1. The present application is being examined under the pre-AIA first to invent provisions.

First Action Interview Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	AIA (First Inventor to File) Status No

The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address.

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

☐ Applicant's request to not have a first-action interview is acknowledged (or the time period for reply set forth in the Pre-Interview Communication has expired and the Office did not receive any reply).

Status

1)☒ Responsive to communication(s) filed on *8/20/2013* and interview conducted on *8/12/2013*.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

3)☒ Claim(s) *40-61* is/are pending in the application.
3a) Of the above claim(s) _____ is/are withdrawn from consideration.

4)☐ Claim(s) _____ is/are allowed.

5)☒ Claim(s) *40-61* is/are rejected.

6)☐ Claim(s) _____ is/are objected to.

7)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

8)☐ The specification is objected to by the Examiner.

9)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

10)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)270-3277

Examiner's Typical Work Schedule: Mon.-Fri. 8:30-5:00

Supervisor's Name: Sreenivasan Padmanabhan

Supervisor's Telephone Number:

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	4) ☐ Other: _____.

First Action Interview Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	40-45,57,60,61	US 2004/006367 (Fox)	102(b)	Fox teaches an composition of an oral dosage form of zoledronic acid and its sodium salt, and does not require bioavailability-enhancing agents, which is preferably in the range of about 1 to about 10 mg for a human.
				This range specifically lists 10 mg. It can be with more than one unit. (para [0063-65],[0070-71],[0078-81]). Such a formulation will inherently possess the bioavailability, aqueous solubility of Applicant's claims.*
				The zoledronic acid can also be from about 1 to about 500 mg. ([0079]). The examples teach formulations with a single active ingredient.
2	46-56	US2004/006367, Chandler	103(a)	Fox is discussed above. It does not explicly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms, which guidelines disclose that such
				units, strength in mg and duration of administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts, timing, duration of administration, and prepare

Expanded Discussion/Commentary		
1		* The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.1% to about 2%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents.
1		* Applicant has argued that the dosage form of Fox may not necessarily have the bioavailability of of Applicant's claims, i.e., it may be in a delayed or prolonged release formulation. However, as addressed above, the dosage form of Fox does not require bioavailability enhancing agents. Such a dosage form is consistent with Applicant's description from its specification in [055].
		Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09 ("Chandler").
34		ODP= obviousness-type double patenting
		Further arguments made by Applicant were addressed by the Examiner in the interview summary from 8/19/2013, and are incorporated by reference herein.

DATE:		

First Action Interview Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
				unit dosage forms labelling with such information. Such optimization is further obvious, as it is mandated by the FDA.
3	40-57,60,61	13/894,262	ODP	of claims 1-19. In order to practice the method, it is necessary to have possession of the oral dosage form.
4	40-57,60,61	13/894,252	ODP	of claims 20-39. In order to practice the method, it is necessary to have possession of the oral dosage form.

Expanded Discussion/Commentary

DATE:	/SVETLANA M. IVANOVA/ Examiner, Art Unit 1627	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
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NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

	1	CULLEN et al., MER-101: A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae. Poster Presentation, November 2007.	☐
	2	LEONARD et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation, October 2007.	☐
	3	LEONARD et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009.	☐
	4	LEONARD et al., Studies of bioavailability and food effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women. Poster Presentation, October 2009.	☐
	5	MCHUGH et al., MER-101-03, A multi center, phase II study to compare MER-101 20mg tablets to intravenous Zometa 4mg in prostate cancer patients. Poster Presentation, May 2009.	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature	/Svetlana Ivanova/	Date Considered	10/29/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

No copies provided.

EFS Web 2.1.17 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-08-20
Name/Print	Brent A. Johnson	Registration Number	51851

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	4	("20040063670" | "20100215743" | "20110028435" | "20120190647").PN.	US-PGPUB	OR	ON	2013/07/12 17:16
S2	2	"1127573"	US-PGPUB; EPO	OR	ON	2013/07/12 17:29

EAST Search History (Interference)

<This search history is empty>

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C:\Users\sivanova\Documents\EAST\Workspaces\13894244.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
PALM inventor search	10/29/2013	si
EAST search	10/29/2013	si

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013							
	1	-	-							
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CLAIM		DATE								
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	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013							
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013							
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	118	-	-							
	119	-	-							

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021

CONFIRMATION NO. 1033

IMPROPER CPOA LETTER

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

Date Mailed: 11/08/2013

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 11/05/2013. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A party who is not the applicant must become the applicant in accordance with 37 CFR 1.46(c) and appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. For a reissue application, reexamination proceeding, or supplemental examination proceeding, a patent owner who was not the applicant under 37 CFR 1.46 must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/hchristian/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**1033**
Appln. No.	:	13/894,244
Applicant	:	Herriot Tabuteau
Filed	:	05/14/2013
Docket No.	:	1958603.00021
Customer No.	:	45200
Title	:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

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UPDATED APPLICATION DATA SHEET IN RESPONSE TO NOTICE REGARDING POWER OF ATTORNEY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sirs:

In response to the Notice Regarding Power of Attorney mailed October 22, 2013, Applicants submit the attached Updated Application Data Sheet with updates underlined. Also attached is the Power of Attorney and 3.73 Statement.

The Commissioner is authorized to charge any fee which may be required in connection with this Notice or credit any overpayment to deposit account No. 50-3207.

Respectfully submitted,

Dated: November 11, 2013

/Brent A. Johnson/
Brent A. Johnson Ph.D.
Registration No. 51851
Customer No. 45,200

K&L GATES, LLP
1 Park Plaza, 12th Floor
Irvine, California 92614-7319
Telephone: 949.253.0900
Facsimile: 949.253.0902

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Herriot		Tabuteau	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	New York	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	260 Park Avenue South, Apt. B		
Address 2			
City	New York	State/Province	NY
Postal Code	10010	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	45200		
Email Address	chicago.patents@klgates.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease		
Attorney Docket Number	1958603.00021	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	Suggested Figure for Publication (if any)	

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	45200		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61646538	2012-05-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61647478	2012-05-15
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654292	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654383	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655527	2012-06-05
Prior Application Status	Pending		Remove

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655541	2012-06-05
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61762225	2013-02-07
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61764563	2013-02-14
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767647	2013-02-21
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767676	2013-02-21
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61803721	2013-03-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Antecip Bioventures II LLC		
Mailing Address Information For Applicant:			
Address 1	630 Fifth Ave.		
Address 2			
City	New York	**State/Province**	NY
Country	US	Postal Code	10111
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Mailing Address Information For Non-Applicant Assignee:			
Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature	/Brent Johnson/			Date (YYYY-MM-DD)	2013-11-05
First Name	Brent	Last Name	Johnson	Registration Number	51851

Additional Signature may be generated within this form by selecting the Add button.

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/96 (01-09)
Approved for use through 02/28/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Herriot Tabuteau

Application No./Patent No.: 13/894,244 Filed/Issue Date: 05/14/2013

Titled: Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Antecip Bioventures II LLC , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 030421, Frame 0213, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Brent A. Johnson/ 10/16/2013

Signature Date

Brent A. Johnson Attorney

Printed or Typed Name Title

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 45200

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 45200

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

Antecip Bioventures II LLC
2711 Centerville Road, Suite 400
Wilmington, DE 19808

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	[signature]	Date	6-20-12
Name	HERRIOT TABUTEAU	Telephone	646-688-2824
Title	MANAGING MEMBER		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	17369131
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	11-NOV-2013
Filing Date:	14-MAY-2013
Time Stamp:	17:31:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1958603-21.pdf	218762 ccf07005331b35e23450008e57d676006ceaf7f2	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Response to Pre-Exam Formalities Notice	1	1
	Application Data Sheet	2	7
	Assignee showing of ownership per 37 CFR 3.73.	8	8

Warnings:					
Information:					
2	Power of Attorney	POA2.pdf	50955 014bf8b206e724f52db94c916244291d6b2a939a	no	1
Warnings:					
Information:					
		Total Files Size (in bytes):	269717		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021

CONFIRMATION NO. 1033

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

PUBLICATION NOTICE

Title: Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Publication No.US-2013-0303485-A1
Publication Date:11/14/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021

CONFIRMATION NO. 1033

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

POA ACCEPTANCE LETTER

OC000000064967429

Date Mailed: 11/15/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/11/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/nhassani/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/894,244	05/14/2013	1627	1030	1958603.00021	20	2

CONFIRMATION NO. 1033

CORRECTED FILING RECEIPT

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

OC000000064967405

Date Mailed: 11/15/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Herriot Tabuteau, New York, NY;

Applicant(s)

Antecip Bioventures II LLC, New York, NY

Assignment For Published Patent Application

Antecip Bioventures II LLC, NEW YORK, NY

Power of Attorney: The patent practitioners associated with Customer Number 45200

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/646,538 05/14/2012
and claims benefit of 61/647,478 05/15/2012
and claims benefit of 61/654,292 06/01/2012
and claims benefit of 61/654,383 06/01/2012
and claims benefit of 61/655,527 06/05/2012
and claims benefit of 61/655,541 06/05/2012
and claims benefit of 61/762,225 02/07/2013
and claims benefit of 61/764,563 02/14/2013
and claims benefit of 61/767,647 02/21/2013
and claims benefit of 61/767,676 02/21/2013
and claims benefit of 61/803,721 03/20/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 06/10/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/894,244**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
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	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

	1	CULLEN et al., MER-101: A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae. Poster Presentation, November 2007.	☐
	2	LEONARD et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation, October 2007.	☐
	3	LEONARD et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009.	☐
	4	LEONARD et al., Studies of bioavailability and food effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women. Poster Presentation, October 2009.	☐
	5	MCHUGH et al., MER-101-03, A multi center, phase II study to compare MER-101 20mg tablets to intravenous Zometa 4mg in prostate cancer patients. Poster Presentation, May 2009.	☐
	6	Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation. European Medicines Agency Science Medicines Health, September 6, 2013.	☐
	7	Opinion of the Committee for Orphan Medicinal Products on orphan medicinal product designation. European Medicines Agency Science Medicines Health, September 4, 2013.	☐
	8	SEBASTIN, SJ. Complex regional pain syndrome. Indian J. Plast. Surg. 44(2): 298-307 (2011).	☐
	9	ENGLISH, A life of pain: woman chooses amputation to deal with painful disorder. http://www.katu.com/news/local/A-life-of-pain-Woman-chooses amputation-to-deal-with... November 18, 2013.	☐

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	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-11-19
Name/Print	Brent A. Johnson	Registration Number	51851

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Electronic Patent Application Fee Transmittal

Application Number:	13894244
Filing Date:	14-May-2013
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman/Georgia Kefallinos
Attorney Docket Number:	1958603.00021

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	17442462
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Georgia Kefallinos
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	19-NOV-2013
Filing Date:	14-MAY-2013
Time Stamp:	14:35:24
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Payment information:

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Warnings:					
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11	Fee Worksheet (SB06)	fee-info.pdf	30195 24e2bfe2419e69bacaa8eec966309395b7dc0c42	no	2
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<u>New International Application Filed with the USPTO as a Receiving Office</u>
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**1033**
Appln. No.	**:**	**13/894,244**
Applicant	**:**	**Herriot Tabuteau**
Filed	**:**	**05/14/2013**
TC/A.U.	**:**	**1627**
Examiner	**:**	**Svetlana M. Ivanova**
Docket No.	**:**	**1958603.00021**
Customer No.	**:**	**45200**
Title	**:**	**COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE**

AMENDMENT AND REMARKS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant submits the following Amendment and Remarks in Response to the Office Action dated November 6, 2013 in the above referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-39. (Canceled)

40. (Currently Amended) An oral dosage form comprising at least about 10 mg of zoledronic acid, wherein the oral bioavailability of zoledronic acid in the dosage form is about ~~about~~ 0.1% to about 2% in a human being, and wherein zoledronic acid is the sole therapeutically active agent in the dosage form.

41. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 300 mg of zoledronic acid.

42. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

43. (Previously Presented) The oral dosage form of claim 40, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 1%.

44. (Original) A pharmaceutical product comprising more than one unit of an oral dosage form of claim 40.

45. (Previously Presented) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

46. (Previously Presented) The pharmaceutical product of claim 45, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about 280 mg to about 1600 mg of zoledronic acid to be administered in about 1 month.

47. (Previously Presented) The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form, for a total of about 850 mg to about 4800 mg of zoledronic acid to be administered in about 3 months.

48. (Previously Presented) The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form, for a total of about 1700 mg to about 10,000 mg of zoledronic acid to be administered in about 6 months.

49. (Previously Presented) The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form, for a total of about 3500 mg to about 19,000 mg of zoledronic acid to be administered in about 1 year.

50. (Original) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 300 mg.

51. (Original) The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form, for a total of about 40 mg to about 1500 mg of zoledronic acid to be administered within a period of about 1 month.

52. (Original) The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form, for a total of about 80 mg to about 2700 mg of zoledronic acid to be administered in about 2 months.

53. (Original) The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form, for a total of about 120 mg to about 4200 mg of zoledronic acid to be administered in about 3 months.

54. (Original) The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form, for a total of about 220 mg to about 9000 mg of zoledronic acid to be administered in about 6 months.

55. (Original) The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form, for a total of about 450 mg to about 18000 mg of zoledronic acid to be administered in about 1 year.

56. (Original) The pharmaceutical product of claim 44, comprising 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid.

57. (Previously Presented) The oral dosage form of claim 40, wherein the zoledronic acid is in the form of a sodium salt.

58-59. (Canceled)

60. (Previously Presented) An oral dosage form comprising zoledronic acid and an excipient, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v), and wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being.

61. (Previously Presented) The oral dosage form of claim 60, wherein the zoledronic acid is in a form that has an aqueous solubility of about 5% (w/v) to about 50% (w/v).

62-119. (Canceled)

120. (New) The oral dosage form of claim 1, wherein the zoledronic acid is present in an amount that provides relief of an inflammatory pain at least 6 hours after administration of the dosage form.

REMARKS/ARGUMENTS

Claim 40 is amended herein to correct a typographical error. Claim 120 is newly added. Claim 120 is supported by at least ¶ 34 of the specification.

In general, Applicant reiterates any arguments made in the previous response that are relevant to the issues of the present rejection. In addition, Applicant adds the arguments below.

35 U.S.C. §102 Rejections

Fox

Claims 40-45, 57, 60, and 61 are rejected as allegedly being anticipated by Fox (US 2004/0063670). Applicant respectfully traverses the rejection. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."[1] In order to anticipate a claim, "the prior art reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference."[2] The rejected claims are not anticipated at least because Fox does not teach the claim elements "an oral dosage form comprising at least about 10 mg of zoledronic acid," or "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being."

[1] MPEP 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

[2] *Net MoneyIN, Inc v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008), quoting *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). Emphasis present in published opinion.

Fox does not teach oral zoledronic acid

Fox does not expressly teach "an oral dosage form comprising…zoledronic acid." Fox only mentions oral dosage forms in ¶¶ 0071, 0072, 0081, and 0082. These paragraphs, as well as ¶¶ 0087 and 0088, are shown below.

> [0071] The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).
>
> [0072] Preferably, the pharmaceutical compositions are adapted to oral or parenteral (especially intravenous, intra-arterial or transdermal) administration. Intravenous and oral, first and foremost intravenous, administration is considered to be of particular importance. Preferably the bisphosphonate active ingredient is in the form of a parenteral, most preferably an intravenous form.
>
> [0081] For example, pharmaceutical-preparations for oral administration can be obtained by combining the active ingredient with solid carriers, where appropriate granulating a resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable adjuncts, into tablets or drage cores. Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating agents and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions that optionally contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in suitable organic solvents or solvent mixtures or, to produce coatings that are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colouring substances or pigments may be added to the tablets or dragee coatings, for example for the purpose of identification or to indicate different doses of active ingredient.
>
> [0082] Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin, and also soft, sealed capsules made of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, where appropriate, stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilisers to be added.
>
> [0087] Capsules containing coated pellets of active ingredient, for example, disodium pamidronate pentahydrate, as active ingredient:

Core pellet:	
active ingredient (ground)	197.3 mg
Microcrystalline cellulose (Avicel ® PH 105)	52.7 mg
	250.0 mg
+ Inner coating:	
Cellulose HP-M 603	10.0 mg
Polyethylene glycol	2.0 mg
Talc	8.0 mg
	270.0 mg
+ Gastric juice-resistant outer coating:	
Eudragit ® L 30 D (solid)	90.0 mg
Triethyl citrate	21.0 mg
Antifoam ®	AF
2.0 mg	Water
Talc	7.0 mg
	390.0 mg

[0088] A mixture of disodium pamidronate with Avicel® PH 105 is moistened with water and kneaded, extruded and formed into spheres. The dried pellets are then successively coated in the fluidized bed with an inner coating, consisting of cellulose HP-M 603, polyethylene glycol (PEG) 8000 and talc, and the aqueous gastric juice-resistant coat, consisting of Eudragit® L 30 D, triethyl citrate and Antifoam AF. The coated pellets are powdered with talc and filled into capsules (capsule size 0) by means of a commercial capsule filling machine, for example Hofliger and Karg.

None of the paragraphs above even mention zoledronic acid, therefore, an oral dosage form comprising zoledronic acid is not "expressly or inherently described" in Fox, and the claim is not anticipated.

The Office Action's allegation that "Fox teaches a composition of an oral dosage form of zoledronic acid"[3] is incorrect. As shown in the paragraphs above, the disclosure of oral dosage form is not directly related to that of zoledronic acid. An oral dosage form of zoledronic acid can only be obtained by "picking, choosing, and combining." For example, one of ordinary skill in the art would have to choose zoledronic acid as the "active ingredient" or the "bisphosphonate active ingredient." Therefore, the Office's conclusion with respect to what Fox teaches is incorrect.

[3] Office Action, p. 2.

Fox does not teach the claimed amount of zoledronic acid in an oral dosage form

The only places where Fox mentions amounts of zoledronic acid are ¶¶ 0078, 0091-0092, 0102, 0104, and 0108, which are reproduced below.

[0078] Preferably, the bisphosphonates are administered in doses which are in the same order of magnitude as those used in the treatment of the diseases classically treated with bisphosphonic acid derivatives, such as Paget's disease, tumour-induced hypercalcemia or osteoporosis. In other words, preferably the bisphosphonic acid derivatives are administered in doses which would likewise be therapeutically effective in the treatment of Paget's disease, tumour-induced hypercalcaemia or osteoporosis, i.e. preferably they are administered in doses which would likewise effectively inhibit bone resorption. For example, for the preferred nitrogen-containing bisphosphonates, e.g. zoledronic acid and salts thereof, doses of bisphosphonate in the range from about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, may be used for treatment of human patients.

[0089] Monolith adhesive transdermal system, containing as active ingredient, for example, 1-hydroxy-2-(imidazol-1-yl)-ethane-1,1-diphosphonic acid:

Composition:	
polyisobutylene (PIB) 300 (Oppanol B1, BASF)	5.0 g
PIB 35000 (Oppanol B10, BASF)	3.0 g
PIB 1200000 (Oppanol B100, BASF)	9.0 g
hydrogenated hydrocarbon resin (Escorez 5320, Exxon)	43.0 g
1-dodecylazacycloheptan-2-one (Azone, Nelson Res., Irvine/CA)	20.0 g
active ingredient	20.0 g
Total	100.0 g

[0090] The above components are together dissolved in 150 g of special boiling point petroleum fraction 100-125 by rolling on a roller gear bed. The solution is applied to a polyester film (Hostaphan, Kalle) by means of a spreading device using a 300 mm doctor blade, giving a coating of about 75 g/m^2. After drying (15 minutes at 60° C.), a silicone-treated polyester film (thickness 75 mm, Laufenberg) is applied as the peel-off film. The finished systems are punched out in sizes in the wanted form of from 5 to 30 cm^2 using a punching tool. The complete systems are sealed individually in sachets of aluminised paper.

Example 3

[0091] Vial containing 1.0 mg dry, lyophilized 1-hydroxy-2-(imidazol-1-yl)- ethane-1,1-diphosphonic acid (mixed sodium salts thereof). After dilution with 1 ml of water, a solution (concentration 1 mg/ml) for i.v. infusion is obtained.

Composition:		
active ingredient (free diphosphonic acid)		1.0 mg
mannitol		46.0 mg
Trisodium citrate × 2 H_2O	ca.	3.0 mg
water		1 ml
water for injection		1 ml.

[0092] In 1 ml of water, the active ingredient is titrated with trisodium citrate•2 H_2O to pH 6.0. Then, the mannitol is added and the solution is lyophilized and the lyophilisate filled into a vial.

[0102] 1. In a model of inflammatory hyperalgesia induced by unilateral hindpaw injection of complete Freund's adjuvant Zoledronate (0.003-0.1 $mgkg^{-1}$ s.c.) produced a dose-dependant reversal of mechanical hyperalgesia. The effect was rapid in onset, with a maximal reversal of 100% within 30 min, and of short duration with no significant activity 3 h following administration. Some contralateral activity was observed at the highest dose.

[0104] 3. In a model of chronic neuropathic pain induced by unilateral partial sciatic nerve ligation. Zoledronate (0.003-0.1 $mgkg^{-1}$ s.c.) produced a moderate 40% reversal of mechanical hyperalgesia which was maximal within 30 min of administration. However, there was also a significant reduction in contralateral paw withdrawal thresholds at the highest dose.

[0108] Adult female rats were given intra-tibial injections of MRMZ1 rat mammary gland carcinoma cells (3 µl, 10^7 cells/ml). These animals gradually developed mechanical hyperalgesia, mechanical allodynia (skin sensitivity to non-noxious stimuli) and hind limb sparing, beginning on day 12-14 following cell injection. Zoledronic acid (ZOL) (10 and 30 µg/kg s.c.) administered 3 times a week from the day of cell injection, produced a profound inhibition of hind limb sparing and mechanical allodynia In comparison to vehicle-treated controls, which showed maximal hind limb sparing by day 19, rats given the higher ZOL dose did not develop any sign of hind limb sparing over 19 days following intra-tibial cell injection. However, when administered as a single injection (100 µg/kg, s.c.) on day 19, ZOL had no acute effect. By contrast, acute treatment with morphine (1-10 mg/kg, s.c.) produced a dose dependent reduction in mechanical allodynia and, at the highest dose only, also a significant reduction in hind limb sparing.

These paragraphs do not even mention an oral dosage form. Therefore "an oral dosage form comprising at least 10 mg zoledronic acid" is not "explicitly or inherently described," and the rejected claims are not anticipated.

The Office Action alleges that "Fox teaches a composition of an oral dosage form of zoledronic acid…which is preferably in the range of about 1 to about 10 mg for a human." As shown in ¶0078 above, the disclosure of oral dosage form is not directly related to "about 1 to about 10 mg." An oral dosage form having "about 1 to about 10 mg" of zoledronic acid can only be achieved by "picking, choosing, and combining." For

example, one of ordinary skill in the art would have to choose an oral "dose" instead of another type of "dose," such as an intravenous "dose," a subcutaneous "dose," a transdermal "dose," etc. Therefore, the Office's conclusion with respect to what Fox teaches is incorrect.[4]

Fox does not teach the claimed oral bioavailability range

Fox does not expressly teach "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being." The Office Action alleges that "Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents"[5] Thus, according to the Office Action, the element of the claims is the same as an element "substantially free of bioavailability-enhancing agents." Applicant respectfully disagrees with the Office Action's modification of this claim element. However, even this alleged revised element is not in Fox. Fox does not even mention bioavailability-enhancing agents, so it cannot teach a limitation such as "substantially free of bioavailability-enhancing agents."

The Office Action alleges that Fox "does not require bioavailability-enhancing agents."[6] But a reference cannot require something that it does not mention, and it is improper to extract a negative limitation from a feature that is not mentioned in a reference. Fox does not expressly say that some of its dosage forms do not have bioavailability enhancing agents, and Fox does not describe any oral dosage forms that contain zoledronic acid and lack a bioavailability enhancing agent. Therefore, Fox teaches neither the element actually in the claims nor the Office Action's incorrect modified version of the claim element.

[4] Applicant also disagrees that "about 1 to about 10 mg" teaches "at least 10 mg," and reserve to right to make this argument at a later time.
[5] Office Action, p. 2.
[6] *Id.*

35 U.S.C. §103 Rejections

Claims 46-56 are rejected as allegedly being obvious over the combination of Day, Fox, and Chandler (Labeling Of Unit Dose Packages Of Drugs, Department Of Pharmacy Policy, University Of Kentucky Hospital Chandler Medical Center, Policy Number: PH-04-06, 11/09). Applicant respectfully traverses the rejection. In order to make a proper *prima facie* case of obviousness, the Office must show: 1) that all elements of the claims are taught or suggested in the prior art;[7] 2) that there is an apparent reason to combine the prior art elements in the manner claimed;[8] and 3) that the result is predictable.[9] In making this determination, the Patent Office must examine the prior art, design demands, marketplace demands, and the background knowledge of a person of ordinary skill in the art.[10] These factors must be considered as a whole, including anything that teaches away from the claimed invention.[11] The rejected claims are not obvious at least because the cited references do not teach or suggest the claimed bioavailability range, the result of using an oral dosage form is not predictable, the claimed oral dosage form can produce unexpected results, the claimed oral dosage form satisfies a long-felt need, and skepticism of experts with respect to the efficacy of the claimed oral dosage form.

The cited references do not teach or suggest the claimed bioavailability range.

All of the cited references are silent with respect to the bioavailability of an oral dosage form of zoledronic acid. As explained above, Fox does not expressly or inherently teach this limitation. Additionally, there is nothing in the combination of Fox and Chandler that suggests "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being." Therefore, the cited

[7] *KSR v. Teleflex*, 127 S. Ct. 1727, 1740-1741 (2007); *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).
[8] *KSR*, 127 S. Ct. at 1740-1741.
[9] *Id.*
[10] *Id.*
[11] *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

references do not teach or suggest all elements of the rejected claims, and the rejected claims are not *prima facie* obvious.

A panel of experts was skeptical with respect to the efficacy of the claimed dosage form.

The claimed composition is also not obvious because a panel of experts expressed disbelief that a claimed composition would be effective. "Expressions of disbelief by experts constitute strong evidence of nonobviousness."[12] Recently, Applicant applied for orphan drug status for a claimed composition with the European Medicines Agency. The application was considered by the Committee for Orphan Medicinal Products ("the Committee"), which includes over thirty experts that are independent of the EMA. Information on this committee, including CVs of the members, was submitted with the previous response.

As explained in the previous response, the Committee denied the application, stating that "[t]he data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS."[13] According to a standard dictionary, the term "plausible" has the meaning "superficially fair, reasonable, or valuable but often specious."[14] Thus, it is fair to say that the Committee, having over 30 experts, expressed disbelief that a claimed composition would be effective in treating CRPS. Furthermore, this demonstrates that the experts on the Committee did not believe there was a reasonable expectation of success in the treatment.

The Interview Summary, incorporated by reference into the Office Action, states that "Examiner indicated that, not being an expert on FDA submissions, it did not seem

[12] MPEP 716.05, quoting *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966), emphasis added.
[13] Draft Public Summary of Opinion prepared by the Committee For Orphan Medicinal Products Of The European Medicines Agency (Draft Public Summary), emphasis added. Submitted previously.
[14] Merriam Webster's Collegiate Dictionary, Tenth Edition, Merriam-Webster, Incorporated, Springfield, Mass., 1997, p. 892.

surprising that the committee would like to see data with the specific product in the application, and not with some other product." If Applicant understands the Interview Summary correctly, it appears that the Office is taking the position that the statement "[t]he data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS"[15] does not actually mean that the committee did not believe that oral zoledronic acid could plausibly be used in the treatment of CRPS. Instead, the Interview Summary seems to be indicating that the Committee denied the application because it failed to meet some higher, unstated, standard of likelihood of success than "plausibly."

Applicant submits herewith the European Medicines Agency Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation, dated September 6, 2013 (COMP Review). This review shows that, for the 1744 orphan drug applications submitted from 2000 to 2013, only 18, or 1%, of these applications received a Final negative COMP opinion.[16] On the other hand, 1196, or 72%, received positive COMP opinions.[17] The remaining applications were withdrawn before a final opinion issued. Thus, there were about 72 times more applications receiving positive opinions than applications receiving negative opinions. Furthermore, of the 147 applications submitted in 2013, only 1 application, that of Applicant, received a final negative opinion.[18] This demonstrates that the COMP's standard for "plausible" is really its plain meaning, i.e. "superficially fair, reasonable, or valuable but often specious," and not some higher standard as alleged by the Interview Summary. Therefore, a panel of experts did express disbelief that the claimed dosage form would be effective, and the rejected claims are not obvious.

Applicant also notes that the standard for a positive COMP opinion is much lower than that required for a drug to be approved for market. From the 1196 applications that

[15] Draft Public Summary, emphasis added.
[16] COMP Review, Annex 1, p. 4. To be submitted in an IDS on the same day as this communication.
[17] *Id.*
[18] *Id.*

received positive COMP opinions from 2000-2013, only 82 orphan medicinal products were authorized for sale.[19]

The result is not predictable.

The rejected claims are not obvious because the efficacy of the claimed oral dosage form is not predictable. "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness."[20] As explained above, the COMP, a panel of experts in the field, asserted that it was not plausible to expect that the claimed dosage form would be effective in treating complex regional pain syndrome.

The Committee observed that "[t]he main data provided in support of the application consisted of a conference abstract describing a study in 24 patients with CRPS treated with zoledronic acid by injection, but lacking relevant details that would be necessary for an in-depth assessment of the results."[21] The Committee further stated that "[n]o data had been provided on zoledronic acid given by mouth, which was the proposed route of administration for the product in this application." [22] The rationale described above is readily applied to Fox. The only data provided in these references are from subcutaneous injection into rats. The references lack the relevant details that would be necessary for an in-depth assessment of the results. Furthermore, there is no data in these references for zoledronic acid given by mouth. Thus, the Committee would likely have said the same thing with respect to Fox: that it was not plausible that an oral zoledronic acid would work for the indications recited in those references. Therefore, at the time of filing, the use of the claimed oral dosage forms in treating the

[19] *Id.*
[20] MPEP 2143.02 (II), citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)
[21] Draft Public Summary
[22] *Id.* Please note that this statement was not included in the published Summary of Opinion because Applicant felt the information was confidential, and did not want it publicly disclosed at that time.

conditions included in the cited references did not have a reasonable expectation of success, and the rejected claims are not *prima facie* obvious.

It is only Applicant's disclosure that has shown that the claimed oral dosage forms could be used to treat conditions such as CRPS. It should be noted that since the rejection of the orphan drug application, Applicant has resubmitted the orphan drug application. The resubmitted application included, *inter alia*, the data from the experiment described in Example 3. With the new information submitted by Applicant, the Committee approved the orphan drug application. The Opinion of the Committee for Orphan Medicinal Products on orphan medicinal product designation approving the application (Positive Opinion), dated September 4, 2013, is submitted herewith. The Positive Opinion stated that "the intention to treat the condition with medicinal product containing zoledronic acid was considered justified…"[23]

The claimed dosage form satisfies a long felt need.

The claimed dosage form is also not obvious because it satisfies a long felt need. Nonobviousness can be demonstrated if the claimed invention satisfies a persistent need that was recognized by those of ordinary skill in the art that has not been satisfied by another before the invention by applicant, and the invention satisfies the long-felt need.[24]

At the time of filing, there was a persistent need for an effective treatment for CRPS that was recognized by those of ordinary skill in the art. For example, the Positive Opinion states "the condition [CRPS] is chronically debilitating due to symptoms such as pain, hyperesthesia or allodynia, oedema, weakness, tremor, dystonia, as well as skill trophic changes."[25] This need has been recognized for a very long time. For example, Sebastin (filed in an IDS filed on the same day as this

[23] Positive Opinion, p. 3, first bullet point. Submitted in an IDS filed on the same day as this communication.
[24] MPEP 716.04(I)
[25] *Id.*, p. 3, second bullet point.

communication) states that "[t]he earliest documented description of CRPS is probably Ambroise Pare's report from the 16th century describing the persistent pain and contractures experienced by King Charles IX after a blood-letting procedure. In 1766, Hunter described the pain syndrome after a joint injury. Silas Weir Mitchell, the father of American neurology gave the first detailed description of CRPS in 1864."

This need remained unsatisfied at the time of filing of the present application. For example, the Positive Opinion states "there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition."[26] A recent news story says the following about Libby Shaffer, a victim of CRPS. Twenty-five years after her original injury, Schaffer was forced to make an agonizing decision. After years of ineffective drugs, therapies and procedures, she decided the only remaining option was to have doctors amputate her leg."[27]

Finally, the claimed dosage form satisfies this need. The Positive Opinion states "the intention to treat the condition with the medicinal product containing zoledronic acid was considered justified based upon the assumption, that zoledronic acid could treat the underlying cause of the condition, which was demonstrated by the reduction of symptoms and signs observed in a preclinical model of the proposed condition."[28]

Therefore, the dosage forms of the rejected claims are not obvious because they satisfy a long-felt need.

An embodiment of a claimed dosage form produces unexpected results.

In addition to the reasons described above, the claimed composition is not obvious because of the unexpected results presented in the specification. "Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of

[26] *Id.*, p. 3, paragraph 7.
[27] Joe English, A life of pain: Woman chooses amputation to deal with painful disorder. KATU.com, August 26, 2013, Accessed Nov. 18, 2013. Submitted in an IDS filed on the same day as this communication.
[28] *Id.*, p. 3, first bullet point.

obviousness."[29] An unexpected therapeutic effect of a composition qualifies as an unexpected result for the purposes of proving nonobviousness. For example, the MPEP states: "unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria."[30]

As shown in the Figure 1, despite the fact that the compositions of Fox had no reversal of inflammatory pain after 3 hours, the claimed composition had extended pain relief that continued for days. This is clearly an unexpected result.

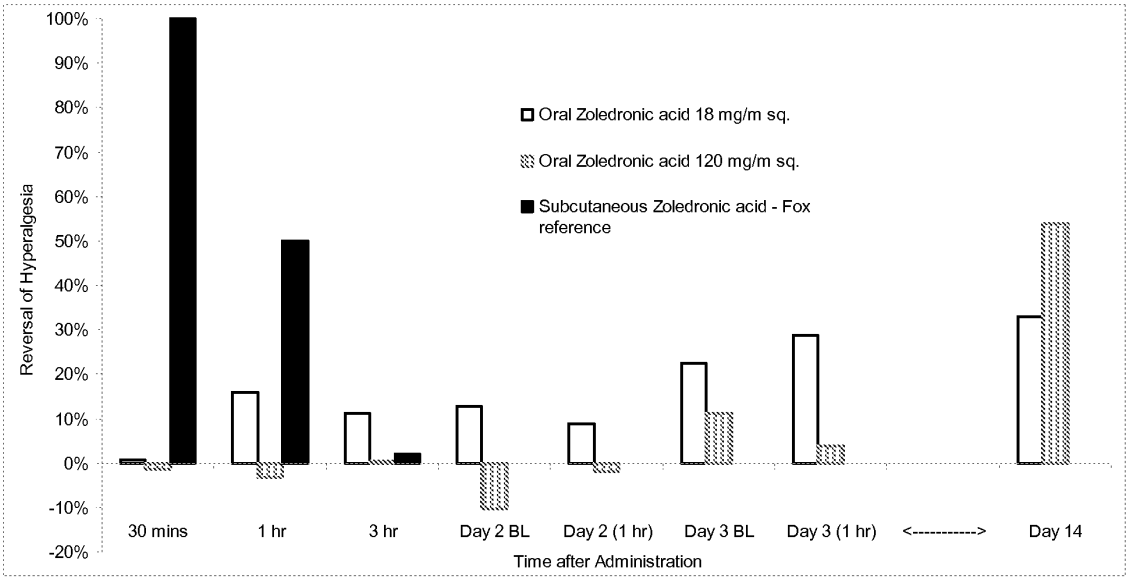

Figure 1

As explained in the previous response, the Figure 1 is a compilation of the data from Examples 1 and 2 of the specification and the Fox reference. This figure clearly demonstrates that the activity of the subcutaneous injection reported in Fox is nearly the opposite of the activity observed for the orally administered zoledronic acid. For the oral

[29] MPEP 2145, citing *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975).
[30] MPEP 716.02 (a)(II), citing *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990), emphasis added.

administration, either no significant effect (18 mg/m^2) or a slight increase in pain (120 mg/m²) was observed at 30 minutes, in contrast with the maximum effect for the subcutaneous administration reported in Fox at the same time point. On the other hand, Fox stated that there was "no significant activity 3 hours following administration." Thus, it is surprising that, at both dosage levels, the oral zoledronic acid had a significant reversal of hyperalgesia 14 days after the first administration and 11 days after administration of the final oral dose (which occurred on day 3).[31] Therefore, the rejected claims are also not obvious because of these unexpected results, and the rejection should be withdrawn.

The Interview Summary states "[t]he Examiner questioned why…2) Applicant is comparing a subcutaneous to an oral formulation, when Fox specifically teaches also an oral formulation, e.g. [071]; 3) Applicant is presenting an argument on method of treatment, when Applicant's claims are directed to a composition."

With respect to point 2), as explained above, Fox does not teach an oral formulation of zoledronic acid. Paragraph [071] cited by the Interview Summary does not even mention zoledronic acid.

> [0071] The pharmaceutical compositions may be, for example, compositions for enteral, such as oral, rectal, aerosol inhalation or nasal administration, compositions for parenteral, such as intravenous or subcutaneous administration, or compositions for transdermal administration (e.g. passive or iontophoretic).

The only zoledronic acid formulations tested in Fox are the subcutaneous formulations which are the subject of Figure 1. Therefore, this comparison is appropriate for demonstrating unexpected results. "[A]pplicant is not required to compare the claimed invention with subject matter that does not exist in the prior art…"[32]

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[31] A higher oral dose was also administered, but the animals were euthanized after 3 days due to the high toxicity level of this dose, so these results are not included in the figure.

[32] MPEP 716.02(e) III.

With respect to point 3), as explained above, an unexpected therapeutic effect of a composition qualifies as an unexpected result for the purposes of obviousness. Thus, Applicant can use unexpected therapeutic effects of the claimed dosage form to demonstrate nonobviousness.

For at least these reasons, the claimed dosage forms are not obvious.

The cited references do not teach or suggest all elements for several of the claims.

There are also a number of claim elements, not present in all of the rejected claims, which are not taught or suggested by the combination of Fox and Chandler. Some representative examples are given below.

Claim 46

The Office Action does not explain how the cited references teach or suggest "comprising 28, 29, 30, or 31 units of the oral dosage form" as recited in claim 46. In fact, Fox would have led a person of ordinary skill in the art to believe that multiple dosage forms would be required per day. Thus, the cited references do not suggest a pharmaceutical dosage form having 28, 29, 30, or 31 units of the dosage form because it would only last for a few days.

Fox includes "a model of inflammatory hyperalgesia."[33] In this model administration of "Zoledronate (0.003-0.1 mgkg-1 s.c.) produced a dose-dependent reversal of mechanical hyperalgesia. The effect was rapid in onset, with maximal reversal of 100% within 30 minutes, and of short duration with no significant activity 3 h following administration." A person of ordinary skill in the art would believe that, in order to provide continuous pain relief, a dose of zoledronic acid should be administered before the pain relief from the previous dose is gone. Therefore, based upon the experiment above, a person of ordinary skill in the art would expect that zoledronic acid

[33] Fox, p. 6, ¶ 102.

would need to be given more often than every three hours, and not once a day. Thus, a product containing 28, 29, 30, or 31 units of a dosage form would not be prepared because it would only last a few days. Chandler contains does not even mention zoledronic acid, and thus does nothing to suggest that zoledronic acid should not be given more often that every three hours. Therefore, the combination of references does not teach or suggest this element of claim 46.

The Office Action does not explain why a person of ordinary skill in the art would ignore this experimental result in Fox, and instead prepare a product with the claimed number of units of the dosage form. The only explanation made by the Office Action is that "Fox…does not explicitly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms which guidelines disclose that such units, strength in mg and duration of administration should be used for labeling drug unit dosage forms. Accordingly, it would have been obvious to optimize the exact amounts, timing, duration of administration and prepare unit dosage forms labelling [sic] with such information. Such optimization is further obvious, as it is mandated by the FDA."[34] As Applicant understands the statement above, the Office Action appears to be saying that this limitation would have been obvious because it is an optimization of a range. But, optimization of a range can only render a claim obvious if the result is predictable based upon the prior art.[35] Thus, it is not appropriate here to rely upon optimization of ranges to show obviousness because the dosage regime is unexpected, or would not be predicted, by the combination of Fox and Chandler.

Claim 47

The cited references do not teach or suggest the claim element "comprising 85 to 95 units of the oral dosage form…to be administered in about 3 months" that is recited

[34] Office Action, pp. 2-3.
[35] *KSR*, 127 S. Ct. at 1740-1741; MPEP 2144.05(III) ("Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing '(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art.' *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1322, 73 USPQ2d 1225, 1228 (Fed. Cir. 2004).")

in claim 47. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 48

The cited references do not teach or suggest the claim element "comprising 170 to 200 units of the oral dosage form…to be administered in about 6 months" that is recited in claim 48. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 49

The cited references do not teach or suggest the claim element "comprising 350 to 380 units of the oral dosage form…to be administered in about 1 year" that is recited in claim 49. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 51

The cited references do not teach or suggest the claim element "comprising 4 or 5 units of the oral dosage form…to be administered within a period of about 1 month" that is recited in claim 51. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 52

The cited references do not teach or suggest the claim element "comprising 8 or 9 units of the oral dosage form…to be administered in about 2 months" that is recited in claim 52. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 53

The cited references do not teach or suggest the claim element "comprising 12, 13, or 14 units of the oral dosage form…to be administered in about 3 months" that is recited in claim 53. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 54

The cited references do not teach or suggest the claim element "comprising 22 to 30 units of the oral dosage form…to be administered in about 6 months" that is recited in claim 54. As explained above, the combination of Fox and Chandler would have led a person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

Claim 55

The cited references do not teach or suggest the claim element "comprising 45 to 60 units of the oral dosage form…to be administered in about 1 year" that is recited in claim 55. As explained above, the combination of Fox and Chandler would have led a

person of ordinary skill in the art to believe that many units of a dosage form should be given a day. Therefore, the combination of Fox and Chandler does not teach or suggest this limitation.

In summary, the rejected claims are not obvious at least because the combination of references does not teach or suggest the claimed bioavailability range, the result of modifying the cited references as required to obtain a claimed dosage form is not predictable, the combination of references does not teach or suggest the number of units of the dosage forms recited in the claims, experts were skeptical about the therapeutic efficacy of the claimed dosage form, the claimed dosage form has unexpected long term pain relieving properties, and the claimed dosage form satisfies a long-felt need for an effective treatment of complex regional pain syndrome.

DOUBLE PATENTING

The Office has indicated that provisional obviousness type double patenting might exist with respect to Application No. 13/894,262, claims 1-19 and Application No. 13/894,252. Without addressing the propriety of any of the Office's rejections above, and specifically the Office's interpretation of what the cited references teach or suggest, Applicant respectfully and properly defers addressing the present rejections until there is otherwise allowable subject matter in each application. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejections, or that the rejections be held in abeyance until claims are allowable in the present application and in at least one of the applications cited above.

CONCLUSION

For at least the reasons given above, Applicant submits that the claims are patentable. Therefore, Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: November 19, 2013

/Brent Johnson/

Brent A. Johnson, Ph.D.
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Electronic Acknowledgement Receipt

EFS ID:	17444480
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
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Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1958603-21Response_to_OA_of_Nov-06-2013.pdf	194061 50fd9ca5995f46318fb2c09b4da07d25721dcd5e	yes	24

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	24
Warnings:			
Information:			
	Total Files Size (in bytes):	194061	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 11/29/2013

K&L Gates LLP
1 Park Plaza
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EXAMINER	
IVANOVA, SVETLANA M	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/29/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USpatentmail@klgates.com
ocpatents@klgates.com

Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/19/2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *40-57,60,61 and 120* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *40-57, 60, 61 and 120* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Response to Arguments

This is a TRACK 1 application. Applicant's response from 11/19/2013 is acknowledged ("Response"). Applicant has not amended the claims, except as to: 1) remove a duplicate word "about" in claim 1, and 2) introduce new claim 120.

Applicant's arguments have been carefully considered, but have not been found to be persuasive.

35 USC 102(b) rejection- Fox

Applicant has argued that Fox does not teach oral zoledronic acid. (Response at pp. 6-7).

In response, it is noted that Fox expressly teaches an oral dosage form, such as in reference to paragraphs [0070-72], as well as teaches the disclosed dosage forms specifically for zoledronic acid, such as with reference to zoledronic acid in paragraphs [0063-65]. There is no picking, choosing and combining involved, to use Applicant's own lingo, as Fox clearly discloses that: "[t]he most preferred bisphosphonate for use in

the invention is zoledronic acid" (*see, e.g.*, Abstract, [0063]); and that "[p]referably, the pharmaceutical compositions are adapted for oral or parenteral […] administration", and that "[i]ntravenous and oral […] administration is considered to be of particular importance" (*see, e.g.*, [0072]).

Applicant has next argued that Fox does not teach the claimed amount of zoledronic acid in an oral dosage form. (Response at pp. 8-10).

The Examiner incorporates by reference and repeats her responses from above. The Examiner further responds that Applicant has not disputed that the claimed amounts are taught. *See also* paragraphs [0078-81] of Fox wherein the claimed amounts are taught. Beyond that, while the law of anticipation requires that all elements of a claim be found in a reference, it does not require that all the elements be present with the exact same word sequence as employed by the Applicant, i.e., a finding of anticipation does not require an *ipsissimis verbis* test.

Applicant's fn. 4 is further noted wherein Applicant has stated that it disagrees with the Examiner, and reserves to make an argument at a later time. In response, if and when such an argument is made, it will be addressed. In the meantime, the Examiner directs Applicant's attention to the office action, wherein the claim limitation at issue was already addressed.

Applicant has next argued that Fox does not teach the claimed oral bioavailability range. (Response at p. 10).

The Examiner incorporates by reference and repeats her responses from above.

The Examiner further responds that Applicant's argument *vis-a-vis* "Applicant respectfully disagrees with the Office Action's modification of this claim element" is not understood. What exactly does it refer to, either procedurally or substantively? Procedurally, Applicant is reminded that this is a TRACK 1 application, which procedurally requires two non-final office actions in step 1 and step 2. As Applicant amended the claims in response to the office action in step 1 to recite the new claim limitation of “about 0.1% to about 2%” with respect to the oral bioavailability of zoledronic acid in the dosage form, the Examiner appropriately modified the office action to address the new claim limitation in the office action in step 2.

Moreover, the Examiner appropriately addressed this claim limitation substantively. Specifically, the office action provides: “The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.1% to about 2%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents. Applicant has argued that the dosage form of Fox may not necessarily have the bioavailability of Applicant's claims, i.e., it may be in a delayed or prolonged release formulation. However, as addressed above, the dosage form of Fox does not require bioavailability enhancing agents. Such a dosage form is consistent with Applicant's description from its specification in [055].” For Applicant’s convenience and in support of the Examiner’

interpretation, paragraph [055] from Applicant's specification is hereto reproduced for the record.

