Example 12:

Zoledronic acid crystal form **I** (2.0g) was stirred in Toluene (20ml) at reflux temperature for 14 hours. Then the suspension was cooled to room temperature, filtered, washed with Toluene (1x15ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.6g of Zoledronic acid crystal form **II**.

Preparation of ZLD-Ac crystal form XII

Example 13:

Zoledronic acid crystal form **XVIII** (10.0g) was dissolved in water (260ml) at reflux temperature. The obtained solution was stirred at reflux temperature for about 20 minutes to obtain a clear solution. Then it was cooled to 75°C during 2 hours and stirred at this temperature for 1 hour. The turbid solution was further cooled to 25°C during 4.5 hours and stirred at this temperature for 1 hour. After cooling to 0°C during 2 hours and stirring at this temperature for 16 hours, the white precipitate was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 7.8g of Zoledronic acid crystal form **XII**.

Example 14:

Zoledronic acid crystal form **I** (2.0g) was stirred in Acetic acid (20ml) at room temperature for 15.5 hours. Then it was filtered, washed with Acetic acid (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 2.0g of Zoledronic acid crystal form **XII**.

Preparation of ZLD-Ac crystal form XV

Example 15:

A 250ml flask was loaded with Zoledronic acid form I (4.8g), Sodium hydroxide (0.7g) and absolute Ethanol (10 volumes per grams of ZLD-Ac) (48ml). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a vacuum oven at 50°C for 23 hours to give 4.9g (96%) of Zoledronate monosodium crystal form XV in a mixture with Zoledronic acid crystal form I (LOD by TGA=5.8%).

Example 16:

A 250ml flask was loaded with Zoledronic acid form I (4.8g), Sodium hydroxide (0.7g) and Methanol (10 volumes per grams of ZLD-Ac) (48ml). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x10ml) and dried in a vacuum oven at 50^0C for 22 hours to give 4.8g (99%) of Zoledronate monosodium crystal form XV (LOD by TGA=0.8%). Purity by HPLC 99.9%.

Example 17:

Zoledronic acid crystal form **XII** (2.0g) was stirred in Methanol (20ml) at reflux temperature for 19 hours. Then the suspension was cooled to room temperature, filtered, washed with Methanol (1x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.8g of a mixture of Zoledronic acid crystal forms **XV** and **XVIII**.

Preparation of ZLD-Ac crystal form XVIII

Example 18:

A 3L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with 1-Imidazoleacetic acid (70.0g, 0.56mole), Phosphorous acid (136.7g, 1.67mole) and Silicon oil (M-350) (490ml). The suspension was heated to 80°C and Phosphorous oxychloride (194.4ml, 2.08mole) was added drop-wise during 4 hours. The reaction mixture was stirred at 80°C for 22 hours. Then water (490ml) was added slowly at 80°C. The mixture was stirred vigorously for about 30 minutes. Then the silicon oil phase and the aqueous phase were separated. The aqueous phase was put in a clean reactor and heated to 97°C for 17.5 hours. Then absolute Ethanol (490ml) was added and the solution was stirred at reflux (87°C) for 2 hours. The solution was then cooled to 70°C-72°C during about 1 hour and was kept at this temperature for 1 hour. After cooling to 25°C during 2.5 hours and stirring at this temperature for 1 hour, half of the product was filtered, washed with small amount of cold water and dried in a vacuum oven at 50°C for 20 hours to obtain 50.8g of Zoledronic acid crystal form **XVIII** (MS-507-crop I, LOD by TGA=1.9%). The rest of the suspension was cooled to 0°C during 2

hours and was stirred at this temperature for about 16 hours. Then the product was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 26g of Zoledronic acid crystal form **XVIII** (MS-507-crop II, LOD by TGA=1.0%). The overall yield of the process is 50% purity by HPLC 97.7%.

Example 19:

Zoledronic acid crystal form **I** (2.0g) was stirred in Methanol (20ml) at room temperature for 14.5 hours. Then it was filtered, washed with Methanol (2x10ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 1.9g of Zoledronic acid crystal form **XVIII**.

Example 20:

Zoledronic acid crystal form **I** (2.0g) was stirred in Methanol (20ml) at reflux temperature for 16 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with Methanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.7g of Zoledronic acid crystal form **XVIII**.

Example 21:

Zoledronic acid crystal form **I** (2.0g) was stirred in 1-Butanol (20ml) at reflux temperature for 15.5 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with 1-Butanol (1x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.8g of Zoledronic acid crystal form **XVIII**.

Example 22:

Zoledronic acid crystal form **I** (2.0g) was stirred in MTBE (20ml) at reflux temperature for 15 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with MTBE (1x10ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 1.4g of Zoledronic acid crystal form **XVIII**.

Example 23:

Zoledronic acid crystal form **I** (2.0g) was stirred in Acetonitrile (20ml) at room temperature for 22 hours. Then the suspension was filtered, washed with Acetonitrile

(2x5ml) and dried in a vacuum oven at 50°C for 23 hours to obtain 2.0g of Zoledronic acid crystal form **XVIII**.

Example 24:

Zoledronic acid crystal form **I** (2.0g) was stirred in a mixture of Methanol/water (1:1 v/v) (20ml) at reflux temperature for 18 hours. Then the suspension was cooled to 0°C, filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 1.8g of Zoledronic acid crystal form **XVIII**.

Example 25:

Zoledronic acid crystal form **I** (2.0g) was stirred in a mixture of Ethanol/water (1:1 v/v) (20ml) at reflux temperature for 18 hours. Then the suspension was cooled to 0°C, filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 1.8g of Zoledronic acid crystal form XVIII.

Preparation of ZLD-Ac crystal form XX

Example 26:

Zoledronic acid crystal form I (2.0g) was stirred in absolute Ethanol (20ml) at reflux temperature for 16 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with absolute Ethanol (2x5ml) and dried in a vacuum oven at 50°C for 22.5 hours to obtain 1.9g of Zoledronic acid crystal form **XX** in a mixture with crystal form **I**.

Example 27:

Zoledronic acid crystal form **I** (2.0g) was stirred in 1-Propanol (20ml) at reflux temperature for 11.5 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with 1-Propanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form **XX**.

Example 28:

Zoledronic acid crystal form **I** (2.0g) was stirred in 2-Propanol (IPA) (20ml) at reflux temperature for 14 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with IPA (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form **XX**. Purity by HPLC 99.8%.

Preparation of ZLD-Ac crystal form XXVI

Example 29:

Zoledronic acid crystal form **I** (2.0g) was stirred in 2-Butanol (20ml) at reflux temperature for about 15 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with 2-Butanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form **XXVI**.

CRYSTAL FORMS OF ZOLEDRONATE MONOSODIUM (ZLD-Na)

Preparation of ZLD-Na crystal form VIII

Example 30:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. Sodium hydroxide (pearls, 1.42g) was added. A pH test of the sodium salt showed pH=4.54. The solution was cooled to 60°C and IPA (10.5ml) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 64 hours. After cooling to 5°C and stirring at this temperature for 1 hour, the white precipitate was filtered, washed with cold water (1x10ml) and dried in a vacuum oven at 50°C for 23.5 hours to obtain 7.0g of Zoledronate monosodium crystal form **VIII** (pH=4.32). Purity by HPLC 100.0%.

Example 31:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to 4°C

during 2 hours and was stirred at this temperature for about 64 hours to obtain a massive precipitate. The white precipitate was filtered, washed with cold water (1x10ml) and dried in a vacuum oven at 50°C for 26 hours to obtain 7.6g (**64%**) of Zoledronate monosodium crystal form **VIII** (LOD by TGA=15.1%).

Example 32→:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3°C and stirring at this temperature for 1.5 hour, the white precipitate was filtered, washed with Methanol (2x15ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 5.8g (**49%**) of Zoledronate monosodium crystal form **VIII** (LOD by TGA=15.1%). The obtained Form VIII (2g) was recrystallized form water (34ml) to give 1.4g (**72%**) of Zoledronic acid crystal form VIII (LOD by TGA=11.3%). Purity by HPLC 100.0%.

[Remark:

Regarding the next examples: the composition of the reflux media is expressed on a volume per volume basis (abbreviated v/v). The amount of water that should be added to the reflux media is calculated according to the following formula:

(10 volumes of alcohol per grams of ZLD-Ac x 100) / X% of alcohol = Y

when Y is the total amount of alcohol and water together →

Y x (100-X)% of water / 100 = Z

when Z is the volume of water that should be added].

Example 33:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (36ml) was added drop-wise to a suspension of Zoledronic acid form I (4.8g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (202ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a

vacuum oven at 50^{0}C for 22 hours to give 4.7g (83%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.5%). Purity by HPLC 99.9%.

Example 34:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac fprm I) (36ml) was added drop-wise to a suspension of Zoledronic acid (4.8g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (202ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x20ml) and dried in a vacuum oven at 50^{0}C for 22 hours to give 4.7g (81%) of Zoledronate monosodium crystal form VIII (LOD by TGA=16.03%). Purity by HPLC 99.9%.

Example 35:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2x20ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 4.7g (79%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.40%). Purity by HPLC 99.95%.

Example 36:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form I) (19ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form I) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was

then filtered, washed with IPA (1x20ml) and dried in a vacuum oven at 50^{0}C for 27 hours to give 0.6g (10%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.0%).

Preparation of ZLD-Na crystal form XVI

Example 37:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / Ethanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (14ml) was added drop-wise to a suspension of Zoledronic acid (4.8g) in a mixture of water (50% v/v) / Ethanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (81ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a vacuum oven at 50^{0}C for 18 hours to give 5.2g (98%) of Zoledronate monosodium crystal form XVI (LOD by TGA=9.9%). Purity by HPLC 99.95%.

Example 38:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / IPA (50% v/v, 10 volumes per grams of ZLD-Ac form I) (15ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (50% v/v) / IPA (50% v/v, 10 volumes per grams of ZLD-Ac form I) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2x20ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 5.2g (94%) of Zoledronate monosodium crystal form XVI (LOD by TGA=9.8%). Purity by HPLC 99.9%.

Example 39:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / Methanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (14ml) was added drop-wise to a suspension of Zoledronic acid form I (4.8g) in a mixture of water (50% v/v) / Ethanol

(50% v/v, 10 volumes per grams of ZLD-Ac form I) (81ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x25ml) and dried in a vacuum oven at 50^{0}C for 25.5 hours to give 4.8g (89%) of Zoledronate monosodium crystal form XVI (LOD by TGA=11.1%). Purity by HPLC 99.9%.

Preparation of ZLD-Na crystal form XVII

Example 40:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 29% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3°C the product was isolated by filtration. Further cooling of the mother-liquid led to the formation of a white precipitate. The precipitate was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 0.6g of Zoledronate monosodium crystal form **XVII** (LOD by TGA=10.3%).

CRYSTAL FORMS OF ZOLEDRONATE DISODIUM (ZLD-Na_2)

Preparation of ZLD-Na_2 crystal form V

Example 41:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (10-15ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate disodium crystal form **V**.