> **[055]** The oral bioavailability of zoledronic acid in a dosage form can vary. Some dosage forms may have ingredients added to enhance the bioavailability. However, bioavailability enhancement is not necessary for an oral dosage form to be effective. In some embodiments, the dosage form is substantially free of bioavailability-enhancing agents. In some embodiments, an oral dosage form may have an oral bioavailability of zoledronic acid of about 0.01% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, etc. Without ingredients or other methods to enhance bioavailability, zoledronic acid typically has a low bioavailability in an oral dosage form. In some embodiments, the oral bioavailability of zoledronic acid is unenhanced or substantially unenhanced. For example, the oral bioavailability of zoledronic acid can be about 0.01% to about 5%, about 0.01% to about 4%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.2% to about 2%, about 0.2% to about 1.5%, about 0.3% to about 1.5%, about 0.3% to about 1%, about 0.1% to about 0.5%, about 0.3% to about 0.5%, about 0.5% to about 1%, about 0.6% to about 0.7%, about 0.7% to about 0.8%, about 0.8% to about 0.9%, about 0.9%, about 1% to about 1.1%, about 1.1% to about 1.2%, about 1.2% to about 1.3%, about 1.3% to about 1.4%, about 1.4% to about 1.5%, about 1.5% to about 1.6%, about 1.6% to about 1.8%, or about 1.8% to about 2%.

Accordingly, the office action appropriately addressed Applicant's claim limitation pertaining to oral bioavailability in view of Applicant's own specification and the disclosure in Fox. Beyond that, the law places no requirement that Fox expressly use the words "bioavailability enhancing agent" or the lack thereof. As the Federal Circuit holds, the elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). *See also* MPEP 2131. Moreover, contrary to Applicant's arguments, it is appropriate to note elements that a reference is silent about. It is then Applicant's burden to rebut such a rejection with evidence, which here Applicant has not done.

35 USC 102(b) rejection- Fox in view of Chandler

Applicant has argued that the cited references do not teach or suggest the claimed bioavailability range. (Response at p. 11-12). Of note, Applicant has stated that the rejection was made over the combination of Day, Fox and Chandler. In response, it is first noted that the record does not reflect a rejection over Day.

The Examiner incorporates by reference and repeats her responses from above. The Examiner already specifically addressed the argument made over the claim limitation of "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being." Applicant has not made any further arguments *vis-à-vis* the teachings of Chandler. The Examiner notes, nonetheless, that the office action further addressed hereto the rejection in view of the combination with Chandler. "Fox does not explicitly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms, which guidelines disclose that such units, strength in mg and duration of administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts, timing, duration of administration, and prepare unit dosage forms labeling with such information. Such optimization is further obvious, as it is mandated by the FDA." As Applicant has not made any further arguments *vis-à-vis* the teachings of Chandler, it is seen as an acquiescence with the Examiner on this issue.

Applicant has next argued that a panel of experts was skeptical with respect to the efficacy of the claimed dosage form (Response at p. 12-14), and that the result is not predictable (Response at p. 14-15).

The Examiner incorporates by reference and repeats her responses from above. The Examiner first responds that Applicant has not made arguments pertaining to the claims rejected on the ground of obviousness, but rather to the claims overall. Applicant has not overcome an anticipation rejection in order to make arguments pertaining to a hypothetical obviousness rejection.

The Examiner has further responded already very clearly and twice on the record- once at the time of the interview, and once in the interview summary, on the findings of the findings of EMA. For Applicant to be attempting to represent some other understanding (of a standard?) of the interview summary is neither genuine, nor in the interest of compact prosecution, nor supported by the record. To restate her clear position, the Examiner responds that the documents Applicant relies on establish that Applicant's application to the Committee for Orphan Medicinal Products ("Committee") was for an oral formulation, but Applicant did not submit before the committee any data for such a formulation, and instead only relied on data from the prior art on an i.v. formulation. Stated differently, Applicant appears to have attempted to ride on the coattails of another entity before the EMA, instead of submitting its own data for the approval it sought. The Committee responded that it would not be plausible to demonstrate based on this data that zolendronate could be used for the treatment of CRPS, where no oral data has been provided. The Examiner indicated that, not being

an expert on FDA submissions, it did not seem surprising that the committee would like to see data with the specific product for regulatory approval in the application, and not with some other product by some other entity on some other route of administration. For instance, considerations for regulatory approval would include considerations of pharmacokinetics, etc. between the different routes of administration. Therefore, Applicant cannot use what appears to be an appropriately denied regulatory approval for lack of data, in a way which elevates it to strong evidence of nonobviousness for purposes of patentability. Simply put, lack of data for regulatory approval is simply lack of data, and not a pronouncement on patentability and/or predictability for purposes of patentability. Rather, for purposes of patentability Applicant was invited to address instead that oral formulations of zoledronic acid were already taught in the art.

Applicant has next argued the claimed dosage form satisfies a long felt need. (Response at pp. 15-16).

The Examiner incorporates by reference and repeats her responses from above. The Examiner first responds that Applicant has not made arguments pertaining to the claims rejected on the ground of obviousness, but rather on the claims overall. Applicant has not overcome an anticipation rejection in order to make arguments pertaining to a hypothetical obviousness rejection.

The Examiner further responds with reference to the criteria which an Applicant must establish in order to demonstrate long-felt need.

Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539, 152 USPQ 602, 605 (CCPA 1967); *Orthopedic Equipment Co., Inc. v. All Orthopedic Appliances, Inc.,* 707 F.2d 1376, 217 USPQ 1281 (Fed. Cir. 1983).

Second, the long-felt need must not have been satisfied by another before the invention by applicant. *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) (Although at one time there was a long-felt need for a "do-it-yourself" window shade material which was adjustable without the use of tools, a prior art product fulfilled the need by using a scored plastic material which could be torn. "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved".)

Third, the invention must in fact satisfy the long-felt need. *In re Cavanagh*, 436 F.2d 491, 168 USPQ 466 (CCPA 1971).

While focusing on the second prong alone, this Applicant has clearly failed to establish that the long-felt need was not have been satisfied by another before the invention by applicant. Fox is a 35 USC 102(b) reference to the contrary of such a position by Applicant.

With respect to the first and third prong, Applicant is reminded that it has made arguments with respect to treating CRPS, which is the subject of another application

with method claims directed to treating CRPS filed by Applicant- 13/894,274, i.e. another invention. It is not with respect to the composition claims of the instant application.

Applicant has next argued an embodiment of a claimed dosage form produces unexpected results. (Response at pp. 16-19).

The Examiner incorporates by reference and repeats her responses from above. The Examiner first responds that Applicant has not made arguments pertaining to the claims rejected on the ground of obviousness, but rather on the claims overall. Applicant has not overcome an anticipation rejection in order to make arguments pertaining to a hypothetical obviousness rejection.

The Examiner further responds with respect to the data in Figure 1 that Applicant is comparing in its own data of an oral formulation to a subcutaneous formulation. However, Fox as the closest art of record already specifically teaches also an oral formulation, e.g. [071]). Further, Applicant is presenting an argument on method of treatment, when Applicant's claims are directed to a composition. As a matter of law, unexpected results must be compared to the closest prior art. *In re Baxter Travenol*, 952 F.2d 383, 392 (Fed. Cir. 1991). Unexpected results must be established by reliable, objective, factual evidence. *In re Johnson*, 747 F.2d 1456, 1460 (Fed. Cir. 1984).

Applicant has next argued that the cited references do not teach or suggest all elements for several of the rejected claims. (Response at pp. 19-23).

The Examiner incorporates by reference and repeats her responses from above. The Examiner further responds that the office action clearly addressed these claim limitations. Specifically, it provides that: "Chandler discloses guidelines for labeling of unit dosage forms, which guidelines disclose that such units, strength in mg and duration of administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts, timing, duration of administration, and prepare unit dosage forms labeling with such information. Such optimization is further obvious, as it is mandated by the FDA." Accordingly, such optimization of unit dosage forms is not only predictable, but more than that, is the standard in the pharmaceutical arts.

Further, there is no requirement that in a combination rejection, one reference alone teach all the claim limitations. In response to Applicant's arguments against Chandler alone, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments pertaining to the model of inflammatory hyperalgesia in Fox are further not persuasive. In Fox, first the model is rat, not human, and second with a sub-cutaneous dose, not oral dose. Thus, quite contrary to Applicant's arguments, a person of skill in the art would know with a reasonable chance of success

to account for interspecies differences, route of administration, and type of disease. Moreover, motivation to establish the therapeutically effective amounts is further explicitly found in paragraphs [0078-79] of Fox.

Double patenting

Applicant has not made arguments, but only deferred addressing the rejections. For Applicant's convenience, the rejections are repeated for the record below.

Claims 40-57, 60, 61 and 120 are pending, and have been examined herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 120 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 120 recites the limitation "the oral dosage form of claim 1" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 is a cancelled claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-45, 57, 60, 61 are rejected under pre-AIA 35 U.S.C. 102(b) as being anticipated by US 2004/006367 to Fox *et al.* ("Fox", of record).

The claims have been examined to the extent they read on an oral dosage form.

Fox teaches a composition of an oral dosage form of zoledronic acid and its sodium salt, and does not require bioavailability-enhancing agents, which is preferably in the range of about 1 to about 10 mg for a human. This range specifically lists 10 mg. It can be with more than one unit. (para [0063-65], [0070-72], [0078-81]). Such a formulation will inherently possess the bioavailability, aqueous solubility of Applicant's claims. The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.1% to about 2%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of

bioavailability-enhancing agents. Applicant has argued that the dosage form of Fox may not necessarily have the bioavailability of Applicant's claims, i.e., it may be in a delayed or prolonged release formulation. However, as addressed above, the dosage form of Fox does not require bioavailability enhancing agents. Such a dosage form is consistent with Applicant's description from its specification in [055].

The zoledronic acid can also be from about 1 to about 500 mg. ([0079]). The examples teach formulations with a single active ingredient.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 46-56 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2004/006367 to Fox *et al.* ("Fox", of record), as applied to claims 40-45, 57, 60, 61 above, further in view of Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09 ("Chandler", of record).

Fox does not explicitly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms, which

guidelines disclose that such units, strength in mg and duration of administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts, timing, duration of administration, and prepare unit dosage forms labeling with such information. Such optimization is further obvious, as it is mandated by the FDA.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 40-61 are provisionally rejected on the ground of nonstatutory double patenting over claims 1-19 of copending Application No. 13/894,262 ("the '262 application"). This is a provisional double patenting rejection because the patentably indistinct claims have not in fact been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: in order to practice the method, it is necessary to have possession of the oral dosage form.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other

copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claims 40-61 are provisionally rejected on the ground of nonstatutory double patenting over claims 20-39 of copending Application No. 13/894,252 ("the '252 application"). This is a provisional double patenting rejection because the patentably indistinct claims have not in fact been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: in order to practice the method, it is necessary to have possession of the oral dosage form.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SVETLANA M. IVANOVA whose telephone number is (571)270-3277. The examiner can normally be reached on Mon.-Fri. 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SVETLANA M. IVANOVA/
Examiner, Art Unit 1627

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013	11/25/2013						
	1	-	-	-						
	2	-	-	-						
	3	-	-	-						
	4	-	-	-						
	5	-	-	-						
	6	-	-	-						
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	36	-	-	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013	11/25/2013						
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	38	-	-	-						
	39	-	-	-						
	40	✓	✓	✓						
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	42	✓	✓	✓						
	43	✓	✓	✓						
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	72	-	-	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013	11/25/2013						
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	106	-	-	-						
	107	-	-	-						
	108	-	-	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013	10/29/2013	11/25/2013						
	109	-	-	-						
	110	-	-	-						
	111	-	-	-						
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	115	-	-	-						
	116	-	-	-						
	117	-	-	-						
	118	-	-	-						
	119	-	-	-						
	120			✓						

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3196	(zoledronic adj acid) or zolendronate	US-PGPUB; USPAT; EPO; JPO	OR	ON	2013/11/25 17:29
L2	357	((zoledronic adj acid) or zolendronate).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:29
L3	563501	oral	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:30
L4	285	2 and 3	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:30
S1	4	("20040063670" | "20100215743" | "20110028435" | "20120190647").PN.	US-PGPUB	OR	ON	2013/07/12 17:16
S2	2	"1127573"	US-PGPUB; EPO	OR	ON	2013/07/12 17:29

EAST Search History (Interference)

<This search history is empty>

11/25/2013 5:38:25 PM
C:\Users\sivanova\Documents\EAST\Workspaces\13894244.wsp

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Published Application citation information please click the Add button.						Add

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button							Add	

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

	1	CULLEN et al., MER-101: A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae. Poster Presentation, November 2007.	☐
	2	LEONARD et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation, October 2007.	☐
	3	LEONARD et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009.	☐
	4	LEONARD et al., Studies of bioavailability and food effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women. Poster Presentation, October 2009.	☐
	5	MCHUGH et al., MER-101-03, A multi center, phase II study to compare MER-101 20mg tablets to intravenous Zometa 4mg in prostate cancer patients. Poster Presentation, May 2009.	☐
	6	Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation. European Medicines Agency Science Medicines Health, September 6, 2013.	☐
	7	Opinion of the Committee for Orphan Medicinal Products on orphan medicinal product designation. European Medicines Agency Science Medicines Health, September 4, 2013.	☐
	8	SEBASTIN, SJ. Complex regional pain syndrome. Indian J. Plast. Surg. 44(2): 298-307 (2011).	☐
	9	ENGLISH, A life of pain: woman chooses amputation to deal with painful disorder. http://www.katu.com/news/local/A-life-of-pain-Woman-chooses amputation-to-deal-with... November 18, 2013.	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature	/Svetlana Ivanova/	Date Considered	11/25/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

References 1-6 were crossed out, because entire poster presentations were shrunk on single individual pages, and then scanned, so they are impossible to read. SI

EFS Web 2.1.17

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-11-19
Name/Print	Brent A. Johnson	Registration Number	51851

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /S.I./

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
PALM inventor search	10/29/2013	si
EAST search	10/29/2013	si
EAST search	11/25/2013	si

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 12/10/2013

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER	
IVANOVA, SVETLANA M	
ART UNIT	**PAPER NUMBER**
1627	

NOTIFICATION DATE	DELIVERY MODE
12/10/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USpatentmail@klgates.com
ocpatents@klgates.com

Applicant-Initiated Interview Summary	**Application No.**	**Applicant(s)**	
	13/894,244	TABUTEAU, HERRIOT	
	Examiner	**Art Unit**	
	SVETLANA M. IVANOVA	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SVETLANA M. IVANOVA*. (3)_____.

(2) *JASON SZCZEPANSKI*. (4)_____.

Date of Interview: *04 December 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Jason Szcaepanski on behalf of Brent Johnson called to inquire whether the office action dated 11/29/2013 was made final since a paragraph at the end of the office action is missing indicating it to be final. The Examiner responded that form PTO-326 already correctly identified the office action as final, and that an interview summary with the inadvertenly missing paragraph at the end of the office action will be supplied with it, as follows.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SVETLANA M. IVANOVA/ Examiner, Art Unit 1627	

U.S. Patent and Trademark Office

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
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———

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- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

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4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 01/30/2014

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER
IVANOVA, SVETLANA M

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
01/30/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspatentmail@klgates.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/894,244	TABUTEAU, HERRIOT	
	Examiner	Art Unit	
	SVETLANA M. IVANOVA	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SVETLANA M. IVANOVA*.

(2) *SREENI PADMANABHAN*.

(3) *BRENT JOHNSON*.

(4) *HERRIOT TABUTEAU*.

Date of Interview: *23 January 2014*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☒ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants came to discuss in person four related patent applications: 13/894,274,13/894,252, 13/894,262 and 13/894,244. An interview agenda (attached) was submitted. There is overlapping art between the applications, and Applicants only specifically discussed the first two applications, for which more detailed interview summaries are provided in the file histories of the corresponding applications. .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/SVETLANA M. IVANOVA/ Examiner, Art Unit 1627	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**1033**
Appln. No.	:	**13/894,244**
Applicant	:	**Herriot Tabuteau**
Filed	:	**05/14/2013**
TC/A.U.	:	**1627**
Examiner	:	**Svetlana M. Ivanova**
Docket No.	:	**1958603.00021**
Customer No.	:	**45200**
Title	:	**COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE**

INTERVIEW SUMMARY

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant thanks the Examiners for agreeing to the in-person interview of January 23, 2014. The interview was attended by Examiner Svetlana Ivanova, Examiner Sreenivasan Padmanabhan, Inventor Dr. Herriot Tabuteau, and Applicant's representative Brent A. Johnson. In the interview, the Fox reference was discussed. Applicant argued that rejected claims were not anticipated because Fox fails to "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." (*Net MoneyIN, Inc v. Verisign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008), quoting *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). Emphasis present in published opinion.) No agreement was reached.

Respectfully submitted,

Dated: March 3, 2014

/Brent A. Johnson/
Brent A. Johnson, Ph.D.
Registration No. 51,851
CUSTOMER NUMBER: 45200

K&L GATES LLP
1 Park Plaza, Twelfth Floor
Irvine, California 92614

Electronic Acknowledgement Receipt

EFS ID:	18355889
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	03-MAR-2014
Filing Date:	14-MAY-2013
Time Stamp:	19:27:59
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	1958603-21_Interview_Summary.pdf	81404 902acfefb0ff2048ac9d0942809d00550eb99f0f	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	81404

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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AMENDMENT AND REMARKS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Applicant submits the following Amendment and Remarks in Response to the Office Action dated November 29, 2013 in the above referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

Applicant requests a two-month extension of time. The extension fee can be charged to the deposit account listed at the end of the Remarks/Arguments section of this document.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-39. (Canceled)

40. (Currently Amended) An oral dosage form comprising ~~at least about 10 mg~~ about 30 mg to about 250 mg of zoledronic acid, wherein the oral bioavailability of zoledronic acid in the dosage form is about ~~about~~ 0.1% to about [[2%]] 3% in a human being~~, and wherein zoledronic acid is the sole therapeutically active agent in the dosage form~~.

41. (Canceled)

42. (Currently Amended) The oral dosage form of claim 40, wherein the oral dosage form contains about [[10]] 30 mg to about 50 mg of zoledronic acid.

43. (Previously Presented) The oral dosage form of claim 40, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 1%.

44. (Currently Amended) A pharmaceutical product comprising more than one unit of an oral dosage form ~~of claim 40~~, wherein the amount of zoledronic to be administered in one month is about 40 mg to about 800 mg.

45. (Previously Presented) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

46. (Currently Amended) The pharmaceutical product of claim [[45]]44, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about ~~280 mg to about 1600 mg~~ 40 mg to about 600 mg of zoledronic acid of zoledronic acid to be administered in about 1 month.

47. (Currently Amended) The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form~~, for a total of about 850 mg to about 4800 mg of zoledronic acid~~ to be administered in about 3 months.

48. (Currently Amended) The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form~~, for a total of about 1700 mg to about 10,000 mg of zoledronic acid~~ to be administered in about 6 months.

49. (Currently Amended) The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form~~, for a total of about 3500 mg to about 19,000 mg of zoledronic acid~~ to be administered in about 1 year.

50. (Original) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 300 mg.

51. (Currently Amended) The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form~~, for a total of about 40 mg to about 1500 mg of zoledronic acid to~~ be administered within a period of about 1 month.

52. (Currently Amended) The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form~~, for a total of about 80 mg to about 2700 mg of zoledronic acid~~ to be administered in about 2 months.

53. (Currently Amended) The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form~~, for a total of about 120 mg to about 4200 mg of zoledronic acid to~~ be administered in about 3 months.

54. (Currently Amended) The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form~~, for a total of about 220 mg to about 9000 mg of zoledronic acid~~ to be administered in about 6 months.

55. (Currently Amended) The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form~~, for a total of about 450 mg to about 18000 mg of zoledronic acid~~ to be administered in about 1 year.

56. (Original) The pharmaceutical product of claim 44, comprising 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid.

57. (Previously Presented) The oral dosage form of claim 40, wherein the zoledronic acid is in the form of a sodium salt.

58-59. (Canceled)

60. (Currently Amended) An oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid and an excipient, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v), and wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about [[2]]3% in a human being.

61. (Previously Presented) The oral dosage form of claim 60, wherein the zoledronic acid is in a form that has an aqueous solubility of about 5% (w/v) to about 50% (w/v).

62-119. (Canceled)

120. (Currently Amended) The oral dosage form of claim [[1]]40, wherein the zoledronic acid is present in an amount that provides relief of an inflammatory pain at least 6 hours after administration of the dosage form.

121. (Previously Presented) The oral dosage form of claim 40, wherein the oral bioavailability of zoledronic acid in the dosage form is about 1% to about 3% in a human being.

REMARKS/ARGUMENTS

Claims 40, 42, 44, 46-49, 51-55, 60, and 120 are amended herein. Claims 1-39, 41, and 62-119 are canceled. The amendments are supported by at least ¶ 049, 053, and 055 of the specification as filed.

Applicant reiterates any relevant arguments made in previous communications with the Office that are not presented herein. There are a number of factual and legal assertions made in the Office Action and in previous communications that are not addressed in this Response. Applicant has not addressed many of these in the interest of expediting prosecution. However, Applicant does not admit that any factual or legal assertion made by the Office, including any factual or legal assertion not addressed herein, is correct.

In general, Applicant reiterates any arguments made in the previous response that are relevant to the issues of the present rejection. In addition, Applicant adds the arguments below.

35 U.S.C. §102 Rejections

Fox

Claims 40-45, 57, 60, and 61 are rejected as allegedly being anticipated by Fox (US 2004/0063670). While Applicant does not admit that the rejection is correct, the claims are amended herein to expedite prosecution.

In Interview Summaries for two related applications, Examiner indicated that if a) Applicant amended the claims so that the doses recited in the claims fall outside of the ranges of paragraph 0078 of Fox, and b) presented data showing that some of the doses in paragraph 0075 of Fox are toxic for zoledronic acid, and that the range of the

claim amendments is below the toxic doses, this may be sufficient to overcome the novelty rejection.[1]

With respect to claims 44 and 45, Applicant will show that the "about 40 mg to about 800 mg of zoledronic acid of zoledronic acid to be administered in about 1 month" is outside of the ranges of paragraph 0078 of Fox. Applicant will also show that some of the doses in paragraph 0075 of Fox are toxic to the extent that they are not tolerated and that the "about 40 mg to about 800 mg of zoledronic acid of zoledronic acid to be administered in about 1 month" can easily be below the dose that is not tolerated. Thus, Applicant believes that the amendment and declaration provided herewith provide what the Examiner indicated may be sufficient to overcome the novelty rejection.

With respect to claim 40, 42, 43, 60, and 61, Applicant will show that "[a]n oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid" is outside of the ranges of paragraph 0078 of Fox. Applicant will also show that some of the doses in paragraph 0075 of Fox are toxic to the extent that they are not tolerated and that "[a]n oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid is below the dose that is not tolerated. Thus, Applicant believes that the amendment and declaration provided herewith provide what the Examiner indicated may be sufficient to overcome the novelty rejection.

The total amount of zoledronic acid to be administered in about a month is outside of the ranges of paragraph 0078 of Fox

The range "about 40 mg to about 800 mg of zoledronic acid of zoledronic acid to be administered in about 1 month" of claim 44 is well above the range of "about 0.5 to about 20 mg, preferably about 1 mg to about 10 mg" recited in ¶ 0078 of Fox. Paragraph 0078 of Fox states that:

[1] March 10, 2014, interview summary for Serial No. 13/894,252 and March 14, 2014 interview summary for Serial No. 13/894,262.

> ...preferably the bisphosphonic acid derivatives are administered in doses which would likewise be therapeutically effective in the treatment of Paget's disease, tumour-induced hypercalcaemia or osteoporosis, i.e. preferably they are administered in doses which would likewise effectively inhibit bone resorption. For example, for the preferred nitrogen-containing bisphosphonates, e.g. zoledronic acid and salts thereof, doses of bisphosphonate in the range from about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, may be used for treatment of human patients.[2]

This paragraph specifically ties the dosage ranges that it recites to doses that are "therapeutically effective in the treatment of Paget's disease, tumour-induced hypercalcaemia, or osteoporosis." Thus, the meaning of this paragraph, or what the paragraph teaches, is best understood in the context of how much zoledronic acid was used for the treatment of these conditions. It is well established law that "additional references may serve to reveal what a reference would have meant to a person of ordinary skill."[3]

The following is what the label for Reclast®, one of two reference FDA approved zoledronic acid intravenous dosage forms, says about "dosage and administration" of zoledronic acid:

> Infusion given intravenously over no less than 15 minutes:
> - Treatment of postmenopausal osteoporosis; treatment to increase bone mass in men with osteoporosis: treatment and prevention of glucocorticoid-induced osteoporosis: 5 mg once a year
> - Prevention of postmenopausal osteoporosis: 5 mg once every 2 years
> - Treatment of Paget's disease of bone: a single 5 mg infusion.[4]

This label makes it clear that, for osteoporosis and Paget's disease, the 5 mg dose is given far less often than once a month.

---

[2] Emphasis added.
[3] *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991). See also MPEP 2131.01 (II) (Extra References or Other Evidence Can Be Used to Show Meaning of a Term Used in the Primary Reference
[4] Reclast® label, attached herewith. Emphasis added and internal citations omitted.

Additionally, the following is what the label for Zometa®, the second of two reference FDA approved zoledronic acid intravenous dosage forms, says about "dosage and administration" of zoledronic acid:

> The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium greater than or equal to 12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes.
>
> Retreatment with Zometa 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and serum creatinine must be assessed prior to retreatment with Zometa.[5]

With respect to the clinical trials of Zometa for Hypercalcemia of Malignancy (HCM), the following table is provided in the label.[6]

Table 11: Secondary Efficacy Variables in Pooled HCM Studies

		Zometa 4 mg		Pamidronate 90 mg
Complete Response	**N**	**Response Rate**	**N**	**Response Rate**
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of Response	**N**	**Median Duration (Days)**	**N**	**Median Duration (Days)**
Time to Relapse	86	30*	99	17
Duration of Complete Response	76	32	69	18

*P less than 0.05 versus pamidronate 90 mg

The values for "Median Duration (Days)" of "30" and "32" clearly demonstrate that Zometa 4 mg is intended to be given no more than twice in a month. Thus, according to the labels for FDA products approved for the conditions recited in ¶ 0078 of Fox, 5 mg of zoledronic acid should be given no more often than yearly, and 4 mg of zoledronic acid should be given no more than twice in a month to a person for the treatment of these conditions. Thus, based upon the dosages of zoledronic acid required by these labels, a person of ordinary skill would understand "about 0.5 to about 20 mg, preferably

[5] Zometa Label, p. 2, section 2.1 Emphasis added and internal citations omitted.
[6] Zometa Label, p. 21.

from about 1 to about 10 mg" to refer to administration of these less often than monthly. Therefore, "about 40 mg to about 800 mg of zoledronic acid of zoledronic acid to be administered in about 1 month" is a higher dose of zoledronic acid than that of ¶ 0078 of Fox.

The total amount of zoledronic acid in a dosage form is outside of the ranges of paragraph 0078 of Fox

"An oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid" as recited in claim 40 and 60, is well above the range of "about 0.5 to about 20 mg, preferably about 1 mg to about 10 mg" recited in ¶ 0078 of Fox.

Some of the doses in paragraph 0075 of Fox are toxic for zoledronic acid

The attached declaration, submitted in co-pending application Serial No. 13/894,252 (the '252 Declaration), demonstrates that a large part of the range of ¶ 0075 of Fox is toxic to the extent that it is not tolerated. Paragraph 0075 of Fox states that "from 0.002-20.0 mg/kg, is administered to a warm-blooded animal weighing approximately 75 kg." A large portion of this range is above the maximum tolerated dose level for zoledronic acid. For example, "[d]ogs did not tolerate daily oral doses of zoledronic acid at 50, 100, or 150 mg/day, which were approximately 5.6, 11.2, and 16.9 mg/kg, respectively, for males and 7.5, 14.9, and 22.4 mg/kg, respectively, for females. Clinical signs of ill health occurred within a few days at all dose levels, which resulted in the death of one dog, the euthanasia of several more dogs in moribund condition or for humane reasons, and the early termination of the study. Other in life findings included emesis, decreased activity, rigidity or stiffness, abnormal gait and posture, muscle tremors and/or twitching."[7] "This demonstrates that the upper end of

[7] '252 Declaration, ¶ 11.

the range 'from 0.002-20.0 mg/kg' in ¶ 0075 of Fox must refer to bisphosphonates that are less toxic than zoledronic acid."[8]

With respect to the monthly dosage range of claim 44, if 5.6 mg/kg of oral zoledronic acid is not tolerable for five days, then it is not tolerable for a month. Thus, within "from 0.002-20.0 mg/kg," at least 5.6 mg/kg to 20 mg/kg, or at least 70% of Fox's range, is not tolerated for five once daily administrations.

The range of the claim amendment of claim 44 is below the doses shown to be not tolerated

There are many ways a total monthly amount of zoledronic acid can be administered in a way that is tolerated. For example, an "amount of zoledronic acid to be administered in one month [of] 40 mg to 800 mg" would correspond to a daily dose of about 0.018 mg/kg to about 0.36 mg/kg for "a warm-blooded animal weighing approximately 75 kg."[9] Less frequent dosing is also possible. Thus, the total monthly amount of zoledronic acid recited in claim 44 can be readily administered in a dosage regime that is well below the portion of the range of Fox that is not tolerated.

The range of the amendment to claims 40 and 60 is below the doses shown to be not tolerated

"An oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid" would, when given to "a warm-blooded animal weighing approximately 75 kg,"[10] correspond to a dose of about 0.4 mg/kg to about 3.3 kg. This is below the range shown not to be tolerated.

Fox does not disclose the monthly dose with sufficient specificity

Claims 44 and 45 are novel at least because Fox does not teach the claim element "wherein the amount of zoledronic to be administered in one month is about 40

[8] '252 Declaration, ¶ 14.
[9] See Fox, ¶ 0075.
[10] See Fox, ¶ 0075.

mg to about 800 mg." "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."[11] With respect to ranges, MPEP 2131 (II) states that "[i]n order to anticipate the claims, the claimed subject matter must be disclosed in the reference with 'sufficient specificity to constitute an anticipation under the statute.' See, e.g., *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory."[12]

Applicant points out that ¶ 0075 refers only to "a single dose of bisphosphonate active ingredient" and does not mention zoledronic acid. Furthermore, according to ¶ 0077 of Fox, "[t]he dose mentioned above...may be repeated for example once daily, once weekly, once every month, once every three months, once every six months or once a year." Thus, for a 75 kg warm-blooded animal, this could correspond to a monthly dose of 0.0125 mg to 46,500 mg.[13] As stated in the MPEP, "a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory." Thus, at least a range that is 30% or less than the range of a prior art reference is not anticipated. Since "about 40 mg to about 800 mg" of "zoledronic acid" is far less than 30% of the range of 0.0125 mg to 46,500 mg of "bisphosphonate," the range derived from Fox does not describe the range of the rejected claims "with sufficient specificity to constitute an anticipation under the statute."

Similarly, ¶ 0079 refers only to "the active ingredient," and does not mention zoledronic acid. Fox contains no explicit connection between this paragraph and any

[11] MPEP 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).
[12] The citation to the *Atofina* case is present in MPEP 2131 (II).
[13] A dose of 0.002 mg/kg given to a 75 kg mammal once a year corresponds to a 0.0125 mg monthly dose. A dose of 20 mg/kg given to a 75 kg mammal once a day corresponds to a 31 day monthly dose of 46,500. However, it is

frequency of dosage. Thus, this reference does not teach any total monthly dose. Applicant points out that ¶ 0077 refers to "[t]he dose mentioned above," and thus does not refer to ¶ 0079, which appears below ¶ 0077.

However, the combination of ¶ 0077 with ¶ 0079 fails to teach "wherein the amount of zoledronic acid to be administered in one month is about 40 mg to about 800 mg" for at least one other reason. According to ¶ 0077 of Fox, "[t]he dose mentioned above…may be repeated for example once daily, once weekly, once every month, once every three months, once every six months or once a year." Thus, "about 1 mg to about 500 mg"[14] could correspond to a monthly dose of 0.083 mg to 15,500 mg.[15] Since "about 40 mg to about 800 mg" of "zoledronic acid" is far less than 30% of the range of 0.083 mg to 15,500 mg of "the active ingredient," the range derived from Fox does not describe the range of claims 44 and 45 "with sufficient specificity to constitute an anticipation under the statute."

For at least these reasons, and those set forth in previous responses, the rejected claims are not anticipated by Fox.

35 U.S.C. §103 Rejections

Claims 46-56 are rejected as allegedly being obvious over the combination of Fox and Chandler (Labeling Of Unit Dose Packages Of Drugs, Department Of Pharmacy Policy, University Of Kentucky Hospital Chandler Medical Center, Policy Number: PH-04-06, 11/09). While Applicant does not admit that the rejection is correct, the claims are amended herein to expedite prosecution.

In Interview Summaries for two related applications, Examiner indicated that Applicant may be able to overcome obviousness issues by showing unexpected results

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Applicant's position that Fox does not teach anything with regard to monthly dose because a monthly dose is obtained by selecting between a dose, a frequency of administration, and in some cases, a length of treatment.
[14] Fox, ¶ 0079.

of the claimed range or by showing that the art teaches away from the claims.[16] Applicant will address unexpected results and teaching away in this response.

Teaching Away

As pointed out in the Interview Summary, "[a] *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)."[17] The claims are not obvious at least because the prior art as a whole teaches away from oral administration of zoledronic acid.

"[I]t was generally believed in the art at the time of filing of the present application that oral zoledronic acid had significant disadvantages that would make its use unsuitable for treatment of medical conditions."[18] For example, one paper (attached herewith) states that "Oral bisphosphonates…have limitations related to long-term compliance, gastrointestinal intolerance, and poor and variable absorption from the gastrointestinal tract. Intermittent intravenous administration of bisphosphonates might address some of these problems…"[19] The observation in the toxicity study reported in the '252 Declaration is consistent with this observation. It stated that "most animals dosed with [oral] zoledronic acid had test article related visible lesions. Findings included, but were not limited to red to dark red mucosa of the stomach, duodenum, jejunum, colon and pancreas, stomach mucosa with lesions, masses and/or multiple foci of various colorations, and thickened edematous mucosa of the pylorus."[20]

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[15] A dose of 1 mg given to a 75 kg mammal once a year corresponds to a 0.083 mg monthly dose. A dose of 500 mg given once a day corresponds to a 31 day monthly dose of 15,500.
[16] March 10, 2014, interview summary for Serial No. 13/894,252 and March 14, 2014 interview summary for Serial No. 13/894,262.
[17] MPEP 2144 (III), citation present in MPEP. Applicants point out that teaching away is not only rebuttal evidence, but evidence of a defective *prima facie* case of obviousness. "[A]s a 'useful general rule'…references that teach away cannot serve to create a *prima facie* case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed. Cir. 1994, citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).
[18] Declaration filed in a recent response for co-pending application Serial No. 13/894,274 (the '274 Declaration), ¶ 19.
[19] Ian R. Reid, et al., *N Engl J Med*, Vol. 346, No. 9, 653-661, right column, first ¶, attached herewith.
[20] '252 Declaration, ¶ 13.

Furthermore, the Office Action cited the following references:

1. Cullen (Cullen et al, MER-101 A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae, Poster Presentation, November 2007),

2. Leonard 2007 (Leonard et al., MER-101 Tablets. A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation October 2007), and

3. Leonard 2009 (Leonard et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009).[21]

All three of these references mention problems associated with oral zoledronic acid. Cullen states that "[a]ll bisphosphonates, including zoledronic acid, have poor oral bioavailability. The current marketed dosage form of zoledronic acid is given as an intravenous infusion to overcome the issues with oral dosing of bisphosphonates, including: Low bioavailability, Gastric irritation, Gastric reflux. The gastric reflux induced by bisphosphonates can result in esophageal erosions."[22] Similarly, Leonard 2007 states "[t]he current marketed dosage form of zoledronic acid is a given as an infusion to overcome the limitations of oral dosing of bisphosphonates, including low bioavailability, gastric irritation, and gastric reflux."[23] Finally, Leonard 2009 states that "[a]ll bisphosphonates, including zoledronic acid, have poor oral bioavailability. This has limited their use in oncological therapies to intravenous infusion to achieve the doses required for efficacy. The local gastric irritation that occurs with existing oral bisphosphonates is also an important consideration in oncological indications, as it can result in esophageal erosions and ulceration."[24] Again, the "visible lesions…red to dark red mucosa of the stomach, duodenum, jejunum, colon and pancreas, stomach mucosa

[21] February 7, 2014 Office Action, p. 4.
[22] Cullen, p. 2, Background section.
[23] Leonard 2007, p. 1, Introduction section.
[24] Leonard 2009, p. 1, Background section.

with lesions, masses and/or multiple foci of various colorations, and thickened edematous mucosa of the pylorus"[25] reported in the toxicity study of the attached declaration are consistent with these statements of Leonard and Cullen.

All three of these references allege that MER-101, which was developed by Merrion Pharmaceuticals, "can improve the oral bioavailability of zoledronic acid and thereby enable the development of an oral dosage form."[26] However, at this time, about seven years after the Cullen presentation, there is no oral dosage form of zoledronic acid available in the United States. Attached is a copy of the FDA's Orange Book listing for zoledronic acid (Orange Book). "...[T]he Orange Book...identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA)..."[27] According to the Orange Book, although there are 19 zoledronic acid products available in the United States, all of them are intravenous and no oral zoledronic acid is available.

Applicant points out that failure by others to obtain FDA approval can be objective evidence of nonobviousness. For example, the Federal Circuit has stated that "evidence of the failure of others...[includes] abandonment of certain FDA registration applications. The so-called 'objective' criteria must always be considered, *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), and given whatever weight is warranted by the evidence presented."[28] Here, the difficulties with oral zoledronic acid expressed in the prior art would have suggested to a person of ordinary skill in the art that failure to obtain FDA approval was likely a result of failure of the oral dosage form. Thus, the fact that, despite apparent attempts to develop an oral zoledronic acid, oral zoledronic acid is not approved by the FDA is significant evidence of the nonobviousness of the claimed method.

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[25] '252 Declaration, ¶ 13.
[26] Leonard 2007, p. 1, Introduction section; see also Leonard 2009, p. 2 and Cullen, p. 2, Background section.
[27] Orange Book Preface, attached herewith, emphasis added.
[28] *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004), citations present in published opinion.

The problems with oral zoledronic acid, as compared to intravenous zoledronic acid, were considered significant by the European Medicine Association's Committee For Orphan Medicinal Products (Committee). As explained in a declaration filed in a recent response for co-pending application Serial No. 13/894,274 (the '274 Declaration), the Committee stated that "since zoledronic acid is known to be poorly absorbed via the oral route, the sponsor was also asked to discuss the expected low bioavailability using the oral formulation."[29]

Even Fox, which the Office alleges teaches oral zoledronic acid,[30] "actually contains no evidence that oral zoledronic acid is effective in the treatment of any condition. Instead, all of the experiments in Fox related to zoledronic acid for treating any condition were carried out with subcutaneous administration."[31] When considered with what is known from the discussion above, it is not at all surprising that Fox makes it clear that intravenous administration of bisphosphonates is preferred to oral administration. For example, Fox stated that "first and foremost, intravenous is considered to be of particular importance. Preferably the bisphosphonate active ingredient is in the form of a parenteral, most preferably an intravenous form."[32] Fox further stated "[m]ost preferably, however, the bisphosphonate is administered intravenously."[33]

Thus, on one hand, any or all of the following would have led a person of ordinary skill in the art away from oral dosage forms of zoledronic acid for treatment of any medical condition: First, in Fox, the zoledronic acid is administered subcutaneously, and Fox clearly states that intravenous administration of bisphosphonates is preferred over oral. Second, all nineteen zoledronic acid products available in the US are intravenous and none are oral. Third, several references cited in

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[29] Exhibit 4, p. 4, ¶2, of the '274 Declaration, which was submitted on March 10, 2014. The '274 Declaration is attached herewith, except that Exhibit 5 is not submitted with its response due to its length, but can be accessed in the file history of 13/894,274.
[30] As explained in previous responses, Applicant's position is that Fox does not teach oral zoledronic acid.
[31] '252 Declaration, ¶ 5; see also Fox, ¶¶ 102-108.
[32] Fox, ¶ 72.

the Office Action describe significant problems associated with oral zoledronic acid. Fourth, the oral zoledronic acid referred to in the publications cited in the Office Action has failed to be approved by the FDA. On the other hand, there is nothing in any of the cited references which suggests that oral administration of zoledronic acid would provide any benefit over intravenous zoledronic acid for the treatment of any medical condition. And there certainly is nothing in the cited references that would have motivated a person of ordinary skill in the art to go to the trouble of formulating an oral dosage form of zoledronic acid when nineteen FDA approved intravenous formulations are conveniently available for purchase. Thus, the prior art as a whole teaches away from oral dosage forms comprising zoledronic acid, and the claims are not obvious.

Unexpected results

The safety and efficacy of an oral dosage form for inflammatory pain was unexpected

As explained above, the prior art as a whole would have led a person of ordinary skill in the art away from oral dosage forms of zoledronic acid for the treatment of any medical condition, including inflammatory pain. Thus, it is unexpected that oral dosage forms related to the doses recited in the claims would be safe and effective in a rat model of inflammatory pain.

Example 1 of the specification describes a test of oral zoledronic acid in a rat model of inflammatory pain. According to ¶ 0090 of the specification, "[o]rally administered zoledronic acid produced a 29% reversal of inflammatory pain at the 18 mg/m^2…dose" administered "on days 1-3."[34] As stated in the attached declaration, "zoledronic acid 54 mg/m^2 (or 9 mg/kg), divided in three equal daily [18 mg/m^2] doses,

[33] Fox, ¶ 73.
[34] Specification, ¶ 085.

was tolerated."[35] Thus, for this group of rats, oral zoledronic acid was unexpectedly proven to be safe and effective in this rat model of inflammatory pain.

The efficacy of the oral dosage form is unexpectedly long lasting as compared to the results reported in Fox for the subcutaneous dosage form

Since Fox states that "[i]n a rat model of inflammatory hyperalgesia…[there was] no significant activity 3 hours following administration," a person of ordinary skill in the art would not have expected an oral dosage form comprising zoledronic to provide extended relief of inflammatory pain. Thus, it is surprising that some embodiments of the claimed composition had extended pain relief that continued for days.

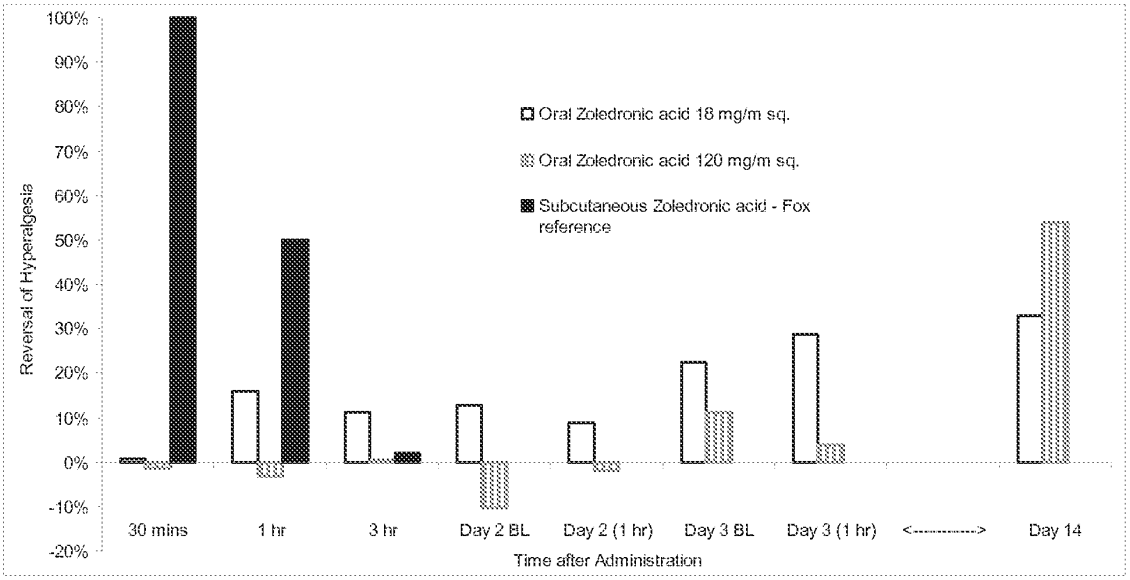

Figure 1

Figure 1 is a compilation of the data from Examples 1 and 2 of the specification and the Fox reference.[36] This figure clearly demonstrates that at the 18 mg/m^2 dosage

[35] '252 Declaration, ¶ 6.
[36] The experiment of Examples 1 and 2 were actually carried out on the same animals, with the effect of the oral administration being a model for either inflammatory pain or arthritis pain, depending upon the time between injection of the CFA and the measurement of paw compression threshold. The values at one hour and 3 hours for the Fox

level, significant pain relief was observed 24 hours after the first (Day 2 BL) and second (Day 3 BL) doses. Furthermore, at both the 18 mg/m^2 and 120 mg/m^2 dosage levels, the oral zoledronic acid had a significant reversal of hyperalgesia 14 days after the first administration and 11 days after administration of the final oral dose (which occurred on day 3).[37] Therefore, the rejected claims are also not obvious because of these unexpected results, and the rejection should be withdrawn.

The results of a dosage form of the claims in a CRPS rat study were unexpected as compared to Fox

Additionally, an embodiment of an oral dosage form of the rejected claims performed significantly better in a CRPS rat study than what would be expected based upon the studies presented in Fox. According to Sebastin, "the International Association for the Study of Pain (IASP) in 1994 introduced the term CRPS to describe a wide variety of post traumatic neuropathic pain conditions of the limbs."[38] Based upon this, a person of ordinary skill in the art would have expected the chronic neuropathic pain model of paragraph 104 of Fox to be relevant to CRPS.[39] At best, a person of ordinary skill in the art might have expected the pain relieving effect for CRPS to be similar to that shown in the rat model of neuropathic pain. Furthermore, as stated in the '274 Declaration, "a person of ordinary skill in the art would likely have expected the pain relieving effect to be lower for oral administration than for subcutaneous administration"[40] due to problems with oral zoledronic acid such as low oral bioavailability. "Thus, it is surprising that, as shown in [Figure 2] below, the pain relieving effect after oral administration in the rat model of CRPS is significantly higher than the pain relieving effect reported after intravenous administration in the rat model

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reference are not actual values reported in Fox, but are added to provide a visual approximation based upon the statement "maximal reversal of 100% within 30 minutes, and a short duration with no significant activity 3 hours following administration." (Fox, ¶ 0102).

[37] A higher oral dose was also administered, but the animals were euthanized after 3 days due to the high toxicity level of this dose, so these results are not included in the figure.

[38] Sebastin, p. 298, first paragraph, emphasis added, submitted in Nov. 19, 2013 IDS.

[40] '274 Declaration, ¶ 22.

of neuropathic pain. It is also surprising that the pain relieving effect of oral zoledronic acid in treating CRPS is significantly longer lasting than the pain relieving effect of subcutaneous zoledronic acid in treating neuropathic pain."[41]

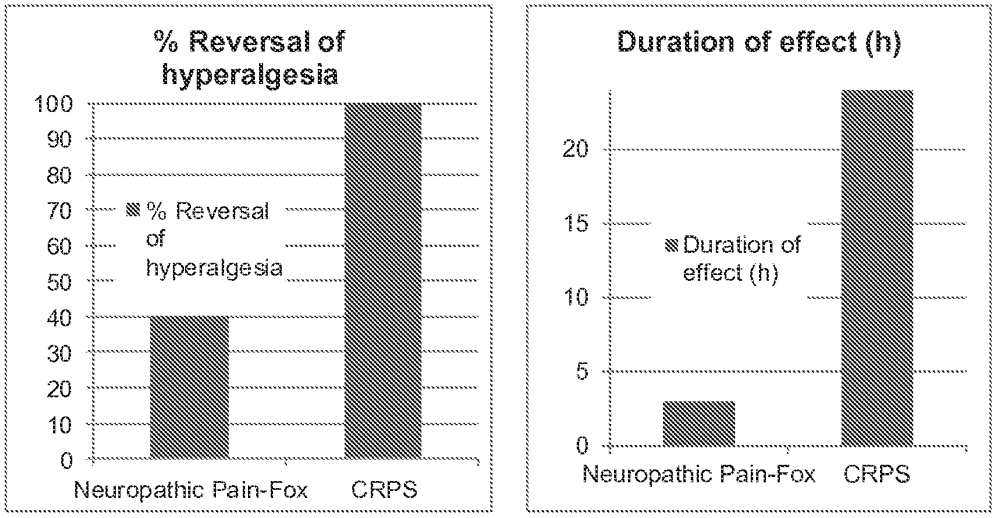

Figure 2

As stated in the '274 Declaration, "In the neuropathic pain model of Fox, the rats were injured two weeks before the zoledronic acid was administered. In the first rat study, administration of zoledronic acid began one day after injury, but in the second rat study, administration of zoledronic acid began 29 days after injury. Thus, the second rat study was deemed to be the appropriate comparison because, like the neuropathic pain model, administration of the zoledronic acid was several weeks after the injury."[42]

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[41] '274 Declaration, ¶ 23.

[42] '274 Declaration, ¶ 24. "Adami" refers to Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. A randomized, double blind, pacebo controlled study. Ann Rheum Dis 1997; 56: 201-4; "Manicourt" refers to Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type 1 of the lower extremity. Arthritis Rheum 2004; 50: 3690-7; "Varenna" refers to Varenna M, Zucchi F, Ghirighelli D, *et al.* Intravenous clodrinate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. J Rheumatol 2000; 27: 1477-83); and "Robinson" refers to Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type 1. Pain Med 2004; 5: 276-80 (Robinson).

The results of a dosage form of the claims in a CRPS rat study were unexpected as compared to other bisphosphonates

"In the rat study, not only is zoledronic acid effective in treating CRPS to a greater extent than would be predicted by the rat model of neuropathic pain in Fox, but it is significantly more effective than what would be predicted based upon studies of other bisphosphonates for the treatment of CRPS. [Figure 3] below compares the results obtained from the second rat study with those reported in Adami, Robinson, Varenna, and Manicourt. It is readily apparent from this Figure that zoledronic acid provides significantly more pain relief than the other bisphosphonates."[43]

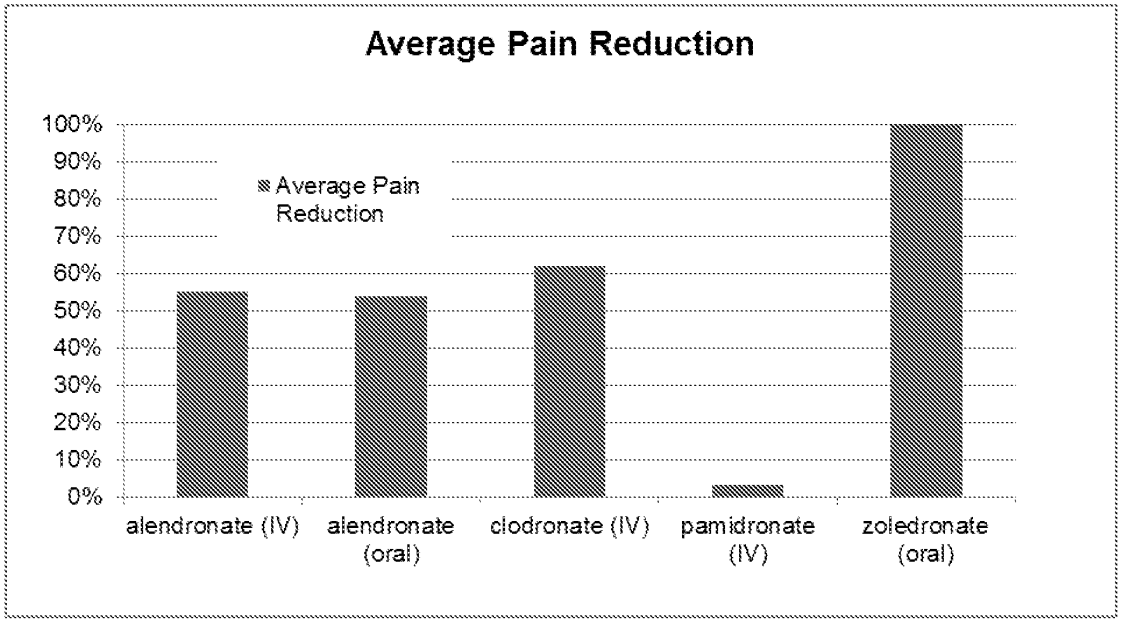

Figure 3

As explained in the '274 Declaration, two studies were performed in a rat model of CRPS. "The data from the second study was used for the comparison because it was more similar in design to the studies done for the other bisphosphonates. In the

[43] Declaration, ¶ 28.

first study, the rats were dosed with zoledronic acid before the animals developed CRPS. In the second study, the rats were dosed with zoledronic acid after the animals had developed CRPS. Since the studies for the other bisphosphonates were carried out after the patients had developed CRPS, the second study was considered to be the more appropriate comparison."[44]

The dosage range of the claims corresponds reasonably well with the unexpected results

The doses shown to be effective in the rat models of inflammatory pain and CRPS are reasonably related to the doses recited in the rejected claims.

Claims 40, 42-43, 60, 61, 120, and 121

In the rat models of inflammatory pain, "[a]nimals were orally administered vehicle (control), zoledronic acid 18 mg/m^2 (or 3 mg/kg)…[or] zoledronic acid 120 mg/m^2 (or 20 mg/kg)…on days 1-3..."[45] In the second study of the rat model of CRPS, animals were "orally administered either vehicle (n=6), or zoledronic acid (n=6) for 3 weeks. Drug treated animals received zoledronic acid at a dose of 126 mg/m^2 (21 mg/kg) on the first day (day 29), followed by 18 mg/m^2/day (3 mg/kg/day) thereafter."[46] As explained in ¶ 109 of the present specification, while individual human surface areas can vary, "under current FDA guidelines, the reference body surface area of a human adult is 1.62 m." Thus, an 18 mg/m^2 dose would correspond to about 29 mg, 120 mg/m^2 would correspond to about 194 mg, and 126 mg/m^2 would correspond to about 204 mg for a human adult having the reference body surface area. These doses are reasonably related to the amount of zoledronic acid in the dosage forms of the claims.

Claims 44-56

[44] '274 Declaration, ¶ 29.
[45] Specification, ¶ 085.
[46] Exhibit 3, p. 5, of the '274 Declaration.

As mentioned above, in these tests, "[a]nimals were orally administered vehicle (control), zoledronic acid 18 mg/m^2 (or 3 mg/kg)…[or] zoledronic acid 120 mg/m^2 (or 20 mg/kg)…on days 1-3..."[47] Administering 18 mg/m^2 of zoledronic acid three times corresponds to a total of 54 mg/m^2 of oral zoledronic acid. Administering 120 mg/m^2 of zoledronic acid three times corresponds to a total of or 360 mg/m^2 of oral zoledronic acid. Administration of both 54 mg/m^2 and 360 mg/m^2 over a three day period resulted a significant reversal of hyperalgesia 14 days after the first administration and 11 days after administration of the final oral dose (which occurred on day 3).[48] In the second study of the rat model of CRPS, animals were "orally administered either vehicle (n=6), or zoledronic acid (n=6) for 3 weeks. Drug treated animals received zoledronic acid at a dose of 126 mg/m^2 (21 mg/kg) on the first day (day 29), followed by 18 mg/m^2/day (3 mg/kg/day) thereafter"[49] for a total of 486 mg/m^2.

Thus, these tests correlate reasonably well to the total amount of zoledronic acid to be administered in a month recited in the rejected claims. Therefore, the rejected claims are not obvious.

Furthermore, based upon Fox, a person of ordinary skill in the art would not have expected the lower end of the monthly dosage range of the claims, administered orally, to be effective in the treatment of arthritis, CRPS, or any chronic inflammatory pain. According to Fox, "0.03-0.1 mgkg^{-1} s.c…produced a dose-dependent reversal of mechanical hyperalgesia. The effect was rapid in onset, with a maximal reversal of 100% within 30 min, and of short duration with no significant activity 3 h following administration."[50] The above 0.1 mgkg^{-1} dose, which is equivalent to about 7.5 mg for a 75 kg person, would need to be administered approximately 5 times in a month to arrive at the lower end of the range "amount of zoledronic acid to be administered in one month [of] about 40 mg to about 800 mg" of claims 44-56. Based upon the 3 hour

[47] Specification, ¶ 085.
[48] A higher oral dose was also administered, but the animals were euthanized after 3 days due to the high toxicity level of this dose, so these results are not included in the figure.
[49] Exhibit 3, p. 5, of the '274 Declaration.

duration of effect reported in Fox, a person of ordinary skill in the art would have expected that, if the 0.1 $mgkg^{-1}$ dose was administered five times in a month, or five times in about 744 hours,[51] pain relief would be experienced for less than a total of 15 hours for the five doses. Thus, for at least 98% of the month, the patient would be expected to experience no pain relief. Furthermore, because of its reported low oral bioavailability, an oral dosage form would have been expected to be even less effective than a subcutaneous dosage form. Therefore, based upon Fox, a person of ordinary skill would not expect a total oral monthly dose of zoledronic acid near or below the lower end of the range of the claims to be effective for the treatment of arthritis, CRPS, or any chronic inflammatory pain.

Thus, Applicant has shown that, based upon Fox, an oral dose lower than that of the total monthly dose recited in the claims would not have been expected to be effective. Further, Applicants have shown that some oral doses higher than the total monthly dose recited in the claims, but within the ranges of ¶ 0075 of Fox, would be expected to be toxic. However, total oral monthly doses reasonably similar to those recited in the claims are unexpectedly shown to be safe and effective in the rat model of arthritis pain.

DOUBLE PATENTING

The Office has indicated that provisional obviousness type double patenting might exist with respect to Application No. 13/894,262, claims 1-19 and Application No. 13/894,252, claims 20-39. While Applicant does not admit the rejection is correct, Applicant has submitted terminal disclaimers in recent responses filed for these patent applications. Thus, the rejection is overcome.

CONCLUSION

[50] Fox, ¶ 0102, emphasis added.

For at least the reasons given above, Applicant submits that the claims are patentable. Therefore, Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: :April 8, 2014

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PTO/SB/434 (05-13)

CERTIFICATION AND REQUEST FOR CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0

Practitioner Docket No.:	Application No.:	Filing Date:
1958603.00021	13/894,244	05/14/2013
First Named Inventor:	**Title:**	
Herriot Tabuteau	COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE	

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS CONSIDERATION UNDER THE AFTER FINAL CONSIDERATION PILOT PROGRAM 2.0 (AFCP 2.0) OF THE ACCOMPANYING RESPONSE UNDER 37 CFR 1.116.

1. The above-identified application is (i) an original utility, plant, or design nonprovisional application filed under 35 U.S.C. 111(a) [a continuing application (*e.g.*, a continuation or divisional application) is filed under 35 U.S.C. 111(a) and is eligible under (i)], or (ii) an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).
2. The above-identified application contains an outstanding final rejection.
3. Submitted herewith is a response under 37 CFR 1.116 to the outstanding final rejection. The response includes an amendment to at least one independent claim, and the amendment does not broaden the scope of the independent claim in any aspect.
4. This certification and request for consideration under AFCP 2.0 is the only AFCP 2.0 certification and request filed in response to the outstanding final rejection.
5. Applicant is willing and available to participate in any interview requested by the examiner concerning the present response.
6. This certification and request is being filed electronically using the Office's electronic filing system (EFS-Web).
7. Any fees that would be necessary consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, extension of time fees, are being concurrently filed herewith. [There is no additional fee required to request consideration under AFCP 2.0.]
8. By filing this certification and request, applicant acknowledges the following:
   - Reissue applications and reexamination proceedings are not eligible to participate in AFCP 2.0.
   - The examiner will verify that the AFCP 2.0 submission is compliant, *i.e.*, that the requirements of the program have been met (see items 1 to 7 above). For compliant submissions:
     - The examiner will review the response under 37 CFR 1.116 to determine if additional search and/or consideration (i) is necessitated by the amendment and (ii) could be completed within the time allotted under AFCP 2.0. If additional search and/or consideration is required but cannot be completed within the allotted time, the examiner will process the submission consistent with current practice concerning responses after final rejection under 37 CFR 1.116, *e.g.*, by mailing an advisory action.
     - If the examiner determines that the amendment does not necessitate additional search and/or consideration, or if the examiner determines that additional search and/or consideration is required and could be completed within the allotted time, then the examiner will consider whether the amendment places the application in condition for allowance (after completing the additional search and/or consideration, if required). If the examiner determines that the amendment does not place the application in condition for allowance, then the examiner will contact the applicant and request an interview.
       - The interview will be conducted by the examiner, and if the examiner does not have negotiation authority, a primary examiner and/or supervisory patent examiner will also participate.
       - If the applicant declines the interview, or if the interview cannot be scheduled within ten (10) calendar days from the date that the examiner first contacts the applicant, then the examiner will proceed consistent with current practice concerning responses after final rejection under 37 CFR 1.116.

Signature	Date
/Brent Johnson/	April 08, 2014
Name (Print/Typed) Brent A. Johnson	**Practitioner Registration No.** 51,851

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☐ * Total of _____ forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**5890**
Appln. No.	:	**13/894,252**
Applicant	:	**Herriot Tabuteau**
Filed	:	**May 14, 2013**
TC/A.U.	:	**1627**
Examiner	:	**Svetlana M. Ivanova**
Docket No.	:	**1958603.00019**
Customer No.	:	**45200**
Title	:	**COMPOSITIONS COMPRISING ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR RELIEVING PAIN ASSOCIATED WITH ARTHRITIS**

DECLARATION UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. I am the inventor of the present application.

2. I have an M.D. degree from Yale University School of Medicine.

3. I have carefully reviewed US 2004/0063670 (Fox).

4. I have also read and understand the Office Action of February 7, 2014 for the present application.

5. Fox actually contains no evidence that oral zoledronic acid is effective in the treatment of any condition. Instead, all of the experiments in Fox related to zoledronic acid for treating any condition were carried out with subcutaneous administration.

6. With respect to Example 2 of the specification of the present application, which describes a test of oral zoledronic acid in a rat model of arthritis, zoledronic acid 54 mg/m^2 (or 9 mg/kg), divided in three equal daily doses, was tolerated.

7. An Oral Repeat Dose Toxicity Study with Zoledronic Acid in Dogs was carried out at my request. The study is described in the following paragraphs.

Objective

8. The purpose of the study was to evaluate the toxicity of zoledronic acid in Beagle dogs when administered orally once daily for up to 14 days. However, due to toxicity resulting in death or necessitating euthanization during the first few days of the study, dosing was stopped in all groups of animals after no more than 5 days.

Methods

9. Groups of 8 dogs (4/sex) were either left untreated to serve as a control group (Group 1) or given daily oral doses of zoledronic acid at 50 or 100 mg (Groups 2 and 3, respectively) or at 150 mg (Groups 4 and 5). At the start of dosing, body weight averaged 8.9 kg for males and 6.7 kg for females, so the zoledronic acid dose levels were approximately 5.6, 11.2, and 16.9 mg/kg, respectively, for males and 7.5, 14.9, and 22.4 mg/kg, respectively, for females.

10. In life, dogs were observed for clinical signs of toxicity and changes in body weight, food consumption, and hematology, coagulation, clinical chemistry, and urinalysis parameters. A complete necropsy was performed on all animals.

Results and Conclusions

11. Dogs did not tolerate daily oral doses of zoledronic acid at 50, 100, or 150 mg/day, which were approximately 5.6, 11.2, and 16.9 mg/kg, respectively, for males and 7.5, 14.9, and 22.4 mg/kg, respectively, for females. Clinical signs of ill health occurred within a few days at all dose levels, which resulted in the death of one dog, the euthanasia of several more dogs in moribund condition or for humane reasons, and the early termination of the study. Other in life findings included emesis, decreased activity, rigidity or stiffness, abnormal gait and posture, muscle tremors and/or twitching.

12. One Group 5 animal was found dead on the morning of Day 4. Based on the mortality and morbidity observed at a dose level of 150 mg/day and the numerous adverse clinical signs seen in almost all animals at this dose level, all Groups 4 and 5 animals were sacrificed early in moribund condition or for humane reasons. In addition, one Group 2 animal and several Group 3 animals were also sacrificed in moribund condition, due to adverse clinical signs of toxicity. Because of the onset of clinical signs similar to the ones seen in the animals sacrificed moribund before, the remaining study animals were sacrificed early for humane

reasons on Day 5 (male Groups 1-3) and Day 4 (female Groups 1-3). This decision was made independently by the contract research laboratory that conducted the study, with the recommendation of their Director of Laboratory Animal Medicine.

13. At necropsy, at all dose levels, most animals dosed with zoledronic acid had test article related visible lesions. Findings included, but were not limited to red to dark red mucosa of the stomach, duodenum, jejunum, colon and pancreas, stomach mucosa with lesions, masses and/or multiple foci of various colorations, and thickened edematous mucosa of the pylorus. No gross necropsy findings were noted for Group 1 (control group) animals.

14. This demonstrates that the upper end of the range "from 0.002-20.0 mg/kg" in ¶ 0075 of Fox must refer to bisphosphonates that are less toxic than zoledronic acid.

15. As a person signing below:

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

SIGNATURE(S)

Full Name: Herriot Tabuteau, M.D.

Signature: _____ Date: 3/28/2014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**7165**
Appln. No.	:	**13/894,274**
Applicant	:	**Herriot Tabuteau**
Filed	:	**13/894,274**
TC/A.U.	:	**1627**
Examiner	:	**Svetlana M. Ivanova**
Docket No.	:	**1958603.00015**
Customer No.	:	**45200**
Title	:	**COMPOSITIONS COMPRISING ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATMENT OF COMPLEX REGIONAL PAIN SYNDROME**

DECLARATION UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

1. I am the inventor of the present application.

2. I have an M.D. degree from Yale University School of Medicine.

3. I am the Chief Executive Officer of Axsome Therapeutics Limited ("Axsome," "we," "us," or "our"), and was personally involved with the application for Orphan Medicinal Product Designation (Orphan Application) of zoledronic acid for the treatment of complex regional pain syndrome submitted by Axsome.

4. I have carefully reviewed 1) US 2004/0063670 (Fox), and 2) Sebastin, Complex Regional Pain Syndrome, Indian J. Plast. Surg., 2011, May-Aug; 44(2): 298-307 (Sebastin). I have also read and understand the Office Action of January 30, 2013 for the present application.

5. When the Committee for Orphan Medicinal Products (the Committee) of the European Medicines Association (EMA) rejected the Orphan Application, it made the statement that "[t]he data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS." At

the time this statement was made, the Committee was in fact in possession of all of the experimental data presented in, or referred to, in Fox and Sebastin.

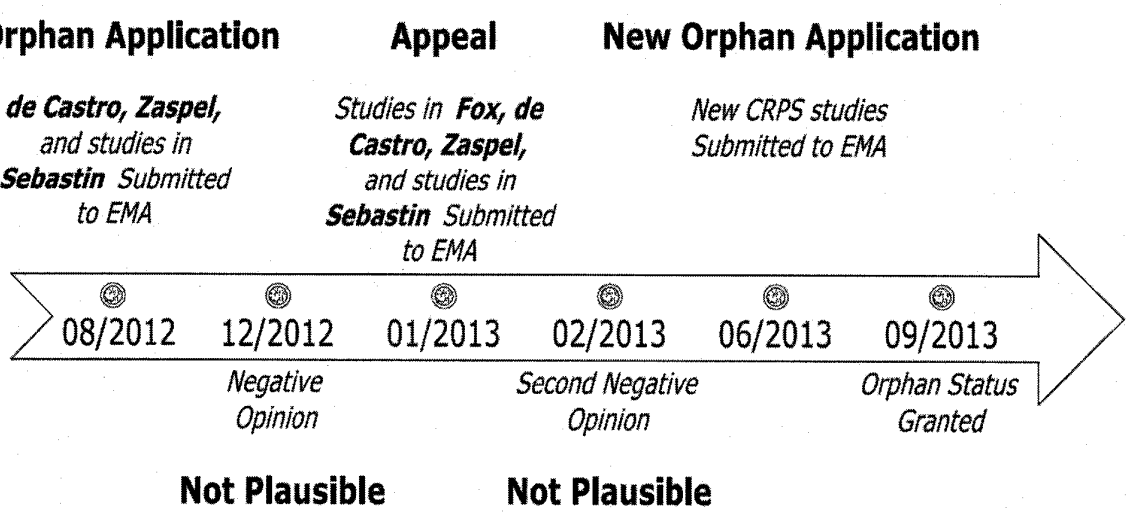

Figure A

6. Figure A depicts a timeline of the Orphan Application process. As shown in Figure A, when the Application for Orphan Medicinal Product Designation (Orphan Application) was filed, the studies referred to in Sebastin, Zaspel, de Castro, and more information, were submitted to the EMA. A list of the literature references provided to the EMA with the Orphan Application are attached herewith as Exhibit 1. Copies of these references are attached herewith as Exhibit 5 (ordered alphabetically by lead author).

7. In the initial Orphan Application, the Committee considered everything relevant to bisphosphonates referred to in Sebastin, and additional information not present in Sebastin. Sebastin states that "[b]isphosphonates (alendronate, pamidronate, and clodronate) are the only class of drugs that have survived placebo controlled clinical trials and shown statistically significant pain reduction in patients with CRPS,"[1] (Sebastin, p. 304) but contains no additional information about treating CRPS with bisphosphonates.

8. The clinical trials referred to in Sebastin are reported in Adami, Manicourt, Varenna, and Robinson.

a. Adami S, Fossaluzza V, Gatti D, Fracassi E, Braga V. Bisphosphonate therapy of reflex sympathetic dystrophy syndrome. A randomized, double blind, pacebo controlled study. Ann Rheum Dis 1997; 56: 201-4 (Adami);
b. Manicourt DH, Brasseur JP, Boutsen Y, Depreseux G, Devogelaer JP. Role of alendronate in therapy for posttraumatic complex regional pain syndrome type 1 of the lower extremity. Arthritis Rheum 2004; 50: 3690-7 (Manicourt);
c. Varenna M, Zucchi F, Ghirighelli D, *et al.* Intravenous clodrinate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study. J Rheumatol 2000; 27: 1477-83 (Varenna); and
d. Robinson JN, Sandom J, Chapman PT. Efficacy of pamidronate in complex regional pain syndrome type 1. Pain Med 2004; 5: 276-80 (Robinson).

9. Figure B shows the relationship between Sebastin and Adami, Manicourt, Varenna, and Robinson. Sebastin contains no direct citations to any original studies, but cites two reviews by Pontell and Tran. Tran directly cites Adami, Manicourt, Varenna, and Robinson. Pontell does not contain any direct citations to any original studies, but cites Sharma, which in turn directly cites Adami, Manicourt, Varenna, and Robinson.

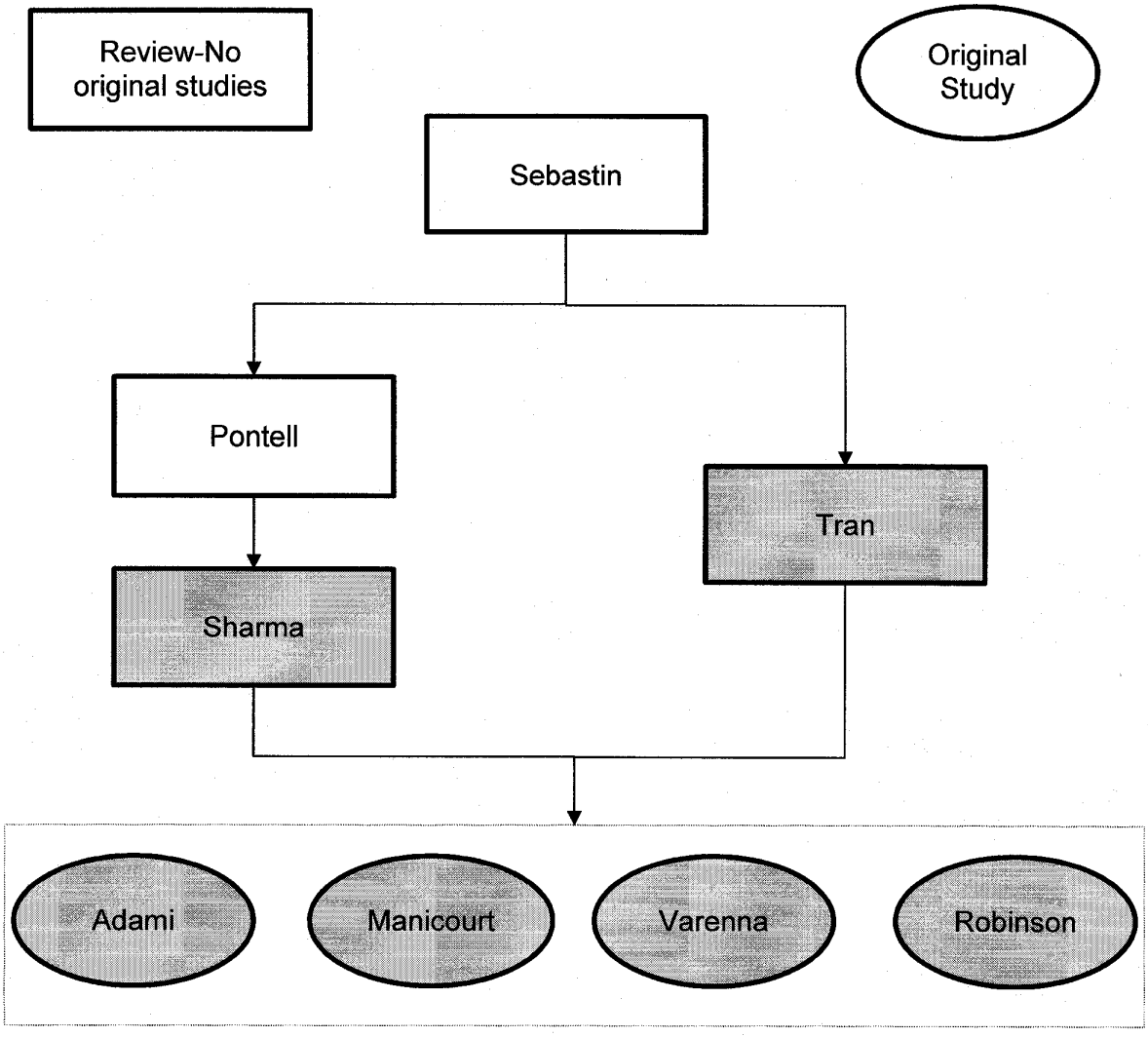

Figure B

10. After receiving the negative opinion, we appealed and submitted the studies referred to in Fox and again submitted the studies in Sebastin, Zaspel, and de Castro. A list of the literature references provided to the EMA with our appeal are attached herewith as Exhibit 2. Copies of these references are attached herewith as Exhibit 5 (ordered alphabetically by lead author).

11. The data from Fox was submitted in the Walker paper (Exhibit 2, reference 115), which described all of the experiments performed in Fox, but with greater experimental detail and a more extensive description and discussion of the results.

12. Thus, the Committee had all of the studies present, or referred to, in Sebastin and Fox, when it stated that "[t]he data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS."

13. Despite the fact that the Committee told us that the method claimed in the present application was not plausible, we continued to develop the method. In collaboration with a third party, we carried out two animal studies to demonstrate that zoledronic acid could be used to treat CRPS. A report of these two animal studies is attached herewith as Exhibit 3.

14. After we generated and submitted the data contained in the patent application (the first animal study), as well as data from an additional study (the second animal study), we filed a new Orphan Application. Based upon the results of these two animal studies, the Committee reversed itself, gave a positive opinion, and Orphan status was granted.

15. Excerpts from the EMA/COMP summary report on our application for orphan medicinal product designation for zoledronic acid for the treatment of complex regional pain syndrome are attached herewith as Exhibit 4. Pages 1-16 are from the original summary report, or Negative Opinion, and pages 17-19 are from the summary report issued after the appeal, or the Second Negative Opinion.

16. As shown in Exhibit 4, the Committee specifically considered Zaspel, as demonstrated by the following statement: "[t]he data presented by the sponsor, based on a single non-sponsor generated abstract (Zaspel et al, 2007, never published as a full article) were not considered sufficient to justify the intention to treat the condition." (Exhibit 3, p. 15, ¶ 3.)

17. The Committee stated that "[Zaspel] was not considered sufficient because the particulars of the study were not available for evaluation." This lack of data is not due to a deficiency in our submission to the EMA, but to a deficiency in the prior art. We diligently attempted to locate the particulars of the study. As far as we can tell, the particulars of the study were not published. In fact, we even contacted the authors of the study, who were unable to provide this information.

18. Additionally, the Committee considered and commented on de Castro as follows: "[t]he other reference is a single case report published in Revista Dor (Brasil), which is a regional peer-reviewed pain journal. The description of the case is lacking details that would be useful for the evaluation of the efficacy of the product, e.g. there is no mentioning of any initiating noxious event, which is a typical criterion for CRPS." (Exhibit 4, p. 3, ¶ 6.) Thus, according to the Committee, not only did this reference have insufficient information "for the evaluation of the efficacy of the product," but the Committee questioned whether the patient studied in the reference even had CRPS.

19. An important difference between Zaspel and de Castro and the presently claimed method is that, in those references, the zoledronic acid was administered intravenously, while the present claims include "administering an oral dosage form containing zoledronic acid." This is a significant difference, as it was generally believed in the art at the time of filing of the present application that oral zoledronic acid had significant disadvantages that would make its use unsuitable for treatment of medical conditions.

20. Fox actually contains no evidence that oral zoledronic acid is effective in the treatment of any condition. Instead, all of the experiments related to zoledronic acid for treating any condition were carried out with subcutaneous administration.

21. Fox makes it clear that intravenous administration of bisphosphonates is preferred to oral administration.

22. Because of statements in the prior art, such as those made in Cullen (MER-101 A bioavailability study of various GIPET formulations in beagle dogs with

intraduodenal cannulae, Poster Presentation, November 2007), Leonard 2007 (MER-101 Tablets. A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation October 2007), and Leonard 2009 (Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009), a person of ordinary skill in the art would likely have expected the pain relieving effect to be lower for oral administration of zoledronic acid than for subcutaneous administration of zoledronic acid.

23. Thus, it is surprising that, as shown in Figure C below, the pain relieving effect after oral administration in the rat model of CRPS is significantly higher than the pain relieving effect reported after intravenous administration in the rat model of neuropathic pain. It is also surprising that the pain relieving effect of oral zoledronic acid in treating CRPS is significantly longer lasting than the pain relieving effect of subcutaneous zoledronic acid in treating neuropathic pain.

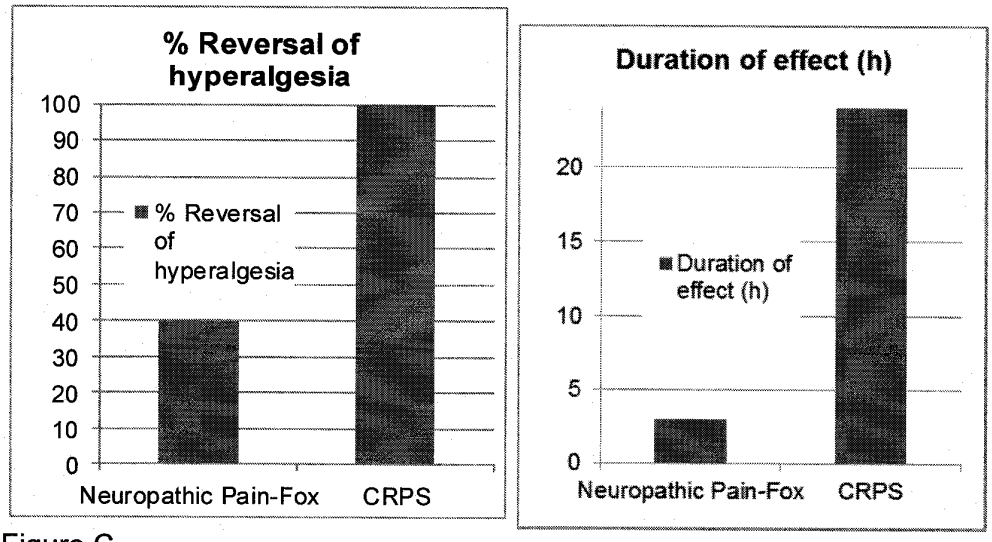

Figure C

24. Two studies of orally administered zoledronic acid in the rat model of CRPS were performed. (Exhibit 3.) In the neuropathic pain model of Fox, the rats were injured two weeks before the zoledronic acid was administered. In the first rat study, administration of zoledronic acid began one day after injury, but in the second rat study, administration of zoledronic acid began 29 days after injury. Thus, the second rat study

was deemed to be the appropriate comparison because, like the neuropathic pain model, administration of the zoledronic acid was several weeks after the injury.

25. The duration of effect depicted above for neuropathic pain from Fox was obtained from Walker, which contains a more detailed description of the experiments of Fox. Walker shows the pain relieving effect is gone within three hours. See Fig. 5, p. 227, of Walker.

26. The data for percent reversal of hyperalgesia in the CRPS model was obtained from p. 11, Figure 7, of Exhibit 3.

27. In the rat study of CRPS, the pain relieving effect reported was 24 hours after the last dose was administered. However, the pain relieving effect may have lasted for significantly longer than 24 hours.

28. In the rat study, not only is zoledronic acid effective in treating CRPS to a greater extent than would be predicted by the rat model of neuropathic pain in Fox, but it is significantly more effective than what would be predicted based upon studies of other bisphosphonates for the treatment of CRPS. Figure D below compares the results obtained from the second rat study with those reported in Adami, Robinson, Varenna, and Manicourt. It is readily apparent from this Figure that zoledronic acid provides significantly more pain relief than would be predicted from studies carried out on other bisphosphonates.

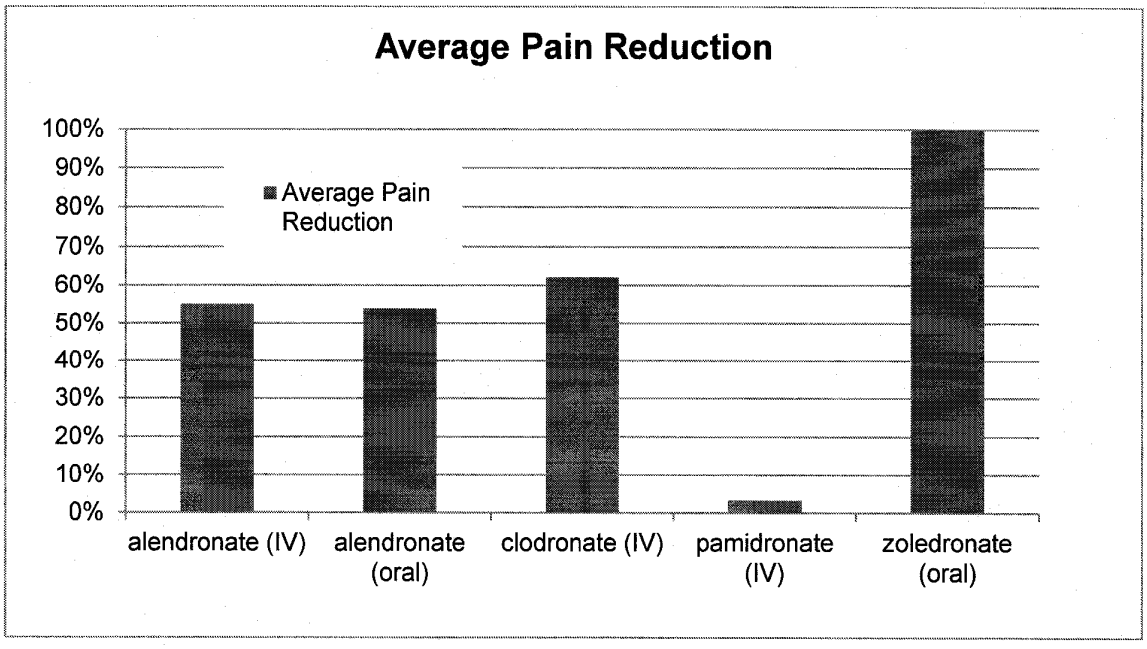

Figure D

29. As mentioned above, two studies of a rat model of CRPS were performed. The data from the second study was used for the comparison because it was more similar in design to the studies done for the other bisphosphonates. In the first study, the rats were dosed with zoledronic acid before the animals developed CRPS. In the second study, the rats were dosed with zoledronic acid after the animals had developed CRPS. Since the studies for the other bisphosphonates were carried out after the patients had developed CRPS, the second study was considered to be the more appropriate comparison.

30. The data for alendronate IV was obtained from the Adami reference. It was an average of two reported values. The first (48.0%) was obtained four weeks after treatment. (Adami, p. 202, right column, lines 38-41.) The second (62.0%) was obtained two weeks after a second treatment and four weeks after the original treatment. (*Id.*)

31. The data for alendronate oral (53.8% pain reduction) was obtained from the Manicourt reference. It was digitized data obtained from Figure 2, p. 3693. The value obtained was that observed after four weeks of treatment.

32. The data for clodronate IV (61.8% pain reduction) was obtained from Table 3, p. 1479 of the Varenna reference. The value was calculated from the VAS scores for the clodronate group at zero days (58.4) and forty days (22.3).

33. The data for pamidronate IV was obtained from the Robinson reference. It was digitized data obtained from Figure A, p. 278 of the reference. The value obtained was that observed after one month of treatment.

34. The data for oral zoledronate was obtained from p. 11, Figure 7, of Exhibit 3.

35. As a person signing below:

I hereby declare that all statements made herein of my own knowledge and belief are true; and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

SIGNATURE(S)

Full Name: Herriot Tabuteau, M.D.

Signature: _____ Date: 6 March 2014

Exhibit 1

1. Raja SN, Grabow TS. Complex regional pain syndrome I (reflex sympathetic dystrophy). Anesthesiology 2002; 96: 1254-1260.

2. Rho RH, Brewer RP, Lamer TJ, Wilson PR. Complex regional pain syndrome. Mayo Clin Proc 2002; 77: 174-180.

3. Wasner G, Backonja M-M, Baron R. Traumatic neuralgias: complex regional pain syndromes (reflex sympathetic dystrophy and causalgia): clinical characteristics, pathophysiologic mechanisms and therapy. Neurol Clin 1998; 16: 851-868.

4. Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle, WA: IASP Press, 1994 p. 40-43.

5. Alvarez-Lario B, Aretxabala-Alcibar I, Alegre-Lopez J, Alonso-Valdivielso JL. Acceptance of the different denominations for reflex sympathetic dystrophy. Ann Rheum Dis 2001; 60: 77-79.

6. Koman LA, Poehling GG, Smith BP, Smith TL, Chloros G. Chapter 59 – Complex Regional Pain Syndrome. Green's Operative Hand Surgery, 6th ed.: Churchill Livingstone, 2010.

7. Sharma A, Williams K, Raja SN. Advances in treatment of regional pain syndrome: recent insights on a perplexing disease. Curr Opin Anaesthesiol 2006; 19: 566-572.

8. Forouzanfar T, Koke AJ, van Kleef M, Weber WE. Treatment of complex regional pain syndrome type I. Eur J Pain 2002; 6: 105-122.

9. Bodde MI, Dijkstra PU, den Dunnen WFA, Geertzen JHB. Therapy-resistant complex regional pain syndrome type I: to amputate or not? J Bone Joint Surg Am 2011; 93: 1799-1805.

10. Dielissen PW, Claassen AT, Veldman PH, Goris RJ. Amputation for reflex sympathetic dystrophy. J Bone Joint Surg Br 1995; 77: 270-273.

11. de Mos M, Huygen FJPM, van der Hoeven-Borgman M, Dieleman JP, Stricker BHC, Sturkenboom MCJM. Outcome of the complex regional pain syndrome. Clin J Pain 2009; 25: 590-597.

12. Green JR, Rogers MJ. Pharmacologic profile of zoledronic acid: a highly potent inhibitor of bone resorption. Drug Dev Res 2002; 55: 210-224.

13. Reid IA, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, Mesenbrink P, Su G, Pak J, Zelenakas K, Luchi M, Richardson P, Hosking D. Comparison of a single infusion

of zoledronic acid with residronate for Paget's disease. N Engl J Med 2005; 353: 898-908.

14. Ripamonti C, Fagnoni E, Campa T, Giardina V, Brunelli C, Pigni A, De Conno F. Decreases in pain at rest and movement-related pain during zoledronic acid treatment in patients with bone metastases due to breast or prostate cancer: a pilot study. Support Care Cancer 2007; 15: 1177-1184.

15. Kretzchmar A, Wiegel T, Al-Batran S, Hinrichs HF, Kindler M, Steck T, Illiger HJ, Heinemann V, Schmidt K, Haus U, Kirner A, Ehninger G. Rapid and sustained influence of intravenous zoledronic acid on course of pain and analgesics consumption in patients with cancer with bone metastases: A multicenter open-label study over 1 year. Supportive Cancer Therapy 2007; 4: 203-210.

16. Ringe JD, Body JJ. A review of bone pain with ibandronate and other bisphosphonates in disorders of increased bone turnover. Clin Exp Rheumatol 2007; 25: 766-774.

17. Ringe JD. Development of clinical utility of zoledronic acid and patient considerations in the treatment of osteoporosis. Patient Prefer Adherence 2010; 4: 231-245.

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Exhibit 2

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FDA Home[2] Drug Databases[1] Orange Book[5]

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Start Over[6] | Back to Search Page

Active Ingredient Search Results from "OB_Rx" table for query on "zoledronic acid."

Displaying records 1 to 19 of 19

Download data

Appl No	TE Code[7]	RLD[8]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N203231	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/100ML	ZOLEDRONIC ACID	ACS DOBFAR INFO SA
A202828	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	ACS DOBFAR INFO SA
A202472	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	ACTAVIS INC
A202650	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	AGILA SPECLTS
A091186	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	DR REDDYS LABS LTD
A091363	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	DR REDDYS LABS LTD
A201783	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	EMCURE PHARMS LTD
A201801	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	EMCURE PHARMS LTD
A202930	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	GLAND PHARMA LTD
A202182	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	HIKMA FARMACEUTICA
A202837	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	HOSPIRA INC
N021223	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/100ML	ZOMETA	NOVARTIS
N021223	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOMETA	NOVARTIS
N021817	AP	Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	RECLAST	NOVARTIS
A091170	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	PHARMACEUTICS
A202163	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 5MG BASE/100ML	ZOLEDRONIC ACID	PHARMACEUTICS
A202571	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	PHARMS
A202746	AP	No	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/5ML	ZOLEDRONIC ACID	SUN PHARMA GLOBAL
A090018		Yes	ZOLEDRONIC ACID	INJECTABLE; IV (INFUSION)	EQ 4MG BASE/VIAL	ZOLEDRONIC ACID	SUN PHARMA GLOBAL

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Office of Generic Drugs
Division of Labeling and Program Support
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Orange Book Preface

Food and Drug Administration
Center for Drug Evaluation and Research
Approved Drug Products with Therapeutic Equivalence Evaluations
32nd Edition

PREFACE

The publication, ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (the List, commonly known as the Orange Book), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products on the List is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the Act.

The therapeutic equivalence evaluations in the List reflect FDA's application of specific criteria to the multisource prescription drug products on the List approved under Section 505 of the Act. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the code appears in the Introduction.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication, October 1980, of the final version of the List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (1984 Amendments). The 1984 Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The ***Approved Drug Products with Therapeutic Equivalence Evaluations*** publication and its monthly Cumulative Supplements satisfy this requirement. The *Addendum*[1] to this publication identifies drugs that qualify under the 1984 Amendments for periods of exclusivity (during which ANDAs or applications described in Section 505(b)(2) of the Act for those drugs may not be submitted for a specified period of time and, if allowed to be submitted, would be tentatively approved) and provides patent information concerning the listed drugs which also may delay the approval of ANDAs or Section 505(b)(2) applications. The *Addendum*[2] also provides additional information that may be helpful to those submitting a new drug application to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Director, Division of Labeling and Program Support HFD-610, Office of Generic Drugs, Center for Drug and Evaluation and Research, 7620 Standish Place, Rockville, MD 20855. Comments received are publicly available to the extent allowable under the Freedom of Information regulations.

INTRODUCTION

Content and Exclusion

The List is composed of four parts: (1) approved prescription drug products with therapeutic equivalence evaluations; (2) approved over-the-counter (OTC) drug products for those drugs that may not be marketed without NDAs or ANDAs because they are not covered under existing OTC monographs; (3) drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research; and (4) a cumulative list of approved products that have never been marketed, are for exportation, are for military use, have been discontinued from marketing, or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. [Note: Newly approved products are added to parts 1, 2, or 3 of the List, depending on the dispensing requirements (prescription or OTC) or approval authority, unless the Orange Book staff is otherwise notified before publication.]

This publication also includes indices of prescription and OTC drug products by trade or established name (if no trade name exists) and by applicant name (holder of the approved application). All established names for active ingredients generally conform to official compendial names or *United States Adopted Names* (USAN) as prescribed in (21 CFR 299.4(e)). The latter list includes applicants' names as abbreviated in this publication; in addition, a list of uniform terms is provided. An *Addendum*[3] contains drug patent and exclusivity information for the Prescription, OTC, Discontinued Drug Product Lists, and for the Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research. The publication may include additional information that the Agency deems appropriate to disseminate.

Prior to the 6th Edition, the publication had excluded OTC drug products and drug products with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research because the main purpose of the publication was to provide information to states regarding FDA's recommendation as to which generic prescription drug products were acceptable candidates for drug product selection. The 1984 Amendments required the Agency to begin publishing an up&€'to&€'date list of all marketed drug products, OTC as well as prescription, that have been approved for safety and efficacy and for which new drug applications are required.

Under the 1984 Amendments, some drug products are given tentative approvals. The Agency will not include drug products with tentative approval in the List; however, they are available at ANDA Approvals[4]. When the tentative approval becomes a full approval through a subsequent action letter to the application holder, the Agency will list the drug product and the final approval date in the appropriate approved drug product list.

Distributors or repackagers of products on the List are not identified. Because distributors or repackagers are not required to notify FDA when they shift their source of supply from one approved manufacturer to another, it is not possible to maintain complete information linking product approval with the distributor or repackager handling the products.

Therapeutic Equivalence-Related Terms

Pharmaceutical Equivalents. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5mg capsules). Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

Pharmaceutical Alternatives. Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.

Therapeutic Equivalents. Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations. *The concept of therapeutic equivalence, as used to develop the List, applies only to drug products containing the same active ingredient(s) and does not encompass a comparison of different therapeutic agents used for the same condition (e.g., ibuprofen vs. naproxen for the treatment of pain).* Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. Therapeutic equivalence determinations are not made for unapproved, off-label indications.

FDA considers drug products to be therapeutically equivalent if they meet the criteria outlined above, even though they may differ in certain other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time and minor aspects of labeling (e.g., the presence of specific pharmacokinetic information) and storage conditions. When such differences are important in the care of a particular patient, it may be appropriate for the prescribing physician to require that a particular brand be dispensed as a medical necessity. With this limitation, however, FDA believes that products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product.