Sample No.	X% H_2O	Y% EtOH	Total volume of solution (H_2O/EtOH)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	4.9g/89%	10.3%
2	40% (33ml)	60% (50ml)	83ml	5.0g/90%	10.3%
3	50% (50ml)	50% (50ml)	100ml	5.1g/91%	10.7%

Example 42:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (13-15ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (70-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V.

Sample No.	X% H_2O	Y% MeOH	Total volume of solution (H_2O/MeOH)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% (50ml)	83ml	4.7g/85%	10.0%
2	50% (50ml)	50% (50ml)	100ml	4.9g/88%	10.8%

Example 43:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (13-15ml) was added drop-wise to a suspension of Zoledronic acid (4.98g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (70-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form **V**.

Sample No.	X% H_2O	Y% IPA	Total volume of solution (H_2O/IPA)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% (50ml)	83ml	4.7g	-
2	50% (50ml)	50% (50ml)	100ml	4.8g/85%	11.2%

Example 44:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (10-15ml) was added drop-wise to a suspension of Zoledronic acid fomr I (5.0g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form **V**. Purity by HPLC 99.9%.

Sample No.	X% H_2O	Y% EtOH	Total volume of solution (H_2O/EtOH)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	6.0g/96%	9.7%
2	50% (50ml)	50% (50ml)	100ml	6.0g/94%	10.9%

Example 45:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (15ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95%.

Sample No.	X% H_2O	Y% MeOH	Total volume of solution (H_2O/MeOH)	Yield (g/%)	LOD by TGA
1	50% (50ml)	50% (50ml)	100ml	6.0g/94%	11.1%

Example 46:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (10-15ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at

reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95%.

Sample No.	X% H_2O	Y% IPA	Total volume of solution (H_2O/IPA)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	5.7g/91%	10.3%
2	50% (50ml)	50% (50ml)	100ml	5.7g/90%	10.6%

Preparation of ZLD-Na_2 crystal form VI

Example 47:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / Ethanol or Methanol (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (60% v/v) / Ethanol or Methanol (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form VI.

Sample No.	X% H_2O	Y% EtOH or MeOH	Total volume of solution (H_2O/EtOH or MeOH)	Yield (g/%)	LOD by TGA
1	60% (75ml)	40% EtOH (50ml)	125ml	4.9g/86%	12.9%
2	60%	40%	125ml	4.5g/78%	13.0%

	(75ml)	MeOH (50ml)			

Example 48:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature and the solution was evaporated to dryness. The obtained solid was dried in a vacuum oven at 50^0C for 5 hours to give 5.2g (78%) of Zoledronate disodium crystal form VI (LOD by TGA=15.4%).Purity by HPLC 99.9%.

Example 49:

Zoledronate disodium crystal form XIX (4.0g) was dissolved in water (10ml) at reflux temperature. After about 30 minutes at reflux temperature a precipitate was obtained. The suspension was then cooled to 0°C using an ice-bath. The solid was isolated by filtration and dried in a vacuum oven at 50^0C for 17 hours to give 2.0g (50%) of Zoledronate disodium crystal form VI.

Preparation of ZLD-Na_2 crystal form VII

Example 50:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10.0g) and water (260ml). The suspension was heated to 80°C to obtain a clear solution. Sodium hydroxide (pearls, 2.84g) was added. A pH test of the sodium salt showed pH=7.35. The solution was cooled to 60°C and IPA (10.5ml) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 16 hours. After cooling to 5°C and stirring at this temperature for 2 hours, the solution was evaporated to dryness to obtain a white solid. The obtained solid was reslurred in water (50ml) and cooled to 4°C. The product

was then isolated by filtration and dried in a vacuum oven at 50°C for 24 hours to obtain 3.2g of Zoledronate disodium crystal form **VII (24%)** (pH=7.27). Purity by HPLC 100.0%.

Example 51:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (130ml). The suspension was heated to reflux temperature to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (6.9g) was added drop-wise. The solution was then cooled to 4°C during 2 hours and was stirred at this temperature for about 1.5 hours. The solution was concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 2.7g **(22%)** of Zoledronate disodium crystal form **VII** (LOD by TGA=10.7%).

Example 52:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (130ml). The suspension was heated to reflux temperature (92°C) to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (6.9g) was added drop-wise. The solution was then cooled to 25°C was stirred at this temperature for about 16 hours. The solution was then concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50°C for 18.5 hours to obtain 2.8g **(23%)** of Zoledronate disodium crystal form **VII** (LOD by TGA=10.2%). Purity by HPLC 100.0%.

Example 53:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered,

washed and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate disodium crystal form **VII**.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	80% (200ml)	20% EtOH (50ml)	250ml	4.9g/89%	9.2%
2	80% (200ml)	20% MeOH (50ml)	250ml	4.5g/83%	7.6%
3	80% (200ml)	20% IPA (50ml)	250ml	4.7g/85%	10.3%

Example 54:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (1x20ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate monosodium crystal form **VIII** (crop I). Then the precipitate from the mother-liquid was isolated by filtration as well, and dried in a vacuum oven at 50^{0}C for 24 hours to give 2.8g (**13%**) of Zoledronate disodium crystal form **VII** (crop II).

Example 55:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 18.5 hours. Then the reaction mixture was cooled to room temperature and the solution was evaporated to dryness to obtain 6.7g (98%) of Zoledronate disodium crystal form VII (LOD by TGA=16.8%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form X

Example 56:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / IPA (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / IPA (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (1x25ml) and dried in a vacuum oven at 50^0C for 24 hours to give 4.7g (91%) of Zoledronate disodium crystal form X (LOD by TGA=2.6%).

Preparation of ZLD-Na_2 crystal form XIII

Example 57:

A solution of sodium hydroxide (1.4g) in a mixture of water (5% v/v) / Ethanol (95% v/v, 10 volumes per grams of ZLD-Ac form I) (8ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (5% v/v) / Ethanol (95% v/v, 10 volumes per grams of ZLD-Ac) (45ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 19.5 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Ethanol (1x10ml) and dried in a vacuum oven

at 50°C for 20 hours to give 4.9g (84%) of Zoledronate disodium crystal form XIII (LOD by TGA=3.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XIV

Example 58:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / DMF (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / DMF (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with DMF (2x10ml) and dried in a vacuum oven at 50°C for 24 hours to give 4.8g (92%) of Zoledronate disodium crystal form XIV (LOD by TGA=1.9%).

Example 59:

A solution of sodium hydroxide (1.4g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac form I) (10ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 17 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x10ml) and dried in a vacuum oven at 50°C for 26 hours to give 5.6g (97%) of Zoledronate disodium crystal form **XIV** (LOD by TGA=1.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XIX

Example 60:

Zoledronate disodium crystal form VII (1.0g) was dissolved in water (19ml) at reflux temperature. After about 30 minutes at reflux temperature a light precipitate was obtained. The suspension was then cooled to 0°C using an ice-bath and was concentrated

under vacuum to obtain a massive precipitation. The solid was isolated by filtration after further stirring at 0°C, and dried in a vacuum oven at 50°C for 27 hours to give 0.4g (40%) of Zoledronate disodium crystal form XIX.

Example 61:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (20.0g) and water (260ml). The suspension was heated to reflux temperature (92°C) to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (13.8g) was added drop-wise. The solution was then cooled to 25°C and was stirred at this temperature for about 16 hours. The solution was then concentrated to half of its volume to obtain a precipitate. After stirring at 0°C for 72 hours, the white precipitate was filtered and dried in a vacuum oven at 50°C for 23 hours to obtain 10.4g of Zoledronate disodium crystal form **XIX**.

Preparation of ZLD-Na_2 crystal form XXV

Example 62:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 19 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The solution was then evaporated to dryness to obtain 6.1g (99%) of Zoledronate disodium crystal form **XXV** (LOD by TGA=7.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XXVII

Example 63:

A 100ml flask was loaded with Zoledronic acid form I (4.9g), Sodium hydroxide (1.4g), Methanol (50ml) and water (2.5ml) [= 5% v/v water in Methanol]. The reaction mixture was heated to reflux temperature for 21 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x75ml) and dried in a vacuum oven at 50°C

for 27.5 hours to give 5.7g (93%) of Zoledronate disodium crystal form XXVII (LOD by TGA=5.3%). Purity by HPLC 99.9%.

Example 64:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x15ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 4.85g (90%) of Zoledronate disodium crystal form XXVII (LOD by TGA=7.5%).

CRYSTAL FORMS OF ZOLEDRONATE TRISODIUM (ZLD-Na_3)

Preparation of ZLD-Na_3 crystal form IX

Example 65:

A solution of sodium hydroxide (1.4g) in a mixture of water (20% v/v) / Ethanol or Methanol or IPA (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (20% v/v) / Ethanol or Methanol or IPA (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate trisodium crystal form **IX**.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA

1	20% (13ml)	80% EtOH (50ml)	63ml	5.6g/84%	13.6%
2	20% (13ml)	80% MeOH (50ml)	63ml	5.9g/88%	13.7%
3	20% (13ml)	80% IPA (50ml)	63ml	5.6g/85%	13.5%

Example 66:

A solution of sodium hydroxide (1.4g) in a mixture of water (40% v/v) / Ethanol or Methanol or IPA (60% v/v, 10 volumes per grams of ZLD-Ac form XII) (13ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (40% v/v) / Ethanol or Methanol or IPA (60% v/v, 10 volumes per grams of ZLD-Ac) (71ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% EtOH (50ml)	83ml	5.7g/68%	13.9%
2	20% (33ml)	60% MeOH (50ml)	83ml	5.5g	-
3	20% (33ml)	60% IPA (50ml)	83ml	5.7g/85%	14.3%

Example 67:

A solution of sodium hydroxide (1.4g) in a mixture of water (50% v/v) / Ethanol or Methanol or IPA (50% v/v, 10 volumes per grams of ZLD-Ac form XII) (15ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (50% v/v) / Ethanol or Methanol or IPA (50% v/v, 10 volumes per grams of ZLD-Ac) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	50% (50ml)	50% EtOH (50ml)	100ml	5.5g/84%	11.6%
2	50% (50ml)	50% MeOH (50ml)	100ml	5.2g/77%	14.6%
3	50% (50ml)	50% IPA (50ml)	100ml	5.3g/85%	8.6%

Example 68:

A solution of sodium hydroxide (1.4g) in a mixture of water (60% v/v) / Ethanol or Methanol or IPA (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (60% v/v) / Ethanol or Methanol or IPA (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and

dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form **IX**.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	60% (75ml)	40% EtOH (50ml)	125ml	5.1g/58%	16.8%
2	60% (75ml)	40% MeOH (50ml)	125ml	4.1g/64%	11.8%
3	60% (75ml)	40% IPA (50ml)	125ml	5.3g/79%	14.1%

Example 69:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form **IX**.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	80%	20%	250ml	5.7g/84%	15.1%

	(200ml)	EtOH (50ml)			
2	80% (200ml)	20% MeOH (50ml)	250ml	5.6g/86%	12.4%
3	80% (200ml)	20% IPA (50ml)	250ml	5.6g/83%	14.5%

Preparation of ZLD-Na_3 crystal form XI

Example 70:

A 250ml flask was loaded with Zoledronic acid form XII (5.0g), Sodium hydroxide (1.4g), absolute Ethanol (50ml) and water (2.5ml) [= 5% v/v water in Ethanol]. The reaction mixture was heated to reflux temperature for 20 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x25ml) and dried in a vacuum oven at 50^0C for 24 hours to give 5.4g (86%) of Zoledronate trisodium crystal form XI (LOD by TGA=8.9%).