Bioavailability. This term means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Bioequivalent Drug Products. This term describes pharmaceutical equivalent or alternative products that display comparable bioavailability when studied under similar experimental conditions. Section 505 (j)(8)(B) of the Act describes one set of conditions under which a test and reference listed drug[5] shall be considered bioequivalent:

the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

the extent of absorption of the test drug does not show a significant difference from the extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the reference drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

Where these above methods are not applicable (e.g., for drug products that are not intended to be absorbed into the bloodstream), other *in vivo* or *in vitro* test methods to demonstrate bioequivalence may be appropriate.

Bioequivalence may sometimes be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may sometimes be demonstrated through comparative clinical trials or pharmacodynamic studies.

Statistical Criteria for Bioequivalence

Under the Drug Price Competition and Patent Term Restoration Act of 1984, manufacturers seeking approval to market a generic drug product must submit data demonstrating that the drug product is bioequivalent to the pioneer (innovator) drug product. A major premise underlying the 1984 law is that bioequivalent drug products[5] are therapeutically equivalent and, therefore, interchangeable.

Bioavailability refers to the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug product and becomes available at the site of drug action (Federal Food, Drug and Cosmetic Act, section 505(j)(8)). Bioequivalence refers to equivalent release of the same drug substance from two or more drug products or formulations. This leads to an equivalent rate and extent of absorption from these formulations. Underlying the concept of bioequivalence is the thesis that, if a drug product contains a drug substance that is chemically identical and is delivered to the site of action at the same rate and extent as another drug product, then it is equivalent and can be substituted for that drug product. Methods used to define bioequivalence can be found in 21 CFR 320.24, and include (1) pharmacokinetic (PK) studies, (2) pharmacodynamic (PD) studies, (3) comparative clinical trials, and (4) in-vitro studies. The choice of study used is based on the site of action of the drug and the ability of the study design to compare drug delivered to that site by the two products.

The standard bioequivalence (PK) study is conducted using a two-treatment crossover study design in a limited number of volunteers, usually 24 to 36 adults. Alternately, a four-period, replicate design crossover study may also be used. Single doses of the test and reference drug products are administered and blood or plasma levels of the drug are measured over time. Pharmacokinetic parameters characterizing rate and extent of drug absorption are evaluated statistically. The PK parameters of interest are the resulting area under the plasma concentration-time curve (AUC), calculated to the last measured concentration (AUC(0-t)) and extrapolated to infinity (AUC(0-inf)), for extent of absorption; and the maximum or peak drug concentrations (Cmax), for rate of absorption. Crossover studies may not be practical in drugs with a long half-life in the body, and a parallel study design may be used instead. Alternate study methods, such as in-vitro studies or equivalence studies with clinical or pharmacodynamic endpoints, are used for drug products where plasma concentrations are not useful to determine delivery of the drug substance to the site of activity (such as inhalers, nasal sprays and topical products applied to the skin).

The statistical methodology for analyzing these bioequivalence studies is called the two one-sided test procedure. Two situations are tested with this statistical methodology. The first of the two one-sided tests determines whether a generic product (test), when substituted for a brand-name product (reference) is significantly less bioavailable. The second of the two one-sided tests determines whether a brand-name product when substituted for a generic product is significantly less bioavailable. Based on the opinions of FDA medical experts, a difference of greater than 20% for each of the above tests was determined to be significant, and therefore, undesirable for all drug products. Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test and a limit of reference-product average/test-product average of 80% for the second statistical test. By convention, all data is expressed as a ratio of the average response (AUC and Cmax) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%).

For statistical reasons, all data is log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance procedure (ANOVA) and calculating a 90% confidence interval for each pharmacokinetic parameter (Cmax and AUC). The confidence interval for both pharmacokinetic parameters, AUC and Cmax, must be entirely within the 80% to 125% boundaries cited above. Because the mean of the study data lies in the center of the 90% confidence interval, the mean of the data is usually close to 100% (a test/reference ratio of 1). Different statistical criteria are sometimes used when bioequivalence is demonstrated through comparative clinical trials pharmacodynamic studies, or comparative in-vitro methodology.

The bioequivalence methodology and criteria described above simultaneously control for both, differences in the average response between test and reference as well as the precision with which the average response in the population is estimated. This precision depends on the within-subject (normal volunteer or patient) variability in the pharmacokinetic parameters (AUC and Cmax) of the two products and on the number of subjects in the study. The width of the 90% confidence interval is a reflection in part of the within-subject variability of the test and reference products in the bioequivalence study. A test product with no differences in the average response when compared to the reference might still fail to pass the bioequivalence criteria if the variability of one or both products is high and the bioequivalence study has insufficient statistical power (i.e., insufficient number of subjects). Likewise, a test product with low variability may pass the bioequivalence criteria, when there are somewhat larger differences in the average response.

This system of assessing bioequivalence of generic products assures that these substitutable products do not deviate substantially in in-vivo performance from the reference product. The Office of Generic Drugs has conducted two surveys to quantify the differences between generic and brand name products. The first survey included 224 bioequivalence studies submitted in approved applications during 1985 and 1986. The observed average differences between reference and generic products for AUC was 3.5% (JAMA, Sept. 4, 1987, Vol. 258, No. 9). The second survey included 127 bioequivalence studies submitted to the agency in 273 ANDAs approved in 1997. The three measures reviewed include AUC(0-t), AUC(0-inf), and Cmax. The observed average differences between the reference and generic products were + 3.47% (SD 2.84) for AUC(0-t), + 3.35% (SD 2.97) for AUC(0-inf), and + 4.29% (SD 3.72) for Cmax (JAMA, Dec. 1, 1999, Vol. 282, No. 21).

The primary concern from the regulatory point of view is the protection of the patient against approval of products that are not bioequivalent. The current practice o carrying out two one-sided tests at the 0.05 level of significance ensures that there is no more than a 5% chance that a generic product that is not truly equivalent t the reference will be approved.

Reference Listed Drug (RLD)

A reference listed drug (21 CFR 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.

FDA has identified in the Prescription Drug Product and OTC Drug Product Lists those reference listed drugs to which the *in vivo* bioequivalence (reference standard) and, in some instances, the *in vitro* bioequivalence of the applicant's product is compared. By designating a single reference listed drug as the standard to which all generic versions must be shown to be bioequivalent, FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart. Such variations could result if generic drugs were compared to different reference listed drugs. However, in some instances when listed drugs are approved for a single drug product, a product not designated as the reference listed drug and not shown to be bioequivalent to the reference listed drug may be shielded from generic competition. A firm wishing to market a generic version of a listed drug that is not designated as the reference listed drug may petition the Agency through the Citizen Petition procedure (see 21 CFR 10.25(a) and CFR 10.30). When the Citizen Petition is approved, the second listed drug will be designated as an additional reference listed drug and the petitioner may submit an Abbreviated New Drug Application citing the designated reference listed drug. *Therapeutic Equivalence Evaluations Codes*[7] *Products meeting necessary bioequivalence requirements* explains the ***AB, AB1, AB2, AB3*** coding system for multisource drug products listed under the same heading with two reference listed drugs.

In addition, there are two situations in which two listed drugs that have been shown to be bioequivalent to each other may both be designated as reference listed drugs. The first situation occurs when the in vivo determination of bioequivalence is self-evident and a waiver of the *in vitro* methodology. The reference listed drug is identified by the symbol "+" in the Prescription and Over-the-Counter (OTC) Drug Product Lists. These identified reference listed drugs represent the best judgment of the Division of Bioequivalence at this time. The Prescription and OTC Drug Product Lists identify reference drugs for oral dosage forms, injectables, ophthalmics, otics, and topical products. It is recommended that a firm planning to conduct an *in vivo* waiver of bioequivalence will be requested, contact the Division of Bioequivalence, Office of Generic Drugs, to confirm the appropriate reference listed drug.

General Policies and Legal Status

The List contains public information and advice. It does not mandate the drug products which may be purchased, prescribed, dispensed, or substituted for one another, nor does it, conversely, mandate the products that should be avoided. To the extent that the List sets forth FDA's evaluations of the therapeutic equivalenc of drug products that have been approved, it contains FDA's advice to the public, to practitioners and to the states regarding drug product selection. These evaluations do not constitute determinations that any product is in violation of the Act or that any product is preferable to any other. Therapeutic equivalence evaluations are a scientific judgment based upon evidence, while generic substitution may involve social and economic policy administered by the states, intended to reduce the cost of drugs to consumers. To the extent that the List identifies drug products approved under Section 505 of the Act, it sets forth information that the Agency is required to publish and that the public is entitled to under the Freedom of Information Act. Exclusion of a drug product from the List does not necessarily mean that the drug product is either in violation of Section 505 of the Act, or that such a product is not safe or effective, or that such a product is not therapeutically equivalent to other drug products. Rather, the exclusion is based on the fact that FDA has not evaluated the safety, effectiveness, and quality of the drug product.

Practitioner/User Responsibilities

Professional care and judgment should be exercised in using the List. Evaluations of therapeutic equivalence for prescription drugs are based on scientific and medical evaluations by FDA. Products evaluated as therapeutically equivalent can be expected, in the judgment of FDA, to have equivalent clinical effect and no difference in their potential for adverse effects when used under the conditions of their labeling. However, these products may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling. If products with such differences are substituted for each other, there is a potential for patient confusion due to differences in color or shape of tablets, inability to provide a given dose using a partial tablet if the proper scoring configuration is not available, or decreased patient acceptance of certain products because of flavor. There may also be better stability of one product over another under adverse storage conditions, or allergic reactions in rare cases due to a coloring or a preservative ingredient, as well as differences in cost to the patient.

FDA evaluation of therapeutic equivalence in no way relieves practitioners of their professional responsibilities in prescribing and dispensing such products with due care and with appropriate information to individual patients. In those circumstances where the characteristics of a specific product, other than its active ingredient, are important in the therapy of a particular patient, the physician's specification of that product is appropriate. Pharmacists must also be familiar with the expiration dates/times and labeling directions for storage of the different products, particularly for reconstituted products, to assure that patients are properly advised when one product is substituted for another.

Multisource and single-source drug products. FDA has evaluated for therapeutic equivalence only multisource prescription drug products approved under Section 505 of the Act, which in most instances means those pharmaceutical equivalents available from more than one manufacturer. For such products, a therapeutic equivalence code is included and, in addition, product information is highlighted in bold face and underlined. Those products with approved applications that are single-source (i.e., there is only one approved product available for that active ingredient, dosage form, route of administration, and strength) are also included on the List, but no therapeutic equivalence code is included with such products. Any drug product in the List repackaged and/or distributed by other than the application holder is considered to be therapeutically equivalent to the application holder's drug product even if the application holder's drug product is single source or coded as non-equivalent (e.g., **BN**). Also, although not identified in the List, distributors or repackagers of an application holder's drug product are considered to have the same code as the application holder. The details of these codes and the policies underlying them are discussed in *Therapeutic Equivalence Evaluations Codes*[8].

Products on the List are identified by the names of the holders of approved applications (applicants) who may not necessarily be the manufacturer of the product. The applicant may have had its product manufactured by a contract manufacturer and may simply be distributing the product for which it has obtained approval. In most instances, however, the manufacturer of the product is also the applicant. The name of the manufacturer is permitted by regulation to appear on the label, even when the manufacturer is not the marketer.

Although the products on the List are identified by the names of the applicants, circumstances, such as changing corporate ownership, have sometimes made identification of the applicant difficult. The Agency believes, based on continuing document review and communication with firms, that the applicant designations on the List are, in most cases, correct.

To relate firm name information on a product label to that on the List, the following should be noted: the applicant's name always appears on the List. This applies whether the applicant (firm name on the Form FDA 356h in the application) is the marketer (firm name in largest letters on the label) or not. However, the applicant's name may not always appear on the label of the product.

If the applicant is the marketer, its name appears on the List and on the label; if the applicant is not the marketer, and the Agency is aware of a corporate relationship (e.g., parent and subsidiary) between the applicant and the marketer, the name of the applicant appears on the List and both firm names may appear o the label. Firms with known corporate relationships are displayed in Appendix B. If there is no known corporate relationship between the applicant and the marketer the applicant's name appears on the List; however, unless the applicant is the manufacturer, packager, or distributor, the applicant's name may not appear on the label. In this case, the practitioner, from labeling alone, will not be able to relate the marketed product to an applicant cited in the List, and hence to a specific approved drug product. In such cases, to assure that the product in question is the subject of an approved application, the firm named on the label should be contacted.

To relate trade name (proprietary name) information on a product label to that on the List, the following should be noted: if the applicant is the marketer, its name appears on the List and on the label; if the Agency is aware of a corporate relationship between the applicant and the marketer, the trade name (proprietary name) of the drug product (established drug name if no trade name exists) appears on the List. If a corporate relationship exists between an application holder and a marketer and both firms are distributing the drug product, the FDA reserves the right to select the trade name of either the marketer or the application holder to appear on the List. If there is no known corporate relationship between the applicant and the marketer, the established drug name appears on the List.

Every product on the List is subject at all times to regulatory action. From time to time, approved products may be found in violation of one or more provisions of the Act. In such circumstances, the Agency will commence appropriate enforcement action to correct the violation, if necessary, by securing removal o the product from the market by voluntary recall, seizure, or other enforcement actions. Such regulatory actions are, however, independent of the inclusion of a product on the List. The main criterion for inclusion of a product is that it has an application with an effective approval that has not been withdrawn for safety or efficacy reasons. FDA believes that retention of a violative product on the List will not have any significant adverse health consequences, because other legal mechanisms are available to the Agency to prevent the product's actual marketing. FDA may however, change a product's therapeutic equivalence rating if the circumstances giving rise to the violation change or otherwise call into question the data upon which the Agency's assessment of whether a product meets the criteri for therapeutic equivalence was made.

Therapeutic Equivalence Evaluations Codes

The coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With few exceptions, the therapeutic equivalence evaluation date is the same as the approval date.

The two basic categories into which multisource drugs have been placed are indicated by the first letter as follows.

A Drug products that FDA considers to be therapeutically equivalent[9] to other pharmaceutically equivalent products, i.e., drug products for which:

(1) there are no known or suspected bioequivalence problems. These are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form; or

(2) actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. These are designated **AB**.

B Drug products that FDA at this time, considers NOT to be therapeutically equivalent to other pharmaceutically equivalent products, i.e.,

drug products for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence. Often the problem is with specific dosage forms rather than with the active ingredients. These are designated **BC**, **BD**, **BE**, **BN**, **BP**, **BR**, **BS**, **BT**, **BX**, or **B***.

Individual drug products have been evaluated as therapeutically equivalent to the reference product in accordance with the definitions and policies outlined below:

"A" CODES

Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products.

"**A**" products are those for which actual or potential bioequivalence problems have been resolved with adequate *in vivo* and/or *in vitro* evidence supporting bioequivalence. Drug products designated with an "**A**" code fall under one of two main policies:

(1) for those active ingredients or dosage forms for which no *in vivo* bioequivalence issue is known or suspected, the information necessary to show bioequivalence between pharmaceutically equivalent products is presumed and considered self-evident based on other data in the application for some dosage forms (e.g., solutions or satisfied for solid oral dosage forms by a showing that an acceptable *in vitro* dissolution standard is met. A therapeutically equivalent rating is assigned such products so long as they are manufactured in accordance with Current Good Manufacturing Practice regulations and meet the other requirements of their approved applications (these are designated **AA**, **AN**, **AO**, **AP**, or **AT**, depending on the dosage form, as described below); or

(2) for those DESI drug products containing active ingredients or dosage forms that have been identified by FDA as having actual or potential bioequivalence problems, and for post-1962 drug products in a dosage form presenting a potential bioequivalence problem, an evaluation of therapeutic equivalence is assigned to pharmaceutical equivalents only if the approved application contains adequate scientific evidence establishing through *in vivo* and/or *in vitro* studies the bioequivalence of the product to a selected reference product (these products are designated as **AB**).

There are some general principles that may affect the substitution of pharmaceutically equivalent products in specific cases. Prescribers and dispensers of drugs should be alert to these principles so as to deal appropriately with situations that require professional judgment and discretion.

There may be labeling differences among pharmaceutically equivalent products that require attention on the part of the health professional. For example, pharmaceutically equivalent powders to be reconstituted for administration as oral or injectable liquids may vary with respect to their expiration time or storage conditions after reconstitution. An FDA evaluation that such products are therapeutically equivalent is applicable only when each product is reconstituted, stored, and used under the conditions specified in the labeling of that product.

The Agency will use notes in this publication to point out special situations such as potential differences between two drug products that have been evaluated as bioequivalent and otherwise therapeutically equivalent, when they should be brought to the attention of health professionals. These notes are contained in *Description of Special Situations*[10].

For example, in rare instances, there may be variations among therapeutically equivalent products in their use or in conditions of administration. Such differences may be due to patent or exclusivity rights associated with such use. When such variations may, in the Agency's opinion, affect prescribing or substitution decisions by health professionals, a note will be added to *Description of Special Situations*[11].

Also, occasionally a situation may arise in which changes in a listed drug product after its approval (for example, a change in dosing interval) may have an impact on the substitutability of already approved generic versions of that product that were rated by the Agency as therapeutically equivalent to the listed product. When such changes in the listed drug product are considered by the Agency to have a significant impact on therapeutic equivalence, the Agency will change the therapeutic equivalence ratings for other versions of the drug product unless the manufacturers of those other versions of the product provide additional information to assure equivalence under the changed conditions. Pending receipt of the additional data, the Agency may add a note to *Description of Special Situations*[12], or, in rare cases may even change the therapeutic equivalence rating.

In some cases (e.g., Isolyte® S w/ Dextrose 5% in Plastic Container and Plasma-Lyte® 148 and Dextrose 5% in Plastic Container), closely related products are listed as containing the same active ingredients, but in somewhat different amounts. In determining which of these products are pharmaceutically equivalent, the Agency has considered products to be pharmaceutically equivalent with labeled strengths of an ingredient that do not vary by more than 1%.

Different salts and esters of the same therapeutic moiety are regarded as pharmaceutical alternatives. For the purpose of this publication, such products are not considered to be therapeutically equivalent. There are no instances in this List where pharmaceutical alternatives are evaluated or coded with regard to therapeutic equivalence. Anhydrous and hydrated entities, as well as different polymorphs, are considered pharmaceutical equivalents and must meet the same standards and, where necessary, as in the case of ampicillin/ampicillin trihydrate, their equivalence is supported by appropriate bioavailability/bioequivalence studies.

The codes in this book are not intended to preclude health care professionals from converting pharmaceutically different concentrations into pharmaceutical equivalents using accepted professional practice.

Where package size variations have therapeutic implications, products so packaged have not been considered pharmaceutically equivalent. For example, some oral contraceptives are supplied in 21-tablet and 28-tablet packets; the 28-tablet packets contain 7 placebo or iron tablets. These two packaging configurations are not regarded as pharmaceutically equivalent; thus, they are not designated as therapeutically equivalent.

Preservatives may differ among some therapeutically equivalent drug products. Differences in preservatives and other inactive ingredients do not affect FDA's evaluation of therapeutic equivalence except in cases where these components may influence bioequivalence or routes of administration.

The specific sub-codes for those drugs evaluated as therapeutically equivalent and the policies underlying these sub-codes follow:

AA Products in conventional dosage forms not presenting bioequivalence problems

Products coded as **AA** contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate *in vitro* bioequivalence standard that is acceptable to the Agency in order to be approved.

AB, AB1, AB2, AB3... Products meeting necessary bioequivalence requirements

Multisource drug products listed under the same heading (i.e., identical active ingredients(s), dosage form, and route(s) of administration) and having the same strength (see *Therapeutic Equivalence-Related Terms, Pharmaceutical Equivalents*[13]) generally will be coded **AB** if a study is submitted demonstrating bioequivalence. In certain instances, a number is added to the end of the **AB** code to make a three character code (i.e., **AB1, AB2, AB3, etc.**). Three-character codes are assigned only in situations when more than one reference listed drug of the same strength has been designated under the same heading. Two or more reference listed drugs are generally selected only when there are at least two potential reference drug products which are not bioequivalent to each other. If a study is submitted that demonstrates bioequivalence to a specific listed drug product, the generic product will be given the same three-character code as the reference listed drug it was compared against. For example, Adalat® CC (Miles) and Procardia XL® (Pfizer), extended-release tablets, are listed under the active ingredient nifedipine. These drug products, listed under the same heading, are not bioequivalent to each other. Generic drug products deemed by FDA to be bioequivalent to Adalat® CC and Procardia XL® have been approved, Adalat® CC and Procardia XL® have been assigned ratings of **AB1** and **AB2**, respectively. The generic drug products bioequivalent to Adalat® CC would be assigned a rating of **AB1** and those bioequivalent to Procardia XL® would be assigned a rating of **AB2**. (The assignment of an **AB1** or **AB2** rating to a specific product does not imply product preference.) Even though drug products of distributors and/or repackagers are not included in the List, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated either with an **AB** or three-character code or is single source in the List. Drugs coded as **AB** under a heading are considered therapeutically equivalent only to other drugs coded as **AB** under that heading. Drugs coded with a three-character code under a heading are considered therapeutically equivalent only to other drugs coded with the same three-character code under that heading.

AN Solutions and powders for aerosolization

Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded **AN**. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded **BN**, unless they have met an appropriate bioequivalence standard. Solutions or suspensions in a specific delivery system will be coded **AN** if the bioequivalence standard is based upon *in vitro* methodology, if bioequivalence needs to be demonstrated by *in vivo* methodology then the drug products will be code **AB**.

AO Injectable oil solutions

The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.

AP Injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions

It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, *Injectable; Injection*. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s of administration stated in the labeling.

Certain commonly used large volume intravenous products in glass containers are not included on the List (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.

The strength of parenteral drugs products is defined as the total drug content of the container. Until recently the strength of liquid parenteral drug products in the Orange Book have not been displayed. The concentration of the liquid parenteral drug product in the Orange Book has been shown as xmg/ml. The amount of dry powder or freeze dried powder in a container has always been identified as the strength.

With the finalization of the Waxman-Hatch amendments that characterized each strength of a drug product as a listed drug it became evident that the format of the Orange Book should be changed to reflect each strength of a parenteral solution. To this end the OGD has started to display the strength of all new approvals of parenteral solutions. Previously we would have displayed only the concentration of an approved parenteral solution, e.g. 50mg/ml. If this drug product had a 20 ml and 60 ml container approved the two products would be shown as 1Gm / 20ml (50mg/ml) and 3Gm / 60ml (50mg/ml).

AT Topical products

There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including creams, gels, lotions, oils, ointments, pastes, solutions, sprays and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of *in vivo* bioequivalence has been granted and for which chemistry and manufacturing processes are adequate to demonstrate bioequivalence, are considered therapeutically equivalent and coded **AT**. Pharmaceutically equivalent topical products that raise questions of bioequivalence, including all post-1962 non-solution topical drug products, are coded **AB** when supported by adequate bioequivaleno data, and **BT** in the absence of such data.

"B" CODES

Drug products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products.

"**B**" products, for which actual or potential bioequivalence problems have not been resolved by adequate evidence of bioequivalence, often have a problem with specific dosage forms rather than with the active ingredients. Drug products designated with a "**B**" code fall under one of three main policies:

(1) the drug products contain active ingredients or are manufactured in dosage forms that have been identified by the Agency as having documented bioequivalence problems or a significant potential for such problems and for which no adequate studies demonstrating bioequivalence have been submitted to FDA; or

(2) the quality standards are inadequate or FDA has an insufficient basis to determine therapeutic equivalence; or

(3) the drug products are under regulatory review.

The specific coding definitions and policies for the "**B**" sub-codes are as follows:

B* Drug products requiring further FDA investigation and review to determine therapeutic equivalence

The code **B*** is assigned to products previously assigned an **A** or **B** code when FDA receives new information that raises a significant question regarding therapeutic equivalence that can be resolved only through further Agency investigation and/or review of data and information submitted by the applicant. The **B*** code signifies that the Agency will take no position regarding the therapeutic equivalence of the product until the Agency completes its investigation and review.

BC Extended-release dosage forms (capsules, injectables and tablets)

Extended-release tablets are formulated in such a manner as to make the contained medicament available over an extended period of time following ingestion.

Although bioavailability studies have been conducted on these dosage forms, they may be subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded **BC**, while those for which such data are available have been coded **AB**.

BD Active ingredients and dosage forms with documented bioequivalence problems

The **BD** code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded **AB**.

BE Delayed-release oral dosage forms

Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach. Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the Agency considers different delayed release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products **BE** in the absence of *in vivo* studies showing bioequivalence. If adequate *in vivo* studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded **AB**

BN Products in aerosol-nebulizer drug delivery systems

This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the Agency does not consider differen metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard, such products are coded **AB**.

BP Active ingredients and dosage forms with potential bioequivalence problems

FDA's bioequivalence regulations (21 CFR 320.33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded **BP** until adequate *in vivo* bioequivalence data are submitted, such products are coded **AB**. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded **BP**. Injectable suspensions are subject to bioequivalence problems because differences in particle size,

polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence, such products would be coded **AB**

BR Suppositories or enemas that deliver drugs for systemic absorption

The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if *in vivo* evidence of bioequivalence is available. In those cases where *in vivo* evidence is available, the product is coded **AB**. If such evidence is not available, the products are coded **BR**.

BS Products having drug standard deficiencies

If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded **BS**. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded **BS**.

BT Topical products with bioequivalence issues

This code applies mainly to post-1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence, will be coded **BT**.

BX Drug products for which the data are insufficient to determine therapeutic equivalence

The code **BX** is assigned to specific drug products for which the data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the Agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.

Description of Special Situations

Certain drugs listed in the Orange Book present special situations that merit further discussion. Following is a description of these special situations:

Amino Acid and Protein Hydrolysate Injections. These products differ in the amount and kinds of amino acids they contain and, therefore, are not considered pharmaceutical equivalents. For this reason, these products are not considered therapeutically equivalent. At the same time, the Agency believes that it is appropriate to point out that where nitrogen balance is the sole therapeutic objective and individual amino acid content is not a consideration, pharmaceutical alternatives with the same total amount of nitrogen content may be considered therapeutically equivalent.

Follitropin Alfa and Beta. Based on available data derived from physico-chemical tests and bioassay, follitropin alfa and follitropin beta are indistinguishable.

Gaviscon®. Gaviscon® is an OTC product which has been marketed since September 1970. The active ingredients in this product, aluminum hydroxide and magnesium trisilicate, were reviewed by the Agency's OTC Antacid Panel and were considered to be safe and effective ingredients (Category I) by that Panel. However, the tablet failed to pass the antacid test which is required of all antacid products. The Agency, therefore, placed the tablet in Category III for lack of effectiveness. A full NDA with clinical studies was submitted by Marion Laboratories, Inc., and approved by FDA on December 9, 1983. Gaviscon® 's activity in treating reflux acidity is made possible by the physical-chemical properties of the inactive ingredients, sodium bicarbonate and alginic acid. Therefore, *all ANDAs which cite Gaviscon® tablets as the listed drug must contain the inactive ingredients sodium bicarbonate and alginic acid.* A full NDA will be required to support the effectiveness of the drug product if different inactive ingredients are to be substituted for sodium bicarbonate or alginic acid or if different proportions of these ingredients are to be used.

Levothyroxine Sodium. Because there are multiple reference listed drugs of levothyroxine sodium tablets and some reference listed drugs' sponsors have conducted studies to establish their drugs' therapeutic equivalence to other reference listed drugs, FDA has determined that its usual practice of assigning two or three character TE codes may be potentially confusing and inadequate for these drug products. Accordingly, FDA provides the following explanation and chart of therapeutic equivalence evaluations for levothyroxine sodium drug products.

Levothyroxine Sodium (Mylan ANDA 76187), tablets have been determined to be therapeutically equivalent to corresponding strengths of Unithroid (Jerome Stevens NDA 021210) tablets.

Levo-T (Alara NDA 021342), Levothyroxine Sodium (Mylan ANDA 76187), Unithroid (Jerome Stevens NDA 021210) and Levothyroxine Sodium (Merck KGAA ANDA 76752)tablets have been determined to be therapeutically equivalent to corresponding strengths of Synthroid (Abbott NDA 021402) tablets.

Levo-T (Alara NDA 021342), Unithroid (Jerome Stevens NDA 021210), Levothyroxine Sodium (Mylan ANDA 076187) and Levothyroxine Sodium (Merck KGAA ANDA 76752) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levoxyl (King Pharms NDA 021301) tablets.

Levothyroxine Sodium (Mylan ANDA 76187) tablets have been determined to be therapeutically equivalent to corresponding strengths of Levothroid (Lloyd NDA 021116) tablets.

The chart outlines TE codes for all 0.025mg products. Other product strenghts may be similar. Therapeutic equivalence has been established between products that have the same AB+number TE code. More than one TE code may apply to some products. One common TE code indicates therapeutic equivalence between products.

Trade Name	Applicant	Potency	TE Code	Appl No	Product No
UNITHROID	STEVENS J	0.025MG	AB1	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB1	76187	001
LEVOXYL	KING PHARMS	0.025MG	AB1	21301	001
SYNTHROID	ABBOTT	0.025MG	AB1	21402	001
LEVO-T	ALARA PHARM	0.025MG	AB1	21342	001
SYNTHROID	ABBOTT	0.025MG	AB2	21402	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB2	76187	001
LEVO-T	ALARA PHARM	0.025MG	AB2	21342	001
UNITHROID	STEVENS J	0.025MG	AB2	21210	001
LEVOTHYROXINE SODIUM	MERCK KGAA	0.025MG	AB2	76752	001
LEVOXYL	KING PHARMS	0.025MG	AB3	21301	001
LEVO-T	ALARA PHARM	0.025MG	AB3	21342	001
UNITHROID	STEVENS J	0.025MG	AB3	21210	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB3	76187	001
LEVOTHYROXINE SODIUM	MERCK KGAA	0.025MG	AB3	76752	001
LEVOTHROID	LLOYD	0.025MG	AB4	21116	001
LEVOTHYROXINE SODIUM	MYLAN	0.025MG	AB4	76187	001

Patent Certification(s) Reference Listed Drug based upon a suitability petition. An abbreviated new drug application that refers to a Reference Listed Drug (RLD) approved pursuant to a suitability petition must demonstrate that the proposed product is bioequivalent to the RLD, and it must include appropriate patent certification(s) and an exclusivity statement with respect to the listed drug which served as the basis for the approved suitability petition. This concept also applies to an ANDA applicant that cites a RLD that was based upon an NDA that is still covered by patent (s) and/or exclusivity, e.g. a second RLD that was selected when the in vivo determination of bioequivalence of the original RLD is self evident and the waiver of the in vivo determination of bioequivalence may be granted

Waived exclusivity. If a new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (Act) qualifies for exclusivity under sections 505(c)(3)(D) and 505(j)(5)(D), the exclusivity is listed in the Patent and Exclusivity Section of the Orange Book. If a drug product has received this exclusivity, the FDA will delay the approval of a 505(b)(2) application or an abbreviated new drug application (ANDA) under section 505(j) of the Act until the expiration of the exclusivity. If the listed drug is also protected by one or more patents, the approval date for the 505(b)(2) application or ANDA will be determined by the latest expiring patent or exclusivity listed in the Orange Book. However, the holder of the NDA may waiver its exclusivity as to any or all 505(b)(2) and ANDA applications referencing the protected drug product. If an NDA sponsor waivers its right to the exclusivity protection, qualified 505(b)(2) or ANDA applications may be approved without regard to the NDA holder's exclusivity. An NDA for which the holder has waived its exclusivity as to all 505(b)(2) and ANDA applications will be coded with a W in the Patent and Exclusivity Section of the Orange Book and be referred to this section. The applicant referencing this listed drug should indicate in the exclusivity statement that the holder of the listed drug has waived its exclusivity.

Therapeutic Equivalence Code Change for a Drug Entity

The Agency will use the following procedures when, in response to a petition or on its own initiative, it is considering a change in the therapeutic equivalence code for approved multi-source drug products. Such changes will generally occur when the Agency becomes aware of new scientific information affecting the therapeutic equivalence of an entire category of drug products in the List (e.g , information concerning the active ingredient or the dosage form), rather than information concerning a single drug product within the category. These procedures will be used when a change in therapeutic equivalence code is under consideration for all drug products found in the Prescription Drug Product List under a specific drug entity and dosage form. The change may be from the code signifying that the drug does not present a bioequivalence problem (e.g., **AA**) to a code signifying a bioequivalence problem (e.g., **BP**), or vice versa. This procedure does not apply to a change of a particular product code (e.g., a change from **BP** to **AB** or from **AB** to **BX**).

Before making a change in a therapeutic equivalence code for an entire category of drugs, the Agency will announce in the *Introduction* that it is considering the change, and will invite comment. Comments, along with scientific data, may be sent to the Director, Division of Bioequivalence, Office of Generic Drugs, Center for Drug Evaluation and Research, (MPN-2) HFD-650, 7620 Standish Place, Rockville, MD 20855. The comment period will generally be 60 days in length, and the closing date for comments will be listed in the description of the proposed change for each drug entity.

The most useful type of scientific data submission is an *in vivo* bioavailability/bioequivalence study conducted on batches of the subject drug products. These submissions should present a full description of the analytical procedures and equipment used, a validation of the analytical methodology, including the standard curve, a description of the method of calculating results, and a description of the pharmacokinetic and statistical models used in analyzing the data. Anecdotal or testimonial information is the least useful to the Agency, and such submissions are discouraged. Copies of supporting reports published in the scientific literature or unpublished material, however, are welcome.

Change of the Therapeutic Equivalence Evaluation for a Single Product

The aforementioned procedure does not apply to a change in a single drug product code. For example, a change in a single drug product's code from **BP** to **AB** as a result of the submission of a bioequivalence study ordinarily will not be the subject of notice and comment. Likewise, a change in a single drug product's code from **AB** to **BX** (e.g., as a result of new information raising a significant question as to bioequivalence) does not require notice and comment. The Agency's responsibility to provide the public with the Agency's most current information related to therapeutic equivalence may require a change in a drug product's code prior to any forma notice and opportunity for the applicant to be heard. The publication in the *Federal Register* of a proposal to withdraw approval of a drug product will ordinarily resul in a change in a product's code from **AB** to **BX** if this action has not already been taken.

Discontinued Section

Those drug products in the Discontinued Section of the Orange Book in which a determination has already been made that the products were not withdrawn for safety or efficacy reasons have "***Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**" following the product strength. Those drug products are only reflective of citizen petitions approved since 1995. The identification of these drug products in the Discontinued Section of the Orange Book should avoid the submission of multiple citizen petitions for the same drug product. FR notices no longer applicable are removed from the Annual Edition (i.e., there is a currently marketed Reference Listed Drug and no applicable patent or exclusivity). Safety or Effectiveness Determinations List[14] lists products that have current and removed notices. The list is updated periodically throughout the year. Notices issued during the year are added to the Electronic Orange Book Query[15] in the month they become effective.

Generally, approved products are added to the Discontinued Section of the Orange Book when the applicant holder notifies the Orange Book staff of the products' non marketed status. Products may also be added if annual reports indicate the product is no longer marketed or other Agency administrative action (e.g., Withdrawal o an Application). Changes to the Orange Book are not affected by the drug registration and listing requirements of Section 510 of the Act

Changes to the Orange Book

Every effort is made to ensure the Annual Edition is current and accurate. Applicant holders are requested to inform the FDA Orange Book Staff (OBS) of any changes or corrections. Please inform the OBS when products are no longer marketed. Notification of the Orange Book staff to include the newly approved product in the Discontinued Drug Product List rather than parts 1, 2 or 3 of the List (as discussed in Section 1.1) must occur by the end of the month in which the product is approved to ensure that the product is not included in the "active" portions of the next published Orange Book update

We can be contacted by email at drugproducts@cder.fda.gov. Send Changes by FAX: 240-276-8974; mail to:

FDA/CDER Orange Book Staff
Office of Generic Drugs, HFD-610
7620 Standish Place
Rockville , MD 20855-2773

Availability of the Edition

Commencing with the 25th edition, the Annual Edition and current monthly Cumulative Supplements are available in a Portable Document Format (PDF) at the EOB home page, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm[16], by clicking on the Publications[17]. The PDF annual format duplicates previous paper versions except for the Orphan Products Designations and Approvals List. An annual subscription of the PDF format may be obtained from the U.S. Government Printing Office, 866-512-1800.

HOW TO USE THE DRUG PRODUCT LISTS

Key Sections for Using the Drug Product Lists

This publication contains illustrations, along with Drug Product Lists, indices, and lists of abbreviations and terms which facilitate their use.

Illustrations. The annotated Drug Product Illustration, see Section 2.2, and the Therapeutic Equivalence Evaluations Illustration, see Section 2.3, are offered to provide further clarification. These depict the format found in the Prescription Drug Product List (the only list in which therapeutic equivalence evaluation codes are displayed).

Drug Product Lists. Drug Product Lists. The Prescription and OTC Drug Product Lists, arranged alphabetically by active ingredient(s), contain product identification information (active ingredients, dosage forms, routes of administration, product names, application holders, strengths) for single and multiple ingredien drug products. Also shown are the application number and drug product number (FDA internal computer data use only) and approval dates for those drug products approved on or after January 1, 1982 . The application number preceded by "N" is a New Drug Application (NDA) or commonly the innovator). The application number preceded by an "A" is an Abbreviated New Drug Application (ANDA or commonly the generic).

The Discontinued Product List, arranged alphabetically by active ingredient(s), contain product identification information (dosage form, product name, strength, and application number).

If a prescription drug product is available from more than one source (multisource), a therapeutic equivalence code will appear in front of the applicant's name. If a product is therapeutically equivalent to one or more products or to an appropriate reference, it will be designated with a code beginning with "A" and the entry will be underlined and printed in bold font for emphasis.

Active ingredient headings for multiple ingredient (combination) drug products are arranged alphabetically. For purposes of this publication, this alphabetical sort takes precedence over United States Pharmacopeia official monograph order (i.e., Reserpine, Hydralazine Hydrochloride, Hydrochlorothiazide). For example, product information labeled as Reserpine, Hydrochlorothiazide and Hydralazine Hydrochloride appears under the active ingredient heading Hydralazine Hydrochloride; Hydrochlorothiazide; Reserpine. A cross-reference to the product information (for prescription and OTC products) appears for each additional active ingredient in the product. For combination drug products, the ingredient strengths are separated by semicolons and appear in the same relative sequence as the ingredients in the heading. Available strengths of the dosage form from an applicant appear on separate lines.

To use the Drug Product Lists, determine by alphabetical order the ingredient under which the product information is listed, using the Product Name Index, if necessary. Then, find the ingredient in the applicable Drug Product List. Proceed to the dosage form and route of administration and compare products within that ingredient heading only. Therapeutic equivalence or inequivalence for prescription products is determined on the basis of the therapeutic equivalence codes provided within that specific dosage form and route heading. The OTC Drug Product List, Discontinued Drug Product List, and Drug Products with Approval under Section 505 of the Act Administered by the Center for Biologics Evaluation and Research List have their data arranged similarly.

The Discontinued Drug Product List contains approved products that have never been marketed, have been discontinued from marketing, are for military use or have had their approvals withdrawn for other than safety or efficacy reasons subsequent to being discontinued from marketing. All products having a "@" in the 12th Cumulative Supplement of the 31st Edition List have been added to the Discontinued Drug Product List appearing in the 32nd Edition. In addition, approved drug products that are not in the commercial distribution channel e.g., approved drug products in applications for export only are also listed in the Discontinued Section of the Orange Book

PATENT AND EXCLUSIVITY INFORMATION ADDENDUM

This *Addendum* identifies drugs that qualify under the Drug Price Competition and Patent Term Restoration Act (1984 Amendments) for periods of exclusivity, during which abbreviated new drug applications (ANDAs) and applications described in Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for those drug products may, in some instances, not be submitted or made effective as described below, and provides patent information concerning the listed drug products. Those drugs that have qualified for Orphan Drug Exclusivity pursuant to Section 527 of the Act and those drugs that have qualified for Pediatric Exclusivity pursuant to Section 505A are also included in this *Addendum*. This section is arranged in alphabetical order by active ingredient name followed the trade name. Active ingredient headings for multiple ingredient (combination) drug products are arranged alphabetically. For an explanation of the codes used in the *Addendum*, see the *Patent and Exclusivity Terms* Section. Exclusivity prevents the submission or effective approval of ANDAs or applications described in Section 505(b)(2) of the Act. It does not prevent the submission or approval of a second 505(b)(1) application except in the case of Orphan Drug exclusivity. Applications qualifying for periods of exclusivity are:

(1) A new drug application approved after September 24, 1984, for a drug product all active ingredients (including any ester or salt of the active ingredient) of which had never been approved in any other new drug application under Section 505 (b) of the Act. No subsequent ANDA or application described in Section 505(b)(2) of the Act for the same drug may be *submitted* for a period of *five years* from the date of approval of the original application, except that such an application may be *submitted* after *four years* if it contains a certification that a patent claiming the drug is invalid or will not be infringed by the product for which approval is sought.

(2) A new drug application approved after September 24, 1984, for a drug product containing an active ingredient (including any ester or salt of that active ingredient) that has been approved in an earlier new drug application and that includes reports of new clinical investigations (other than bioavailability studies). Such investigations must have been conducted or sponsored by the applicant and must have been essential to approval of the application. If these requirements are met, the approval of a subsequent ANDA or an application described in Section 505(b)(2) of the Act may not be *made effective* for the same drug or use, if for a new indication, before the expiration of *three years* from the date of approval of the original application. If an applicant has exclusivity for a new application or 505(b)(2) application for the drug product with indications or use, this does not preclude the approval of an ANDA or 505(b)(2) application not covered by the exclusivity.

(3) A supplement to a new drug application for a drug containing a previously approved active ingredient including (any ester or salt of the active ingredient) approved after September 24, 1984, that contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the applicant. The approval of a subsequent ANDA or 505(b)(2) application for a change approved in the supplement may not be *made effective* for *three years* from the date of approval of the original supplement.

The Act requires that patent information be filed with all newly submitted Section 505(b) drug applications. No NDA may be approved after September 24, 1984, without the submission of patent information to the Agency. Effective August 18, 2003, this information must be filed using FDA Form 3542a "Patent Information Submitted with the Filing of an NDA, Amendment or Supplement".

Effective August 18, 2003, upon approval of an application, patent information for purposes of listing in the Orange Book must be submitted to the agency within 30 days of approval on FDA Form 3542 "Patent Information Submitted Upon and After Approval of an NDA or Supplement". Patent information on unapproved applications or on patents beyond the scope of the Act (i.e., process or manufacturing patents) will not be published. FDA form 3542 will be the only form used for the purposes of this publication.

The patents that FDA regards as covered by the statutory provisions for submission of patent information are: patents that claim the active ingredient(s); drug product patents which include formulation/composition patents; use patents for a particular approved indication or method of using the product; and certain other patents as detailed on FDA Form 3542. This information, as provided by the sponsor on FDA form 3542, will be published as described above.

A requirement for submission of patent information to FDA for certain old antibiotics became effective October 7, 2008 under section 4(b)(1) of the QI Act. A guidance for industry on this subject is available[19]. Upon approval, patent numbers and expiration dates, in addition to certain other information on appropriate patents claiming drug products that are the subject of approved applications, will be published on a daily basis in the Electronic Orange Book, http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm[19]. The Addendum lists patent and exclusivity information up to January of the Edition year. The monthly Cumulative Supplements to the annual edition list patent and exclusivity information changes since the Annual Edition Addendum. Since all parts of this publication are subject to changes, additions, or deletions, the Electronic Orange Book, updated daily, should be consulted for the most recent patent and exclusivity information.

Search the Orange Book[20]

Page Last Updated: 02/03/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

Links on this page:

1. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
2. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
3. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#patent_addendum
4. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugAppro
5. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Reference%20Listed%20Drug
6. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Bioequivalent%20Drug%20Products
7. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Therapeutic%20Equivalence%20Evaluations%20Codes
8. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Section%201.7,%20Therapeutic%20Equivalence%20Evaluations%20Codes
9. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Therapeutic%20Equivalents
10. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#1.8%20Description%20of%20Special%20Situations
11. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#1.8%20Description%20of%20Special%20Situations
12. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#1.8%20Description%20of%20Special%20Situations
13. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#Therapeutic%20Equivalence-Related%20Terms
14. http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ApprovedDrugProductswithTherapeuticEquivalenceEvaluationsOrangeBook/ucm119198.i
15. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
16. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
17. http://www.accessdata.fda.gov/scripts/cder/ob/faqlink.cfm
18. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080579.pdf
19. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm
20. http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RECLAST safely and effectively. See full prescribing information for RECLAST.

Reclast® (zoledronic acid) Injection
Initial U.S. Approval: 2001

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.6) 04/2013

----------INDICATIONS AND USAGE----------

Reclast is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis (1.1, 1.2)
- Treatment to increase bone mass in men with osteoporosis (1.3)
- Treatment and prevention of glucocorticoid-induced osteoporosis (1.4)
- Treatment of Paget's disease of bone in men and women (1.5)

Limitations of Use
Optimal duration of use has not been determined. For patients at low-risk for fracture, consider drug discontinuation after 3 to 5 years of use (1.6)

----------DOSAGE AND ADMINISTRATION----------

Infusion given intravenously over no less than 15 minutes:

- Treatment of postmenopausal osteoporosis (2.2); treatment to increase bone mass in men with osteoporosis (2.4); treatment and prevention of glucocorticoid-induced osteoporosis (2.5): 5 mg once a year
- Prevention of postmenopausal osteoporosis: 5 mg once every 2 years (2.3)
- Treatment of Paget's disease of bone: a single 5 mg infusion. Patients should receive 1500 mg elemental calcium and 800 international units vitamin D daily (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

5 mg in a 100 mL ready-to-infuse solution (3)

----------CONTRAINDICATIONS----------

- Hypocalcemia (4)
- Patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment (4, 5.3)
- Hypersensitivity to any component of Reclast (4, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- *Products Containing Same Active Ingredient*: Patients receiving Zometa should not receive Reclast (5.1)
- *Hypocalcemia* may worsen during treatment. Patients must be adequately supplemented with calcium and vitamin D (5.2)
- *Renal Impairment*: A single dose should not exceed 5 mg and the duration of infusion should be no less than 15 minutes. Renal toxicity may be greater in patients with underlying renal impairment or with other risk factors, including advanced age or dehydration. Monitor creatinine clearance before each dose (2.7, 5.3)
- *Osteonecrosis of the Jaw (ONJ)* has been reported. All patients should have a routine oral exam by the prescriber prior to treatment (5.4)
- *Atypical Femur Fractures* have been reported. Patients with thigh or groin pain should be evaluated to rule out a femoral fracture (5.5)
- *Pregnancy*: Reclast can cause fetal harm. Women of childbearing potential should be advised (5.6, 8.1)
- *Severe Bone, Joint, and Muscle Pain* may occur. Withhold future doses of Reclast if severe symptoms occur (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (greater than 10%) were pyrexia, myalgia, headache, arthralgia, pain in extremity (6.1). Other important adverse reactions were flu-like illness, nausea, vomiting, diarrhea (6.2), and eye inflammation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Aminoglycosides: May lower serum calcium for prolonged periods (7.1)
- Loop diuretics: May increase risk of hypocalcemia (7.2)
- Nephrotoxic drugs: Use with caution (7.3)
- Drugs primarily excreted by the kidney: Exposure may be increased with renal impairment. Monitor serum creatinine in patients at risk (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Nursing Mothers: Reclast should not be given to nursing women (8.3)
Pediatric Use: Not indicated for use in pediatric patients (8.4)
Geriatric Use: Special care to monitor renal function (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Osteoporosis in Postmenopausal Women

Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures [*see Clinical Studies (14.1)*].

1.2 Prevention of Osteoporosis in Postmenopausal Women

Reclast is indicated for prevention of osteoporosis in postmenopausal women [*see Clinical Studies (14.2)*].

1.3 Osteoporosis in Men

Reclast is indicated for treatment to increase bone mass in men with osteoporosis [*see Clinical Studies (14.3)*].

1.4 Glucocorticoid-Induced Osteoporosis

Reclast is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months [*see Clinical Studies (14.4)*].

1.5 Paget's Disease of Bone

Reclast is indicated for treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease [*see Clinical Studies (14.5)*].

1.6 Important Limitations of Use

The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. Patients at low-risk for fracture should be considered for drug discontinuation after 3 to 5 years of use. Patients who discontinue therapy should have their risk for fracture re-evaluated periodically.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Reclast injection must be administered as an intravenous infusion over no less than 15 minutes.

- Patients must be appropriately hydrated prior to administration of Reclast [*see Warnings and Precautions (5.3)*].
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Intravenous infusion should be followed by a 10 mL normal saline flush of the intravenous line.
- Administration of acetaminophen following Reclast administration may reduce the incidence of acute-phase reaction symptoms.

2.2 Treatment of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

2.3 Prevention of Osteoporosis in Postmenopausal Women

The recommended regimen is a 5 mg infusion given once every 2 years intravenously over no less than 15 minutes.

2.4 Osteoporosis in Men

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

2.5 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The recommended regimen is a 5 mg infusion once a year given intravenously over no less than 15 minutes.

2.6 Treatment of Paget's Disease of Bone

The recommended dose is a 5 mg infusion. The infusion time must not be less than 15 minutes given over a constant infusion rate.

Re-treatment of Paget's Disease

After a single treatment with Reclast in Paget's disease an extended remission period is observed. Specific re-treatment data are not available. However, re-treatment with Reclast may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, or in those patients who failed to achieve normalization of their serum alkaline phosphatase, or in those patients with symptoms, as dictated by medical practice.

2.7 Laboratory Testing and Oral Examination Prior to Administration

- Prior to administration of each dose of Reclast, obtain a serum creatinine and creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Reclast dose. Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment. A 5 mg dose of Reclast administered intravenously is recommended for patients with creatinine clearance greater than or equal to 35 mL/min. There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dose adjustment is required in patients with CrCl greater than or equal to 35 mL/min [*see Contraindications (4), Warnings and Precautions (5.3)*].
- A routine oral examination should be performed by the prescriber prior to initiation of Reclast treatment [*see Warnings and Precautions (5.4)*].

2.8 Calcium and Vitamin D Supplementation

- Instruct patients being treated for Paget's disease of bone on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia. All patients should take 1500 mg elemental calcium daily in divided doses (750 mg two times a day, or 500 mg three times a day) and 800 international units vitamin D daily, particularly in the 2 weeks following Reclast administration [*see Warnings and Precautions (5.2)*].
- Instruct patients being treated for osteoporosis to take supplemental calcium and vitamin D if their dietary intake is inadequate. An average of at least 1200 mg calcium and 800-1000 international units vitamin D daily is recommended.

2.9 Method of Administration

The Reclast infusion time must not be less than 15 minutes given over a constant infusion rate.

The i.v. infusion should be followed by a 10 mL normal saline flush of the intravenous line.

Reclast solution for infusion must not be allowed to come in contact with any calcium or other divalent cation-containing solutions, and should be administered as a single intravenous solution through a separate vented infusion line.

If refrigerated, allow the refrigerated solution to reach room temperature before administration. After opening, the solution is stable for 24 hours at 2°C–8°C (36°F - 46°F) [*see How Supplied/Storage and Handling (16)*].

3 DOSAGE FORMS AND STRENGTHS

5 mg in a 100 mL ready to infuse solution.

4 CONTRAINDICATIONS

Reclast is contraindicated in patients with the following conditions:

- Hypocalcemia [*see Warnings and Precautions (5.2)*]
- Creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [*see Warnings and Precautions (5.3)*].
- Known hypersensitivity to zoledronic acid or any components of Reclast. Hypersensitivity reactions including urticaria, angioedema, and anaphylactic reaction/shock have been reported [*see Post-Marketing Experience (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Reclast contains the same active ingredient found in Zometa, used for oncology indications, and a patient being treated with Zometa should not be treated with Reclast.

5.2 Hypocalcemia and Mineral Metabolism

Pre-existing hypocalcemia and disturbances of mineral metabolism (e.g., hypoparathyroidism, thyroid surgery, parathyroid surgery; malabsorption syndromes, excision of small intestine) must be effectively treated before initiating therapy with Reclast. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended for these patients [*see Contraindications (4)*].

Hypocalcemia following Reclast administration is a significant risk in Paget's disease. All patients should be instructed about the symptoms of hypocalcemia and the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2.8), Adverse Reactions (6.1), Information for Patients (17)*].

All osteoporosis patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels [*see Dosage and Administration (2.8), Adverse Reactions (6.1), Information for Patients (17)*].

5.3 Renal Impairment

A single dose of Reclast should not exceed 5 mg and the duration of infusion should be no less than 15 minutes [*see Dosage and Administration (2)*].

Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment [*see Contraindications (4)*]. If history or physical signs suggest dehydration, Reclast therapy should be withheld until normovolemic status has been achieved [*see Post-Marketing Experience (6.2)*].

Reclast should be used with caution in patients with chronic renal impairment. Acute renal impairment, including renal failure, has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise, advanced age, concomitant nephrotoxic medications, concomitant diuretic therapy, or severe dehydration occurring before or after Reclast administration. Acute renal failure (ARF) has been observed in patients after a single administration. Rare reports of hospitalization and/or dialysis or fatal outcome occurred in patients with underlying moderate to severe renal impairment or with any of the risk factors described in this section [*see Post-Marketing Experience (6.2)*]. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted [*see Drug Interactions (7.4)*].

Creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each Reclast dose. Transient increase in serum creatinine may be greater in patients with impaired renal function; interim monitoring of creatinine clearance should be performed in at-risk patients. Elderly patients and those receiving diuretic therapy are at increased risk of acute renal failure. These patients should have their fluid status assessed and be appropriately hydrated prior to administration of Reclast. Reclast should be used with caution with other nephrotoxic drugs [*see Drug Interactions (7.3)*]. Consider monitoring creatinine clearance in patients at-risk for ARF who are taking concomitant medications that are primarily excreted by the kidney [*see Drug Interactions (7.4)*].

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with bisphosphonates, including zoledronic acid. Most cases have been in cancer patients treated with intravenous bisphosphonates undergoing dental procedures. Some cases have occurred in patients with postmenopausal osteoporosis treated with either oral or intravenous bisphosphonates. A routine oral examination should be performed by the prescriber prior to initiation of bisphosphonate treatment. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with a history of concomitant risk factors (e.g., cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene, pre-existing dental disease or infection, anemia, coagulopathy).

While on treatment, patients with concomitant risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.1)*].

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g., prednisone) at the time of fracture.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Pregnancy

RECLAST SHOULD NOT BE USED DURING PREGNANCY. Reclast may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while on Reclast therapy [*see Use in Specific Populations (8.1)*].

5.7 Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. The time to onset of symptoms varied from one day to several months after starting the drug. Consider withholding future Reclast treatment if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [*see Adverse Reactions (6.2)*].

5.8 Patients with Asthma

While not observed in clinical trials with Reclast, there have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates. Use Reclast with caution in aspirin-sensitive patients.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Treatment of Osteoporosis in Postmenopausal Women

The safety of Reclast in the treatment of postmenopausal osteoporosis was assessed in Study 1, a large, randomized, double-blind, placebo-controlled, multinational study of 7736 postmenopausal women aged 65-89 years with osteoporosis, diagnosed by bone mineral density or the presence of a prevalent vertebral fracture. The duration of the trial was three years with 3862 patients exposed to Reclast and 3852 patients exposed to placebo administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 international units of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between groups: 3.4% in the Reclast group and 2.9% in the placebo group. The incidence of serious adverse events was 29.2% in the Reclast group and 30.1% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.4% and 4.8% for the Reclast and placebo groups, respectively.

The safety of Reclast in the treatment of osteoporosis patients with a recent (within 90 days) low-trauma hip fracture was assessed in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint-driven study of 2127 men and women aged 50-95 years; 1065 patients were randomized to Reclast and 1062 patients were randomized to placebo. Reclast was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. The study continued until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of approximately 2 years on study drug. Vitamin D levels were not routinely measured but a loading dose of

vitamin D (50,000 to 125,000 international units orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 international units of vitamin D supplementation per day for at least 14 days prior to the study drug infusions.

The incidence of all-cause mortality was 9.6% in the Reclast group and 13.3% in the placebo group. The incidence of serious adverse events was 38.3% in the Reclast group and 41.3% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.3% and 4.7% for the Reclast and placebo groups, respectively.

Adverse reactions reported in at least 2% of patients with osteoporosis and more frequently in the Reclast-treated patients than placebo-treated patients in either osteoporosis trial are shown below in Table 1.

Table 1. Adverse Reactions Occurring in greater than or equal to 2.0% of Patients with Osteoporosis and More Frequently than in Placebo-Treated Patients

	Study 1		Study 2	
System Organ Class	5 mg IV Reclast once per year % (N=3862)	Placebo once per year % (N=3852)	5 mg IV Reclast once per year % (N=1054)	Placebo once per year % (N=1057)
Blood and the Lymphatic System Disorders				
Anemia	4.4	3.6	5.3	5.2
Metabolism and Nutrition Disorders				
Dehydration	0.6	0.6	2.5	2.3
Anorexia	2.0	1.1	1.0	1.0
Nervous System Disorders				
Headache	12.4	8.1	3.9	2.5
Dizziness	7.6	6.7	2.0	4.0
Ear and Labyrinth Disorders				
Vertigo	4.3	4.0	1.3	1.7
Cardiac Disorders				
Atrial Fibrillation	2.4	1.9	2.8	2.6
Vascular Disorders				
Hypertension	12.7	12.4	6.8	5.4
Gastrointestinal Disorders				
Nausea	8.5	5.2	4.5	4.5
Diarrhea	6.0	5.6	5.2	4.7
Vomiting	4.6	3.2	3.4	3.4
Abdominal Pain Upper	4.6	3.1	0.9	1.5
Dyspepsia	4.3	4.0	1.7	1.6
Musculoskeletal, Connective Tissue and Bone Disorders				
Arthralgia	23.8	20.4	17.9	18.3
Myalgia	11.7	3.7	4.9	2.7
Pain in Extremity	11.3	9.9	5.9	4.8
Shoulder Pain	6.9	5.6	0.0	0.0
Bone Pain	5.8	2.3	3.2	1.0
Neck Pain	4.4	3.8	1.4	1.1
Muscle Spasms	3.7	3.4	1.5	1.7
Osteoarthritis	9.1	9.7	5.7	4.5
Musculoskeletal Pain	0.4	0.3	3.1	1.2
General Disorders and Administrative Site Conditions				
Pyrexia	17.9	4.6	8.7	3.1
Influenza-like Illness	8.8	2.7	0.8	0.4
Fatigue	5.4	3.5	2.1	1.2
Chills	5.4	1.0	1.5	0.5
Asthenia	5.3	2.9	3.2	3.0
Peripheral Edema	4.6	4.2	5.5	5.3
Pain	3.3	1.3	1.5	0.5
Malaise	2.0	1.0	1.1	0.5
Hyperthermia	0.3	<0.1	2.3	0.3
Chest Pain	1.3	1.1	2.4	1.8
Investigations				
Creatinine Renal Clearance Decreased	2.0	2.4	2.1	1.7

Renal Impairment

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal impairment manifested as deterioration in renal function (i.e., increased serum creatinine) and in rare cases, acute renal failure. In the clinical trial for postmenopausal osteoporosis, patients with baseline creatinine clearance less than 30 mL/min (based on actual body weight), urine dipstick greater than or equal to 2+ protein or increase in serum creatinine of greater than 0.5 mg/dL during the screening visits were excluded. The change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the Reclast and placebo treatment groups over 3 years, including patients with creatinine clearance between 30-60 mL/min at baseline. Overall, there was a transient increase in serum creatinine observed within 10 days of dosing in 1.8% of Reclast-treated patients versus 0.8% of placebo-treated patients which resolved without specific therapy [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

The signs and symptoms of acute phase reaction occurred in Study 1 following Reclast infusion including fever (18%), myalgia (9%), flu-like symptoms (8%), headache (7%), and arthralgia (7%). The majority of these symptoms occurred within the first 3 days following the dose of Reclast and usually resolved within 3 days of onset but resolution could take up to 7-14 days. In Study 2, patients without a contraindication to acetaminophen were provided with a standard oral dose at the time of the IV infusion and instructed to use additional acetaminophen at home for the next 72 hours as needed. Reclast was associated with fewer signs and symptoms of a transient acute phase reaction in this trial: fever (7%) and arthralgia (3%). The incidence of these symptoms decreased with subsequent doses of Reclast.

Laboratory Findings

In Study 1, in women with postmenopausal osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 7.5 mg/dL) following Reclast administration. No symptomatic cases of hypocalcemia were observed. In Study 2, following pre-treatment with vitamin D, no patients had treatment emergent serum calcium levels below 7.5 mg/dL.

Injection Site Reactions

In the osteoporosis trials, local reactions at the infusion site such as itching, redness and/or pain have been reported in 0% to 0.7% of patients following the administration of Reclast and 0% to 0.5% of patients following administration of placebo.

Osteonecrosis of the Jaw

In the postmenopausal osteoporosis trial, Study 1, in 7736 patients, after initiation of therapy, symptoms consistent with ONJ occurred in one patient treated with placebo and one patient treated with Reclast. Both cases resolved after appropriate treatment [*see Warnings and Precautions (5.4)*]. No reports of osteonecrosis of the jaw were reported in either treatment group in Study 2.

Atrial Fibrillation

In the postmenopausal osteoporosis trial, Study 1, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.3% of patients (50 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group. The overall incidence of all atrial fibrillation adverse events in the zoledronic acid treatment group was reported in 2.5% of patients (96 out of 3862) in the Reclast group vs. 1.9% of patients (75 out of 3852) in the placebo group. Over 90% of these events in both treatment groups occurred more than a month after the infusion. In an ECG sub-study, ECG measurements were performed on a subset of 559 patients before and 9 to 11 days after treatment. There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusions. In Study 2, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.0% of patients (11 out of 1054) compared to 1.2% (13 out of 1057) in the placebo group demonstrating no difference between treatment groups.

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis trials, 1 (less than 0.1%) to 9 (0.2%) patients treated with Reclast and 0 (0%) to 1 (less than 0.1%) patient treated with placebo developed iritis/uveitis/episcleritis.

Prevention of Osteoporosis in Postmenopausal Women

The safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged greater than or equal to 45 years. Patients were randomized to one of three treatment groups: (1) Reclast given at randomization and Month 12 (n=198); (2) Reclast given at randomization and placebo at Month 12 (n=181); and (3) placebo given at randomization and Month 12 (n=202). Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 international units vitamin D supplementation per day.

The incidence of serious adverse events was similar for subjects given (1) Reclast at randomization and at Month 12 (10.6%), (2) Reclast at randomization and placebo given at Month 12 (9.4%), and (3) placebo at randomization and at Month 12 (11.4%). The percentages of patients who withdrew from the study due to adverse events were 7.1%, 7.2%, and 3.0% in the two Reclast groups and placebo group, respectively. Adverse reactions reported in at least 2% of patients with osteopenia and more frequently in the Reclast-treated patients than placebo-treated patients are shown in Table 2.

Table 2. Adverse Reactions Occurring in greater than or equal to 2% of Patients with Osteopenia and More Frequently than in Placebo-Treated Patients

System Organ Class	5 mg IV Reclast Once Per Year % (n=198)	5 mg IV Reclast Once % (n=181)	Placebo once per year % (n=202)
Metabolism and nutrition disorders			
Anorexia	2.0	0.6	0.0
Nervous system disorders			
Headache	14.6	20.4	11.4
Dizziness	7.6	6.1	3.5
Hypoesthesia	5.6	2.2	2.0
Ear and labyrinth disorders			
Vertigo	2.0	1.7	1.0
Vascular disorders			
Hypertension	5.1	8.3	6.9
Gastrointestinal disorders			
Nausea	17.7	11.6	7.9
Diarrhea	8.1	6.6	7.9
Vomiting	7.6	5.0	4.5
Dyspepsia	7.1	6.6	5.0
Abdominal pain*	8.6	6.6	7.9
Constipation	6.6	7.2	6.9
Abdominal discomfort	2.0	1.1	0.5
Abdominal distension	2.0	0.6	0.0
Skin and subcutaneous tissue disorders			
Rash	3.0	2.2	2.5
Musculoskeletal and connective tissue disorders			
Arthralgia	27.3	18.8	19.3
Myalgia	19.2	22.7	6.9
Back pain	18.2	16.6	11.9
Pain in extremity	11.1	16.0	9.9
Muscle spasms	5.6	2.8	5.0
Musculoskeletal pain**	8.1	7.2	7.9
Bone pain	5.1	3.3	1.0
Neck pain	5.1	6.6	5.0
Arthritis	4.0	2.2	1.5
Joint stiffness	3.5	1.1	2.0
Joint swelling	3.0	0.6	0.0
Flank pain	2.0	0.6	0.0
Pain in jaw	2.0	3.9	2.5

General disorders and administration site conditions			
Pain	24.2	14.9	3.5
Pyrexia	21.7	21.0	4.5
Chills	18.2	18.2	3.0
Fatigue	14.6	9.9	4.0
Asthenia	6.1	2.8	1.0
Peripheral edema	5.6	3.9	3.5
Non-cardiac chest pain	3.5	7.7	3.0
Influenza-like illness	1.5	3.3	2.0
Malaise	1.0	2.2	0.5

* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR
** Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

Ocular Adverse Events

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the osteoporosis prevention trial, 4 (1.1%) patients treated with Reclast and 0 (0%) patients treated with placebo developed iritis/uveitis.

Acute Phase Reaction

In patients given Reclast at randomization and placebo at Month 12, Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (20.4%), fever (19.3%), chills (18.2%), pain (13.8%), headache (13.3%), fatigue (8.3%), arthralgia (6.1%), pain in extremity (3.9%), influenza-like illness (3.3%), and back pain (1.7%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days.

Osteoporosis in Men

The safety of Reclast in men with osteoporosis or osteoporosis secondary to hypogonadism was assessed in a two year randomized, multicenter, double-blind, active controlled group study of 302 men aged 25-86 years. One hundred fifty three (153) patients were exposed to Reclast administered once annually with a 5 mg dose in 100 mL infused over 15 minutes for up to a total of two doses, and 148 patients were exposed to a commercially-available oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 international units of vitamin D supplementation per day.

The incidence of all-cause mortality (one in each group) and serious adverse events were similar between the Reclast and active control treatment groups. The percentage of patients experiencing at least one adverse event was comparable between the Reclast and active control groups, with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability of Reclast was similar to the active control.

Adverse reactions reported in at least 2% of men with osteoporosis and more frequently in the Reclast-treated patients than the active control-treated patients and either (1) not reported in the postmenopausal osteoporosis treatment trial or (2) reported more frequently in the trial of osteoporosis in men are presented in Table 3. Therefore, Table 3 should be viewed in conjunction with Table 1.

Table 3: Adverse Reactions Occurring in greater than or equal to 2% of Men with Osteoporosis and More Frequently in the Reclast-Treated Patients than the Active Control-Treated Patients and either (1) Not Reported in the Postmenopausal Osteoporosis Treatment Trial or (2) Reported More Frequently in this Trial

System Organ Class	5 mg IV Reclast once per year % (N=153)	Active Control once weekly % (N=148)
Nervous System Disorders		
Headache	15.0	6.1
Lethargy	3.3	1.4
Eye Disorders		
Eye pain	2.0	0.0
Cardiac Disorders		
Atrial fibrillation	3.3	2.0
Palpitations	2.6	0.0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	6.5	4.7
Abdominal pain*	7.9	4.1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	2.6	2.0
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	19.6	6.8
Musculoskeletal pain**	12.4	10.8
Musculoskeletal stiffness	4.6	0.0
Renal and Urinary Disorders		
Blood creatinine increased	2.0	0.7
General Disorders and Administrative Site Conditions		
Fatigue	17.6	6.1
Pain	11.8	4.1
Chills	9.8	2.7
Influenza-like illness	9.2	2.0
Malaise	7.2	0.7
Acute phase reaction	3.9	0.0
Investigations		
C-reactive protein increased	4.6	1.4

* Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR
** Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

Renal Impairment

Creatinine clearance was measured annually prior to dosing and changes in long-term renal function over 24 months were comparable in the Reclast and active control groups [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

Reclast was associated with signs and symptoms of an acute phase reaction: myalgia (17.1%), fever (15.7%), fatigue (12.4%), arthralgia (11.1%), pain (10.5%), chills (9.8%), headache (9.8%), influenza-like illness (8.5%), malaise (5.2%), and back pain (3.3%), which occurred within the first 3 days following the dose of Reclast. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset but resolution could take up to 7-14 days. The incidence of these symptoms decreased with subsequent doses of Reclast.

Atrial Fibrillation

The incidence of all atrial fibrillation adverse events in the Reclast treatment group was 3.3% (5 out of 153) compared to 2.0% (3 out of 148) in the active control group. However, there were no patients with adjudicated serious adverse events of atrial fibrillation in the Reclast treatment group.

Laboratory Findings

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

Injection Site Reactions

There were 4 patients (2.6%) on Reclast vs. 2 patients (1.4%) on active control with local site reactions.

Osteonecrosis of the Jaw

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

Glucocorticoid-Induced Osteoporosis

The safety of Reclast in men and women in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in a randomized, multicenter, double-blind, active controlled, stratified study of 833 men and women aged 18-85 years treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy: less than or equal to 3 months prior to randomization (prevention subpopulation), and greater than 3 months prior to randomization (treatment subpopulation).

The duration of the trial was one year with 416 patients exposed to Reclast administered once as a single 5 mg dose in 100 mL infused over 15 minutes, and 417 patients exposed to a commercially-available oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 international units of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between treatment groups: 0.9% in the Reclast group and 0.7% in the active control group. The incidence of serious adverse events was similar between the Reclast treatment and prevention groups, 18.4% and 18.1%, respectively, and the active control treatment and prevention groups, 19.8% and 16.0%, respectively. The percentage of subjects who withdrew from the study due to adverse events was 2.2% in the Reclast group vs. 1.4% in the active control group. The overall safety and tolerability were similar between Reclast and active control groups with the exception of a higher incidence of post-dose symptoms in the Reclast group that occurred within 3 days after infusion. The overall safety and tolerability profile of Reclast in glucocorticoid-induced osteoporosis was similar to the adverse events reported in the Reclast postmenopausal osteoporosis clinical trial.

Adverse reactions reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis treatment trial or reported more frequently in the treatment and prevention of glucocorticoid-induced osteoporosis trial included the following: abdominal pain (Reclast 7.5%; active control 5.0%), and musculoskeletal pain (Reclast 3.1%; active control 1.7%). Other musculoskeletal events included back pain (Reclast 4.3%, active control 6.2%), bone pain (Reclast 3.1%, active control 2.2%), and pain in the extremity (Reclast 3.1%, active control 1.2%). In addition, the following adverse events occurred more frequently than in the postmenopausal osteoporosis trial: nausea (Reclast 9.6%; active control 8.4%), and dyspepsia (Reclast 5.5%; active control 4.3%).

Renal Impairment

Renal function measured prior to dosing and at the end of the 12 month study was comparable in the Reclast and active control groups [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

Reclast was associated with signs and symptoms of a transient acute phase reaction that was similar to that seen in the Reclast postmenopausal osteoporosis clinical trial.

Atrial Fibrillation

The incidence of atrial fibrillation adverse events was 0.7% (3 of 416) in the Reclast group compared to no adverse events in the active control group. All subjects had a prior history of atrial fibrillation and no cases were adjudicated as serious adverse events. One patient had atrial flutter in the active control group.

Laboratory Findings

There were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

Injection Site Reactions

There were no local reactions at the infusion site.

Osteonecrosis of the Jaw

In this trial there were no cases of osteonecrosis of the jaw [*see Warnings and Precautions (5.4)*].

Paget's Disease of Bone

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged greater than 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Reclast and 172 patients exposed to risedronate. Reclast was administered once as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The incidence of serious adverse events was 5.1% in the Reclast group and 6.4% in the risedronate group. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 1.2% for the Reclast and risedronate groups, respectively.

Adverse reactions occurring in at least 2% of the Paget's patients receiving Reclast (single 5 mg intravenous infusion) or risedronate (30 mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 4.

Table 4. Adverse Reactions Reported in at Least 2% of Paget's Patients Receiving Reclast (Single 5 mg intravenous Infusion) or Risedronate (Oral 30 mg Daily for 2 Months) Over a 6-Month Follow-Up Period

System Organ Class	5 mg IV Reclast % (N = 177)	30 mg/day x 2 Months risedronate % (N = 172)
Infections and Infestations		
Influenza	7	5
Metabolism and Nutrition Disorders		
Hypocalcemia	3	1
Anorexia	2	2
Nervous System Disorders		
Headache	11	10
Dizziness	9	4
Lethargy	5	1
Paresthesia	2	0
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5	1
Gastrointestinal Disorders		
Nausea	9	6
Diarrhea	6	6
Constipation	6	5
Dyspepsia	5	4
Abdominal Distension	2	1
Abdominal Pain	2	2
Vomiting	2	2
Abdominal Pain Upper	1	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	2
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	9	11
Bone Pain	9	5
Myalgia	7	4
Back Pain	4	7
Musculoskeletal Stiffness	2	1
General Disorders and Administrative Site Conditions		
Influenza-like Illness	11	6
Pyrexia	9	2
Fatigue	8	4
Rigors	8	1
Pain	5	4
Peripheral Edema	3	1
Asthenia	2	1

Laboratory Findings

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels were observed. Approximately 21% of patients had serum calcium levels less than 8.4 mg/dL 9-11 days following Reclast administration.

Renal Impairment

In clinical trials in Paget's disease there were no cases of renal deterioration following a single 5 mg 15-minute infusion [*see Warnings and Precautions (5.3)*].

Acute Phase Reaction

The signs and symptoms of acute phase reaction (influenza-like illness, pyrexia, myalgia, arthralgia, and bone pain) were reported in 25% of patients in the Reclast-treated group compared to 8% in the risedronate-treated group. Symptoms usually occur within the first 3 days following Reclast administration. The majority of these symptoms resolved within 4 days of onset.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported with zoledronic acid [*see Warnings and Precautions (5.4)*].

6.2 Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post approval use of Reclast:

Acute Phase Reactions

Fever, headache, flu-like symptoms, nausea, vomiting, diarrhea, arthralgia, and myalgia. Symptoms may be significant and lead to dehydration.

Acute Renal Failure

Acute renal failure requiring hospitalization and/or dialysis or with a fatal outcome have been rarely reported. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as advanced age, or concomitant nephrotoxic drugs in the post-infusion period. Transient rise in serum creatinine can be correctable with intravenous fluids.

Allergic Reactions

Allergic reaction with intravenous zoledronic acid including anaphylactic reaction/shock, urticaria, angioedema, and bronchoconstriction have been reported.

Asthma Exacerbations

Asthma exacerbations have been reported.

Hypocalcemia

Hypocalcemia has been reported.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported.

Ocular Adverse Events

Cases of the following events have been reported: conjunctivitis, iritis, iridocyclitis, uveitis, episcleritis, scleritis and orbital inflammation/edema.

Other

Hypotension in patients with underlying risk factors has been reported.

7 DRUG INTERACTIONS

No *in vivo* drug interaction studies have been performed for Reclast. *In vitro* and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates, including zoledronic acid, are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.

7.2 Loop Diuretics

Caution should also be exercised when Reclast is used in combination with loop diuretics due to an increased risk of hypocalcemia.

7.3 Nephrotoxic Drugs

Caution is indicated when Reclast is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

7.4 Drugs Primarily Excreted by the Kidney

Renal impairment has been observed following the administration of zoledronic acid in patients with pre-existing renal compromise or other risk factors [*see Warnings and Precautions (5.3)*]. In patients with renal impairment, the exposure to concomitant medications that are primarily renally excreted (e.g., digoxin) may increase. Consider monitoring serum creatinine in patients at risk for renal impairment who are taking concomitant medications that are primarily excreted by the kidney.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precautions (5.6)*].

RECLAST SHOULD NOT BE USED DURING PREGNANCY. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving Reclast.

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception space, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female rats given daily subcutaneous doses of zoledronic acid beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased at approximately greater than or equal to 0.3 times the anticipated human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison). Adverse maternal effects were observed in all dose groups at greater than or equal to 0.1 times the human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality was considered related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid during gestation, adverse fetal effects were observed at about 2 and 4 times human systemic exposure following a 5 mg intravenous dose (based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations.

In pregnant rabbits given daily subcutaneous doses of zoledronic acid during gestation at doses less than or equal to 0.4 times the anticipated human systemic exposure following a 5 mg intravenous dose (based on a mg/m^2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses greater than or equal to 0.04 times the human 5 mg intravenous dose, based on a mg/m^2 comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia [*see Nonclinical Toxicology (13.3)*].

8.3 Nursing Mothers

It is not known whether Reclast is excreted in human milk. Because many drugs are excreted in human milk, and because Reclast binds to bone long-term, Reclast should not be administered to a nursing woman.

8.4 Pediatric Use

Reclast is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with zoledronic acid use in children did not raise any new safety findings beyond those previously seen in adults treated for Paget's disease of bone and treatment of osteoporosis including osteonecrosis of the jaw (ONJ) and renal impairment. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within three days after the first infusion and became less common with repeat dosing. No cases of ONJ or renal impairment were observed in this study. Because of long-term retention in bone, Reclast should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 minutes. Mean C_{max} and $AUC_{(0\text{-last})}$ was 167 ng/mL and 220 ng.h/mL respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use

The combined osteoporosis trials included 4863 Reclast-treated patients who were at least 65 years of age, while 2101 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

Of the patients receiving Reclast in the osteoporosis study in men, glucocorticoid-induced osteoporosis, and Paget's disease studies, 83, 116, and 132 patients, respectively were 65 years of age or over, while 24, 29, and 68 patients, respectively were at least 75 years of age.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

8.6 Renal Impairment

Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment. There are no safety or efficacy data to support the adjustment of the Reclast dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of greater than or equal to 35 mL/min [*see Warnings and Precautions (5.3), Clinical Pharmacology (12.3)*]. Risk of acute renal failure may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc. [*see Post-Marketing Experience (6.2)*].

8.7 Hepatic Impairment

Reclast is not metabolized in the liver. No clinical data are available for use of Reclast in patients with hepatic impairment.

10 OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid (Reclast) solution for intravenous infusion is limited. Patients who have received doses higher than those recommended should be carefully monitored. Overdosage may cause clinically significant renal impairment, hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

Single doses of Reclast should not exceed 5 mg and the duration of the intravenous infusion should be no less than 15 minutes [*see Dosage and Administration (2)*].

11 DESCRIPTION

Reclast contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is:

Zoledronic acid monohydrate is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and a molar mass of 290.1 g/Mol. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of the Reclast solution for infusion is approximately 6.0 – 7.0.

Reclast Injection is available as a sterile solution in bottles for intravenous infusion. One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis.

Inactive Ingredients: 4950 mg of mannitol, USP; and 30 mg of sodium citrate, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Reclast is a bisphosphonate and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity to bone mineral.

12.2 Pharmacodynamics

In the osteoporosis treatment trial, the effect of Reclast treatment on markers of bone resorption (serum beta-C-telopeptides [b-CTx]) and bone formation (bone specific alkaline phosphatase [BSAP], serum N-terminal propeptide of type I collagen [P1NP]) was evaluated in patients (subsets ranging from 517 to 1246 patients) at periodic intervals. Treatment with a 5 mg annual dose of Reclast reduces bone turnover markers to the pre-menopausal range with an approximate 55% reduction in b-CTx, a 29% reduction in BSAP and a 52% reduction in P1NP over 36 months. There was no progressive reduction of bone turnover markers with repeated annual dosing.

12.3 Pharmacokinetics

Pharmacokinetic data in patients with osteoporosis and Paget's disease of bone are not available.

Distribution: Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to less than 1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hour and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL.

Metabolism: Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion: In 64 patients with cancer and bone metastases on average (± SD) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs. 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs. 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Specific Populations

Pediatrics: Reclast is not indicated for use in children [*see Pediatric Use (8.4)*].

Geriatrics: The pharmacokinetics of zoledronic acid was not affected by age in patients with cancer and bone metastases whose age ranged from 38 years to 84 years.

Race: The pharmacokinetics of zoledronic acid was not affected by race in patients with cancer and bone metastases.

Hepatic Impairment: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Impairment: The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately-impaired renal function. Compared to patients with creatinine clearance greater than 80 mL/min (N=37), patients with creatinine clearance = 50-80 mL/min (N=15) showed an average increase in plasma AUC of 15%, whereas patients with creatinine clearance = 30-50 mL/min (N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of greater than or equal to 35 mL/min. Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure [*see Contraindications (4), Warnings and Precautions (5.3), Use in Specific Populations (8.6)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses greater than or equal to 0.002 times the human intravenous dose of 5 mg, based on a mg/m^2 comparison). Rats were given daily oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses less than or equal to 0.1 times the human intravenous dose of 5 mg, based on a mg/m^2 comparison).

Mutagenesis: Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Impairment of Fertility: Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

13.2 Animal Pharmacology

Bone Safety Studies: Zoledronic acid is a potent inhibitor of osteoclastic bone resorption. In the ovariectomized rat, single IV doses of zoledronic acid of 4-500 µg/kg (less than 0.1 to 3.5 times human exposure at the 5 mg intravenous dose, based on a mg/m^2 comparison) suppressed bone turnover and protected against trabecular bone loss, cortical thinning and the reduction in vertebral and femoral bone strength in a dose-dependent manner. At a dose equivalent to human exposure at the 5 mg intravenous dose, the effect persisted for 8 months, which corresponds to approximately 8 remodeling cycles or 3 years in humans.

In ovariectomized rats and monkeys, weekly treatment with zoledronic acid dose-dependently suppressed bone turnover and prevented the decrease in cancellous and cortical BMD and bone strength, at yearly cumulative doses up to 3.5 times the intravenous human dose of 5 mg, based on a mg/m^2 comparison. Bone tissue was normal and there was no evidence of a mineralization defect, no accumulation of osteoid, and no woven bone.

13.3 Reproductive and Developmental Toxicology

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (greater than or equal to 0.3 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (greater than or equal to 0.1 times the human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality was considered related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given daily subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg during gestation, adverse fetal effects were observed in the mid- and high-dose groups (about 2 and 4 times human systemic exposure following a 5 mg intravenous dose, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (about 1.2 times the anticipated human systemic exposure, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (at doses less than or equal to 0.4 times the anticipated human systemic exposure following a 5 mg intravenous dose, based on a mg/m^2 comparison) no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses greater than or equal to 0.04 times the human 5 mg intravenous dose, based on a mg/m^2 comparison). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

14 CLINICAL STUDIES

14.1 Treatment of Postmenopausal Osteoporosis

Study 1: The efficacy and safety of Reclast in the treatment of postmenopausal osteoporosis was demonstrated in Study 1, a randomized, double-blind, placebo-controlled, multinational study of 7736 women aged 65-89 years (mean age of 73) with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Women were stratified into two groups: Stratum I: no concomitant use of osteoporosis therapy or Stratum II: baseline concomitant use of osteoporosis therapies which included calcitonin, raloxifene, tamoxifen, and hormone replacement therapy, but excluded other bisphosphonates.

Women enrolled in Stratum I (n=5661) were evaluated annually for incidence of vertebral fractures. All women (Strata I and II) were evaluated for the incidence of hip and other clinical fractures. Reclast was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 international units of vitamin D supplementation per day.

The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years and the incidence of hip fractures over a median duration of 3 years. The diagnosis of an incident vertebral fracture was based on both qualitative diagnosis by the radiologist and quantitative morphometric criterion. The morphometric criterion required the dual occurrence of 2 events: a relative height ratio or relative height reduction in a vertebral body of at least 20%, together with at least a 4 mm absolute decrease in height.

Effect on Vertebral Fractures

Reclast significantly decreased the incidence of new vertebral fractures at one, two, and three years as shown in Table 5.

Table 5. Proportion of Patients with New Morphometric Vertebral Fractures

Outcome	Reclast (%)	Placebo (%)	Absolute Reduction in Fracture Incidence % (95% CI)	Relative Reduction in Fracture Incidence % (95% CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)*
At least one new vertebral fracture (0–2 years)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)*
At least one new vertebral fracture (0–3 years)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)*

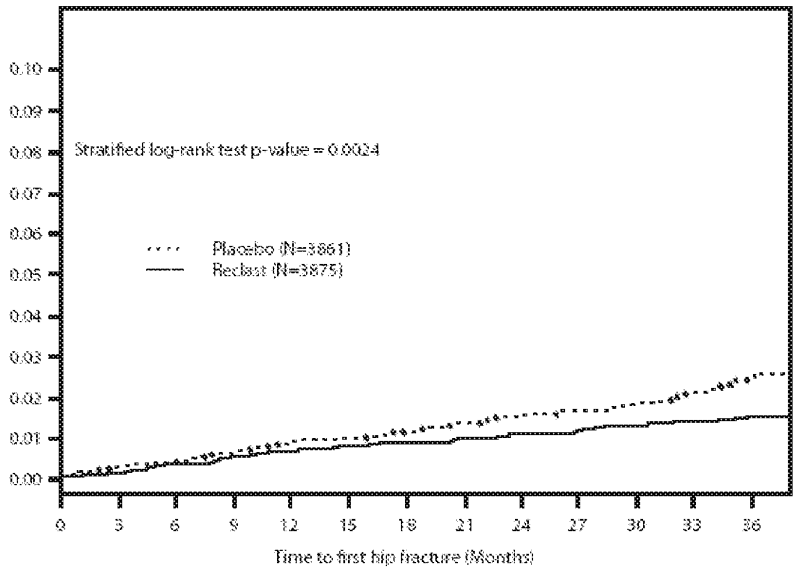
* p <0.0001

The reductions in vertebral fractures over three years were consistent (including new/worsening and multiple vertebral fractures) and significantly greater than placebo regardless of age, geographical region, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score, or prior bisphosphonate usage.

Effect on Hip Fracture over 3 years

Reclast demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The hip fracture event rate was 1.4% for Reclast-treated patients compared to 2.5% for placebo-treated patients.

Figure 1. Cumulative Incidence of Hip Fracture Over 3 Years



The reductions in hip fractures over three years were greater for Reclast than placebo regardless of femoral neck BMD T-score.

Effect on All Clinical Fractures

Reclast demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical (symptomatic) vertebral and non-vertebral fractures (excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures). All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 6.

Table 6. Between–Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years

Outcome	Reclast (N= 3875) Event Rate n (%)[+]	Placebo (N= 3861) Event Rate n (%)[+]	Absolute Reduction in Fracture Incidence % (95% CI)[+]	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture [(1)]	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture [(2)]	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture [(3)]	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36)*

*p-value < 0.001, **p-value <0.0001

[+] Event rates based on Kaplan-Meier estimates at 36 months

[(1)] Excluding finger, toe, and facial fractures

[(2)] Includes clinical thoracic and clinical lumbar vertebral fractures

[(3)] Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)

Reclast significantly increased BMD at the lumbar spine, total hip and femoral neck, relative to treatment with placebo at time points 12, 24, and 36 months. Treatment with Reclast resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.1% at the femoral neck, over 3 years as compared to placebo.

Bone Histology

Bone biopsy specimens were obtained between Months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Reclast. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76 specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralization defects.

Effect on Height

In the 3-year osteoporosis study, standing height was measured annually using a stadiometer. The Reclast group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively [p<0.001]).

Study 2: The efficacy and safety of Reclast in the treatment of patients with osteoporosis who suffered a recent low-trauma hip fracture was demonstrated in Study 2, a randomized, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years (mean age of 74.5). Concomitant osteoporosis therapies excluding other bisphosphonates and parathyroid hormone were allowed. Reclast was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes. The study continued until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 international units orally or IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 international units of vitamin D supplementation per day for at least 14 days prior to the study drug infusions. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Reclast significantly reduced the incidence of any clinical fracture by 35%. There was also a 46% reduction in the risk of a clinical vertebral fracture (Table 7).

Table 7. Between-Treatment Comparisons of the Incidence of Key Clinical Fracture Variables

Outcome	Reclast (N=1065) Event Rate n (%)[+]	Placebo (N=1062) Event Rate n (%)[+]	Absolute Reduction in Fracture Incidence % (95% CI)[+]	Relative Risk Reduction in Fracture Incidence % (95% CI)
Any clinical fracture [(1)]	92 (8.6)	139 (13.9)	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture [(2)]	21 (1.7)	39 (3.8)	2.1 (0.5, 3.7)	46 (8, 68)*

*p-value <0.05, **p-value <0.005
[+] Event rates based on Kaplan-Meier estimates at 24 months
[(1)] Excluding finger, toe and facial fractures
[(2)] Including clinical thoracic and clinical lumbar vertebral fractures

Effect on Bone Mineral Density (BMD)

Reclast significantly increased BMD relative to placebo at the hip and femoral neck at all timepoints (12, 24, and 36 months). Treatment with Reclast resulted in a 6.4% increase in BMD at the total hip and a 4.3% increase at the femoral neck over 36 months as compared to placebo.

14.2 Prevention of Postmenopausal Osteoporosis

The efficacy and safety of Reclast in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, multi-center, double-blind, placebo-controlled study of 581 postmenopausal women aged greater than or equal to 45 years, who were stratified by years since menopause: Stratum I women less than 5 years from menopause (n=224); Stratum II women greater than or equal to 5 years from menopause (n=357). Patients within Stratum I and II were randomized to one of three treatment groups: (1) Reclast given at randomization and at Month 12 (n=77) in Stratum I and (n=121) in Stratum II; (2) Reclast given at randomization and placebo at Month 12 (n=70) in Stratum I and (n=111) in Stratum II; and (3) Placebo given at randomization and Month 12 (n=202). Reclast was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 international units vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

Effect on Bone Mineral Density (BMD)

Reclast significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 6.3% increase in BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

Reclast also significantly increased total hip BMD relative to placebo at Month 24 across both strata. Reclast given once at randomization (and placebo given at Month 12) resulted in 2.6% increase in BMD in Stratum I patients and 2.1% in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.1% decrease in BMD in Stratum I patients and 1.0% decrease in BMD in Stratum II patients over 24 months. Therefore, Reclast given once at randomization (and placebo given at Month 12) resulted in a 4.7% increase in BMD in Stratum I patients and 3.2% increase in Stratum II patients over 24 months as compared to placebo (both p<0.0001).

14.3 Osteoporosis in Men

The efficacy and safety of Reclast in men with osteoporosis or significant osteoporosis secondary to hypogonadism, was assessed in a randomized, multicenter, double-blind, active controlled, study of 302 men aged 25-86 years (mean age of 64). The duration of the trial was two years. Patients were randomized to either Reclast which was administered once annually as a 5 mg dose in 100 mL infused over 15 minutes for a total of up to two doses, or to an oral weekly bisphosphonate (active control) for up to two years. All participants received 1000 mg of elemental calcium plus 800 to 1000 international units of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

An annual infusion of Reclast was non-inferior to the oral weekly bisphosphonate active control based on the percentage change in lumbar spine BMD at Month 24 relative to baseline (Reclast: 6.1% increase; active control: 6.2% increase).

14.4 Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

The efficacy and safety of Reclast to prevent and treat glucocorticoid-induced osteoporosis (GIO) was assessed in a randomized, multicenter, double-blind, stratified, active controlled study of 833 men and women aged 18-85 years (mean age of 54.4 years) treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent). Patients were stratified according to the duration of their pre-study corticosteroid therapy: less than or equal to 3 months prior to randomization (prevention subpopulation), and greater than 3 months prior to randomization (treatment subpopulation). The duration of the trial was one year. Patients were randomized to either Reclast which was administered once as a 5 mg dose in 100 mL infused over 15 minutes, or to an oral daily bisphosphonate (active control) for one year. All participants received 1000 mg of elemental calcium plus 400 to 1000 international units of vitamin D supplementation per day.

Effect on Bone Mineral Density (BMD)

In the GIO treatment subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to the active control at one year (Reclast 4.1%, active control 2.7%) with a treatment difference of 1.4% ($p<0.001$). In the GIO prevention subpopulation, Reclast demonstrated a significant mean increase in lumbar spine BMD compared to active control at one year (Reclast 2.6%, active control 0.6%) with a treatment difference of 2.0% ($p<0.001$).

Bone Histology

Bone biopsy specimens were obtained from 23 patients (12 in the Reclast treatment group and 11 in the active control treatment group) at Month 12 treated with an annual dose of Reclast or daily oral active control. Qualitative assessments showed bone of normal architecture and quality without mineralization defects. Apparent reductions in activation frequency and remodeling rates were seen when compared with the histomorphometry results seen with Reclast in the postmenopausal osteoporosis population. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

14.5 Treatment of Paget's Disease of Bone

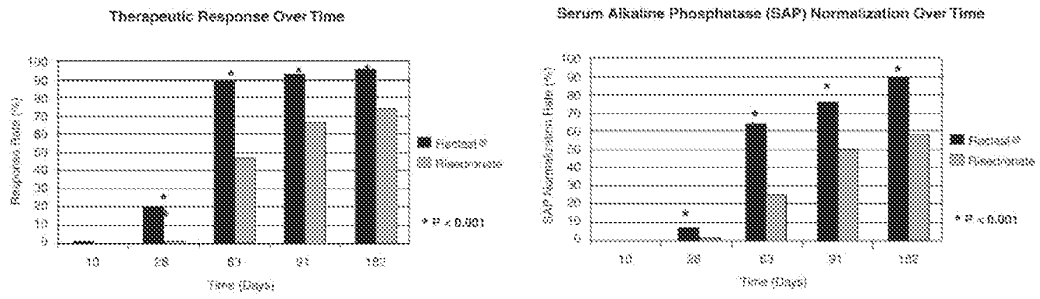
Reclast was studied in male and female patients with moderate to severe Paget's disease of bone, defined as serum alkaline phosphatase level at least twice the upper limit of the age-specific normal reference range at the time of study entry. Diagnosis was confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Reclast vs. oral daily doses of 30 mg risedronate for 2 months was demonstrated in two identically designed 6-month randomized, double blind trials. The mean age of patients in the two trials was 70. Ninety-three percent (93%) of patients were Caucasian. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of normal range.

In both trials Reclast demonstrated a superior and more rapid therapeutic response compared with risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of formation (SAP, serum N-terminal propeptide of type I collagen [P1NP]) and resorption (serum CTx 1 [cross-linked C-telopeptides of type I collagen] and urine α-CTx).

The 6-month combined data from both trials showed that 96% (169/176) of Reclast-treated patients achieved a therapeutic response as compared with 74% (127/171) of patients treated with risedronate. Most Reclast patients achieved a therapeutic response by the Day 63 visit. In addition, at 6 months, 89% (156/176) of Reclast-treated patients achieved normalization of SAP levels, compared to 58% (99/171) of patients treated with risedronate ($p<0.0001$) (see Figure 2).

Figure 2. Therapeutic Response/Serum Alkaline Phosphatase (SAP) Normalization Over Time



The therapeutic response to Reclast was similar across demographic and disease-severity groups defined by gender, age, previous bisphosphonate use, and disease severity. At 6 months, the percentage of Reclast-treated patients who achieved therapeutic response was 97% and 95%, respectively, in each of the baseline disease severity subgroups (baseline SAP less than 3xULN, greater than or equal to 3xULN) compared to 75% and 74%, respectively, for the same disease severity subgroups of risedronate-treated patients.