Example 71:

A 250ml flask was loaded with Zoledronic acid form XII (5.0g), Sodium hydroxide (1.4g), Methanol (50ml) and water (2.5ml) [= 5% v/v water in Methanol]. The reaction mixture was heated to reflux temperature for 22 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x50ml) and dried in a vacuum oven at 50^0C for 24 hours to give 5.4g (84%) of Zoledronate trisodium crystal form XI in a mixture with crystal form IX (LOD by TGA=10.5%).

General procedure for the preparation of amorphous Zoledronate sodium

Example 72:

A 100ml flask was loaded with Zoledronic acid crystal form XII (2.0g), Sodium hydroxide (0.57g) and water (10ml). The reaction mixture was stirred at room

temperature to obtain a clear solution. Then the solution was concentrated under vacuum to obtain a precipitate. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with water (2x10ml) and dried in a vacuum oven at 50^0C for 24 hours to give 0.76g of amorphous Zoledronate sodium.

Summarizing tables – crystals forms of Zoledronate sodium salts

1. Preparation of Zoledronate monosodium salt:

	EtOH	MeOH	IPA
0% v/v H_2O	I (ZLD-Ac)+XV(ZLD-Ac)	XV(ZLD-Ac)	reaction
20% v/v H_2O	**XII** (ZLD-Ac) >**IV**		
50% v/v H_2O	XVI	No reaction	XVI
80% v/v H_2O	VIII>>XII (ZLD-Ac)	VIII	VIII

- ***Using ZLD-Ac (assay 100%, Form I) as a starting material***

2. Preparation of Zoledronate disodium salt:

	EtOH	MeOH	IPA
5% v/v H_2O	XIII	XXVII	No reaction
20% v/v H_2O	V	XIV	V
50% v/v H_2O	V>VI+IX	V>>IX?	V
80% v/v H_2O	VII	XXV	VI

- ***Using ZLD-Ac (assay 100%, Form I) as a starting materia***

	EtOH	MeOH	IPA	DMF
20% v/v H_2O	V	V+XXVII	X	XIV
40% v/v H_2O	V	V>XII	V	=
50% v/v H_2O	V	V>VIII	V>VIII	=
60% v/v H_2O	VI	VI+11.3	VIII (crop I) VII+8.2 (crop II)	=
80% v/v H_2O	VII	VII	VII+8.2,9.1	-
100% v/v H_2O	Amorphous			

- *Using ZLD-Ac (assay 90%, Form XII) as a starting material*

3. Preparation of Zoledronate trisodium salt:

	EtOH	MeOH	IPA
5% v/v H_2O	XI	IX+XI	-
20% v/v H_2O	IX+IV	IX>IV+9.9	IX+6.4,6.7
40% v/v H_2O	IX	IX+V	IX+IV
50% v/v H_2O	IX+IV	IX+V>>IV	IX+IV+amorph.+7.1
60% v/v H_2O	IX+IV	IX>IV	IX
80% v/v H_2O	IX	IX	IX
100% v/v H_2O	Amorphous		

- *Using ZLD-Ac (assay 90%, Form XII) as a starting material*

What is claimed is:

1. Crystalline solid zoledronic acid (Form I) characterized by a powder X-ray diffraction pattern having peaks at 12.1, 12.8, 15.7, and 18.9 ± 0.2 °2θ.
2. The crystalline solid zoledronic acid of claim 1 further characterized by a powder X-ray diffraction pattern with peaks at 20.9, 21.3, 21.8, 22.2, 25.8, 27.6, 29.2, 32.5, and 32.9 ±0.2 °2θ.
3. The crystalline solid zoledronic acid of claim 1, which contains less than about 5% of other polymorphic forms of zoledronic acid.
4. The crystalline solid zoledronic acid of claim 1, of which no more than about 5% transforms to zoledronic acid Form II upon exposure to 100% relative humidity (RH) for 7 days.
5. The crystalline solid zoledronic acid of claim 4, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 100% relative humidity (RH) for 7 days.
6. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 100% relative humidity (RH) for 7 days, absorbs less than about 0.2% water.
7. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 100% relative humidity (RH) for 7 days, retains its X-ray diffraction pattern substantially as shown in figure no.1.
8. The crystalline solid zoledronic acid of claim 1, of which no more than about 5% transforms to zoledronic acid form II upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
9. The crystalline solid zoledronic acid of claim 8, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
10. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, absorbs less than about 0.2% water.
11. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, retains its X-ray diffraction pattern substantially as shown in figure no.1.
12. A pharmaceutical composition comprising the crystalline zoledronic acid of claim 1.

13. The crystalline solid zoledronic acid of claim 1, which is a monohydrate.
14. Crystalline solid zoledronic acid (Form II) characterized by a powder X-ray diffraction pattern having peaks at 14.6, 15.4, 19.1, 22.9, and 23.9 ± 0.2 °2θ.
15. The crystalline zoledronic acid of claim 14, further characterized by a powder X-ray diffraction pattern with peaks at 20.8, 21.7, 25.1, 26.7, 29.5, 29.9, and ±0.2 °2θ.
16. The crystalline solid zoledronic acid of claim 14, which is a monohydrate.
17. Crystalline solid zoledronic acid (Form XII) characterized by a powder X-ray pattern having peaks at 9.0, 13.9, 14.8, 21.5, 24.7, and 29.8 ± 0.2 °2θ.
18. The crystalline zoledronic acid of claim 17, further characterized by a powder X-ray diffraction pattern with peaks at 17.0, 20.6, 20.8, 22.4, 25.8, 27.7, 28.4, 28.7, 29.1, 30.8, 3.19, 32.3, and 32.9 ±0.2 °2θ.
19. The crystalline solid zoledronic acid of claim 17, which is a monohydrate.
20. Crystalline solid zoledronic acid (Form XV) characterized by a powder X-ray diffraction pattern having peaks at 10.1, 17.3, 19.3, and 23.2 ± 0.2 °2θ.
21. The crystalline zoledronic acid of claim 20, further characterized by a powder X-ray diffraction pattern with peaks at 14.5, 16.7, 18.1, 24.5, 25.1, 25.7, 28.5, 29.1, 29.6, and 30.4 ±0.2 °2θ.
22. The crystalline solid zoledronic acid of claim 20, which is anhydrous.
23. Crystalline solid zoledronic acid (Form XVIII) characterized by a powder X-ray diffraction pattern having peaks at 10.7, 13.0, 16.4, 17.4, and 28.5 ± 0.2 °2θ.
24. The crystalline zoledronic acid of claim 23, further characterized by a powder X-ray diffraction pattern with peaks at 13.3, 18.1, 19.3, 21.3, 23.7, 25.9, 31.5, and 34.5 ±0.2 °2θ.
25. The crystalline solid zoledronic acid of claim 23, which is a monohydrate.
26. Crystalline solid zoledronic acid (Form XX) characterized by a powder X-ray diffraction pattern having peaks at 12.2, 19.3, 20.2, 21.3, 25.1, and 27.25 ± 0.2 °2θ.
27. The crystalline zoledronic acid of claim 26, further characterized by a powder XRD pattern with peaks at 11.4, 14.9, 15.5, 17.2, 18.2 and 30.5 ±0.2 °2θ.
28. The crystalline solid zoledronic acid of claim 26, which is anhydrous.

29. Crystalline solid zoledronic acid (Form XXVI) characterized by a powder X-ray diffraction pattern having peaks at 9.8, 14.5, 17.1, 17.6, and 18.3 ± 0.2 °2θ.
30. The crystalline zoledronic acid of claim 29, further characterized by a powder X-ray diffraction pattern with peaks at 18.8, 19.7, 21.4, 25.7, 26.6, and 28.1 ±0.2 °2θ.
31. The crystalline solid zoledronic acid of claim 29, which is anhydrous.
32. A pharmaceutical composition comprising the crystalline solid zoledronic acid of claim 14.
33. Crystalline solid zoledronate monosodium.
34. Crystalline solid zoledronate monosodium hydrate.
35. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 15.5, 18.6, 23.6, and 26.8 ± 0.2 °2θ (Form VIII).
36. The crystalline solid zoledronate monosodium of claim 35, further characterized by a powder X-ray diffraction pattern with peaks at 11.8, 17.6, 20.1, 24.7, 25.0, 28.4, 31.7, and 32.8 ± 0.2 °2θ.
37. The crystalline solid zoledronate monosodium of claim 35, which is a trihydrate.
38. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 7.3, 8.8, 14.7, 21.8, and 29.6 ± 0.2 °2θ (form XVI).
39. The crystalline solid zoledronate monosodium of claim 38, further characterized by a powder X-ray diffraction pattern with peaks at 13.8, 16.8, 20.4, 21.4, 24.4, 25.6, 27.5, 28.2, and 31.7 ± 0.2 °2θ.
40. The crystalline solid zoledronate monosodium of claim 38, which is a dihydrate.
41. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 9.0, 14.5, 21.4, 24.5, and 29.2 ± 0.2 °2θ (Form XVII).
42. The crystalline solid zoledronate monosodium of claim 41, further characterized by a powder X-ray diffraction pattern with peaks at 13.9, 15.5, 16.8, 18.6, 22.3, 23.6, 26.7, 27.7, and 32.3 ± 0.2 °2θ.
43. The crystalline solid zoledronate monosodium of claim 41, which is a dihydrate.
44. Crystalline solid zoledronate disodium.

45. Crystalline solid zoledronate disodium hydrate.

46. Crystalline solid zoledronate disodium anhydrous.

47. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having at 11.3, 14.8, 15.5, 17.4, and 19.9 ± 0.2 °2θ (Form V).

48. The crystalline solid zoledronate disodium of claim 47, further characterized by a powder X-ray diffraction pattern with peaks at 18.0, 18.9, 19.7, 22.7, 25.0, 26.7, 30.9, and 34.5 ± 0.2 °2θ.

49. The crystalline solid zoledronate disodium of claim 47, which is a dihydrate.

50. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 7.2, 13.3, 13.7, 14.5, and 21.7 ± 0.2 °2θ (Form VI).

51. The crystalline solid zoledronate disodium of claim 50, further characterized by a powder X-ray diffraction pattern with peaks at 8.2, 16.6, 16.9, 17.3, 25.9, 26.6, 30.7, 31.9, and 32.9± 0.2 °2θ.

52. The crystalline solid zoledronate disodium of claim 50, which is a trihydrate.

53. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.2 11.6, 12.6, 13.7 ± 0.2 °2θ (Form VII).