In patients who had previously received treatment with oral bisphosphonates, therapeutic response rates were 96% and 55% for Reclast and risedronate, respectively. The comparatively low risedronate response was due to the low response rate (7/23, 30%) in patients previously treated with risedronate. In patients naïve to previous treatment, a greater therapeutic response was also observed with Reclast (98%) relative to risedronate (86%). In patients with symptomatic pain at screening, therapeutic response rates were 94% and 70% for Reclast and risedronate respectively. For patients without pain at screening, therapeutic response rates were 100% and 82% for Reclast and risedronate respectively.

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with Reclast 5 mg. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each bottle contains 5 mg/100 mL. NDC 0078-0435-61

Handling

After opening the solution, it is stable for 24 hours at 2°C–8°C (36°F-46°F).

If refrigerated, allow the refrigerated solution to reach room temperature before administration.

Storage

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

Information for Patients

Patients should be made aware that Reclast contains the same active ingredient (zoledronic acid) found in Zometa®, and that patients being treated with Zometa should not be treated with Reclast.

Reclast is contraindicated in patients with creatinine clearance less than 35 mL/min [*see Contraindications (4)*].

Before being given Reclast, patients should tell their doctor if they have kidney problems and what medications they are taking.

Reclast should not be given if the patient is pregnant or plans to become pregnant, or if she is breast-feeding [*see Warnings and Precautions (5.6)*].

There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including Reclast. Before being given Reclast, patients should tell their doctor if they are aspirin-sensitive.

If the patient had surgery to remove some or all of the parathyroid glands in their neck, or had sections of their intestine removed, or are unable to take calcium supplements they should tell their doctor.

Reclast is given as an infusion into a vein by a nurse or a doctor, and the infusion time must not be less than 15 minutes.

On the day of treatment the patient should eat and drink normally, which includes drinking at least 2 glasses of fluid such as water within a few hours prior to the infusion, as directed by their doctor, before receiving Reclast.

After getting Reclast it is strongly recommended patients with Paget's disease take calcium in divided doses (for example, 2 to 4 times a day) for a total of 1500 mg calcium a day to prevent low blood calcium levels. This is especially important for the two weeks after getting Reclast [*see Warnings and Precautions (5.2)*].

Adequate calcium and vitamin D intake is important in patients with osteoporosis and the current recommended daily intake of calcium is 1200 mg and vitamin D is 800 international units – 1000 international units daily. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels.

Patients should be aware of the most commonly associated side effects of therapy. Patients may experience one or more side effects that could include: fever, flu-like symptoms, myalgia, arthralgia, and headache. Most of these side effects occur within the first 3 days following the dose of Reclast. They usually resolve within 3 days of onset but may last for up to 7 to 14 days. Patients should consult their physician if they have questions or if these symptoms persist. The incidence of these symptoms decreased markedly with subsequent doses of Reclast.

Administration of acetaminophen following Reclast administration may reduce the incidence of these symptoms.

Physicians should inform their patients that there have been reports of persistent pain and/or a non-healing sore of the mouth or jaw, primarily in patients treated with bisphosphonates for other illnesses. If they experience these symptoms, they should inform their physician or dentist.

Severe and occasionally incapacitating bone, joint, and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Reclast. Consider withholding future Reclast treatment if severe symptoms develop.

Atypical femur fractures in patients on bisphosphonate therapy have been reported; patients with thigh or groin pain should be evaluated to rule out a femoral fracture.

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MEDICATION GUIDE

Reclast® (RE-clast)

(zoledronic acid)

Injection

Read the Medication Guide that comes with Reclast before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. Talk to your doctor if you have any questions about Reclast.

What is the most important information I should know about Reclast?

You should not receive Reclast if you are already receiving Zometa. Both Reclast and Zometa contain zoledronic acid.

Reclast can cause serious side effects including:

1. Low calcium levels in your blood (hypocalcemia)
2. Severe kidney problems
3. Severe jaw bone problems (osteonecrosis)
4. Bone, joint or muscle pain
5. Unusual thigh bone fractures

1. **Low calcium levels in your blood (hypocalcemia)**.
Reclast may lower the calcium levels in your blood. If you have low blood calcium before you start taking Reclast, it may get worse during treatment. Your low blood calcium must be treated before you take Reclast. Most people with low blood calcium levels do not have symptoms, but some people may have symptoms. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles
- Numbness or tingling in your fingers, toes, or around your mouth

Your doctor may prescribe calcium and vitamin D to help prevent low calcium levels in your blood, while you take Reclast. Take calcium and vitamin D as your doctor tells you to.

2. **Severe kidney problems.**
Severe kidney problems may happen when you take Reclast. Severe kidney problems may lead to hospitalization or kidney dialysis and can be life-threatening. Your risk of kidney problems is higher if you:

- already have kidney problems
- take a diuretic or "water pill"
- do not have enough water in your body (dehydrated) before or after you receive Reclast
- are of advanced age since the risk increases as you get older
- take any medicines known to harm your kidneys

You should drink at least 2 glasses of fluid within a few hours before receiving Reclast to reduce the risk of kidney problems.

3. **Severe jaw bone problems (osteonecrosis).**
Severe jaw bone problems may happen when you take Reclast. Your doctor should examine your mouth before you start Reclast. Your doctor may tell you to see your dentist before you start Reclast. It is important for you to practice good mouth care during treatment with Reclast.

4. **Unusual thigh bone fractures.**
Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh.

5. **Possible harm to your unborn baby.**
Reclast should not be used if you are pregnant. Tell your doctor right away if you are pregnant or plan to become pregnant. Reclast may harm your unborn baby.

6. **Bone, joint, or muscle pain.**
Some people who take bisphosphonates develop severe bone, joint, or muscle pain.

Call your doctor right away if you have any of these side effects.

What is Reclast?

Reclast is a prescription medicine used to:

- Treat or prevent osteoporosis in women after menopause. Reclast helps reduce the chance of having a hip or spinal fracture (break).
- Increase bone mass in men with osteoporosis.
- Treat or prevent osteoporosis in either men or women who will be taking corticosteroid medicines for at least one year.
- Treat certain men and women who have Paget's disease of the bone.

It is not known how long Reclast works for the treatment and prevention of osteoporosis. You should see your doctor regularly to determine if Reclast is still right for you.

Reclast is not for use in children.

Who should not take Reclast?

Do not take Reclast if you:

- Have low levels of calcium in your blood
- Have kidney problems
- Are allergic to zoledronic acid or any of its ingredients. A list of ingredients is at the end of this leaflet.

What should I tell my doctor before taking Reclast?

Before you start Reclast, be sure to talk to your doctor if you:

- Have low blood calcium.
- Have kidney problems.
- Had parathyroid or thyroid surgery (glands in your neck).
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome) or have had parts of your intestine removed.
- Have asthma (wheezing) from taking aspirin.
- Plan to have dental surgery or teeth removed.
- Are pregnant, or plan to become pregnant. Reclast may harm your unborn baby. **Reclast should not be used if you are pregnant.**
- Are breastfeeding or plan to breastfeed. It is not known if Reclast passes into your milk and may harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may affect how Reclast works.

Especially tell your doctor if you are taking:

- An antibiotic. Certain antibiotic medicines called aminoglycosides may increase the effect of Reclast in lowering your blood calcium for a long period of time.
- A diuretic or "water pill".
- Non-steroidal anti-inflammatory medicines (NSAIDS).

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get a new medicine.

How will I receive Reclast?

- Your doctor will tell you how often you will receive Reclast.
- Reclast is given by infusion into your vein (intravenously). Your infusion should last at least 15 minutes.
- Before you receive Reclast, drink at least 2 glasses of fluid (such as water) within a few hours as directed by your doctor.
- You may eat before your treatment with Reclast.
- If you miss a dose of Reclast, call your doctor or healthcare provider to schedule your next dose.

What are the possible side effects of Reclast?

Reclast may cause serious side effects.

- See "**What is the most important information I should know about Reclast?**"

The most common side effects of Reclast included:

- Fever
- Pain in your bones, joints or muscles
- Pain in your arms and legs
- Headache
- Flu-like illness (fever, chills, bone, joint, or muscle pain, fatigue)
- Nausea
- Vomiting
- Diarrhea

Talk to your doctor about things you can do to help decrease some of these side effects that might happen with a Reclast infusion.

You may get allergic reactions, such as hives, swelling of your face, lips, tongue, or throat.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Reclast. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of Reclast.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide summarizes the most important information about Reclast. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Reclast that is written for health professionals.

For more information, go to: www.RECLAST.com or call 1-866-732-5278.

What are the ingredients in Reclast?

Active ingredient: zoledronic acid monohydrate.

Inactive ingredients: mannitol and sodium citrate.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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INTRAVENOUS ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

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ABSTRACT

Background Bisphosphonates are effective agents for the management of osteoporosis. Their low bioavailability and low potency necessitate frequent administration on an empty stomach, which may reduce compliance. Gastrointestinal intolerance limits maximal dosing. Although intermittent intravenous treatments have been used, the optimal doses and dosing interval have not been systematically explored.

Methods We studied the effects of five regimens of zoledronic acid, the most potent bisphosphonate, on bone turnover and density in 351 postmenopausal women with low bone mineral density in a one-year, randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25 mg, 0.5 mg, or 1 mg at three-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, six months apart. Lumbar-spine bone mineral density was the primary end point.

Results There were similar increases in bone mineral density in all the zoledronic acid groups to values for the spine that were 4.3 to 5.1 percent higher than those in the placebo group ($P<0.001$) and values for the femoral neck that were 3.1 to 3.5 percent higher than those in the placebo group ($P<0.001$). Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Myalgia and pyrexia occurred more commonly in the zoledronic acid groups, but treatment-related dropout rates were similar to that in the placebo group.

Conclusions Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis. (N Engl J Med 2002;346:653-61.)

ORAL bisphosphonates are widely used for treating osteoporosis and have been shown to increase bone mineral density and decrease the rate of fracture.[1,2] However, they do have limitations related to long-term compliance, gastrointestinal intolerance, and poor and variable absorption from the gastrointestinal tract. Intermittent intravenous administration of bisphosphonates might address some of these problems and has been shown to be effective in the treatment of malignant hypercalcemia and Paget's disease and to reduce the rate of skeletal complications in patients with breast carcinoma or multiple myeloma. Evidence suggests that intravenous bisphosphonates increase bone mineral density in patients with osteoporosis, but most relevant studies have been small, unblinded, and short-term and have not systematically examined the effects of the dose and dosing interval on changes in bone mineral density and markers of bone turnover.[3-6]

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Zoledronic acid is the most potent bisphosphonate that has been studied in clinical trials to date.[7] It is superior to pamidronate in the treatment of cancer-related hypercalcemia.[8] Because it has high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used. We undertook a phase 2 study to examine the effect of intravenous zoledronic acid on bone density and bone turnover in postmenopausal women with low bone density and to assess the effects of varying the total dose administered and the dosing interval.

METHODS

Study Subjects

A total of 351 postmenopausal women 45 to 80 years of age were studied at 24 centers in 10 countries. In all the women, menopause had occurred at least five years previously, either naturally or as the result of bilateral oophorectomy. All women had a bone mineral density at the lumbar spine (L1 to L4) that was at least 2.0 SD below the mean value for young adults (a T score lower than −2) and had no more than one vertebral fracture at screening. The date of onset of menopause was defined as the date of oophorectomy when applicable or as 12 months after the cessation of menses in women over 50 years of age and 18 months after the cessation of menses in women between 45 and 49 years of age. Major criteria for exclusion included systemic estrogen treatment within the previous three months, evidence of secondary osteoporosis, clinical or laboratory evidence of hepatic or renal disease, disorders of the parathyroid or thyroid glands, a serum 25-hydroxyvitamin D concentration of 15 ng per milliliter (37 nmol per liter) or less, a history of cancer, previous treatment with bisphosphonates or fluoride, and current therapy with any other drug known to affect the skeleton. The protocol was approved by the ethics committee at each center, and all the women gave written informed consent. Thirty-five women withdrew from the study, most commonly for personal reasons (in the case of 15 women) or because of adverse events (14 women). Thus, 316 women completed the study.

Treatment

All women received a calcium supplement (1 g per day). At study entry the women were randomly assigned to receive one of six treatment regimens in a double-blind fashion. Three groups received zoledronic acid by intravenous infusion every three months, one group at a dose of 0.25 mg, one at a dose of 0.5 mg, and one at a dose of 1 mg. Two other groups received a total dose of 4 mg of zoledronic acid — one group receiving a single 4-mg infusion at the beginning of the trial and the other group receiving two doses of 2 mg each, one at base line and the other at six months. Thus, there were three groups that received a total dose of 4 mg in one year. The sixth group received only placebo (saline). To maintain blinding, all women received an intravenous infusion of either zoledronic acid or placebo every three months. All infusions were 20 ml in volume and were infused over a period of five minutes. A dose of 4 mg given in this way produces a mean (±SD) peak serum concentration of zoledronic acid of 393±100 ng per milliliter. Infusions were prepared at each center by a pharmacist who had no contact with the patients and were labeled with the subject's study number and supplied to the study personnel.

Bone Density Measurement

The bone mineral density of the lumbar spine, the nondominant proximal femur and forearm, and the total body were measured by dual-energy x-ray absorptiometry at base line and at 6, 9, and 12 months with the use of Hologic QDR (Hologic, Waltham, Mass.) or Lunar (Madison, Wis.) instruments. Data were converted to Hologic-equivalent values by the method of Hui et al.[9] A central laboratory (Institut für Funktionsanalyse, Hamburg, Germany) was responsible for the supervision of quality control for these measurements and notified investigators if any patient had a decrease in bone density of more than 5 percent from the base-line values.

Markers of Bone Turnover

Measurement of biochemical markers was performed in a central laboratory with the use of established methods. For serum bone-specific alkaline phosphatase, the Tandem-MP Ostase assay was used (Hybritech, Liege, Belgium). Serum osteocalcin was measured with the N-MID one-step enzyme-linked immunosorbent assay (Osteometer, Herlev, Denmark). Urinary type I collagen cross-linked N-telopeptide was measured with the Osteomark assay (Ostex, Seattle). Serum type I collagen C-telopeptide was measured with the CrossLaps assay (Osteometer).

Statistical Analysis

The necessary sample size was calculated as the number of patients needed to detect a difference between the zoledronic acid groups and the placebo group of at least 4 percent in the degree of change in lumbar-spine bone mineral density from base line to 12 months. Bonferroni's correction was used to adjust for multiple comparisons in order to ensure an overall nominal significance level of 0.05. Given a noncentral t distribution with a type I error of 0.025, a power of 80 percent, a two-sided alternative, and a standard deviation of 5.7 percent, we calculated that 40 patients were needed in each treatment group in order to allow detection of a difference of 4 percent. To allow for a possible 15 percent dropout rate, a total sample size of 290 was selected.

All analyses were performed according to the intention-to-treat principle with the use of all available data from all patients who received study drug. Missing values were not imputed or replaced. Analysis of covariance was performed (with the Proc Mixed procedure of SAS software [SAS Institute, Cary, N.C.]) to estimate differences between the treatment groups. The statistical fixed-effects model considered center and treatment as main variables. In addition, the base-line values, if measured, were used as covariates. The analyses were repeated with the last observation carried forward and produced essentially the same results (data not shown).

For the primary variable, adjustment for multiple comparisons between placebo and the active doses of zoledronic acid was performed at a one-sided alpha level of 0.025, according to the method of Marcus et al.[10] For secondary variables, pairwise comparisons were investigated in the exploratory analysis (unadjusted for multiple comparisons). The pairwise comparisons were tested at a two-sided level of significance of 0.05. In addition to the P value for the comparisons between treatment groups, estimates of the differences and associated 95 percent confidence intervals were calculated.

The protocol was designed and developed by the sponsor and submitted to the investigators for comments and amendments. The final protocol was then accepted by the investigators and submitted to the ethics review committees of their institutions for approval. Data management and statistical analysis were performed by the sponsor. Interpretation of the data and preparation of the manuscript were performed by a publication committee that included three academic researchers who were investigators in the trial (Drs. Reid, Brown, and Burckhardt) and Dr. Trechsel, the author of the study protocol, as a representative of the sponsor. These authors had full and unfettered access to the data and take full responsibility for the completeness and accuracy of the reported data. The study sponsor placed no limits on statements made in the final paper.

RESULTS

Study Subjects

The base-line characteristics of the women who participated in the study are summarized in Table 1.

All but two women were white, and none had vertebral fractures at study entry.

Bone Mineral Density

Mean bone-mineral-density values in the lumbar spine corresponded to a T score of −2.9. All groups receiving zoledronic acid regimens had a progressive increase in bone mineral density in the lumbar spine throughout the 12-month study period, although the rate of increase tended to slow in the second half of the study (Fig. 1A). Throughout the study, the values for lumbar-spine bone mineral density achieved with all zoledronic acid regimens were significantly higher than those in the placebo group ($P<0.001$), and there were no significant differences among the zoledronic acid groups. At 12 months, the mean lumbar-spine bone mineral density in the groups receiving zoledronic acid was 4.3 to 5.1 percent higher than the mean value in the placebo group, which remained stable. The bone mineral density in the femoral neck also increased progressively throughout the study period; all zoledronic acid groups had similar increases to values that were significantly higher than those in the placebo group (differences of 3.1 to 3.5 percent at 12 months, $P<0.001$) (Fig. 1B). The femoral-neck bone mineral density declined by 0.4 percent in the placebo group.

Bone mineral density at the distal radius responded to zoledronic acid treatment to a lesser extent, resulting in differences from the placebo group of 0.8 to 1.6 percent at 12 months (data not shown); in the placebo group, distal radial bone mineral density decreased by 0.8 percent. All zoledronic acid regimens except the four doses of 0.25 mg each resulted in distal radial bone mineral density that was significantly greater than that in the placebo group ($P\leq0.05$ for all comparisons). The results for total-body bone mineral density were similar (data not shown). At 12 months, the differences in total-body bone mineral density between the zoledronic acid groups and the placebo group ranged from 0.9 percent to 1.3 percent and were significant ($P<0.03$ for all comparisons) for all regimens except the four doses of 0.5 mg each.

Markers of Bone Turnover

Markers of bone resorption reached a nadir at one month (median decreases of 65 to 83 percent in serum C-telopeptide and 50 to 69 percent in the urinary N-telopeptide:creatinine ratio), whereas there were no significant changes in the placebo group (Fig. 2). The decrease in markers of resorption tended to be dose-dependent, particularly at three months — a pattern that is consistent with previous reports that higher doses of bisphosphonates increase the duration of action of the drug.[11] We do not have full documentation of the immediate reductions in bone resorption after each infusion, because most samples were obtained only every three months. The suppression of

TABLE 1. BASE-LINE CHARACTERISTICS.*

CHARACTERISTIC	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
No. of women completing the study	51	52	48	55	53	57
Age (yr)	64±6	64±7	65±7	63±7	65±7	64±6
Weight (kg)	60±10	62±10	61±9	63±13	62±11	63±10
Height (cm)	158±6	158±6	158±6	159±6	159±6	160±6
Urinary N-telopeptide:creatinine ratio†	48±32	56±43	45±21	46±27	48±24	45±26
Serum C-telopeptide (nmol/liter)	5.5±2.8	5.3±2.2	4.7±1.8	4.8±1.9	5.1±1.9	4.8±1.8
Serum bone-specific alkaline phosphatase (μg/liter)	17±8	18±6	15±5	15±5	15±6	16±7
Serum osteocalcin (μg/liter)	26±10	24±11	26±9	22±10	24±11	24±13
Bone mineral density (g/cm²)‡						
Lumbar spine	0.74±0.06	0.72±0.08	0.73±0.06	0.73±0.07	0.73±0.08	0.74±0.07
Femur	0.70±0.09	0.71±0.11	0.71±0.09	0.72±0.09	0.74±0.11	0.71±0.08
Radial	0.43±0.05	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06
Total body	0.90±0.09	0.90±0.10	0.90±0.09	0.90±0.09	0.90±0.09	0.88±0.08

*Plus–minus values are means ±SD.

†N-telopeptide was measured in nanomoles, and creatinine in millimoles.

‡Data have been converted to Hologic-equivalent values.

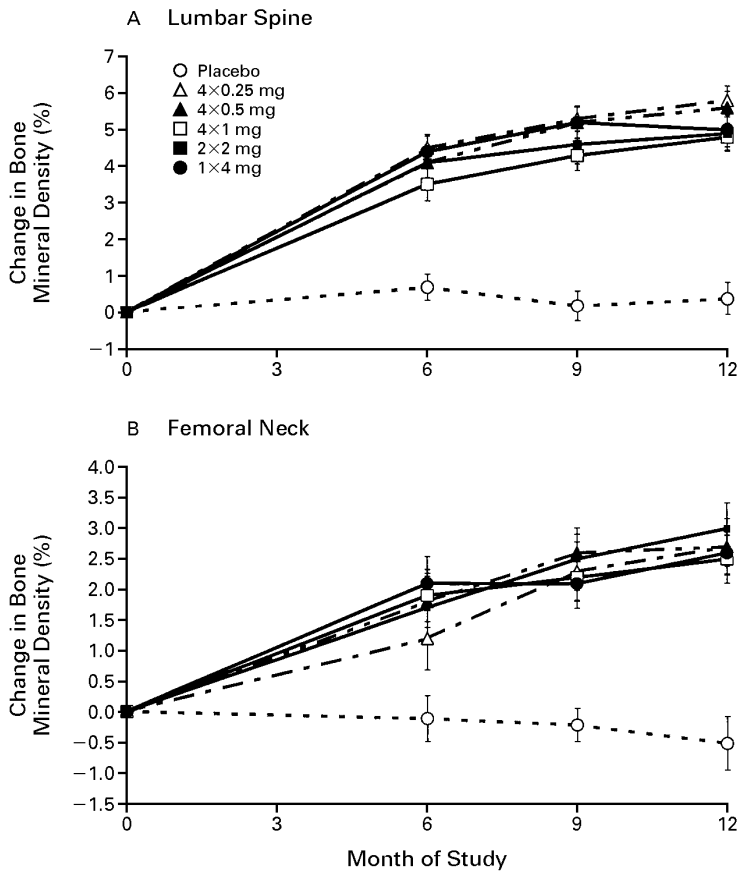

Figure 1. Effects of Various Regimens of Zoledronic Acid and Placebo on Bone Mineral Density in the Lumbar Spine (Panel A) and the Femoral Neck (Panel B) in Postmenopausal Women with Low Bone Mineral Density.

The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Achieved density with all regimens of zoledronic acid was significantly higher than that with placebo, and there were no significant differences among the zoledronic acid groups. I bars represent standard errors.

resorption was maintained at 12 months. At 12 months, the zoledronic acid regimens were associated with decreases of 49 to 52 percent in serum C-telopeptide (as compared with a decrease of 8 percent in the placebo group) and decreases of 54 to 65 percent in the ratio of urinary N-telopeptide to creatinine (as compared with an increase of 3 percent in the placebo group). All zoledronic acid groups had values for these markers of resorption that were significantly different from those in the placebo group ($P<0.01$ for all comparisons), but there were no significant differences among the zoledronic acid groups. Bone-specific alkaline phosphatase and osteocalcin, which are serum markers of bone formation, showed similar responses, but there was no sharp decrease apparent at one month (Fig. 3). Again, suppression persisted at 12 months with all doses ($P<0.001$).

Bone Biopsies

A 7.5-mm transiliac biopsy specimen was obtained from 43 women and double-labeled with tetracycline. Of these specimens, 27 were complete and suitable for histomorphometric analysis. The sections were undecalcified and stained with Goldner's trichrome, except for tetracycline measurements, which were made on unstained sections. Women treated with zoledronic

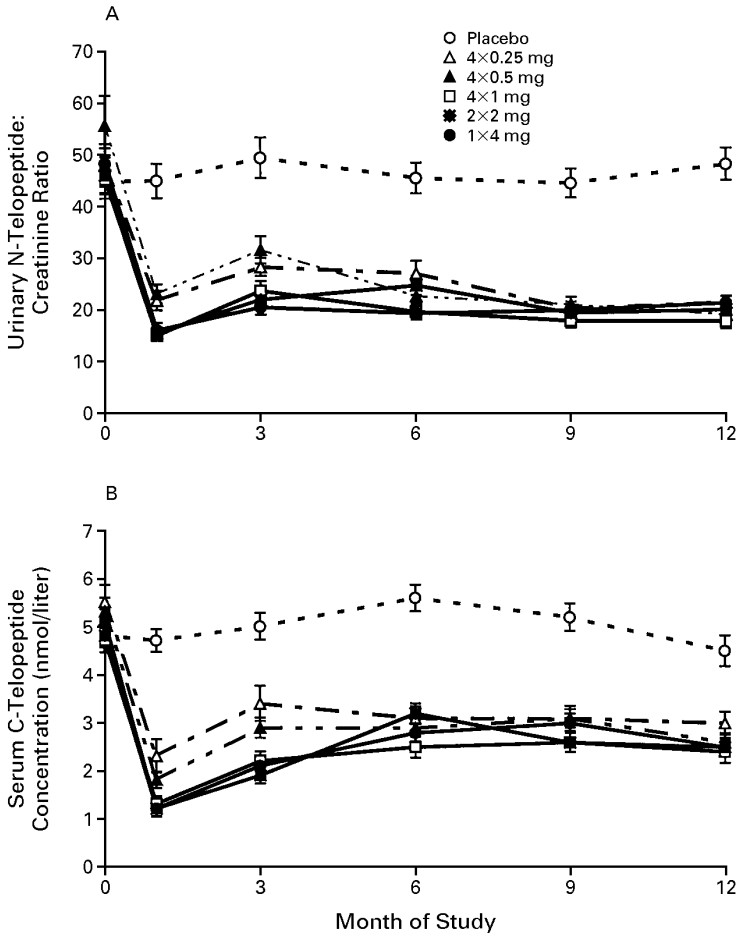

Figure 2. Effects of Various Regimens of Zoledronic Acid and Placebo on Biochemical Markers of Bone Resorption.

The ratio of N-telopeptide of type I collagen (in nanomoles) to creatinine (in millimoles) was measured in urine (Panel A). C-telopeptide was measured in serum (Panel B). The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at one month, the effects of all regimens were significantly different from those of placebo. The I bars represent standard errors.

acid at any dose had significantly lower proportions of mineralizing surfaces, rates of bone formation, adjusted mineral apposition rates, and activation frequencies than the women in the placebo group (differences of 71 percent to 84 percent, $P<0.05$); there were nonsignificant differences in the proportion of eroded surface (39 percent lower than that in the placebo group, $P<0.06$) and in eroded volume (48 percent lower, $P<0.07$). No change was noted in cortical bone thickness or porosity; cancellous bone volume; trabecular thickness, separation, or number; wall width of trabecular bone packets; number of nodes per volume of tissue; or osteoid maturation time. No dose effect was found with respect to any of these factors. No evidence of osteomalacia was found, either by qualitative assessment or on the basis of such quantitative measures as osteoid thickness and volume or the mineral apposition rate. No other qualitative abnormalities were apparent.

Fractures

Spinal radiographs at base line and one year showed no vertebral fractures during the study. No nonver-

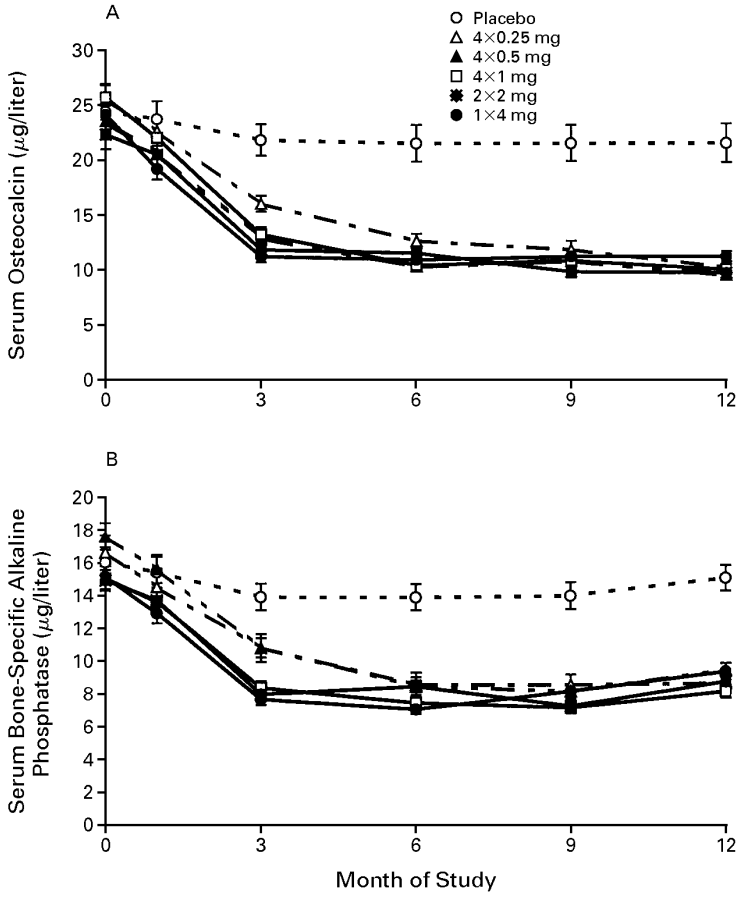

Figure 3. Effects of Various Regimens of Zoledronic Acid and Placebo on Serum Markers of Bone Formation.

The curves show the mean changes from base line in serum osteocalcin (Panel A) and serum bone-specific alkaline phosphatase (Panel B) in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at three months, the serum concentrations with all regimens of zoledronic acid were significantly lower than base-line values. The I bars represent standard errors.

tebral fractures occurred in the group receiving four doses of 0.25 mg of zoledronic acid; two nonvertebral fractures occurred in the group receiving four doses of 1 mg of zoledronic acid; and one nonvertebral fracture occurred in each of the other groups.

Safety

Mean serum calcium concentrations in the zoledronic acid groups declined significantly ($P<0.05$ for all comparisons), by approximately 0.08 mmol per liter, between base line and one month but were similar to those in the placebo group from three months onward. Serum phosphate concentrations in the zoledronic acid groups had decreased by 0.06 to 0.12 mmol per liter at one month and generally remained about 0.05 mmol per liter below those in the placebo group throughout the study period, although they did not differ significantly from those in the placebo group at one year. Intact parathyroid hormone was measured in serum at base line and 12 months. There were no significant differences among the groups at the 12-month follow-up, although the mean value was about 30 percent higher than the base-line value in the women in the group receiving four doses of 1 mg of zole-

dronic acid, possibly because sampling was performed only three months after the last dose had been administered in this group.

The rates of adverse events were similar in all the active-treatment groups (Table 2). However, treatment-related adverse events were significantly more common in the zoledronic acid groups than in the placebo group (rates of 45 to 67 percent vs. 27 percent; data not shown). In the zoledronic acid groups, most adverse events were instances of musculoskeletal pain, nausea, or fever, most of which were rated as mild. Most occurred the first time the drug was administered. Five women withdrew from the study because of drug-related adverse events, all of which were reactions after the first infusion of zoledronic acid. These withdrawals were not dose-related; two occurred in women who were receiving the lowest dose and two in women receiving the highest dose. There was no evidence of adverse effects on renal function with any of these regimens. Overall, the proportions of women who withdrew from the study because of adverse events were similar in all groups. Symptoms at the infusion site were uncommon in all groups (e.g., reported in no patients receiving a single 4-mg dose of zoledronic acid and in two patients receiving placebo). Iritis did not develop in any patients, and the occurrence of any eye disorder was uncommon (e.g., reported in two patients receiving a single 4-mg dose of zoledronic acid and in nine patients receiving placebo).

DISCUSSION

Intermittent intravenous administration of the potent bisphosphonate zoledronic acid results in changes in biochemical markers of bone turnover and in bone mineral density that are similar to those observed with daily oral bisphosphonate therapy. Thus, the reductions in markers at one year in the present study are similar to those seen with 5 mg of risedronate per day,[12] 2.5 to 5 mg of ibandronate per day,[13] and 10 mg of alendronate per day.[14-16] Zoledronic acid increases spinal bone mineral density at 12 months to 5 percent above values found in patients receiving placebo — an increase similar to that achieved with a daily 10-mg dose of alendronate (5 percent),[17] a daily 5-mg dose of risedronate (3 percent),[12] or a daily 150-mg dose of pamidronate (5 percent).[18] Intravenous zoledronic acid also produced results similar to those of the oral regimens at the femoral neck (alendronate, 3 percent increase in bone density; risedronate, 2 percent; pamidronate, 3 percent) and in the total body (alendronate, 1.5 percent increase; pamidronate, 1 percent).

Our study assessed longer intervals between doses than have been assessed by previous studies of intermittent bisphosphonate therapy. Etidronate has been used for many years in two-week oral courses administered at three-month intervals.[19,20] There is also evidence that intravenous pamidronate[3] or ibandronate,[4] given every three months, has beneficial effects on bone density in women with postmenopausal osteoporosis. The disappointing data on fractures from a recent study of intermittent ibandronate therapy (1 mg intravenously every three months)[21] has been interpreted as indicating that a dosing interval of three months is too long. However, this ibandronate regimen did not stably suppress markers of bone resorption; a substantial maximal suppression of C-telopeptide excretion (by 50 percent) was rapidly offset, so that the level before the next dose was only 10 to 20 percent below that in the placebo group.[4] As a result, the changes in bone density (increases of 2.9 percent

TABLE 2. ADVERSE EVENTS.*

VARIABLE	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
Adverse events — no.	236	236	255	271	269	210
Women with an adverse event — no. (%)						
Any	52 (87)	50 (86)	50 (94)	56 (92)	54 (90)	45 (76)
Myalgia	12 (20)	6 (10)	7 (13)	10 (16)	6 (10)	1 (2)
Pyrexia	6 (10)	5 (9)	7 (13)	12 (20)	9 (15)	2 (3)
Arthralgia	9 (15)	8 (14)	9 (17)	15 (25)	5 (8)	9 (15)
Influenza-like illness	1 (2)	4 (7)	2 (4)	10 (16)	9 (15)	4 (7)
Nausea	3 (5)	4 (7)	5 (9)	6 (10)	8 (13)	3 (5)
Any leading to withdrawal from study	4 (7)	2 (3)	2 (4)	2 (3)	3 (5)	1 (2)
Any serious	4 (7)	4 (7)	7 (13)	5 (8)	6 (10)	3 (5)

*Data are for all adverse events in each category, not just those classified as drug-related.

in the spine at 12 months[4] or to 4 percent higher than the spinal bone mineral density in the placebo group at 3 years[21]) were smaller than those found in our study; this effect is consistent with the moderate effect of this dose of ibandronate on the incidence of vertebral fracture (a 26 percent reduction at 3 years). Our data indicate that much longer dosing intervals are compatible with efficacy (in terms of both suppression of bone turnover and increase in bone density) if the dose of bisphosphonate is sufficiently large. Indeed, the present study does not establish a maximal dosing interval, since turnover remained suppressed at 12 months. Thus, it is possible that a longer interval between doses could be effective, particularly if larger doses of zoledronic acid were used.

How a single infusion of zoledronic acid suppresses bone turnover for so long remains to be determined. Prolonged suppression is not the result of the persistence of the drug in the circulation, given that by 24 hours after administration, drug levels are less than 1 percent of the postadministration peak and 40 percent of the dose has been excreted in the urine. The balance of the dose is presumably bound to bone and is slowly released back into the circulation, giving rise to a 167-hour terminal half-life in plasma. It has been thought that bisphosphonates are located exclusively on osteoclastic surfaces[22] and that short-term exposure inhibits activity in a single generation of basic multicellular units in bone. The life span of the basic multicellular unit (about three months) then determines the duration of action of the drug. However, evidence suggests that bisphosphonates are also deposited on osteoblastic and resting bone surfaces and remain there for the long term.[23] The existence of such deposits would provide a possible explanation for our results, since residue from a single dose could interfere with the future development of basic multicellular units at these surfaces. It is also possible that direct effects on existing basic multicellular units and osteocytes[24,25] result in reduced formation of succeeding basic multicellular units.

Zoledronic acid was generally well tolerated, and the rate of retention of subjects in the study was high. The adverse events that were more common in women receiving zoledronic acid are those that have occurred previously in patients receiving intravenous aminobisphosphonates and are transient. Infrequent doses may increase tolerance of these side effects.

The inclusion of a placebo group in this study permits quantification of the size of the therapeutic effect and facilitates comparison of the present data with those from other studies. We believe this use of a placebo is ethical, since the bone density used as a criterion for entry (a T score of less than −2) is higher than that required at the participating centers for a diagnosis of osteoporosis and would certainly not be considered to be a threshold for therapeutic intervention at these centers. Thus, the study was conducted in a low-risk population — a characterization supported by the fact that no spinal fractures occurred during the study period. Only one sixth of these low-risk subjects received placebo, and they received it for a maximum of 12 months, after which all women received active therapy.

Osteoporosis has been regarded as requiring daily therapy, and maintaining compliance with daily regimens for a predominantly asymptomatic condition has been a major problem.[26,27] Administration of treatment at intervals of 6 to 12 months or more is likely to be much more acceptable to patients and could reduce costs. A greater proportion of the at-risk population might take advantage of prophylaxis against osteoporosis if an intermittent regimen were used, and the rate of fractures might therefore decrease. However, studies that demonstrate an effect on the rate of fractures are needed before any recommendation can be made.

Supported by a grant from Novartis Pharma.

We are indebted to Esther Hagin of Novartis Pharma, Basel, Switzerland, for her expert work in conducting the trial.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOMETA safely and effectively. See full prescribing information for ZOMETA.

Zometa® (zoledronic acid) Injection
Ready-to-Use Solution for Intravenous Infusion (For Single Use)
Concentrate for Intravenous Infusion
Initial U.S. Approval: 2001

RECENT MAJOR CHANGES

Warnings and Precautions, Hypocalcemia (5.10) 9/2013

INDICATIONS AND USAGE

Zometa is a bisphosphonate indicated for the treatment of:

- Hypercalcemia of malignancy. (1.1)
- Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. (1.2)

Important limitation of use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or nontumor-related hypercalcemia. (1.3)

DOSAGE AND ADMINISTRATION

Hypercalcemia of malignancy (2.1)

- 4 mg as a single-use intravenous infusion over no less than 15 minutes.
- 4 mg as retreatment after a minimum of 7 days.

Multiple myeloma and bone metastasis from solid tumors. (2.2)

- 4 mg as a single-use intravenous infusion over no less than 15 minutes every 3-4 weeks for patients with creatinine clearance of greater than 60 mL/min.
- Reduce the dose for patients with renal impairment.
- Coadminister oral calcium supplements of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Administer through a separate vented infusion line and do not allow to come in contact with any calcium or divalent cation-containing solutions. (2.3)

DOSAGE FORMS AND STRENGTHS

4 mg/100 mL single-use ready-to-use bottle (3)
4 mg/5 mL single-use vial of concentrate (3)

CONTRAINDICATIONS

Hypersensitivity to any component of Zometa. (4)

WARNINGS AND PRECAUTIONS

- Patients being treated with Zometa should not be treated with Reclast®. (5.1)
- Adequately rehydrate patients with hypercalcemia of malignancy prior to administration of Zometa and monitor electrolytes during treatment. (5.2)
- Renal toxicity may be greater in patients with renal impairment. Do not use doses greater than 4 mg. Treatment in patients with severe renal impairment is not recommended. Monitor serum creatinine before each dose. (5.3)
- Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting Zometa. Avoid invasive dental procedures. (5.4)
- Severe incapacitating bone, joint, muscle pain may occur. Discontinue Zometa if severe symptoms occur. (5.5)
- Zometa can cause fetal harm. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.9, 8.1)
- Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy. These fractures may occur after minimal or no trauma. Evaluate patients with thigh or groin pain to rule out a femoral fracture. Consider drug discontinuation in patients suspected to have an atypical femur fracture. (5.6)
- Hypocalcemia: Correct before initiating Zometa. Adequately supplement patients with calcium and vitamin D (5.10)

ADVERSE REACTIONS

The most common adverse events (greater than 25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Aminoglycosides: May have an additive effect to lower serum calcium for prolonged periods. (7.1)
- Loop diuretics: Concomitant use with Zometa may increase risk of hypocalcemia. (7.2)
- Nephrotoxic drugs: Use with caution. (7.3)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known whether Zometa is excreted in human milk. (8.3)
- Pediatric Use: Not indicated for use in pediatric patients. (8.4)
- Geriatric Use: Special care to monitor renal function. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypercalcemia of Malignancy

Zometa is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin (g/dL)).

1.2 Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

1.3 Important Limitation of Use

The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions have not been established.

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.1 Hypercalcemia of Malignancy

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium greater than or equal to 12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over **no less than 15 minutes**. Patients who receive Zometa should have serum creatinine assessed prior to each treatment.

Dose adjustments of Zometa are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine less than 400 μmol/L or less than 4.5 mg/dL).

Patients should be adequately rehydrated prior to administration of Zometa [*see Warnings and Precautions (5.2)*].

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa. Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia.

Retreatment with Zometa 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and serum creatinine must be assessed prior to retreatment with Zometa [*see Warnings and Precautions (5.2)*].

2.2 Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance greater than 60 mL/min is 4 mg infused over **no less than 15 minutes** every 3-4 weeks. The optimal duration of therapy is not known.

Upon treatment initiation, the recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are listed in Table 1. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula [*see Warnings and Precautions (5.2)*].

Table 1: Reduced Doses for Patients with Baseline CrCl Less Than or Equal to 60 mL/min

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose*
greater than 60	4 mg
50–60	3.5 mg
40–49	3.3 mg
30–39	3 mg

*Doses calculated assuming target AUC of 0.66(mg•hr/L) (CrCl=75 mL/min)

During treatment, serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

For patients with normal baseline creatinine, increase of 0.5 mg/dL
For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be reinitiated at the same dose as that prior to treatment interruption.

Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

2.3 Preparation of Solution

Zometa must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

4 mg/100 mL Single-Use Ready-to-Use Bottle

Bottles of Zometa ready-to-use solution for infusion contain overfill allowing for the administration of 100 mL of solution (equivalent to 4 mg zoledronic acid). This solution is ready-to-use and may be administered directly to the patient without further preparation. For single use only

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa solution from the bottle (see Table 2) and replace with an equal volume of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Administer the newly-prepared dose-adjusted solution to the patient by infusion. Follow proper aseptic technique. Properly discard previously withdrawn volume of ready-to-use solution - do not store or reuse.

Table 2: Preparation of Reduced Doses–Zometa Ready-to-Use Bottle

Remove and discard the following Zometa ready-to-use solution (mL)	Replace with the following volume of sterile 0.9% Sodium Chloride, USP or 5% Dextrose Injection, USP (mL)	Dose (mg)
12.0	12.0	3.5
18.0	18.0	3.3
25.0	25.0	3.0

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C–8°C (36°F–46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

4 mg/5 mL Single-Use Vial

Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, following proper aseptic technique, and administered to the patient by infusion. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the Zometa concentrate from the vial for the dose required (see Table 3).

Table 3: Preparation of Reduced Doses – Zometa Concentrate

Remove and Use Zometa Volume (mL)	Dose (mg)
4.4	3.5
4.1	3.3
3.8	3.0

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

2.4 Method of Administration

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of Zometa should not exceed 4 mg and the duration of infusion should be no less than 15 minutes [*see Warnings and Precautions (5.3)*]. In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis, have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial Zometa dose.

3 DOSAGE FORMS AND STRENGTHS

4 mg/100 mL single-use ready-to-use bottle

4 mg/5 mL single-use vial of concentrate

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Zoledronic Acid or Any Components of Zometa

Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drugs with Same Active Ingredient or in the Same Drug Class

Zometa contains the same active ingredient as found in Reclast® (zoledronic acid). Patients being treated with Zometa should not be treated with Reclast or other bisphosphonates.

5.2 Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

5.3 Renal Impairment

Zometa is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased [*see Adverse Reactions (6.1)*]. Preexisting renal insufficiency and multiple cycles of Zometa and other bisphosphonates are risk factors for subsequent renal deterioration with Zometa. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zometa treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine greater than 400 µmol/L or greater than 4.5 mg/dL were excluded.

Zometa treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine greater than 265 µmol/L or greater than 3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine greater than 2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance less than 30 mL/min [*see Clinical Pharmacology (12.3)*].

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.2)*].

5.5 Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, including Zometa. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [*see Adverse Reactions (6.2)*].

5.6 Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including Zometa. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. These fractures occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain in the absence of trauma should be suspected of having an atypical fracture and should be evaluated. Discontinuation of Zometa therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

5.7 Patients with Asthma

While not observed in clinical trials with Zometa, there have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

5.8 Hepatic Impairment

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

5.9 Use in Pregnancy

Bisphosphonates, such as Zometa, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy.

Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in pregnant rats, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure resulted in pre- and postimplantation losses, decreases in viable fetuses and fetal skeletal, visceral, and external malformations. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (8.1)*].

5.10 Hypocalcemia

Hypocalcemia has been reported in patients treated with Zometa. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcemia. In some instances, hypocalcemia may be life-threatening. Hypocalcemia must be corrected before initiating Zometa. Adequately supplement patients with calcium and vitamin D.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypercalcemia of Malignancy

The safety of Zometa was studied in 185 patients with hypercalcemia of malignancy (HCM) who received either Zometa 4 mg given as a 5-minute intravenous infusion (n=86) or pamidronate 90 mg given as a 2-hour intravenous infusion (n=103). The population was aged 33-84 years, 60% male and 81% Caucasian, with breast, lung, head and neck, and renal cancer as the most common forms of malignancy. NOTE: pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Renal Toxicity

Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [*see Warnings and Precautions (5) and Dosage and Administration (2)*].

The most frequently observed adverse events were fever, nausea, constipation, anemia, and dyspnea (see Table 4).

Table 4 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or pamidronate 90 mg from the two HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 4: Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)	
Patients Studied				
Total No. of Patients Studied	86	(100)	103	(100)
Total No. of Patients with any AE	81	(94)	95	(92)
Body as a Whole				
Fever	38	(44)	34	(33)
Progression of Cancer	14	(16)	21	(20)
Cardiovascular				
Hypotension	9	(11)	2	(2)
Digestive				
Nausea	25	(29)	28	(27)
Constipation	23	(27)	13	(13)
Diarrhea	15	(17)	17	(17)
Abdominal Pain	14	(16)	13	(13)
Vomiting	12	(14)	17	(17)
Anorexia	8	(9)	14	(14)
Hemic and Lymphatic System				

Anemia	19	(22)	18	(18)
Infections				
Moniliasis	10	(12)	4	(4)
Laboratory Abnormalities				
Hypophosphatemia	11	(13)	2	(2)
Hypokalemia	10	(12)	16	(16)
Hypomagnesemia	9	(11)	5	(5)
Musculoskeletal				
Skeletal Pain	10	(12)	10	(10)
Nervous				
Insomnia	13	(15)	10	(10)
Anxiety	12	(14)	8	(8)
Confusion	11	(13)	13	(13)
Agitation	11	(13)	8	(8)
Respiratory				
Dyspnea	19	(22)	20	(19)
Coughing	10	(12)	12	(12)
Urogenital				
Urinary Tract Infection	12	(14)	15	(15)

The following adverse events from the two controlled multicenter HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug: asthenia, chest pain, leg edema, mucositis, dysphagia, granulocytopenia, thrombocytopenia, pancytopenia, nonspecific infection, hypocalcemia, dehydration, arthralgias, headache and somnolence.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

Acute Phase Reaction

Within three days after Zometa administration, an acute phase reaction has been reported in patients, with symptoms including pyrexia, fatigue, bone pain and/or arthralgias, myalgias, chills, and influenza-like illness; these symptoms usually resolve within a few days. Pyrexia has been the most commonly associated symptom, occurring in 44% of patients.