54. The crystalline solid zoledronate disodium of claim 53, further characterized by a powder X-ray diffraction pattern with peaks at 22.0, 23.2, 26.4, 27.1, 28.6, 28.8, 34.2± 0.2 °2θ.

55. The crystalline solid zoledronate disodium of claim 53, which is a tetrahydrate.

56. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.7, 14.4, 18.2, 20.4, and 20.7 ± 0.2 °2θ (Form X).

57. The crystalline solid zoledronate disodium of claim 56, further characterized by a powder X-ray diffraction pattern with peaks at 8.8, 13.7, 17.0, 19.8, 21.3, 24.4, 27.5, 27.9, 30.9, and 33.4± 0.2 °2θ.

58. The crystalline solid zoledronate disodium of claim 56, which is a hemihydrate.

59. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.5, 13.0, 16.1, 17.2, and 30.7 ± 0.2 °2θ (Form XIII).

60. The crystalline solid zoledronate disodium of claim 59, further characterized by a powder X-ray diffraction pattern with peaks at 10.2, 19.0, 20.0, 20.6, 22.3, 27.4, 28.6, 28.9, and 34.8± 0.2 °2θ.

61. The crystalline solid zoledronate disodium of claim 59, which is a hemihydrate.

62. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.6, 19.9, 28.5, and 34.8 ± 0.2 °2θ (Form XIV).

63. The crystalline solid zoledronate disodium of claim 62, further characterized by a powder X-ray diffraction pattern with peaks at 13.0, 15.1, 17.1, 20.5, 27.7, 29.6, 30.7, and 33.5± 0.2 °2θ.

64. The crystalline solid zoledronate disodium of claim 62, which is anhydrous.

65. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 11.6, 12.5, 13.7, 22.0, and 23.1 ± 0.2 °2θ (Form XIX).

66. The crystalline solid zoledronate disodium of claim 65, further characterized by a powder X-ray diffraction pattern with peaks at 6.2, 14.3, 15.3, 16.0, 18.5, 24.3, and 28.6 ± 0.2 °2θ.

67. The crystalline solid zoledronate disodium of claim 65, which is a pentahydrate.

68. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 7.4, 13.7, 17.6, and 21.9 ± 0.2 °2θ (Form XXV).

69. The crystalline solid zoledronate disodium of claim 68, further characterized by a powder X-ray diffraction pattern with peaks at 6.3, 9.5, 12.6, 14.6, 26.2, 27.1, and 28.6 ± 0.2 °2θ.

70. The crystalline solid zoledronate disodium of claim 68, which is a sesquihydrate.

71. The crystalline solid zoledronate disodium of claim 44, which is a monohydrate characterized by a powder X-ray diffraction pattern having peaks at 6.4, 8.2, 16.0, 17.4, 19.0, and 28.8 ± 0.2 °2θ (Form XXVII).

72. The crystalline solid zoledronate disodium of claim 71, further characterized by a powder X-ray diffraction pattern with peaks at 7.7, 10.2, 17.2, 18.1, 21.6, 25.7, and 25.9 ± 0.2 °2θ.

73. The crystalline solid zoledronate disodium of claim 71, which is a monohydrate.

74. Crystalline solid zoledronate trisodium.

75. The crystalline solid zoledronate trisodium of claim 74, characterized by a powder X-ray diffraction pattern having peaks at 8.3, 10.9, 15.0, 16.6, and 22.8 ± 0.2 °2θ (Form IX).

76. The crystalline solid zoledronate trisodium of claim 75, further characterized by a powder X-ray diffraction pattern with peaks at 13.1, 20.2, 20.6, 20.9, 25.0, 27.8, and 29.0 ± 0.2 °2θ.

77. The crystalline solid zoledronate trisodium of claim 75, which is a trihydrate.

78. The crystalline solid zoledronate trisodium of claim 74, characterized by a powder X-ray diffraction pattern having peaks at 6.2, 7.9, 8.8, 10.6, and 12.2 ± 0.2 °2θ (Form XI).

79. The crystalline solid zoledronate trisodium of claim 78, further characterized by a powder X-ray diffraction pattern with peaks at 15.0, 15.4, 17.5, 18.8, 19.6, 20.5, 22.3, 23.7, 25.7, 29.6, and 31.7 0.2 °2θ.

80. The crystalline solid zoledronate trisodium of claim 78, which is a dihydrate.

81. A process for preparing a solid crystalline zoledronate sodium salt comprising:
    a) dissolving zoledronic acid in water to form a solution;
    b) adding a base to the solution; and
    c) cooling the solution to precipitate crystalline zoledronate sodium.

82. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

83. The process of claim 82, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

84. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

85. The process of claim 84, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

86. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

87. The process of claim 86, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

88. A process for preparing a crystalline solid zoledronate sodium salt comprising:
   a) suspending zoledronic acid in a mixture of alcohol/water
   b) adding to the suspension of a) a solution of a base, in an equivalent mixture of alcohol/water as that used in the suspension of a), to form a reaction mixture; and
   c) stirring the reaction mixture for a time sufficient to precipitate a crystalline solid zoledronate sodium salt.

89. The process of claim 88, wherein the reaction mixture is stirred at reflux for about 10 to about 20 hours.

90. The process of claim 88, wherein the volume ratio of alcohol/water to zoledronic acid in a) and b) is 6-14 volumes.

91. The process of claim 88, wherein the alcohol in a) and b) is selected from the group consisting of methanol, ethanol, isopropanol and dimethylformamide.

92. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:1.

93. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:2.

94. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:1.1.

95. The process of claim 92, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

96. The process of claim 95, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

97. The process of claim 93 or claim 94, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

98. The process of claim 97, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

99. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:2.1.

100. The process of claim 99, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

101. The process of claim 100, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

102. A process for preparing a solid crystalline zoledronate sodium salt comprising:
   a) dissolving a crystal form of zoledronate sodium in water to form a solution; and
   b) cooling the solution to precipitate a crystal form of zoledronate sodium which is different from the starting form in a).

103. The process of claim 102, wherein the water is added in an amount of between 20-30 volumes per volume of zoledronate sodium.

104. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:
   a) adding a solution of a base in an 80%/20% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/ethanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form VIII.

105. The process of claim 104, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

106. The process of claim 104, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14.

107. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:
   a) adding a solution of a base in an 80%/20% v/v mixture of water/methanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/methanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form VIII.

108. The process of claim 107, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

109. The process of claim 107, wherein the volume ratio of water/methanol to zoledronic acid form I in the suspension and the solution is between 6-14.

110. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:
   a) adding a solution of a base in an 60%/40% v/v mixture of water/isopropanol to a suspension of zoledronic acid form I in an 60%/40% v/v mixture of water/isopropanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form VIII.

111. The process of claim 110, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

112. The process of claim 110, wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14.

113. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:
   a) adding a solution of a base in a 50%/50% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form XVI.

114. The process of claim 113, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

115. The process of claim 113, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14.

116. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:
   a) adding a solution of a base in a 50%/50% v/v mixture of water/isopropanol to a suspension of zoledronic acid Form I in a 50%/50% v/v mixture of water/isopropanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form XVI.

117. The process of claim 116, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

118. The process of claim 116 wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14.

119. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:
   a) adding a solution of a base in a 50%/50% v/v mixture of water/methanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature;
   b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
   c) precipitating zoledronate monosodium Form XVI.

120. The process of claim 119, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

121. The process of claim 119, wherein the volume ratio of water/methanol to zoledronic acid form I in the solution is between 6-14 and the volume ratio of water/ethanol in the suspension is between 6-14.

122. A process for preparing solid crystalline zoledronate sodium Form XVII comprising:
   a) dissolving zoledronic acid Form I in water to form a solution;
   b) adding a base to the solution; and
   c) cooling the solution, optionally with the addition of an organic solvent, to precipitate crystalline zoledronate sodium Form XVII.

123. A pharmaceutical composition comprising the crystalline solid zoledronate monosodium of claim 33.

124. A pharmaceutical composition comprising the crystalline solid zoledronate disodium of claim 44.

125. A pharmaceutical composition comprising the crystalline solid zoledronate trisodium of claim 74.

126. Amorphous monosodium zoledronate.

127. Amorphous disodium zoledronate.

128. Amorphous trisodium zoledronate.

129. A pharmaceutical composition comprising the amorphous solid zoledronate of claim 126.

130. A process for preparing zoledronate amorphous sodium comprising:

treating zoledronic acid and a base, in water at room temperature and precipitating zoledronate amorphous sodium.

131. The process of claim 130, wherein the ratio of acid:base is 1:1.1.

132. The process of claim 130, wherein the ratio of acid:base is 1:2.1.

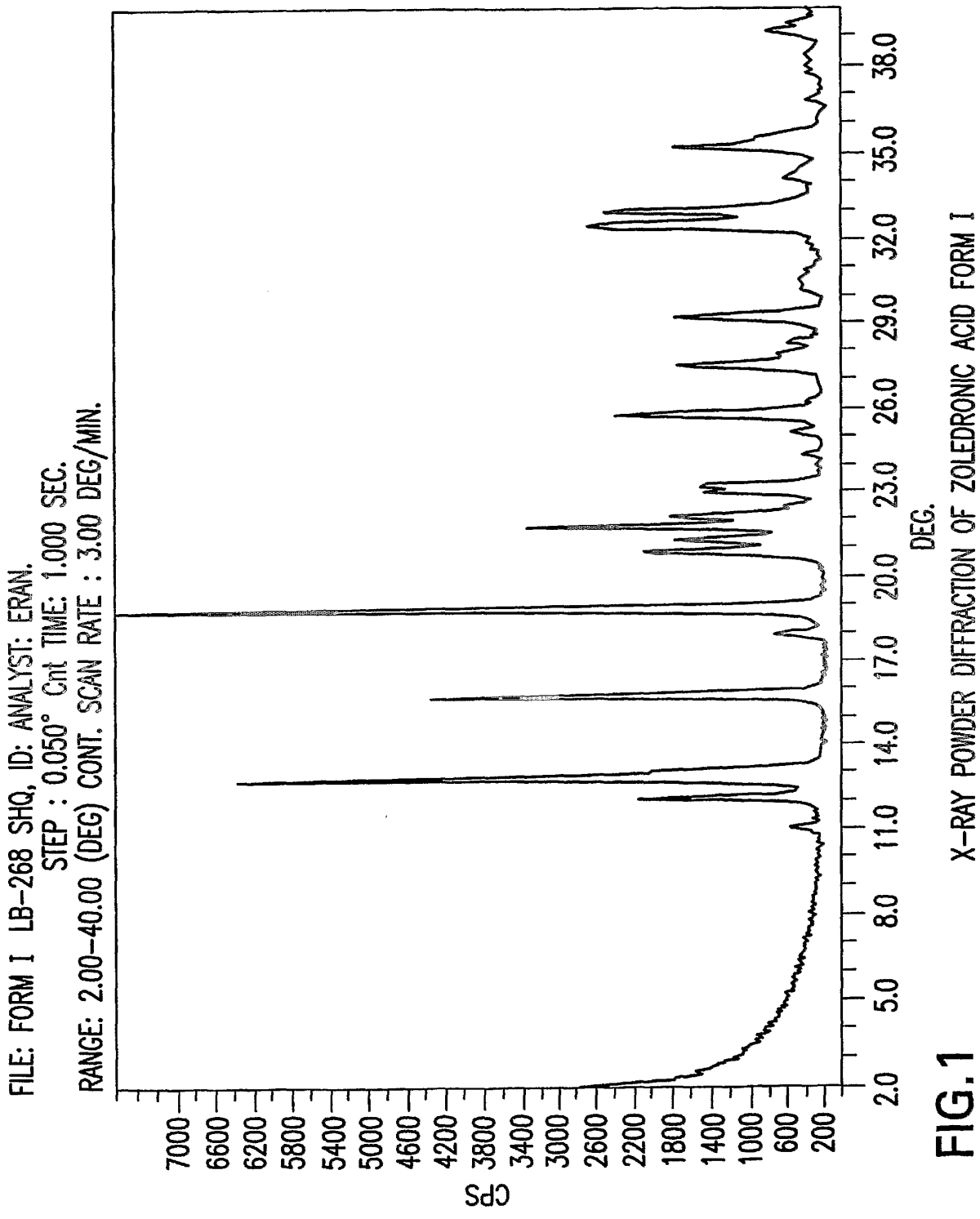
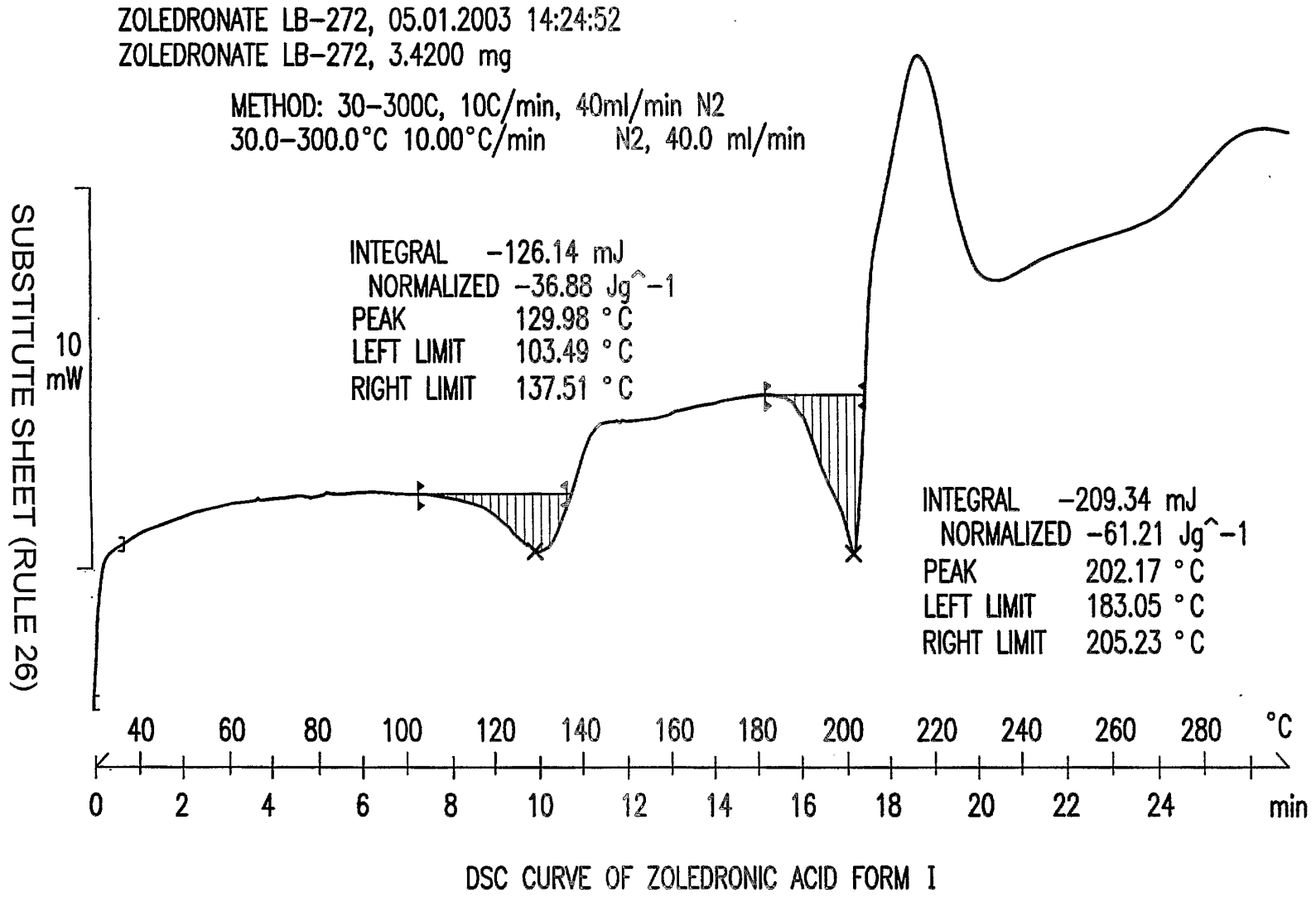