Mineral and Electrolyte Abnormalities

Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 5 and 6.

Table 5: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

Laboratory Parameter	Grade 3			
	Zometa 4 mg		Pamidronate 90 mg	
	n/N	(%)	n/N	(%)
Serum Creatinine[1]	2/86	(2%)	3/100	(3%)
Hypocalcemia[2]	1/86	(1%)	2/100	(2%)
Hypophosphatemia[3]	36/70	(51%)	27/81	(33%)
Hypomagnesemia[4]	0/71	—	0/84	—

Table 6: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

Laboratory Parameter	Grade 4			
	Zometa 4 mg		Pamidronate 90 mg	
	n/N	(%)	n/N	(%)
Serum Creatinine[1]	0/86	—	1/100	(1%)
Hypocalcemia[2]	0/86	—	0/100	—
Hypophosphatemia[3]	1/70	(1%)	4/81	(5%)
Hypomagnesemia[4]	0/71	—	1/84	(1%)

[1]Grade 3 (greater than 3x Upper Limit of Normal); Grade 4 (greater than 6x Upper Limit of Normal)
[2]Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)
[3]Grade 3 (less than 2 mg/dL); Grade 4 (less than 1 mg/dL)
[4]Grade 3 (less than 0.8 mEq/L); Grade 4 (less than 0.5 mEq/L)

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Ocular Adverse Events

Ocular inflammation such as uveitis and scleritis can occur with bisphosphonate use, including Zometa. No cases of iritis, scleritis or uveitis were reported during these clinical trials. However, cases have been seen in postmarketing use [*see Adverse Reactions (6.2)*].

Multiple Myeloma and Bone Metastases of Solid Tumors

The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2042 patients treated with Zometa 4 mg, pamidronate 90 mg, or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for 2 years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for Zometa 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

Table 7 describes adverse events that were reported by 10% or more of patients. Adverse events are listed regardless of presumed causality to study drug.

Table 7: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)		Placebo n (%)	
Patients Studied						
Total No. of Patients	1031	(100)	556	(100)	455	(100)
Total No. of Patients with any AE	1015	(98)	548	(99)	445	(98)
Blood and Lymphatic						
Anemia	344	(33)	175	(32)	128	(28)
Neutropenia	124	(12)	83	(15)	35	(8)
Thrombocytopenia	102	(10)	53	(10)	20	(4)
Gastrointestinal						
Nausea	476	(46)	266	(48)	171	(38)
Vomiting	333	(32)	183	(33)	122	(27)
Constipation	320	(31)	162	(29)	174	(38)
Diarrhea	249	(24)	162	(29)	83	(18)
Abdominal Pain	143	(14)	81	(15)	48	(11)
Dyspepsia	105	(10)	74	(13)	31	(7)
Stomatitis	86	(8)	65	(12)	14	(3)
Sore Throat	82	(8)	61	(11)	17	(4)
General Disorders and Administration Site						
Fatigue	398	(39)	240	(43)	130	(29)
Pyrexia	328	(32)	172	(31)	89	(20)
Weakness	252	(24)	108	(19)	114	(25)
Edema Lower Limb	215	(21)	126	(23)	84	(19)
Rigors	112	(11)	62	(11)	28	(6)
Infections						
Urinary Tract Infection	124	(12)	50	(9)	41	(9)
Upper Respiratory Tract Infection	101	(10)	82	(15)	30	(7)
Metabolism						
Anorexia	231	(22)	81	(15)	105	(23)
Weight Decreased	164	(16)	50	(9)	61	(13)
Dehydration	145	(14)	60	(11)	59	(13)
Appetite Decreased	130	(13)	48	(9)	45	(10)
Musculoskeletal						
Bone Pain	569	(55)	316	(57)	284	(62)
Myalgia	239	(23)	143	(26)	74	(16)
Arthralgia	216	(21)	131	(24)	73	(16)
Back Pain	156	(15)	106	(19)	40	(9)
Pain in Limb	143	(14)	84	(15)	52	(11)
Neoplasms						
Malignant Neoplasm Aggravated	205	(20)	97	(17)	89	(20)
Nervous						
Headache	191	(19)	149	(27)	50	(11)
Dizziness (excluding vertigo)	180	(18)	91	(16)	58	(13)
Insomnia	166	(16)	111	(20)	73	(16)
Paresthesia	149	(15)	85	(15)	35	(8)
Hypoesthesia	127	(12)	65	(12)	43	(10)

Psychiatric						
Depression	146	(14)	95	(17)	49	(11)
Anxiety	112	(11)	73	(13)	37	(8)
Confusion	74	(7)	39	(7)	47	(10)
Respiratory						
Dyspnea	282	(27)	155	(28)	107	(24)
Cough	224	(22)	129	(23)	65	(14)
Skin						
Alopecia	125	(12)	80	(14)	36	(8)
Dermatitis	114	(11)	74	(13)	38	(8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of Zometa in patients with bone metastases are shown in Tables 8 and 9.

Table 8: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

Laboratory Parameter	Zometa 4 mg		Grade 3 Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	7/529	(1%)	4/268	(2%)	4/241	(2%)
Hypocalcemia[2]	6/973	(<1%)	4/536	(<1%)	0/415	—
Hypophosphatemia[3]	115/973	(12%)	38/537	(7%)	14/415	(3%)
Hypermagnesemia[4]	19/971	(2%)	2/535	(<1%)	8/415	(2%)
Hypomagnesemia[5]	1/971	(<1%)	0/535	—	1/415	(<1%)

[1]Grade 3 (greater than 3x Upper Limit of Normal); Grade 4 (greater than 6x Upper Limit of Normal)
*Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2]Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)
[3]Grade 3 (less than 2 mg/dL); Grade 4 (less than 1 mg/dL)
[4]Grade 3 (greater than 3 mEq/L); Grade 4 (greater than 8 mEq/L)
[5]Grade 3 (less than 0.9 mEq/L); Grade 4 (less than 0.7 mEq/L)

Table 9: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

Laboratory Parameter	Zometa 4 mg		Grade 4 Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine[1*]	2/529	(<1%)	1/268	(<1%)	0/241	—
Hypocalcemia[2]	7/973	(<1%)	3/536	(<1%)	2/415	(<1%)
Hypophosphatemia[3]	5/973	(<1%)	0/537	—	1/415	(<1%)
Hypermagnesemia[4]	0/971	—	0/535	—	2/415	(<1%)
Hypomagnesemia[5]	2/971	(<1%)	1/535	(<1%)	0/415	—

[1]Grade 3 (greater than 3x Upper Limit of Normal); Grade 4 (greater than 6x Upper Limit of Normal)
*Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2]Grade 3 (less than 7 mg/dL); Grade 4 (less than 6 mg/dL)
[3]Grade 3 (less than 2 mg/dL); Grade 4 (less than 1 mg/dL)
[4]Grade 3 (greater than 3 mEq/L); Grade 4 (greater than 8 mEq/L)
[5]Grade 3 (less than 0.9 mEq/L); Grade 4 (less than 0.7 mEq/L)

Among the less frequently occurring adverse events (less than 15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the Zometa 4 mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the Zometa 4 mg group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

Renal Toxicity

In the bone metastases trials, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (less than 1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (greater than or equal to1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials (see Table 10).

Table 10: Percentage of Patients with Treatment Emergent Renal Function Deterioration by Baseline Serum Creatinine*

Patient Population/Baseline Creatinine				
Multiple Myeloma and Breast Cancer	**Zometa 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	27/246	(11%)	23/246	(9%)
Abnormal	2/26	(8%)	2/22	(9%)
Total	29/272	(11%)	25/268	(9%)
Solid Tumors	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9%)	1/20	(5%)
Total	18/165	(11%)	11/163	(7%)
Prostate Cancer	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	12/82	(15%)	8/68	(12%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17%)	10/78	(13%)

*Table includes only patients who were randomized to the trial after a protocol amendment that lengthened the infusion duration of Zometa to 15 minutes.

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of Zometa. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Osteonecrosis of the Jaw

Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients treated with intravenous bisphosphonates including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be a risk factor for ONJ. Data suggests a greater frequency of reports of ONJ in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of the reported cases are in cancer patients following invasive dental procedures, such as tooth extraction. It is therefore prudent to avoid invasive dental procedures as recovery may be prolonged [*see Warnings and Precautions (5)*].

Acute Phase Reaction

Within three days after Zometa administration, an acute phase reaction has been reported, with symptoms including pyrexia, fatigue, bone pain and/or arthralgias, myalgias, chills, and influenza-like illness; these symptoms usually resolve within three days of onset, but resolution could take up to 7 to 14 days. However, some of these symptoms have been reported to persist for a longer duration.

Musculoskeletal Pain

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use [*see Warnings and Precautions (5*)].

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including Zometa [*see Warnings and Precautions (5.6)*].

Ocular Adverse Events

Cases of uveitis, scleritis, episcleritis, conjunctivitis, iritis, and orbital inflammation including orbital edema have been reported during postmarketing use. In some cases, symptoms resolved with topical steroids.

Hypersensitivity Reactions

There have been rare reports of allergic reaction with intravenous zoledronic acid including angioedema and bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

Additional adverse reactions reported in postmarketing use include:

CNS: taste disturbance, hyperesthesia, tremor; ***Special Senses:*** blurred vision; ***Gastrointestinal:*** dry mouth; ***Skin:*** Increased sweating; ***Musculoskeletal:*** muscle cramps; ***Cardiovascular:*** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors); ***Respiratory:*** bronchospasms, interstitial lung disease (ILD) with positive rechallenge; ***Renal:*** hematuria, proteinuria; ***General Disorders and Administration Site:*** weight increase, influenza-like illness (pyrexia, asthenia, fatigue, or malaise) persisting for greater than 30 days; ***Laboratory Abnormalities:*** hyperkalemia, hypernatremia.

7 DRUG INTERACTIONS

In vitro studies indicate that the plasma protein binding of zoledronic acid is low, with the unbound fraction ranging from 60-77%. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in Zometa clinical trials.

7.2 Loop Diuretics

Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia.

7.3 Nephrotoxic Drugs

Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

7.4 Thalidomide

No dose adjustment for Zometa 4 mg is needed when coadministered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zometa 4 mg given as a 15 minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1–14 and 200 mg once daily on days 15–28). Coadministration of thalidomide with Zometa did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [*see Warnings and Precaution (5.9)*]

There are no adequate and well-controlled studies of Zometa in pregnant women. Zometa may cause fetal harm when administered to a pregnant woman. Bisphosphonates, such as Zometa, are incorporated into the bone matrix and are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established. If this drug is used during pregnancy or if the patient becomes pregnant while taking or after taking this drug, the patient should be apprised of the potential hazard to the fetus.

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate-class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and postimplantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose

group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥0.05 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

8.3 Nursing Mothers

It is not known whether zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Zometa, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Zoledronic acid binds to bone long term and may be released over weeks to years.

8.4 Pediatric Use

Zometa is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active-controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with Zometa use in children did not raise any new safety findings beyond those previously seen in adults treated for hypercalcemia of malignancy or bone metastases. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 min. Mean C_{max} and $AUC_{(0\text{-last})}$ was 167 ng/mL and 220 ng•h/mL, respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

10 OVERDOSAGE

Clinical experience with acute overdosage of Zometa is limited. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

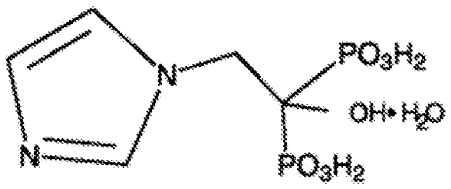
In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose, the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100 U/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy [*see Dosage and Administration (2.4)*].

11 DESCRIPTION

Zometa contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is:



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1 g/mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa is available in 100-mL bottles as a sterile liquid ready-to-use solution for intravenous infusion and in 5-mL vials as a sterile liquid concentrate solution for intravenous infusion.

- Each 100 mL ready-to-use bottle contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 5100 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.
- Each 5 mL concentrate vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.

Inactive Ingredients: mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

12.2 Pharmacodynamics

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous cell malignancies of the lung or head and neck or in genitourinary tumors such as renal cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation [*see Dosage and Administration (2)*].

12.3 Pharmacokinetics

Pharmacokinetic data in patients with hypercalcemia are not available.

Distribution

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8, or 16 mg Zometa were given to 64 patients with cancer and bone metastases. The postinfusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end of infusion to less than 1% of C_{max} 24 hours postinfusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 postinfusion, and a terminal

elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0\text{-}24h}$) of zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0\text{-}24h}$ ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5000 ng/mL. *In vitro,* the plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases, on average (± SD) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post-Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4-mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL versus 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL versus 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pediatrics

Zometa is not indicated for use in children [*see Pediatric Use (8.4)*].

Geriatrics

The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

Race

Population pharmacokinetic analyses did not indicate any differences in pharmacokinetics among Japanese and North American (Caucasian and African American) patients with cancer and bone metastases.

Hepatic Insufficiency

No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

Renal Insufficiency

The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula:

$$CrCl = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa, CL (L/h)=$6.5(CL_{cr}/90)^{0.4}$. These formulae can be used to predict the Zometa AUC in patients, where CL=Dose/$AUC_{0-\infty}$. The average AUC_{0-24} in patients with normal renal function was 0.42 mg•h/L and the calculated $AUC_{0-\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mg•h/L following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed [*see Warnings and Precautions (5.2)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses ≤0.2 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in preimplantation losses and a decrease in the number of implantations and live fetuses.

14 CLINICAL STUDIES

14.1 Hypercalcemia of Malignancy

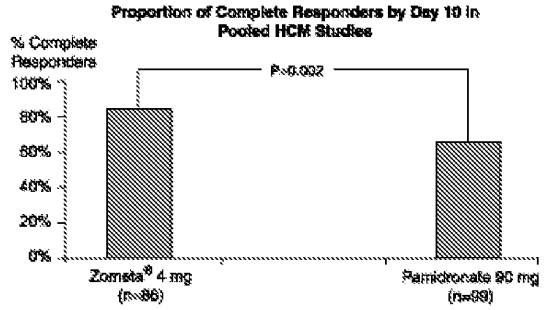
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [*see Warnings and Precautions (5.1 and 5.2) and Dosage and Administration (2.4)*]. The treatment groups in the clinical studies

were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were black, and 4% were of other races. 60% of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of greater than or equal to 12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to less than or equal to 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a preplanned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002) (see Figure 1). In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value less than 11.6 mg/dL (less than 2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 11.

Table 11: Secondary Efficacy Variables in Pooled HCM Studies

	Zometa 4 mg		Pamidronate 90 mg	
Complete Response	**N**	**Response Rate**	**N**	**Response Rate**
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
Duration of Response	**N**	**Median Duration (Days)**	**N**	**Median Duration (Days)**
Time to Relapse	86	30*	99	17
Duration of Complete Response	76	32	69	18

*P less than 0.05 versus pamidronate 90 mg.

14.2 Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 12 describes an overview of the efficacy population in three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These trials included a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer, and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, including NSCLC, renal cell cancer, small cell lung cancer, colorectal cancer, bladder cancer, GI/genitourinary cancer, head and neck cancer, and others. These trials were comprised of a core phase and an extension phase. In the solid tumor, breast cancer and multiple myeloma trials, only the core phase was evaluated for efficacy as a high percentage of patients did not choose to participate in the extension phase. In the prostate cancer trials, both the core and extension phases were evaluated for efficacy showing the Zometa effect during the first 15 months was maintained without decrement or improvement for another 9 months. The design of these clinical trials does not permit assessment of whether more than one-year administration of Zometa is beneficial. The optimal duration of Zometa administration is not known.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8 mg Zometa treatment arm were switched to 4 mg due to toxicity. Patients who were randomized to the Zometa 8 mg group are not included in these analyses.

Table 12: Overview of Efficacy Population for Phase III Studies

Patient Population	No. of Patients	Zometa Dose	Control	Median Duration (Planned Duration) Zometa 4 mg
Multiple myeloma or metastatic breast cancer	1,648	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	12.0 months (13 months)
Metastatic prostate cancer	643	4 and 8* mg Q3 weeks	Placebo	10.5 months (15 months)
Metastatic solid tumor other than breast or prostate cancer	773	4 and 8* mg Q3 weeks	Placebo	3.8 months (9 months)

*Patients who were randomized to the 8 mg Zometa group are not included in any of the analyses in this package insert.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study and time to the first SRE. Results for the two Zometa placebo-controlled studies are given in Table 13.

Table 13: Zometa Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	**Study Arm & Patient Number**	**Proportion**	**Difference[2] & 95% CI**	**P-value**	**Median (Days)**	**Hazard Ratio[3] & 95% CI**	**P-value**
Prostate Cancer	Zometa 4 mg (n=214)	33%	-11% (-20%, -1%)	0.02	Not Reached	0.67 (0.49, 0.91)	0.011
	Placebo (n=208)	44%			321		
Solid Tumors	Zometa 4 mg (n=257)	38%	-7% (-15%, 2%)	0.13	230	0.73 (0.55, 0.96)	0.023
	Placebo (n=250)	44%			163		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus placebo.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus placebo.

In the breast cancer and myeloma trial, efficacy was determined by a noninferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1,128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI = 7.3%, 18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 14.

Table 14: Zometa Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer

		I. Analysis of Proportion of Patients with a SRE[1]			II. Analysis of Time to the First SRE		
Study	**Study Arm & Patient Number**	**Proportion**	**Difference[2] & 95% CI**	**P-value**	**Median (Days)**	**Hazard Ratio[3] & 95% CI**	**P-value**
Multiple Myeloma & Breast Cancer	Zometa 4 mg (n=561)	44%	-2% (-7.9%, 3.7%)	0.46	373	0.92 (0.77, 1.09)	0.32
	Pamidronate (n=555)	46%			363		

[1]SRE=Skeletal-Related Event
[2]Difference for the proportion of patients with a SRE of Zometa 4 mg versus pamidronate 90 mg.
[3]Hazard ratio for the first occurrence of a SRE of Zometa 4 mg versus pamidronate 90 mg.

16 HOW SUPPLIED/STORAGE AND HANDLING

4 mg/100 mL single-use ready-to-use bottle

Carton of 1 bottle.....NDC 0078-0590-61

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

4 mg/5 mL single-use vial of concentrate

Carton of 1 vial.....NDC 0078-0387-25

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

- Patients should be instructed to tell their doctor if they have kidney problems before being given Zometa.
- Patients should be informed of the importance of getting their blood tests (serum creatinine) during the course of their Zometa therapy.
- Zometa should not be given if the patient is pregnant or plans to become pregnant, or if she is breastfeeding.
- Patients should be advised to have a dental examination prior to treatment with Zometa and should avoid invasive dental procedures during treatment.
- Patients should be informed of the importance of good dental hygiene and routine dental care.
- Patients with multiple myeloma and bone metastasis of solid tumors should be advised to take an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.
- Patients should be advised to report any thigh, hip, or groin pain. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.
- Patients should be aware of the most common side effects including: anemia, nausea, vomiting, constipation, diarrhea, fatigue, fever, weakness, lower limb edema, anorexia, decreased weight, bone pain, myalgia, arthralgia, back pain, malignant neoplasm aggravated, headache, dizziness, insomnia, paresthesia, dyspnea, cough, and abdominal pain.
- There have been reports of bronchoconstriction in aspirin-sensitive patients receiving bisphosphonates, including zoledronic acid. Before being given zoledronic acid, patients should tell their doctor if they are aspirin-sensitive.

Manufactured by
Novartis Pharma Stein AG
Stein, Switzerland for
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2013-75
September 2013

Exhibit 3

STUDY REPORT

Title: **Effect of Orally Administered Zoledronic Acid in the Rat Tibia Fracture Model of Complex Regional Pain Syndrome**

Study 1 and Study 2

Study Sponsor: **Axsome Therapeutics, Inc.**
New York, NY, USA

CONTENTS

1 EXECUTIVE SUMMARY

Background. Tibia fracture in rats evokes chronic hindpaw pain, edema, warmth, and regional osteopenia, a syndrome resembling complex regional pain syndrome (CRPS). The effect of orally administered zoledronic acid was tested in this model of CRPS.

Methods. Two studies were performed. In both studies, the distal tibia was fractured and the hindlimb casted for 4 weeks followed by cast removal. In study 1, the rats were administered vehicle (distilled water) or zoledronic acid by oral gavage starting the day after fracture and continuing for 4 weeks, after which time the cast was removed and multiple assessments were performed in the hindpaw. In study 2, dosing was started after cast removal and continued for 3 weeks thereafter. Bilateral hindpaw nociceptive thresholds, thickness, and temperature were determined.

Results. Fracture and casting significantly reduced nociceptive threshold and weight bearing, and increased paw thickness and temperature in the ipsilateral fracture limb as compared to the contralateral normal limb. In study 1, oral zoledronic acid treatment reversed fracture induced hyperalgesia by 77% as compared to vehicle control, and significantly improved weight bearing in the fracture limb (86% of normal for zoledronic acid versus 55% of normal for vehicle). Zoledronic acid treatment reduced fracture induced hindpaw edema by 60% as compared to vehicle. There was a small zoledronic acid effect on hindpaw temperature. In study 2, oral zoledronic acid significantly reversed hyperalgesia and restored weight bearing as compared to vehicle treatment. Zoledronic acid administration resulted in a complete reversal of hyperalgesia after 3 weeks of treatment. Hindpaw warmth and edema resolved in both treatment groups with no significant difference noted between the two groups for these parameters.

Conclusion. Oral administration of zoledronate reversed pain, restored weight bearing, and prevented edema as compared to vehicle in the rat tibia fracture model of CRPS.

2 OBJECTIVE

The objective of the study was to examine the effects of oral administration of zoledronate on hindlimb nociception, edema and temperature in the rat tibia fracture of model of CRPS.

3 OVERVIEW OF ANIMAL MODEL

The rat tibia fracture model of CRPS has been shown to replicate the inciting trauma, natural history and complex multi-organ pathologic changes observed in CRPS patients. Distal tibia fracture in rats followed by 4-week cast immobilization results in chronic unilateral hindlimb pain, edema, warmth, postural unweighting, periarticular osteoporosis, facilitated spontaneous protein extravasation, and increased expression of pro-inflammatory cytokines (Guo et al. 2004, Guo et al. 2006, Kingery 2010, Wei et al. 2012). These post-fracture changes closely resemble the clinical presentation of patients with acute CRPS.

4 MATERIALS AND METHODS

Surgery

Tibia fracture was performed under under 2-4% isoflurane to maintain surgical anesthesia as previously described (Guo et al. 2004). The right distal tibia was fractured using pliers with an adjustable stop that had been modified with a three-point jaw. The hind limb was then casted so the hip, knee, and ankle were flexed. The cast extended from the metatarsals of the hindpaw up to a spica formed around the abdomen. The rats were given subcutaneous saline and buprenorphine immediately after the procedure and on the first day after fracture for postoperative hydration and analgesia. At 4 weeks, the rats were anesthetized with isoflurane and the cast removed with a vibrating cast saw. All rats used in this study had union at the fracture site after 4 weeks of cast immobilization.

Drug

Zoledronic acid, in the form of the disodium salt, was dissolved in distilled water for oral administration by gavage. A gavage volume of 80 µl/100g body weight was used.

Hindpaw nociception

To measure mechanical hyperalgesia in the rats, an up-down von Frey testing paradigm was used as previously described (Kingery et al. 2003, Guo et al. 2004, Guo et al. 2006). Von Frey hairs ranging in thickness from 0.41 g to 15.14 g were applied against the hindpaw plantar skin at approximately midsole. The fiber was pushed until it slightly bowed and then it was jiggled in that position for 6 seconds. Hindpaw withdrawal from the fiber was considered a positive response. The initial fiber presentation was 2.1 g and the fibers were presented according to the up-down method of Dixon to generate six responses in the immediate vicinity of the 50% threshold.

To measure hindpaw unweighting, a postural effect of hindlimb nociception, an incapacitance device was used. The rats were manually held in a vertical position over the apparatus with the hindpaws resting on separate metal scale plates and the entire weight of the rat was supported on the hindpaws. The duration of each measurement was 6 seconds and 10 consecutive measurements were taken at 60-second intervals. Eight readings (excluding the highest and lowest ones) were averaged to calculate the bilateral hindpaw weight-bearing values.

Hindpaw thickness

A laser sensor technique was used to determine the dorsal-ventral thickness of the hindpaw, as previously described (Guo et al. 2006). For laser measurements, each rat was briefly anesthetized with isoflurane and its hindpaw was placed on a table top below the laser. Using optical triangulation, a laser with a distance measuring sensor was used to determine the distance to the table top and to the top of the hindpaw, and the difference was used to calculate the dorsal-ventral paw thickness. The

measurement sensor device used in these experiments has a measurement range of 200 mm with a 0.01 mm resolution.

Hindpaw temperature

The room temperature was maintained at 23° C and humidity ranged between 25 and 45%. The temperature of the hindpaw was measured using a fine wire thermocouple applied to the paw skin, as previously described (Kingery et al. 2003, Guo et al. 2004, Guo et al. 2006). Six sites were tested on each hindpaw and the measurements averaged for the mean temperature.

Study 1 design

A total of 20 animals were used in the study. After baseline tests, the rats underwent a right distal tibia fracture with casting.

Animals were orally administered either vehicle (n=12), or zoledronic acid (n=8) in a dosage of 18 mg/m^2/day (3 mg/kg/day)for 28 days, starting the day after fracture and casting. Drug was dissolved in distilled water and administered by gavage. Animals were fasted for 4 hours before and 2 hours after dosing.

The casts were removed on the 28th day after fracture, and on the following day, bilateral testing of hindpaw mechanical nociceptive withdrawal thresholds, weight bearing, thickness, and temperature was performed.

Hindpaw temperature and thickness data were analyzed as the difference between the fracture (right) side and the contralateral normal (left) side. Weight bearing data were analyzed as the ratio between right and left hindpaw weight bearing values ((2R/(R+L)) ×100%).

Study 2 design

A total of 12 animals were used in the study. After baseline tests, the rats underwent a right distal tibia fracture with casting.

The casts were removed on the 28th day after fracture. Starting on day 29 after fracture, animals were orally administered either vehicle (n=6), or zoledronic acid (n=6) for 3 weeks. Drug treated animals received zoledronic acid at a dose of 126 mg/m^2 (21 mg/kg) on the first day (day 29), followed by 18 mg/m^2/day (3 mg/kg/day) thereafter. Drug was dissolved in distilled water and administered by gavage. Animals were fasted for 4 hours before and 2 hours after dosing.

Bilateral testing of hindpaw mechanical nociceptive withdrawal thresholds, weight bearing, thickness, and temperature was performed at baseline, on day 29 after fracture, and then weekly for three weeks.

Hindpaw nociceptive threshold, temperature and thickness data were analyzed as the difference between the fracture (right) side and the contralateral normal (left) side. Weight bearing data were analyzed as the ratio between right and left hindpaw weight bearing values ((2R/(R+L)) ×100%).

5 STUDY 1 RESULTS

Study 1 Results

In Study 1, oral administration of zoledronic acid significantly reversed pain, restored weight bearing, and prevented edema as compared to vehicle control in the rat tibia fracture model of CRPS. As shown in Figure 2, zoledronic acid treatment reduced hyperalgesia by 77% and edema by 60% as compared to vehicle treatment. Zoledronic acid treatment also improved weight bearing on the affected limb by 56% as compared to vehicle control.

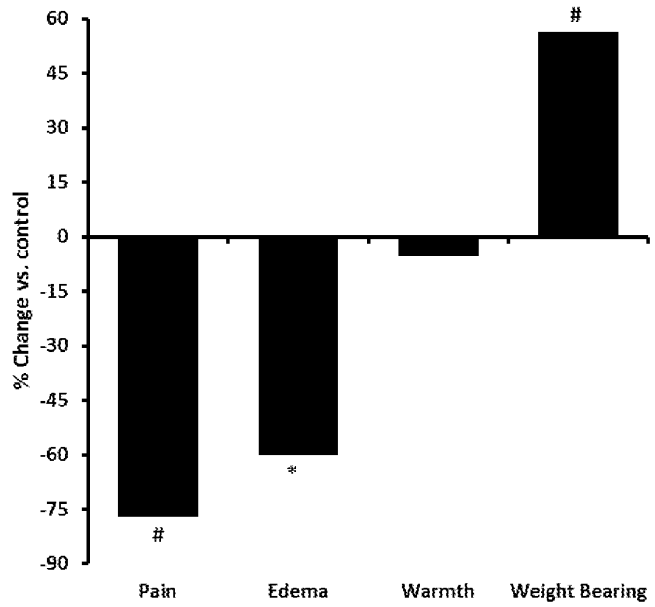


Figure 2. Summary of effects of zoledronic acid in the rat CRPS model. CRPS was induced by distal tibia fracture followed by 4-week cast immobilization. Animals were treated with orally administered zoledronic acid 18 mg/m^2/day (3 mg/kg/day)or vehicle control (distilled water, n=12). #p<0.001 versus control, *p=0.03 versus control.

The results of Study 1 are presented below.

Effect on nociception

Nociception was assessed by measuring mechanical hyperalgesia and reduction in weight bearing, a postural effect of hindlimb pain.

Von Frey nociceptive thresholds for the right (fracture) hindpaw were reduced by 72% versus the contralateral (normal) hindpaw in vehicle treated animals ($p<0.001$). Zoledronic acid treatment reversed fracture induced hyperalgesia by 77% as compared to vehicle treatment ($p<0.001$), as shown in Figure 3.

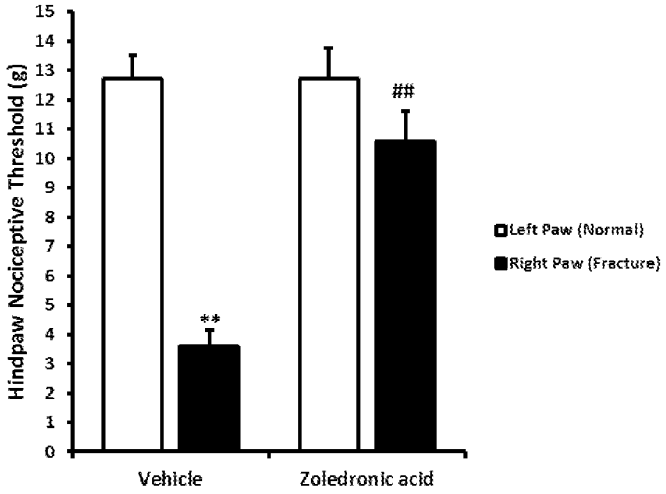


Figure 3. Effect of zoledronic acid on nociception (pain thresholds) in the rat CRPS model. Hindpaw mechanical hyperalgesia was measured using the up-down von Frey fiber paradigm 4 weeks post injury. Animals were treated with vehicle (distilled water, n=12) or zoledronic acid 18 mg/m^2/day (3 mg/kg/day) (n=8). **$p<0.001$ versus contralateral paw, ##$p<0.001$ versus vehicle control.

Reduction in weight bearing (unweighting) was greater in the vehicle treated group than in the zoledronic acid treated group, as shown in Figure 4. Weight bearing on the fracture hindlimb was reduced to 55% of normal in the vehicle treated group. Zoledronic acid treatment significantly restored hindlimb weight bearing to 86% of normal ($p<0.001$ versus vehicle).

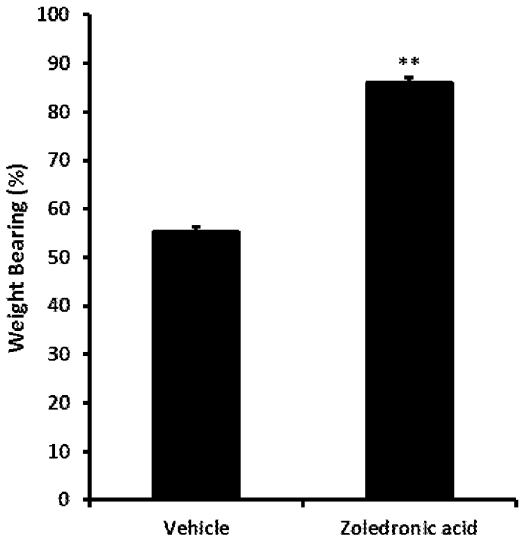


Figure 4. Effect of zoledronic acid on nociception (weight bearing) in the rat CRPS model. Weight bearing on the fracture hindlimb was measured 4 weeks post injury. Animals were treated with vehicle (distilled water, n=12) or zoledronic acid 18 mg/m^2/day (3 mg/kg/day) (n=8). Measurements represent weight bearing on the fracture hindlimb as a ratio to 50% of the total bilateral hindlimb loading, thus a percentage lower than 100% represents hindlimb unweighting. **p<0.001 versus vehicle control.

Effect on edema

Edema was assessed by measuring the changes in paw thickness of the affected limb relative to the contralateral normal paw.

Fracture and casting induced edema as evidenced by a significant increase in hindpaw thickness in the right (fracture) limb compared to the contralateral normal limb. Hindpaw edema was significantly greater in the vehicle treated group than in the zoledronic acid treated group (p=0.03), as shown in Figure 5. Zoledronic acid treatment reduced hindpaw edema by 60% versus vehicle treatment.

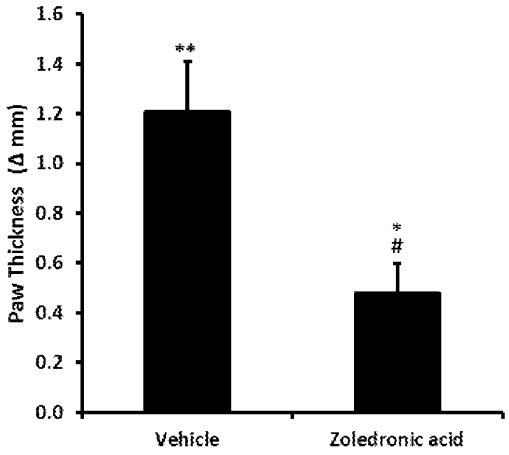


Figure 5. Effect of zoledronic acid on edema in the rat CRPS model. Edema in the fracture hindlimb was measured 4 weeks post injury. Animals were treated with vehicle (distilled water, n=12) or zoledronic acid 18 mg/m^2/day (3 mg/kg/day) (n=8). Data are presented as the difference between the fracture side and the contralateral limb, thus a positive value represents an increase in paw thickness. *p<0.01 and **p<0.001 versus contralateral limb, #p=0.03 versus vehicle control.

Effect on hindpaw warmth

Fracture and casting induced hindpaw warmth as evidenced by a significant increase in temperature in the right (fracture) limb compared to the contralateral normal limb in both cohorts, as shown in Figure 6. There was no significant zoledronic acid effect on the change in hindpaw temperature.

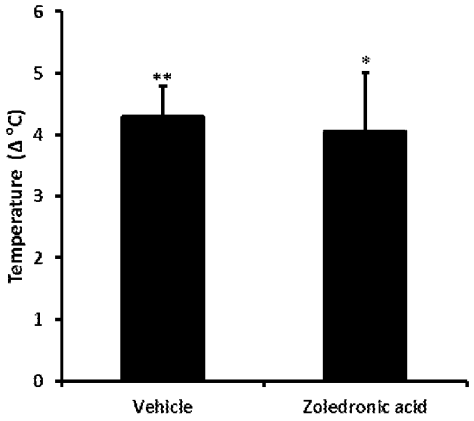


Figure 6. Effect of zoledronic acid on warmth in the rat CRPS model. Temperature in the fracture hindlimb was measured 4 weeks post injury. Animals were treated with vehicle (distilled water, n=12) or zoledronic acid 18 mg/m^2/day (3 mg/kg/day) (n=8). Data are presented as the difference between the fracture side and the contralateral limb, thus a positive value represents an increase in paw temperature. *p<0.01 and **p<0.001 versus contralateral limb.

6 STUDY 2 RESULTS

In Study 2, oral administration of zoledronic acid significantly reversed pain and restored weight bearing as compared to vehicle treatment in the rat tibia fracture model of CRPS. A complete reversal of hyperalgesia was seen with zoledronic acid administration after 3 weeks of treatment. The effects on weight bearing were observed as early as 1 week after the start of treatment.

The results of Study 2 are presented below.

Effect on nociception

Nociception was assessed by measuring mechanical hyperalgesia and reduction in weight bearing, a postural effect of hindlimb pain.

Hyperalgesia developed 4 weeks after fracture and casting as reflected by the decrease in pain thresholds (Figure 7). Treatment with zoledronic acid or vehicle was then started. Zoledronic acid administration resulted in a 65% reversal of fracture-induced hyperalgesia 2 weeks after treatment start ($p<0.05$ versus vehicle). A complete reversal of hyperalgesia was observed in the zoledronic acid group 3 weeks after the start of treatment ($p<0.05$ versus vehicle).

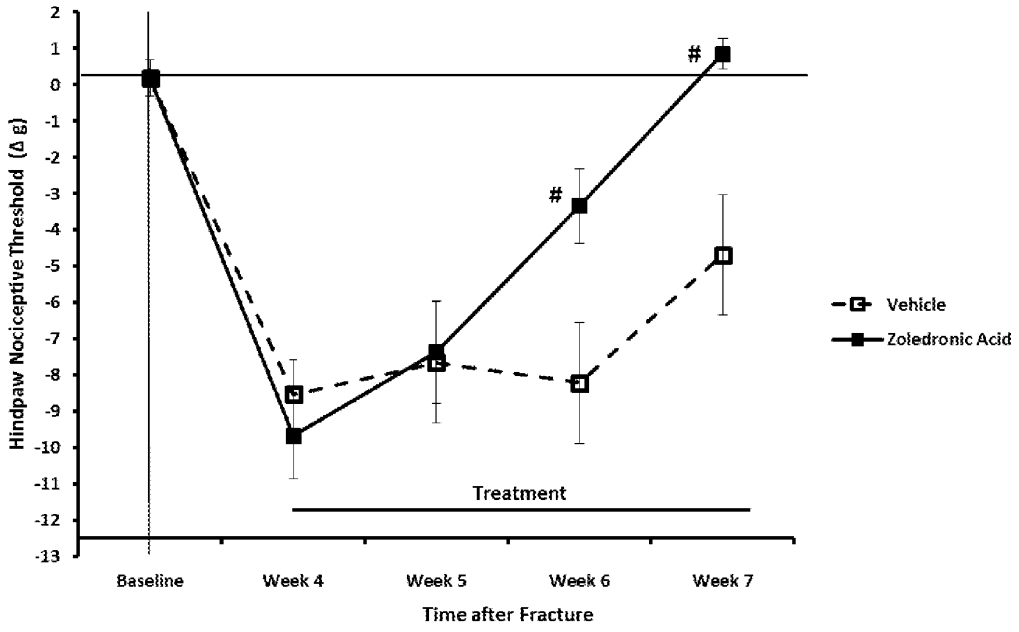


Figure 7. Effect of zoledronic acid on nociception (pain thresholds) in the rat CRPS model. Hindpaw mechanical hyperalgesia was measured using the up-down von Frey fiber paradigm. Animals were treated with vehicle (distilled water, n=6) or zoledronic acid (126 mg/m^2 first day, 18 mg/m^2/day thereafter, n=6) starting 4 weeks after fracture. Data are presented as the difference between the fracture side and the contralateral limb, thus a negative value represents a reduction in pain threshold. #$p<0.05$ versus vehicle control.

Weight bearing was significantly reduced in all animals 4 weeks after fracture and casting, and improved thereafter (Figure 8). Administration of zoledronic acid resulted in greater weight bearing than vehicle at every time point the start of treatment ($p<0.01$ versus vehicle).

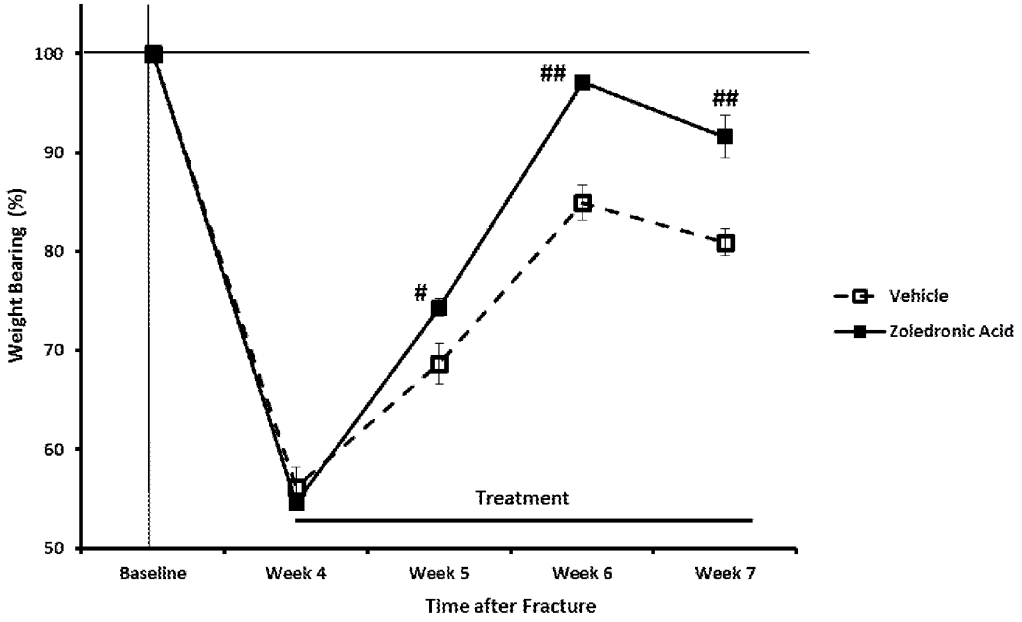


Figure 8. Effect of zoledronic acid on nociception (weight bearing) in the rat CRPS model. Weight bearing on the fracture hindlimb was measured. Animals were treated with vehicle (distilled water, n=6) or zoledronic acid (126 mg/m^2 first day, 18 mg/m^2/day thereafter, n=6) starting 4 weeks after fracture. Measurements represent weight bearing on the fracture hindlimb as a ratio to 50% of the total bilateral hindlimb loading, thus a percentage lower than 100% represents hindlimb unweighting. #$p<0.05$, ##$p<0.01$ versus vehicle control.

Effect on hindpaw edema and warmth

Fracture and casting induced an increase in hindpaw temperature and edema in the fracture limb. These parameters resolved over time. Resolution of edema and warmth in the zoledronic acid and vehicle groups were similar (Figure 9).

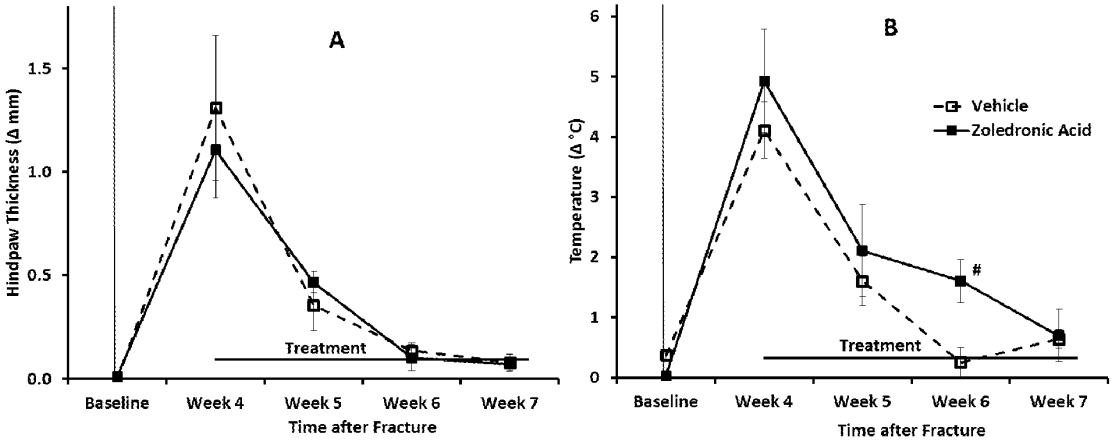


Figure 9. Effect of zoledronic acid on edema and warmth in the rat CRPS model. Edema (A) and warmth (B) in the fracture hindlimb was measured. Edema and warmth were assessed by measuring changes in paw thickness and temperature, respectively. Animals were treated with vehicle (distilled water, n=6) or zoledronic acid (126 mg/m^2 first day, 18 mg/m^2/day thereafter, n=6) starting 4 weeks after fracture. Data are presented as the difference between the fracture side and the contralateral limb, thus a positive value represents an increase in paw thickness (A) or temperature (B). #p<0.05 versus vehicle control.

7 REFERENCES

Guo TZ, Offley SC, Boyd EA, Jacobs CR, Kingery WS. Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. Pain 2004; 108: 95–107.

Guo TZ, Wei T, Kingery WS. Glucocorticoid inhibition of vascular abnormalities in a tibia fracture rat model of complex regional pain syndrome type I. Pain 2006; 121: 158–167.

Kingery WS, Davies MF, Clark JD. A substance P receptor (NK1) antagonist can reverse vascular and nociceptive abnormalities in a rat model of complex regional pain syndrome type II. Pain 2003; 104: 75–84.

Kingery WS. Role of neuropeptide, cytokine, and growth factor signaling in complex regional pain syndrome. Pain Med 2010; 11: 1239-1250.

Wei T, Guo TZ, Li WW, Hou S, Kingery WS, Clark JD. Keratinocyte expression of inflammatory mediators plays a crucial role in substance P-induced acute and chronic pain. J Neuroinflammation 2012; 9: 181.

Exhibit 4

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 December 2012
EMA/COMP/595031/2012 [redacted]
Committee for Orphan Medicinal Products

EMA/COMP summary report

On an application for orphan medicinal product designation

Zoledronic acid
Treatment of complex regional pain syndrome
EMA/OD/125/12
Sponsor: Axsome Therapeutics Limited

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[redacted]

pharmacological action by binding to the bone matrix, to osteoblasts and to osteoclasts. They directly inhibit osteoclast activity, formation and recruitment, and can cause osteoclast apoptosis. Nitrogren containing bisphosphonates, such as zoledronic acid, also inhibit the mevalonate pathway in the osteoclast thereby interrupting normal osteoclast function [12].

[redacted] Plausibility of the orphan condition; rationale for use of the medicinal product

The scientific rationale for the use of zoledronic acid in the treatment of CRPS is as follows:

a) A key feature of CRPS is patchy osteoporosis and bone marrow edema which are the result of osteoclast hyperactivity [1-4]. Zoledronic acid is a potent inhibitor of bone resorption and osteoclast activity [12-13, 31-32].

b) Pain is the primary symptom of CRPS [1-4]. Zoledronic acid has been shown to relieve pain in other disease settings both clinically as well as in animal models [14-19].

c) Zoledronic acid has been used to successfully treat CRPS patients in a controlled study and case report [21, 22].

CRPS is associated with localized bone resorption and bone marrow edema in the affected limb which are the result of osteoclastic hyperactivity. Consequently, investigators have theorized that bisphosphonates might be beneficial in the treatment of CRPS since these compounds inhibit bone resorption and have analgesic efficacy [20]. As will be discussed below, initial clinical reports are supportive of the potential efficacy of zoledronic acid in the treatment of CRPS [21, 22].

The analgesic efficacy of zoledronic acid has been demonstrated in patients with bone pain associated with both malignant and non-malignant disorders [14-19]. Animal studies, as reviewed by Yanow et al. [19] have demonstrated the antinociceptive effects of zoledronic acid and other bisphosphonates in non-bone-related pain. These clinical and preclinical observations support the potential analgesic activity of zoledronic acid in CRPS.