FIG. 1

X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM I



DSC CURVE OF ZOLEDRONIC ACID FORM I

FIG.2

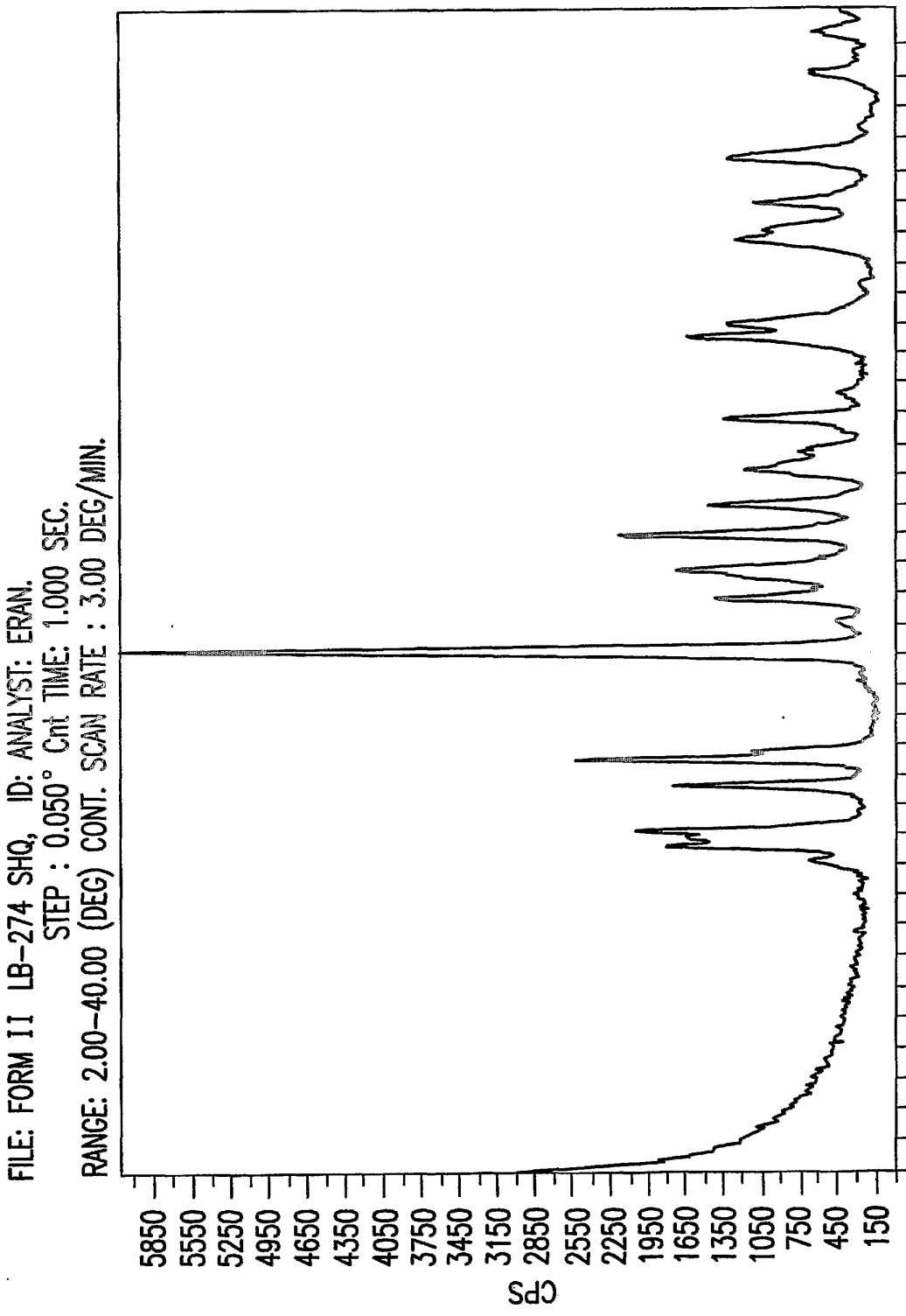


FIG.3 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM II

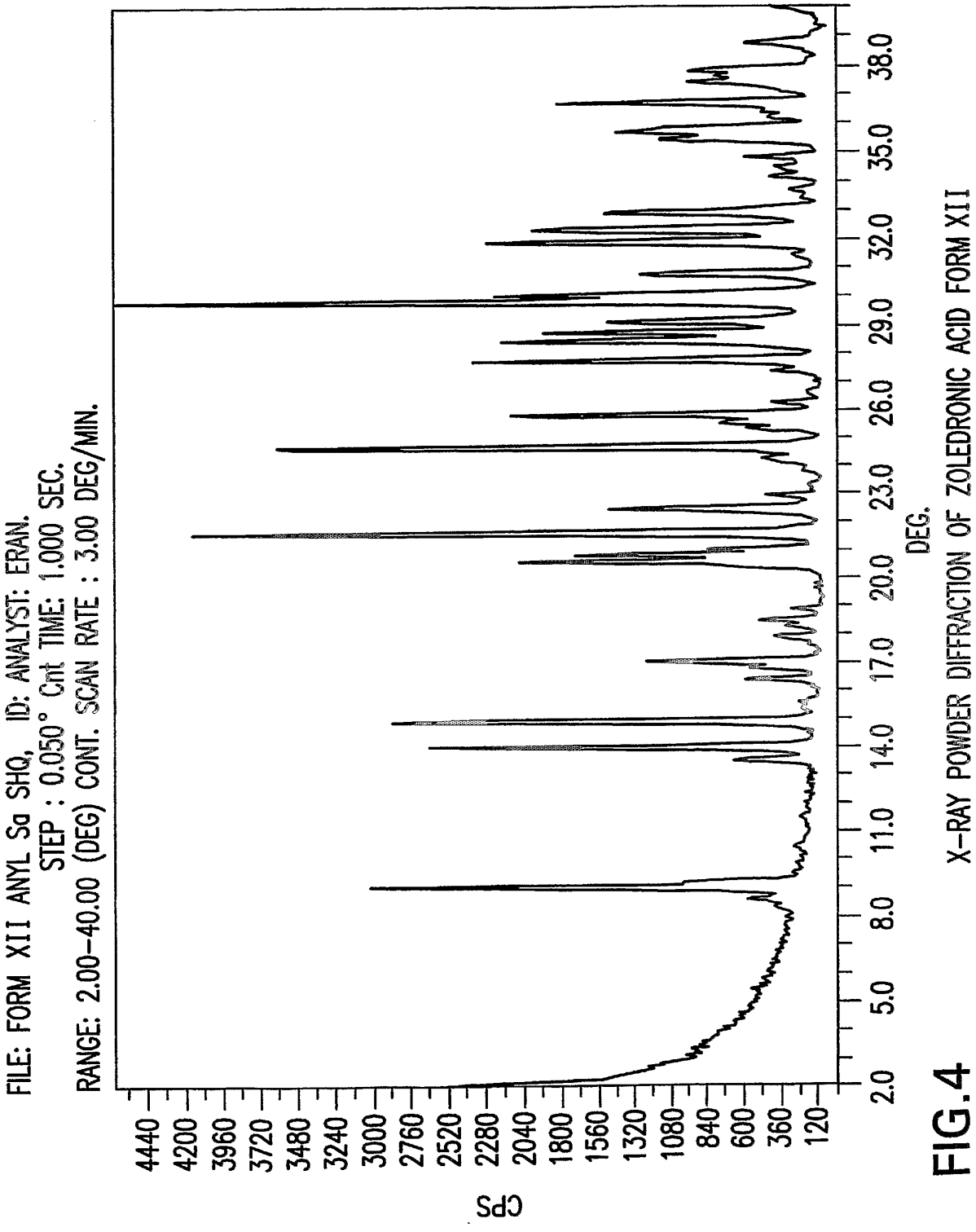
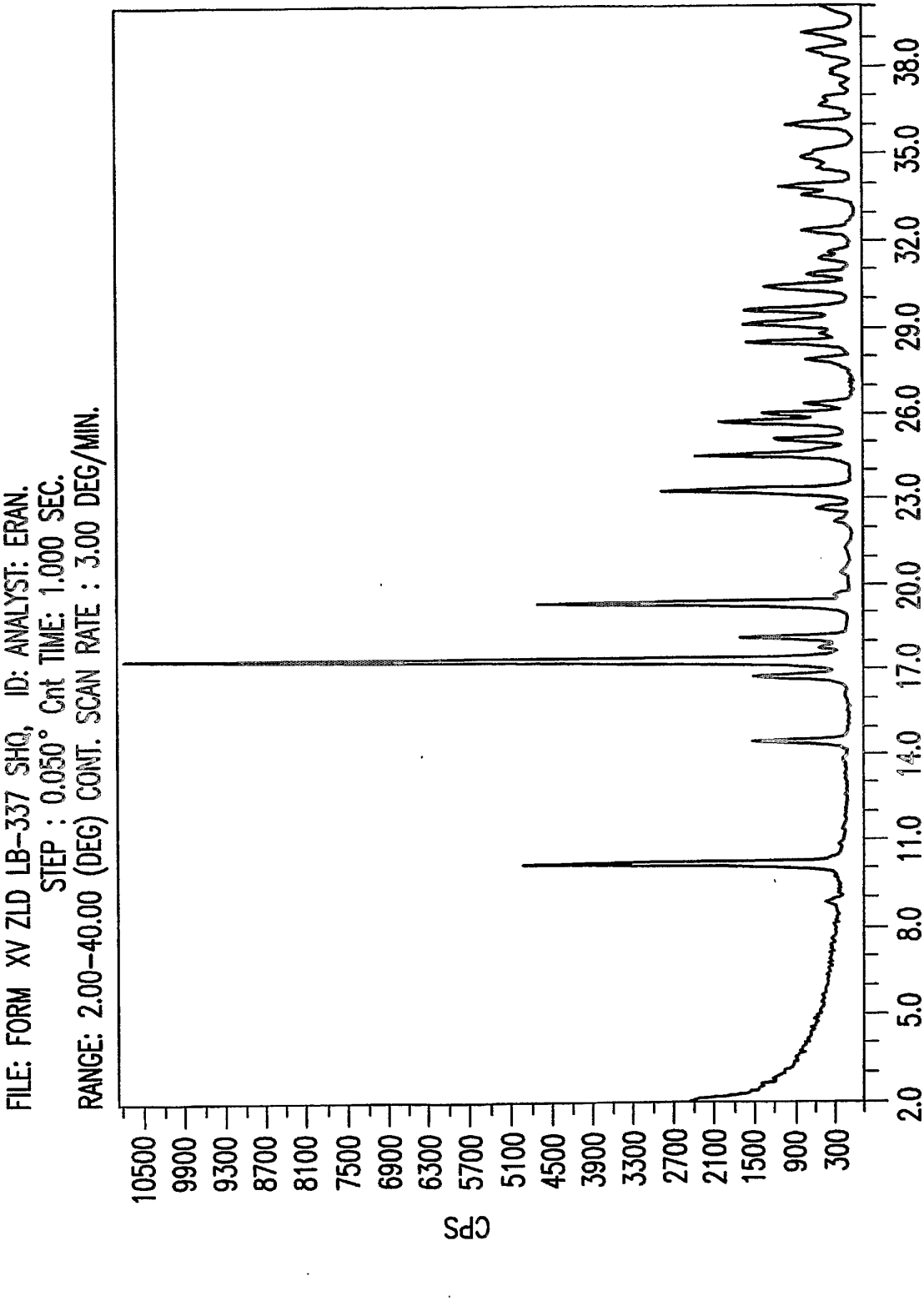


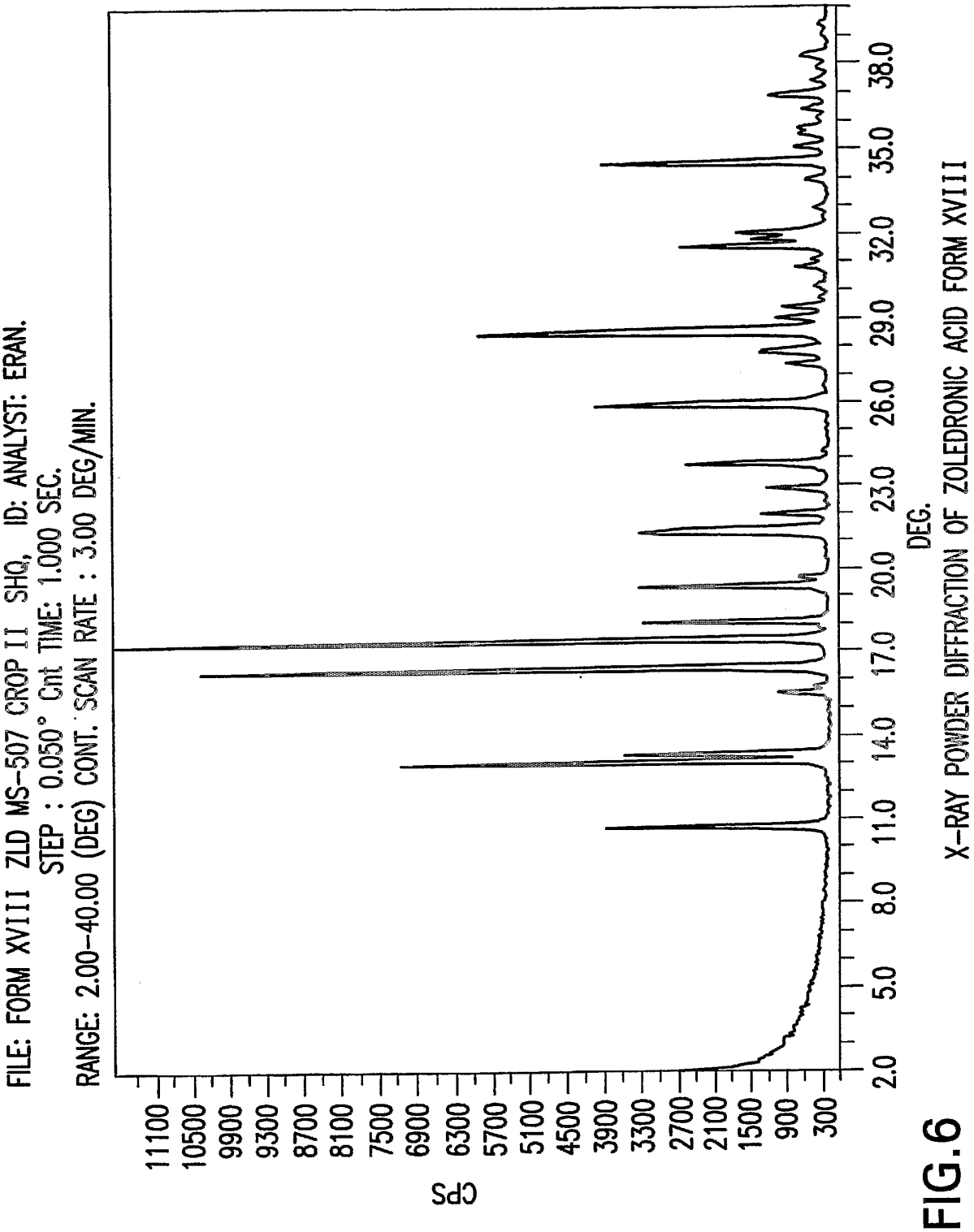
FIG.4

X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XII



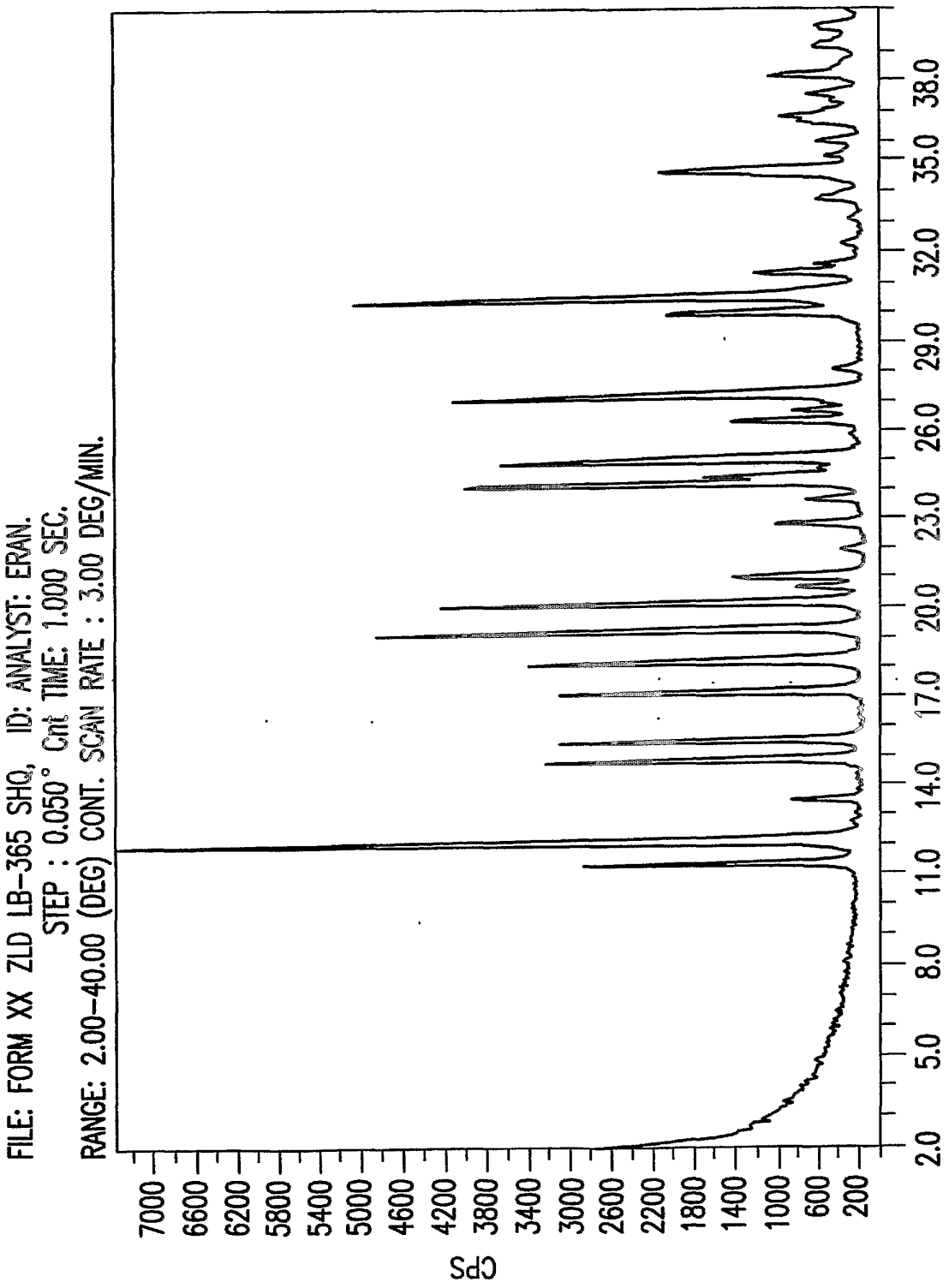
X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XV