The mechanism by which bisphosphonates provide pain relief in CRPS is unknown but may involve inhibition of osteoclast activity as well as inhibition of prostaglandin E2, proteolytic enzymes, and lactic acid [7, 19]. Activated osteoclasts produce an acidic microenvironment in bone thereby activating acid-sensing nociceptors, and release nerve growth factor (NGF) which is also thought to contribute to hyperalgesia [19].

Clinical Experience with Zoledronic Acid in the Treatment of CRPS

Zoledronic acid has been successfully used to treat patients with CRPS as reported in a controlled study and case report [21, 22]. These reports are summarized in Table 4.

Zaspel et al. tested zoledronic acid in a prospective active control study of 24 patients with CRPS [21]. Patients in the treatment group received a 5 mg single infusion of zoledronic acid while those in the control group received methylprednisolone. Patients were followed for six months, and pain was measured using the VAS (visual analog pain scale). The zoledronic acid group experienced a 70% reduction in pain, an effect that was maintained over the entire six-month observation period. Furthermore this effect was statistically significant versus control ($p<0.001$). The control group, in contrast, showed only transient pain relief through month 1 versus baseline. No reduction in pain was seen in the control at other time points.

[redacted] Trial and Case Report Investigating the Use of Zoledronic Acid for Complex Regional Pain Syndrome

Study	Dosage, administration	Outcomes	Patient(s) and follow-up duration	Results
Zaspel et al., 2007 [21]	5mg IV single infusion	VAS, dystrophic symptoms, edema, sudomotor activity	24 patients (10 zoledronic acid, 14 methylprednisolone), 6 months	70% pain reduction with zoledronic acid lasting 6 months, statist. signif. versus control. Tendency towards improvement of dystrophic symptoms.
de Castro et al., 2011 [22]	5mg IV single infusion	Pain, edema	31-year old patient with CRPS-I for 16 years refractory to multiple treatments, 6 months	Total regression of pain and edema with no recurrence for 6 months.

IV, intravenous; VAS, Visual Analog Pain Scale

de Castro et al. reported the successful use of zoledronic acid in a 31-year old patient who had suffered from CRPS for 16 years [22]. This patient presented with severe pain and had failed multiple therapeutic interventions including steroids, NSAIDs, amitriptyline, other antidepressants, carbamezapine, other anti-convulsants, sympathetic nerve blocks with lidocaine and bupivacaine, opioids, neuromuscular blockers, dexmedetomidine, magnesium sulfate and chlorpromazine over a two-year period. Given the lack of response to these measures, the patient was treated with a 5 mg infusion of zoledronic acid. The result was total regression of pain and edema lasting six months.

Corroborating the potential for zoledronic acid in this disease setting are the positive results from several randomized controlled studies using other bisphosphonates to treat CRPS [23-25]. These reports are summarized in Table 5.

[redacted] Trials Investigating the Use of other Bisphosphonates for Complex Regional Pain Syndrome

Study	Drug studied	Type of study	Patients and follow-up duration	Results
Manicourt et al., 2004 [23]	Alendronate 40mg oral daily for 8 weeks	RCT, double-blind, placebo-controlled	39 patients (19 drug, 20 placebo), 12 weeks	Statist. signif. improvement in spontaneous pain, pressure tolerance, and joint mobility.
Robinson et al., 2004 [24]	Pamidronate 60mg IV, one time	RCT, double-blind, placebo-controlled	27 (14 drug, 13 placebo), 3 months	Statist. signif. improvement in pain score, global assessment of disease severity score, and physical function.
Varenna et al., 2000 [25]	Clodronate 300mg IV for 10 days	RCT, double-blind, placebo-controlled	32 patients (15 drug, 17 placebo), 40 days	Statist. signif. improvement in pain score and clinical global

Study	Drug studied	Type of study	Patients and follow-up duration	Results
				assessment.

Of all the bisphosphonate compounds available clinically, zoledronic acid has been shown to be the most potent inhibitor of osteoclast-mediated bone resorption [12]. For example, by some in vitro measures it is approximately 20 times as potent as alendronate (Fosamax) and over 60 times as potent as pamidronate (Aredia) [12]. This increased potency has translated into more rapid, more complete and more sustained clinically therapeutic effects than other bisphosphonates [13]. Therefore zoledronic acid may potentially provide greater efficacy, faster onset of action, and less frequent dosing than other bisphosphonates in the treatment of CRPS.

As a whole, we believe the signals of efficacy from these reports support the development of this potentially promising therapy for a debilitating, difficult-to-treat condition with few safe and effective treatment options, and for which there is currently no medicinal product authorized in the E.U.

Comment [redacted]

Zoledronic acid (zoledronate) belongs to the class of bisphosphonates; molecules used for the treatment of osteoporosis and other osteoclastic conditions based on their inhibition of osteoclastic bone resorption. The sponsor is applying for orphan designation of zoledronic acid for oral use, and (as described in section E1) is developing zoledronic acid as disodium salt. The sponsor states that zoledronate is currently available as an intravenous formulation only. The company is in the process of completing the initial manufacture of the sodium salt.

The sponsor proposes the product for the treatment of CRPS base on the potentialto treat some of the clinical features of CRPS, namely patchy osteoporosis and bone marrow oedema. In addition, the sponsor claims that zoledronic acid has been able to reduce pain associated to different diseases, and the reduction of pain could be extrapolated to the proposed condition.

The sponsor provides only 2 citations directly related to the use of intravenous zoledronic acid in CRPS. The first of these references (Zaspel et al, 2007), is a meeting abstract that apparently has not been subsequently published as a full paper. As reported in this abstract, 24 patients with CRPS (type I, early stage) received treatment either with zoledronic acid (10 patients) or methylprednisolone (14 patients). The sponsor reports that zoledronic acid seemed to induce reduction of pain as compared to methylprednisolone. However the authors stated also that *"over the entire period, compared to the bisphosphonate, cortisone showed a significant ($p < 0.001$) impact on the improvement of dystrophic symptoms such as oedema and sudomotor activity"*. From this study it seems that the product would be active on pain but not necessarily on oedema. In addition, being the the study reported as a short communication and not published in a peer-reviewed journal, it lacks relevant information that would be necessary for an in-depth assessment of the results

The other reference is a single case report published in Revista Dor (Brasil), which is a regional peer-reviewed pain journal. The description of the case is lacking details that would be useful for the evaluation of the efficacy of the product, e.g. there is no mentioning of any initiating noxious event, which is a typical criterion for CRPS.

Even though there are more relevant references to published studies on other bisphosphonates in CRPS, the sponsor provides no specific data or discussion as to whether such data can be extrapolated to their product.

The COMP questioned the scientific rationale of using bisphosphonates, and in particular the proposed product, in CPRS, and on the available clinical data. It is also not clear from the description of the condition provided by the sponsor in section A1, how relevant and frequent bone reabsorption (the main target of treatment with bisphosphonate) is in CRPS, and this might need better clarification in order to justify the use of the proposed product in this condition.

The Committee also asked the sponsor to provide more specific information on the development of the product, which apparently is at a very early stage. Since zoledronic acid is known to be poorly absorbed via the oral route, the sponsor was also asked to discuss the expected low bioavailability using the oral formulation (see List of Questions).

Redacted

[redacted] COMP discussion and request for a list of issues

On the basis of the assessment of the application as reflected in the different parts of this summary report, and according to the discussion held at the COMP meeting, the COMP requests the sponsor to answer the following list of issues.

Written responses to the outstanding issues should be addressed to the EMA Co-ordinator by 20 November 2012. The sponsor will be invited to an oral explanation before the COMP at their meeting on 5-6 December 2012.

[redacted] Medical plausibility

To establish correctly if there exists a scientific rationale for the development of zoledronic acid for the treatment of CRPS, the sponsor is invited to further elaborate on:

-the extent and relevance of bone reabsorption and other osteoclastic mechanisms in CRPS;

- the methodology, the scientific validity and relevance of the two cited references on zoledronic acid in CRPS, as the only study on 24 CRPS patients has been published as an abstract (Zaspel et al), and never as a full article;

- the characteristics of the patients that responded to treatment with zolendronic acid in the abstract from Zaspel et al, and in particular on whether the responders had local or generalized osteoporosis;

- the extrapolation of data from conditions other than CRPS in relation to the proposed action of the product in reducing pain;

- the possible extrapolation to zolendronic acid of data from other bisphosphonates tested in CRPS.

In addition the sponsor is invited to comment on the expected low bioavailability using the oral route of administration, and how this would influence the expected action of the product on pain and on bone reabsorption in CRPS.

[redacted] Prevalence

In order to correctly establish the prevalence of CRPS in the Eu the sponsor is invited to elaborate on:

Redacted

[redacted] Development of Medicinal Product

It appears unclear to what extent zoledronic acid is developed into a medicinal product for oral administration. As yet the pharmaceutical formulation is briefly described in prospected terms.

The sponsor is invited to provide a description of the medicinal product as developed at this stage.

[redacted]. Randomized, double-blind, placebo-controlled trials of bisphosphonates in CRPS

Study	Drug studied	Type of study	Patients and follow-up duration	Results
Manicourt et al., 2004 [5]	Alendronate 40mg oral daily for 8 weeks	RCT, double-blind, placebo-controlled	39 patients (19 drug, 20 placebo), 12 weeks	Statist. signif. improvement in spontaneous pain, pressure tolerance, and joint mobility.
Robinson et al., 2004 [22]	Pamidronate 60mg IV, one time	RCT, double-blind, placebo-controlled	27 (14 drug, 13 placebo), 3 months	Statist. signif. improvement in pain score, global assessment of disease severity score, and physical function.
Varenna et al., 2000 [6]	Clodronate 300mg IV for 10 days	RCT, double-blind, placebo-controlled	32 patients (15 drug, 17 placebo), 40 days	Statist. signif. improvement in pain score and clinical global assessment.
Adami et al., 1997 [23]	Alendronate 7.5mg IV daily for 3 days	RCT, double-blind, placebo-controlled	20 patients (10 drug, 10 placebo), 2 weeks	Statist. signif. improvement in pain, tenderness, swelling, range of motion.

RCT, randomized controlled trial; IV, intravenous

Comments to the sponsor's response and summary of the oral explanation:

The first question from the COMP addressed the proposed mechanism of action of zoledronic acid in CRPS, with particular regard to the extent and relevance of osteoporosis in this specific condition, as osteoporosis is one of the main targets of bisphosphonate treatment.

The sponsor cited in the written response and the oral explanation some publications to support the role of bone reabsorption and osteoclastic activity in CRPS.

From the sources cited by the sponsor, Rho 2002 is a review article stating that osteoporosis can occur but no insights are provided in the publication about the pathophysiologic and clinical relevance of osteoporosis in CRPS, which would support its rationale as therapeutic target in CRPS.

The second article, from Raja 2002, is another review on CRPS but it does not mention osteoporosis. The only brief mention to osteopenia is on page 1256 and reads: "*The subgroup of patients who exhibited CRPS features, including motor or trophic changes and osteopenia, had the briefest disease duration*". The article from Bickerstaff et al (1991, ref. 2 in the sponsor's responses to the List of Questions) concludes that the radiographic appearances of algodystrophy "*are not specific for the disorder but are qualitatively similar to those which follow fracture and immobilisation*", though the radiographic changes in patients with Colles' fracture were more marked in those patients who developed algodystrophy. The authors concluded that there might be a common pathogenesis to the two conditions, which is accelerated by algodystrophy. Even though this article provides insights into loss of bone density in algodystrophy, it does not provide any information which has been considered by the Committee as supporting the extent and relevance of osteoporosis in the condition. In addition, osteoporosis is not listed in the IASP nor in the Budapest diagnostic criteria, which are the recognized diagnostic criteria of the condition as stated by the sponsor in the original application (see section A1).

Other articles cited by the sponsor in the written answer to this question do not seem to be relevant to the discussion. The article from Bickerstaff 1994 (ref. 28) does not address osteoporosis as a feature of CRPS, and the one from Leitha 1995 (ref. 3) is not conclusive and does not provide information on the role of osteoporosis as target of treatment in CRPS. The study from Atkins 1989 (ref. 33) addresses dolorimetry, and it is not understood how the results of this study could be extrapolated to the role of osteoporosis/osteoclast activity/bone reabsorption in CRPS.

The article from Maincourt 2004 (ref. 5 in the sponsors' responses to the List of Questions) provides theoretical discussion into the possible role of osteoclasts and bone reabsorption in CRPS in relation to the therapeutic action of alendronate, a product belonging to the class of bisphosphonates. The sponsor did not present or discuss any of the bibliographic references relevant to such discussion cited by Manincourt et al. The evidence of osteoporosis reported at baseline in the study of Manincourt could have been further elaborated by the sponsor for supporting the plausibility of zoledronic acid treatment in CRPS. These baseline data indicate that osteoporosis is present but do not *per se* support its relevance as therapeutic target.

In conclusion, even though the COMP acknowledged the presence of osteoporosis in CRPS, the written answers and the discussion provided by the sponsor during the oral explanation were not considered by the COMP sufficient to satisfactorily justify the relevance of bone reabsorption and other osteoclastic mechanisms in CRPS to support the scientific rationale for the development of zoledronic acid in CRPS. The second question from the Committee was focused on the two main references presented by the sponsor as data supporting the plausibility of zoledronic acid in the CRPS, i.e., the abstract from Zaspel at al. and the case study from de Castro et al.

The COMP was of the opinion that an abstract which has never been published and that therefore has not been subject to review by other experts in the field does not constitute a valid source of evidence.

The sponsor argued that some peer review is expected also for the acceptance of an abstract at a conference. However the COMP was of the opinion that even if this principle would be accepted, by being very brief by nature the abstract is not tailored to provide sufficient information for supporting the validity of its methodology and results. The COMP considered that necessary information was missing in the abstract regarding the study population (e.g. diagnostic criteria, main features of CRPS, patient's age, presence of regional and/or diffuse osteoporosis,), the study methodology (e.g. treatment schedule, dosage, methodology used for evaluating pain), the endpoints besides pain, and the results (e.g. complete overview of the endpoints, figures of the effect –only p values are provided), among others. In absence of more extensive information on this study, which would have been provided in a full article or a study report, the COMP considered that such abstract cannot be considered as containing conclusive information.

A case report, such as the one presented by the sponsor from de Castro et al (Rev Dor Sao Paulo, 2011) is usually considered by the COMP as supportive data rather than a main argument for establishing the medical plausibility of a proposed treatment. The COMP considered that information was missing in the report of this case which would have been relevant for the evaluation of the efficacy of zoledronic acid in the proposed condition, such as e.g. the method for the establishment of the primary diagnosis, the description of the diagnostic criteria in the clinical history, and the quantification of the different signs and symptoms pre and post-treatment, among others. Further, the discussion in the oral explanation was focused on the possibility of extrapolating data from other bisphosphonates to the use of zoledronic acid for the treatment of CRPS. The sponsor had cited in the written responses four published clinical trials where bisphosphonates were used in CRPS (Manincourt 2004; Adami 1997; Robinson 2004; Varenna 2000).

In two of these studies the product was alendronate, in one study it was pamidronate, and in one study clodronate. In all studies, the bisphosphonates were administered intravenously, similarly to zoledronic acid in the case report of de Castro et al, while the sponsor is proposing the development of an oral formulation of zoledronic acid for orphan designation in the present application.

The sponsor presented the conclusions of the studies but did not perform a critical review of such studies neither in the written responses not during the discussion, even though this was requested by the Committee. A critical discussion of the trials would have been useful for the purpose of evaluating their relevance to the extrapolation of the results to zolendronic acid in the treatment of CRPS. This would have included e.g.:

- discussion on the patient population of these trials and how the results on this population could be extrapolated to the condition for which the sponsor is seeking designation. Among the four trials presented, two addressed only CRPS type I, and two refer to reflex sympathetic dystrophy (which would likely nowadays encompass type I and type II CRPS according to some authors, or only to CRPS type I according to other authors namely Varenna et al, the authors of one of the clinical trials presented by the sponsor). Systematic reviews on clinical trials in CRPS have indicated the need of using uniform diagnostic criteria in order to allow evaluation of treatment efficacy of bisphosphonates and in general of treatments for CRPS (Tran et al, Can J Anesth 2010; 57:149-166; Brunner et al Eur J Pain 2009;13 (1) 17-21), and the discussion on the different diagnostic criteria in the different studies would have been appropriate, being the present a bibliographic-only application.

- discussion on the methodology and the study endpoints, in relation to the proposed mechanism of action of zoledronic acid and the relative relevance of pain and osteoporosis in the study population, and the endpoints and outcome in these studies. For example, a discussion on the comparability of endpoints of reversal of trophic changes and of improvement of functionality across the studies would have been useful to the evaluation of the possibility to generalize the results of these trials to the whole class of bisphosphonates. Of note, Tran et al noted in the systematic review that future trials

are needed for better understanding of treatment efficacy in CRPS, namely trials including sample size justification, and endpoints of functionality and reversal of trophic changes.

- clear reasoning on the extrapolation of data obtained using bisphosphonates intravenously to the oral use proposed by the sponsor in the present application. Of note, in the abstract from Zaspel *et al.* and the case report from de Castro presented by the sponsor, zoledronic acid had been always used intravenously.

In addition it is to be noted that the aforementioned two different systematic reviews (Brunner et al, and Tran et al) reached different conclusions on the efficacy of bisphosphonates in the treatment of CRPS, and a discussion on these conclusions, their meaning and their relevance would have been useful to the evaluation of the medical plausibility of zoledronic acid in the treatment of CRPS. The sponsor did not present any of these two systematic reviews in the bibliography provided for this application, although systematic reviews are considered to be at one of the highest levels in the scale of scientific evidence. One of the systematic reviews considered the four clinical trials to be of moderate quality, and a discussion on this point would have also been appropriate from the side of the sponsor.

Conclusion

The COMP considered that the data provided by the sponsor were not robust enough to satisfactorily establish the intention to treat the condition. In particular the sponsor did not provide adequate justifications to support the pharmacological action of zoledronic acid in the proposed condition (i.e. CRPS) and to clarify the role of its pathophysiologic target in the syndrome.

The sponsor did not present own generated data in the proposed condition CRPS. The bibliographic data presented in the proposed condition CRPS were considered by the COMP as not containing sufficient level of detail to be fully evaluable, due to the lack of essential information and relevant details for data evaluation.

The four bibliographic clinical trials presented by the sponsor where other bisphosphonates were used were not considered by the COMP sufficiently discussed and elaborated by the sponsor to the aim of supporting the possible extrapolation of the data to the use of zoledronic acid in its intention to treat CRPS.

For this reasons the COMP adopted a negative opinion on the orphan designation of zoledronic acid for the treatment of CRPS.

COMP discussion and conclusion at day 88

Complex regional pain syndrome is a distinct medical entity and thus a valid condition.

The sponsor has established that the condition was affecting approximately not more than 3 in 10,000 persons in the European Union, at the time the application was made. The prevalence estimate was based on relevant international literature.

The sponsor has established that the condition is chronically debilitating in those cases which do not undergo spontaneous resolution. In those cases, the chronically debilitating nature of the disease is due to symptoms such as pain, oedema, motor, sensorial, and vasomotor disturbances in the affected region. Continuous disabling pain has been described as the hallmark of the disease; it is disproportionate to the inciting event and lasts beyond the healing period. As the disease progresses, the pain often spreads beyond the affected limb. Autonomic symptoms and motor dysfunction can develop, including dystonia, tremor, myoclonus and muscle weakness.

The Committee has considered that the sponsor has not established that the product is intended for the treatment of the proposed condition as required for orphan designation under Article 3(1)(a) of Regulation (EC) No 141/2000. The intention to treat the condition with the above-mentioned product has been considered by the Committee not to be sufficiently justified by the sponsor. The sponsor did not provide a satisfactory discussion of the pharmacological action of the product in the proposed condition. In addition, the Committee was of the opinion that the sponsor did not provide sufficient data to support the potential clinical use of the product in complex regional pain syndrome. The data presented by the sponsor, based on a single non-sponsor generated abstract (Zaspel et al, 2007, never published as a full article) were not considered sufficient to justify the intention to treat the condition. Similarly, the bibliographic case report (De Castro et al, 2011) presented by the sponsor was considered to lack sufficient details for evaluation. Further, the sponsor did not sufficiently justify the extrapolation of data from clinical trials of other bisphosphonates in complex regional pain syndrome, to the proposed product.

There is at present no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

Grounds for the opinion on orphan medicinal product designation

The sponsor Axsome Therapeutics Limited – UK, submitted on 28 August 2012 an application for designation as an orphan medicinal product to the European Medicines Agency for zoledronic acid for treatment of complex regional pain syndrome.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- complex regional pain syndrome (hereinafter referred to as "the condition") was estimated to be affecting not more than 3 in 10,000 persons in the European Union, at the time the application was made. The prevalence estimate was based on relevant international literature.
- the condition is chronically debilitating in those cases which do not undergo spontaneous resolution. In those cases, the chronically debilitating nature of the disease is due to symptoms such as pain, oedema, motor, sensorial, and vasomotor disturbances in the affected region. Continuous disabling pain has been described as the hallmark of the disease; it is disproportionate to the inciting event and lasts beyond the healing period. As the disease progresses, the pain often spreads beyond the affected limb. Autonomic symptoms and motor dysfunction can develop, including dystonia, tremor, myoclonus and muscle weakness.
- However, the intention to treat the condition with the above-mentioned product has been considered by the Committee not to be sufficiently justified by the sponsor. The sponsor did not provide a satisfactory discussion of the pharmacological action of the product in the proposed condition. In addition, the Committee was of the opinion that the sponsor did not provide sufficient data to support the potential clinical use of the product in complex regional pain syndrome. The data presented by the sponsor, based on a single non-sponsor generated abstract (Zaspel et al, 2007, never published as a full article) were not considered sufficient to justify the intention to treat the condition. Similarly, the bibliographic case report (De Castro et al, 2011) presented by the sponsor was considered to lack sufficient details for evaluation. Further, the sponsor did not sufficiently justify the extrapolation of data from clinical trials of other bisphosphonates in complex regional pain syndrome, to the proposed product.
- the Committee has therefore considered that the sponsor has not established that the product is intended for the treatment of the proposed condition as required for orphan designation under Article 3(1)(a) of Regulation (EC) No 141/2000;
- the sponsor has demonstrated, as required under Article 3(1)(b), Regulation (EC) No 141/2000 of 16 December 1999, that there exists no satisfactory method of treatment of the condition in question that has been authorised in the European Union. Therefore a demonstration of significant benefit has not been required.

The Committee for Orphan Medicinal Products has recommended the refusal of the granting of the designation of zoledronic acid as an orphan medicinal product for treatment of complex regional pain syndrome.

Comments to the sponsor's grounds for appeal and summary of the oral explanation:

In its written comments, and during an oral explanation before the COMP on 6 February 2013, the sponsor presented its grounds for appeal, and defended in particular the intention to treat the proposed condition with the product subject of this application. The sponsor discussed again the proposed pharmacological properties of zoledronic acid and other biophosphonates, spanning anti-inflammatory, anti-osteoclastic, and direct analgesic effects based on literature studies. These pharmacodynamic effects were considered to be relevant for the treatment of the condition, based on its clinical features and in particular pain. The sponsor also re-discussed published randomised controlled clinical trials with other bisphosphonates in patients with the proposed condition, and based on the results from these studies and from other published literature, proposed a class effect of bisphosphonates in the treatment of CRPS. The sponsor also presented arguments to justify the validity of the abstract by Zaspel et al, including reviewers' opinions, as well as expert opinions on the medical plausibility argument. The full study report from the cited abstract was not presented to the Committee.

In the subsequent discussion, the COMP explained to the sponsor that a designation is given to a specific product in relation to a specific proposed indication, and that so far the sponsor has not presented data with the proposed product to justify satisfactorily the intention to treat the condition as applied for. Of all the arguments presented in the appeal, the most direct data pertained to a non-sponsor generated abstract with a different formulation of the active substance (Zaspel et al, 2007) which was not considered sufficient because the particulars of the study were not available for evaluation. In particular there is no data on important methodological aspects of the study that would affect the interpretation of the results, such as the randomisation to the experimental groups or any measures to conceal allocation. In addition the results on pain are presented as a relative value but there is no data about baseline values. Finally the analysis of data is not described. All these elements affect negatively the possibility to draw valid conclusions from the data presented. In conclusion and in consensus, the Committee for Orphan Medicinal Products has recommended the refusal of the granting of the designation of zoledronic acid as an orphan medicinal product for treatment of complex regional pain syndrome.

7. Grounds for the final opinion on orphan medicinal product designation adopted by the COMP on 6 February 2013

The sponsor Axsome Therapeutics Limited – UK, submitted on 28 August 2012 an application for designation as an orphan medicinal product to the European Medicines Agency for zoledronic acid for treatment of complex regional pain syndrome.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- complex regional pain syndrome (hereinafter referred to as "the condition") was estimated to be affecting not more than 3 in 10,000 people in the European Union, at the time the application was made. The prevalence estimate was based on relevant international literature.
- the condition is chronically debilitating in those cases which do not undergo spontaneous resolution. In those cases, the chronically debilitating nature of the disease is due to symptoms such as pain, oedema, motor, sensorial, and vasomotor disturbances in the affected region. Continuous disabling pain has been described as the hallmark of the disease; it is disproportionate to the inciting event and lasts beyond the healing period. As the disease progresses, the pain often spreads beyond the affected limb. Autonomic symptoms and motor dysfunction can develop, including dystonia, tremor, myoclonus and muscle weakness.
- the intention to treat the condition with the above-mentioned product has been considered by the Committee not to be justified by the sponsor. The Committee was of the opinion that the sponsor did not provide sufficient data to support the potential clinical use of the product in complex regional pain syndrome. The most direct data presented by the sponsor, pertained to a non-sponsor generated abstract with a different formulation of the active substance (Zaspel et al, 2007) which was not considered sufficient because the particulars of the study were not available for evaluation. The sponsor did not present any data with the proposed route of administration as applied for designation.
- the Committee has therefore considered that the sponsor has not established that the product is intended for the treatment of the proposed condition as required for orphan designation under Article 3(1)(a) of Regulation (EC) No 141/2000;
- the sponsor has demonstrated, as required under Article 3(1)(b), Regulation (EC) No 141/2000 of 16 December 1999, that there exists no satisfactory method of treatment of the condition in question that has been authorised in the European Union.

The Committee for Orphan Medicinal Products recommends the refusal of the granting of the designation of zoledronic acid as an orphan medicinal product for treatment of complex regional pain syndrome.

Electronic Patent Application Fee Transmittal

Application Number:	13894244
Filing Date:	14-May-2013
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman
Attorney Docket Number:	1958603.00021

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	2252	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**300**

Electronic Acknowledgement Receipt

EFS ID:	18706343
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman
Filer Authorized By:	
Attorney Docket Number:	1958603.00021
Receipt Date:	08-APR-2014
Filing Date:	14-MAY-2013
Time Stamp:	17:18:57
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$300
RAM confirmation Number	3934
Deposit Account	503207
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1958603-21_Response_to_OA_Nov-29-2013.pdf	210002 53ba26659f724e71283a02caad57a9c3e5941f40	yes	25

Multipart Description/PDF files in .zip description

Document Description	Start	End
Response After Final Action	1	1
Claims	2	4
Applicant Arguments/Remarks Made in an Amendment	5	25

Warnings:

Information:

2	After Final Consideration Program Request	1958603-21_After_Final_Pilot_Form.pdf	226648 a988ee742cc65501f9503c34cfffe8c9c8c8527b	no	2

Warnings:

Information:

3	Affidavit-traversing rejectns or objectns rule 132	252_Declaration.pdf	792298 1efa55b08998675b5dd3244a5ffc0b702886836d	no	3

Warnings:

Information:

4	Affidavit-traversing rejectns or objectns rule 132	274_Declaration.pdf	8961914 c10fdf5964d8a1825028cdd1d5a4af7dd0243761	no	27

Warnings:

Information:

5	Applicant Arguments/Remarks Made in an Amendment	Orange_Book.PDF	99727 dd1b0f9585f01ac62bf53abf0a5bce958496bf00	no	2

Warnings:

Information:

6	Applicant Arguments/Remarks Made in an Amendment	Orange_Book_Preface.PDF	336171 282ca68b53345e2507594ba6a5422e04a0fa5192	no	9

Warnings:

Information:

7	Applicant Arguments/Remarks Made in an Amendment	reclast.PDF	461751 850f5606667c4e70a7451f318c24f8c8622a5517	no	28

Warnings:					
Information:					
8	Applicant Arguments/Remarks Made in an Amendment	Reid2002l.PDF	128771 65e272e7018af15ee8b91e83a36dd2e5e9e481e0	no	9
Warnings:					
Information:					
9	Applicant Arguments/Remarks Made in an Amendment	Zometa.PDF	336527 c42ab5f80f61753a35153d7d07ed1d7a9be5f331	no	23
Warnings:					
Information:					
10	Applicant Arguments/Remarks Made in an Amendment	Exhibit3.pdf	273006 4861f5e75cb15b8d245319f86018f8740a069f86	no	15
Warnings:					
Information:					
11	Applicant Arguments/Remarks Made in an Amendment	Exhibit4.pdf	1738886 f73c4ceb7c8913095ba78b91ab60da2bef3a3701	no	15
Warnings:					
Information:					
12	Fee Worksheet (SB06)	fee-info.pdf	30209 6d63960377f8de6d7f04109ccf968fbe476b6406	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	13595910	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/894,244	Filing Date 05/14/2013	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	11/19/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	X $40 =	40
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**40**

AMENDMENT	04/08/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/PAUL STANBACK/

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	13894244	Filing Date	2013-05-14	Docket Number (if applicable)	1958603.00021	Art Unit	1627
First Named Inventor	Herriot Tabuteau			Examiner Name	Ivanova, Svetlana M.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☐ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other Certification and Request for Prioritize Examination

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 503207

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2014-04-09
Name	Brent A. Johnson	Registration Number	51851

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Herriot Tabuteau	Nonprovisional Application Number (if known):	13894244
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Brent A. Johnson/	Date 2014-04-09
Name (Print/Typed) Brent A. Johnson	Practitioner Registration Number 51851

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	13894244
Filing Date:	14-May-2013
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman/Maria Nadal
Attorney Docket Number:	1958603.00021

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for Continued Examination	2801	1	600	600
		Total in USD ($)		**2600**

Electronic Acknowledgement Receipt

EFS ID:	18721923
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Maria Nadal
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	09-APR-2014
Filing Date:	14-MAY-2013
Time Stamp:	20:08:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2600
RAM confirmation Number	6487
Deposit Account	503207
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	1958603_00021_US_TRANSMITTAL_LETTER_RCE_TRACK_ONE.pdf	61846 99d50f38b73b9fc9e3be1741461d32f38b39868f	no	1
Warnings:					
Information:					
2	Request for Continued Examination (RCE)	1958603_00021_US_RCE.pdf	697891 c196e260b59467b8a9951a29631657d7f69f07f0	no	3
Warnings:					
Information:					
3	TrackOne Request	1958603_00021_US_REQUEST_FOR_PRIORITIZED_EXAMINATION.pdf	152748 fbc09a6fcdb0a6f7ebb15707fa85ac9425203903	no	2
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32098 7ad3a61e52b18f714871ff988f0fb1321a77de31	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	944583		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**1033**
Appln. No.	**:**	**13/894,244**
Applicant	**:**	**Herriot Tabuteau**
Filed	**:**	**05/14/2013**
TC/A.U.	**:**	**1627**
Examiner	**:**	**Ivanova, Svetlana M.**
Docket No.	**:**	**1958603.00021**
Customer No.	**:**	**45200**
Title	**:**	**Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease**

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sirs:

Applicant submits a Request for Continued Examination and Certification and Request for Prioritized Examination. An After Final Consideration Pilot Program Request was submitted in error in this application.

The Commissioner is authorized to charge any fee which may be required in connection with this Notice or credit any overpayment to deposit account No. 50-3207.

Respectfully submitted,

Dated: 9 April 2014

/Brent A. Johnson/
Brent A. Johnson
Registration No. 51851
Customer No. 45,200

K&L GATES, LLP
1 Park Plaza, 12th Floor
Irvine, California 92614-7319
Telephone: 949.253.0900
Facsimile: 949.253.0902

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/894,244	Filing Date 05/14/2013	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 04/09/2014

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 21	Minus	** 21	= 0	X $40 =	0
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $210 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/GLORIA ANTHONY/

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE CA 92614

MAILED
APR 14 2014
OFFICE OF PETITIONS

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13/894,244

1. THE REQUEST FILED April 9, 2014 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Brian W. Brown at 571-272-5338.

/Brian W. Brown/
[*Signature*]

Petitions Examiner, Office of Petitions
(Title)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 04/30/2014

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER	
IVANOVA, SVETLANA M	
ART UNIT	**PAPER NUMBER**
1627	

NOTIFICATION DATE	DELIVERY MODE
04/30/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspatentmail@klgates.com

Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/11/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *40,42-57,60,61,120 and 121* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *40,42-57,60,61,120 and 121* is/are rejected.

8)☒ Claim(s) *121* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection on 04/09/2014. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Response to Arguments

This is a TRACK 1 application. Applicant's response from 04/09/2014 is acknowledged ("Response"). Applicant's arguments have been carefully considered, but have not been found to be persuasive.

35 USC 102(b) rejection- Fox

35 USC 103(a) rejection- Fox in view of Chandler

In view of Applicant's claim amendment, the 102(b) rejection over Fox has been modified to a 103(a) rejection. The following responses to Applicant's arguments to both apply.

Applicant has argued that the total amount of zoledronic acid to be administered in about a mouth is outside of the ranges of paragraph 0078 of Fox, that the range of claims 44, 40 and 60 is below the doses shown to not be tolerated, and that Fox does not disclose the monthly dose with sufficient specificity. (Response at pages 6-12).

In response, the rejection has been modified to provide the following. Applicant's claims, as amended, recite that the oral dosage form comprised about 30 mg to about 400 mg of zoledronic acid. For a 75 kg man, this corresponds to about 0.4 mg/kg to about 5.3 mg/kg of zoledronic acid. Fox discusses doses in several main paragraphs, such as [0075], [0078] and [0079]. Paragraph [0075] of Fox recites that the preferred dose of the bisphosphonate is 0.01-10 mg/kg of the bisphosphonate for a 75 kg warm blooded animal. The dose can be given as a single dose, once daily, once weekly, or once every month [0075-77]. Per Fox, zoledronic acid is the most preferred bisphosphonate. [0063]. Thus, Applicant's range of about 0.4 mg/kg to about 5.3 mg/kg is a range within the preferred range of Fox of [0075]. Fox also provides broader disclosure for the dose ranges, i.e. tablets or capsules from about 1 mg to about 500 mg of the active ingredient. ([0079]). Thus, Applicant's range of about 0.4 mg/kg to about 5.3 mg/kg is a range within the preferred range of Fox of [0079]. Fox in paragraph [0078] also discloses that the preferred bisphosphonate zoledronic acid is in the range of about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, for a human. This

range specifically lists 10 mg. It can be with more than one unit. (para [0063-65], [0070-72], [0078-81]). This last dose range of [0078] only does not explicitly fall within Applicant's claimed range of independent claims 40 and 60, and constitutes the reason as to why the previously made rejection is presently modified from an anticipation rejection to an obviousness rejection.

In view of the above, it would have been obvious to a person of skill in the art to modify the dose range in a way such as claimed by Applicant in order to achieve therapeutic efficacy, as per the particular disease or condition for which such oral dosage form is administered. Motivation to do so is found in Fox itself which explicitly discloses broader ranges in [0075] and [0079], and that adjusting such doses is a result-effective variable, i.e. in the order of magnitude, which is therapeutically effective (e.g. as in [0078]). "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). It has been held that it is within the skills in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. *In re Boesch*, 205 USPQ 215 (CCPA 1980). MPEP 2114.04.

Such motivation to optimize the dose and frequency of administration is further found in Leonard. This reference teaches the development of an oral tablet of

zoledronic acid, which is well tolerated and has no serious side effects associated with its administration. Leonard further teaches that for oral tablets of zoledronic acid, the dose administered via a 20 mg tablet is equivalent to 1 mg intravenous infusion, which enables once weekly treatment regimen (i.e. approximately 80 mg monthly). Thus, even assuming, arguendo, that the dose is not anticipated in view of Applican't claim amendments, because Fox does not state in *ipsis verbis* as Applicant the total montly range, this dose range is at least rendered obvious. Motivation to optimize this dose is found in Fox itself, as well as additionally in the prior art as a whole, to include for instance Leonard, which discloses that there is a 20-fold difference in the dose between oral and intravenous zoledronic acid, and which further provides that the oral tablets are an improved alternative to bisphosphonate products currently marketed, that this oral bisphosphonate tablet meets an unmet market need in oncology, and that advantages of oral tablets include: improved quality of life for the patient, flexibility in the dosing regimen, and improved compliance.

Of note, independent claim 44 recites that the amount to be administered in one month is about 40 mg to about 800 mg in a pharmaceutical product with more than one unit. A dependent claim 50 discloses a unit of 10 mg. With respect to this independent claim 44, and the claims that depend from it, even paragraph [0078] of Fox in accordance with paragraph [0077] continues to disclose the range of Applicant's claims. For instance, paragraph [0077] of Fox discloses that the drug can be administered once daily, once weekly, once a month. To take a dose of Fox's 20 mg, or 10 mg dose, even given once weekly, this translates into a monthly dose of approximately 80 mg, or 40

mg, which both fall squarely within the scope of Applicant's claims. Assuming once daily administration, such doses of Fox increase for 30 days to 600 mg, or 300 mg, which both fall squarely within the scope of Applicant's claims.

Applicant has further made arguments that the doses of paragraph [0078] as they pertain to the treatment of Paget's disease, hypercalcinemia or osteoporosis. What the paragraph states is that "[p]referably, the bisphosphonates are administered in doses which are in the same order of magnitude as those used in the treatment of diseases classically treated with bisphosphonate acid derivates, such as Paget's disease, tumour-induced hypercalcinemia or osteoporosis". Applicant has further offered a reading, based on the labels of Reclast® and Zometa®, that since the doses used in the labels are considerably lower than those in Fox, a person of skill in the art would understand the doses in Fox to mean administration of less often than monthly, or no more than twice in a month given at low doses.

In response, first, as shown in paragraph [0077], this is clearly what Fox expressly teaches- a single dose, once daily, once weekly, or once every month. Second, the discussed labels pertain to treatment of different diseases and with a different route of administration- intravenous. Third, as the prior teaches, for oral tablets of zoledronic acid, the dose administered via a 20 mg tablet is equivalent to 1 mg intravenous infusion, which enables once weekly treatment regimen. *See, e.g.* Leonard. Fourth, even the doses in the label for Zometa, discussed by Applicant, 4 mg no more than twice in a month correspond to the doses in Applicant's claimed range (80

mg if once a month, or 160 mg if twice a month administration is calculated for oral administration equivalents to intravenous doses, per Leonard).

Even assuming, arguendo, that the dose is not anticipated in view of Applican't claim amendments, because Fox does not state in *ipsis verbis* as Applicant the total montly range, this dose range is at least rendered obvious. Motivation to optimize this dose is found in Fox itself, as well as additionally in the prior art as a whole, to include for instance Leonard, which discloses that there is a 20-fold difference in the dose between oral and intravenous zoledronic acid, and which further provides that the oral tablets are an improved alternative to bisphosphonate products currently marketed. Such motivation is further found in the drug labels for different indications of zoledronic acid, which show that depending on the condition being treated, the therapeutic dose and frequency of administration of zoledronic acid varies as well. Such optimization is further obvious, to include additionally for frequency of administration, as it is mandated by the FDA.

Regarding obviousness, Applicant has stated that interview summaries for the two related applications 13/894,252 and 13/894,262 indicate that Applicant may be able to overcome obviousness issues by showing unexpected results of the claimed range of by showing that the art teaches away from the claims. (Response at pp. 12-13 *et seq.*). For clarity of the record, the Examiner observes that the '252 and the '262 applications recite method claims, whereas the instant claims are directed to an oral dosage form and a pharmaceutical product. Here, Applicant has not discovered an oral dosage form or a pharmaceutical product of an oral dosage form. Here, Applicant has not presented

arguments directed to an oral dosage form with unexpected results over an oral dosage form of the prior art (e.g. with ingredients affording better stability, solubility, etc.). Applicant has mostly made arguments as they pertain to the method of use of this (pharmaceutical product of) oral dosage form, which is not the subject of the instant claims.

Applicant has also argued that oral administration has been noted to have problems. In response, it is noted that the overall disclosure of the references pertaining to MER-101 does not teach away from using such oral zoledronic acid. To the contrary, while discussing both problems and potential, the references clearly teach in favor or using oral zoledronic acid as an improved alternative to bisphosphonate products currently marketed. *See, e.g.,* Leonard (discussed above). Such conclusion is also clearly buttressed by Fox, which provides that the preferred mode of administration, "of particular importance", are intravenous or oral. [0073].

Applicant's arguments that no FDA product is currently approved for oral administration are noted. However, Applicant has provided no evidence whatsover that this amounts to failure of the oral dosage form, nor is such approval of the oral dosage form by the FDA a requirement for finding patentability or lack thereof. At the same time, actual evidence on the preferability or not of oral zoledronic acid is from the art of record, Fox- that intravenous and oral are the preferred modes of administration. That Fox teaches that intravenous is preferred over oral is not a teaching away from oral administration, especially where Fox explicitly states that the two are both preferred. This conclusion is further supported by the discussion pertaining to Leonard above,

which advocates the use of oral administration over other currently marketed formulations of zoledronic acid. This is despite what Applicant has argued- that the prior art also reports problems associated with an oral dosage form. Stated differently, even where potential side effects are noted, the art still discloses a strong overall preference in favor of use of an oral dosage form. That the art has expressed some preference for intravenous dosage forms over oral dosage forms (e.g. in Fox, but to the contrary- not in e.g., Leonard), does not take away from the fact, that it also expresses a preference for oral dosage forms, and does not constitute evidence of teaching away. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use (here, in some, but not all references- e.g., Fox, but not Leondard). *See, e.g., In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.).

Lastly, Applicant has failed to establish unexpected results. The safety and efficacy of Applicant's oral dosage form cannot be unexpected, because Applicant's

claimed doses are disclosed by the prior art. Moreover, comparison with Figure 1 in Fox is not a comparison to the closest prior art, at least because it pertains to an example of an inflammatory hyperalgesia of a subcutaneous, not oral, dosage form, where Fox explicitly teaches an oral dosage form. Lastly, as stated above, Applicant has mostly made arguments as they pertain to the method of use of this (pharmaceutical product of) oral dosage form, which is the subject of related patent applications, but not the subject of the instant claims.

Double patenting

Applicant has stated that the rejection has been overcome, because Applicant has submitted terminal disclaimers in the '252 and the '262 applications. However, in order to overcome a provisional non-statutory double patenting rejection, where both applications (the instant and the one rejected over) are filed on the same day (as they are here) the provisional double patenting rejection should be maintained until filing a terminal disclaimer in both applications. Accordingly, for Applicant's convenience, the rejections are repeated for the record below.

Claims 40, 42-57, 60, 61, 120 and 121 are pending, and have been examined herewith.

Claim 121 is objected to as lacking the proper status identifier. Claim 121 is new, but has been presented instead as Previously Presented. In the interest of

compact prosecution, the Examiner has examined the application in lieu of sending a Notice of Non-Compliant Amendment (37 CFR. 1.121), and solely makes a notation for the record.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 42-57, 60, 61, 120 and 121 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over US 2004/006367 to Fox *et al.* ("Fox", of record), further in view of Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09 ("Chandler", of record) and Leonard et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster presentation, October 2007. ("Leonard", of record).

The claims have been examined to the extent they read on an oral dosage form.

Fox teaches a composition of an oral dosage form of zoledronic acid and its sodium salt, and does not require bioavailability-enhancing agents, wherein the zoledronic acid is the preferred bisphosphonate. (para [0063-65], [0070-72], [0078-81]).

Such a formulation will inherently possess the bioavailability, aqueous solubility of Applicant's claims. The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.1% to about 2%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents. Applicant has argued that the dosage form of Fox may not necessarily have the bioavailability of Applicant's claims, i.e., it may be in a delayed or prolonged release formulation. However, as addressed above, the dosage form of Fox does not require bioavailability enhancing agents. Such a dosage form is consistent with Applicant's description from its specification in [055]. The examples teach formulations with a single active ingredient.

It is noted that Fox expressly teaches an oral dosage form, such as in reference to paragraphs [0070-72], as well as teaches the disclosed dosage forms specifically for zoledronic acid, such as with reference to zoledronic acid in paragraphs [0063-65]. There is no picking, choosing and combining involved, to use Applicant's own lingo, as Fox clearly discloses that: "[t]he most preferred bisphosphonate for use in the invention is zoledronic acid" (*see, e.g.*, Abstract, [0063]); and that "[p]referably, the pharmaceutical compositions are adapted for oral or parenteral […] administration", and that "[i]ntravenous and oral […] administration is considered to be of particular importance" (*see, e.g.*, [0072]).

Applicant's claims, as amended, recite that the oral dosage form comprised about 30 mg to about 400 mg of zoledronic acid. For a 75 kg man, this corresponds to

about 0.4 mg/kg to about 5.3 mg/kg of zoledronic acid. Fox discusses doses in several main paragraphs, such as [0075], [0078] and [0079]. Paragraph [0075] of Fox recites that the preferred dose of the bisphosphonate is 0.01-10 mg/kg of the bisphosphonate for a 75 kg warm blooded animal. The dose can be given as a single dose, once daily, once weekly, or once every month [0075-77]. Per Fox, zoledronic acid is the most preferred bisphosphonate. [0063]. Thus, Applicant's range of about 0.4 mg/kg to about 5.3 mg/kg is a range within the preferred range of Fox of [0075]. Fox also provides broader disclosure for the dose ranges, i.e. tablets or capsules from about 1 mg to about 500 mg of the active ingredient. ([0079]). Thus, Applicant's range of about 0.4 mg/kg to about 5.3 mg/kg is a range within the preferred range of Fox of [0079]. Fox in paragraph [0078] also discloses that the preferred bisphosphonate zoledronic acid is in the range of about 0.5 to about 20 mg, preferably from about 1 to about 10 mg, for a human. This range specifically lists 10 mg. It can be with more than one unit. (para [0063-65], [0070-72], [0078-81]). This last dose range of [0078] only does not fall within Applicant’s claimed range of independent claims 40 and 60, and constitutes the reason as to why the previously made rejection is presently modified from an anticipation rejection to an obviousness rejection.

Of note, independent claim 44 recites that the amount to be administered in one month is about 40 mg to about 800 mg in a pharmaceutical product with more than one unit. A dependent claim 50 discloses a unit of 10 mg. With respect to this independent claim 44, and the claims that depend from it, even paragraph [0078] of Fox continues to disclose the range of Applicant's claims. For instance, paragraph [0077] of Fox

discloses that the drug can be administered once daily, once weekly, once a month. To take a dose of Fox's 20 mg, or 10 mg dose, even given once weekly, this translates into a monthly dose of approximately 80 mg, or 40 mg, which both fall squarely within the scope of Applicant's claims. Assuming once daily administration, such doses of Fox increase for 30 days to 600 mg, or 300 mg, which both fall squarely within the scope of Applicant's claims.

In view of the above, it would have been obvious to a person of skill in the art to modify the dose range in a way such as claimed by Applicant in order to achieve therapeutic efficacy, as per the particular disease or condition for which such oral dosage form is administered. Motivation to do so is found in Fox itself which explicitly discloses broader ranges in [0075] and [0079], and that adjusting such doses is a result-effective variable, i.e. in the order of magnitude, which is therapeutically effective (e.g. as in [0078]). "When the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimal or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). It has been held that it is within the skills in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. *In re Boesch*, 205 USPQ 215 (CCPA 1980). MPEP 2114.04.