FIG.5



X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XVIII

FIG.6



X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XX

FIG.7

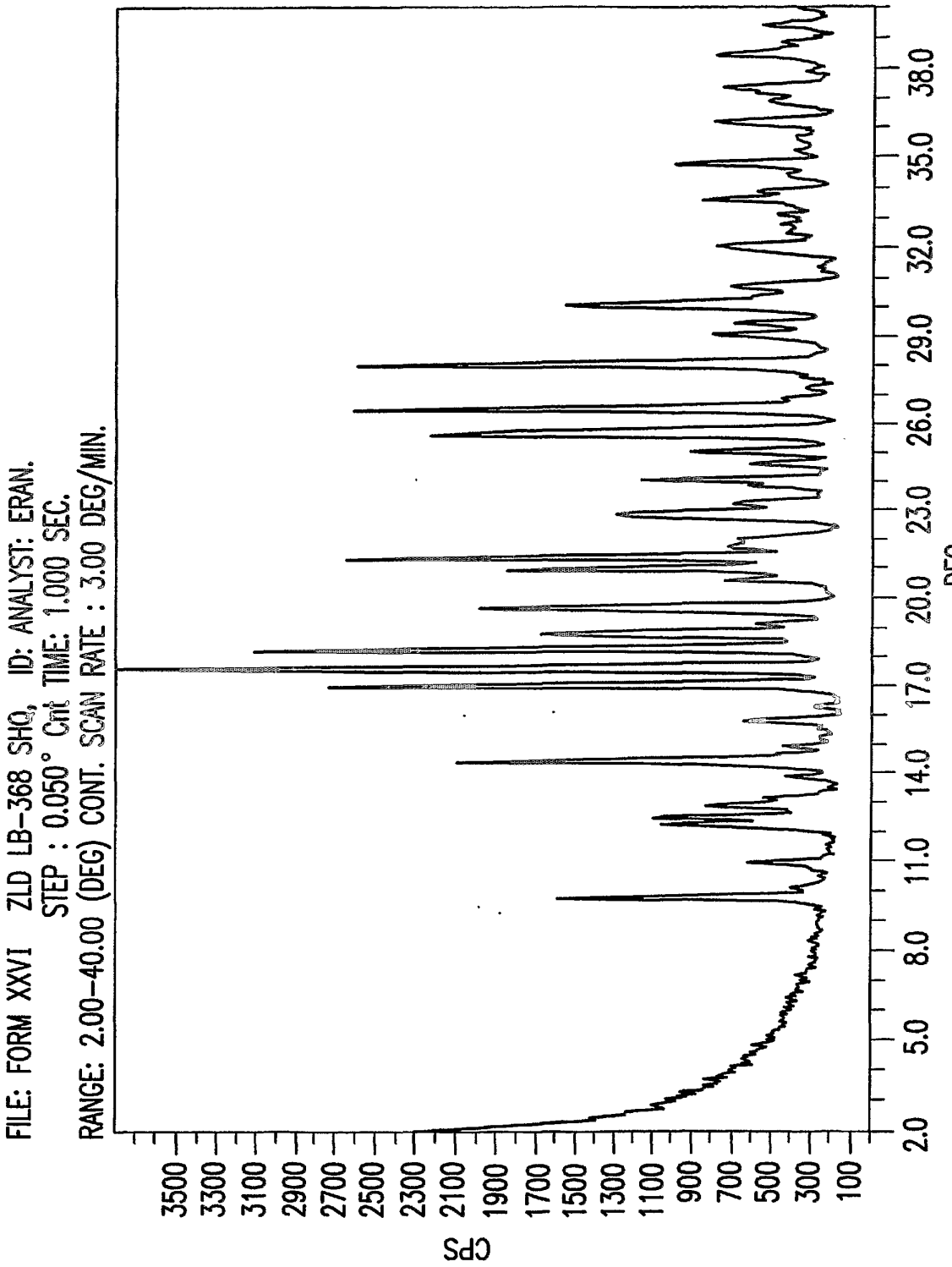


FIG.8

X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XXVI

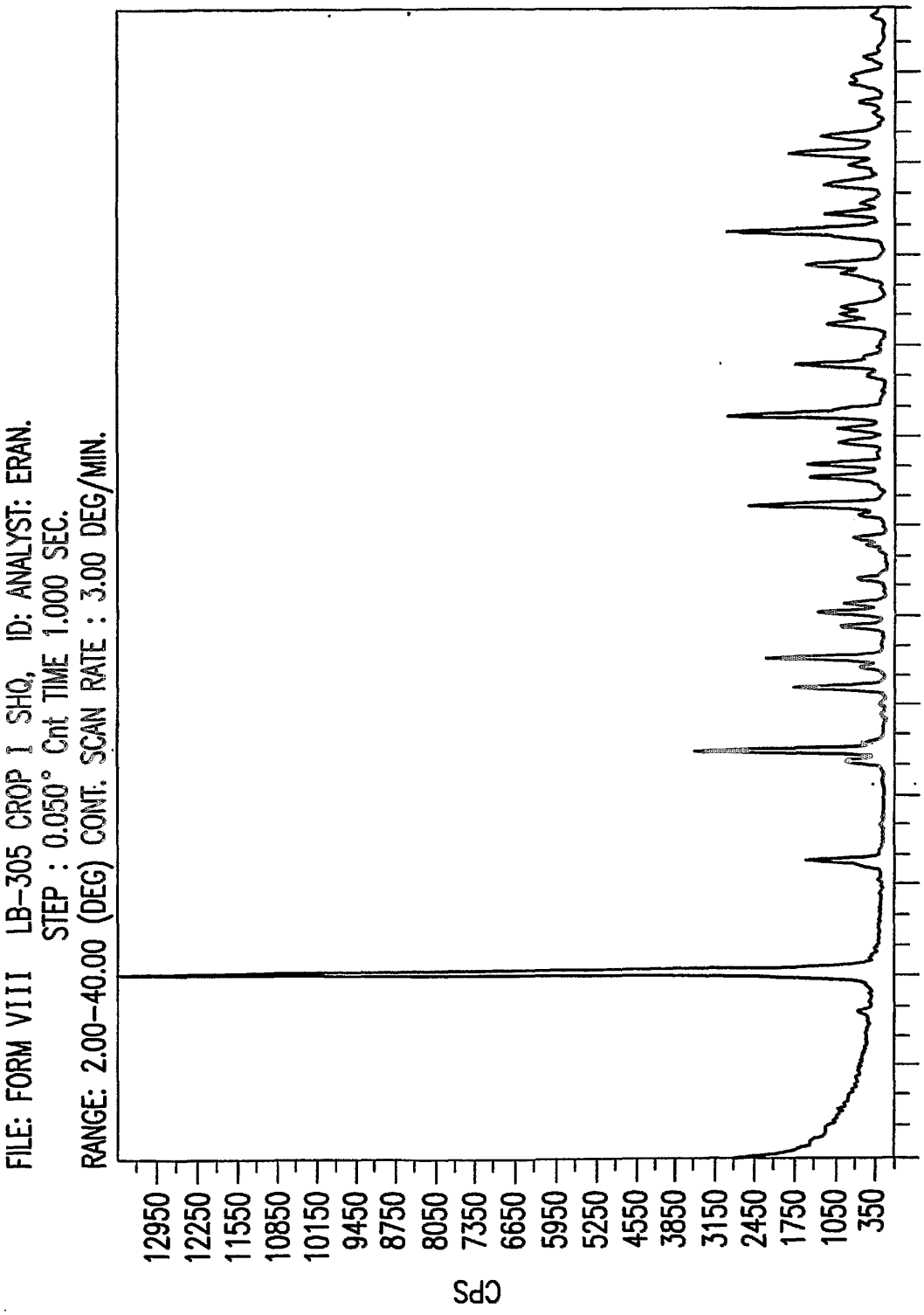


FIG.9 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM VIII

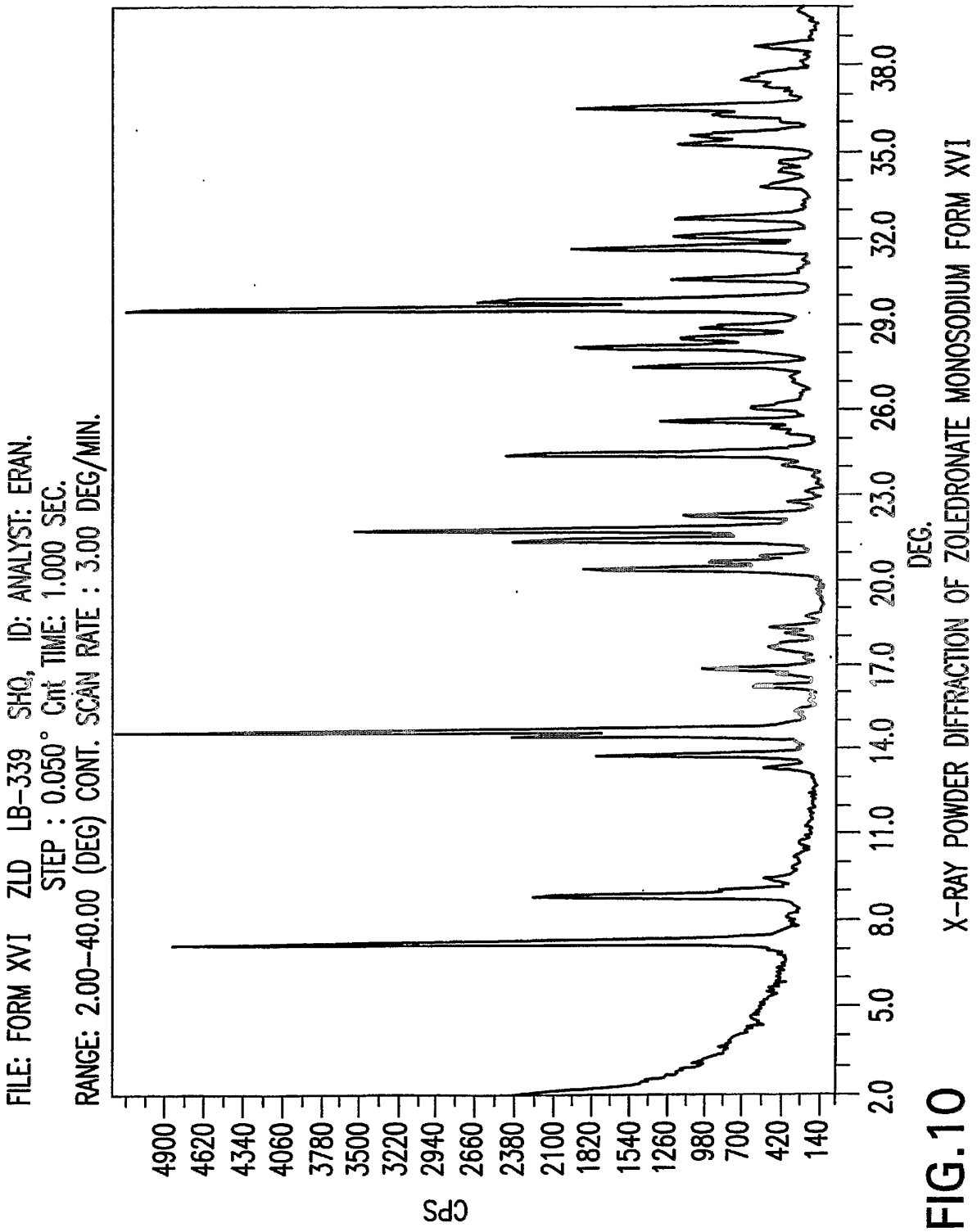


FIG.10

X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM XVI

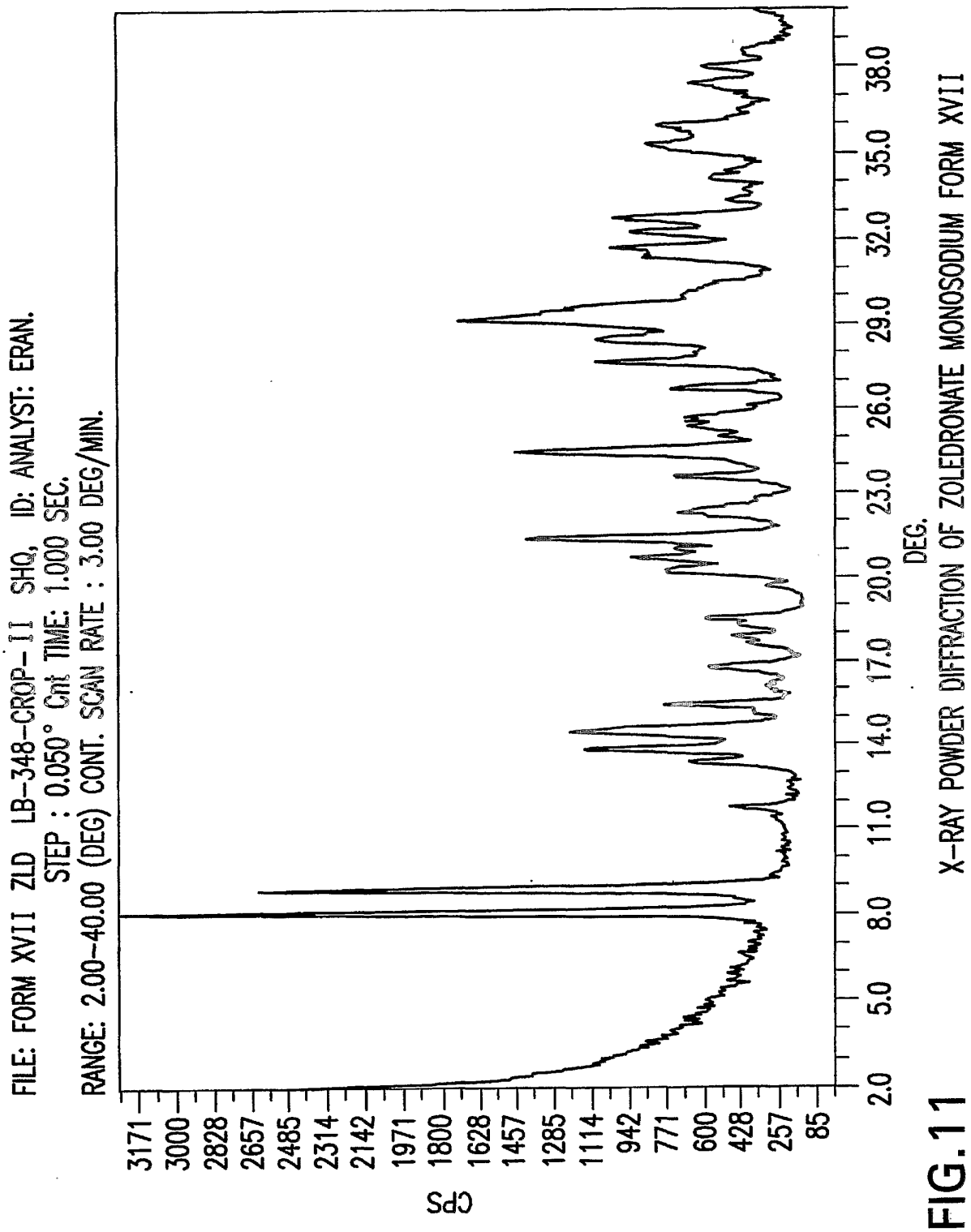


FIG. 11

X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM XVII

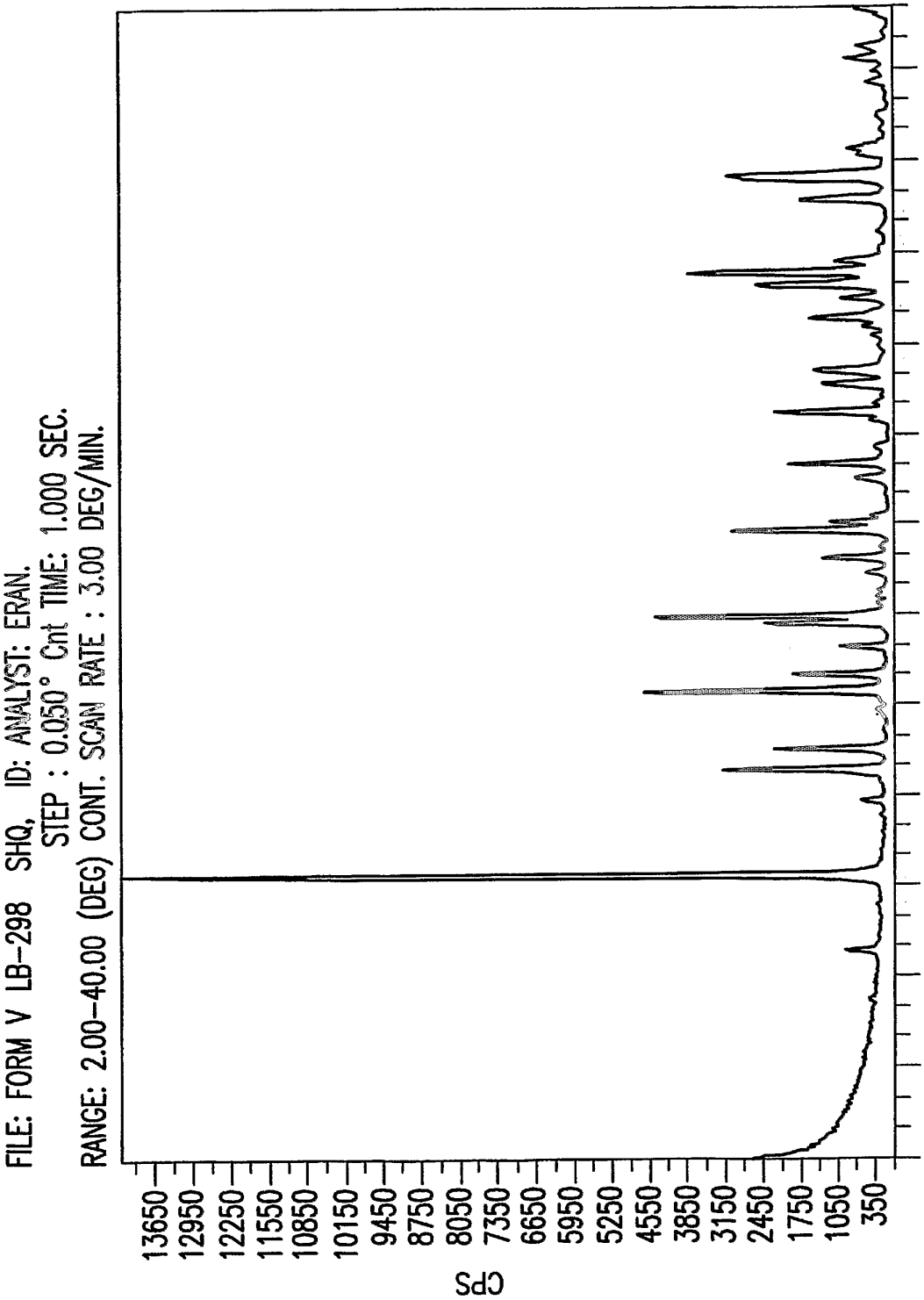


FIG.12 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM V

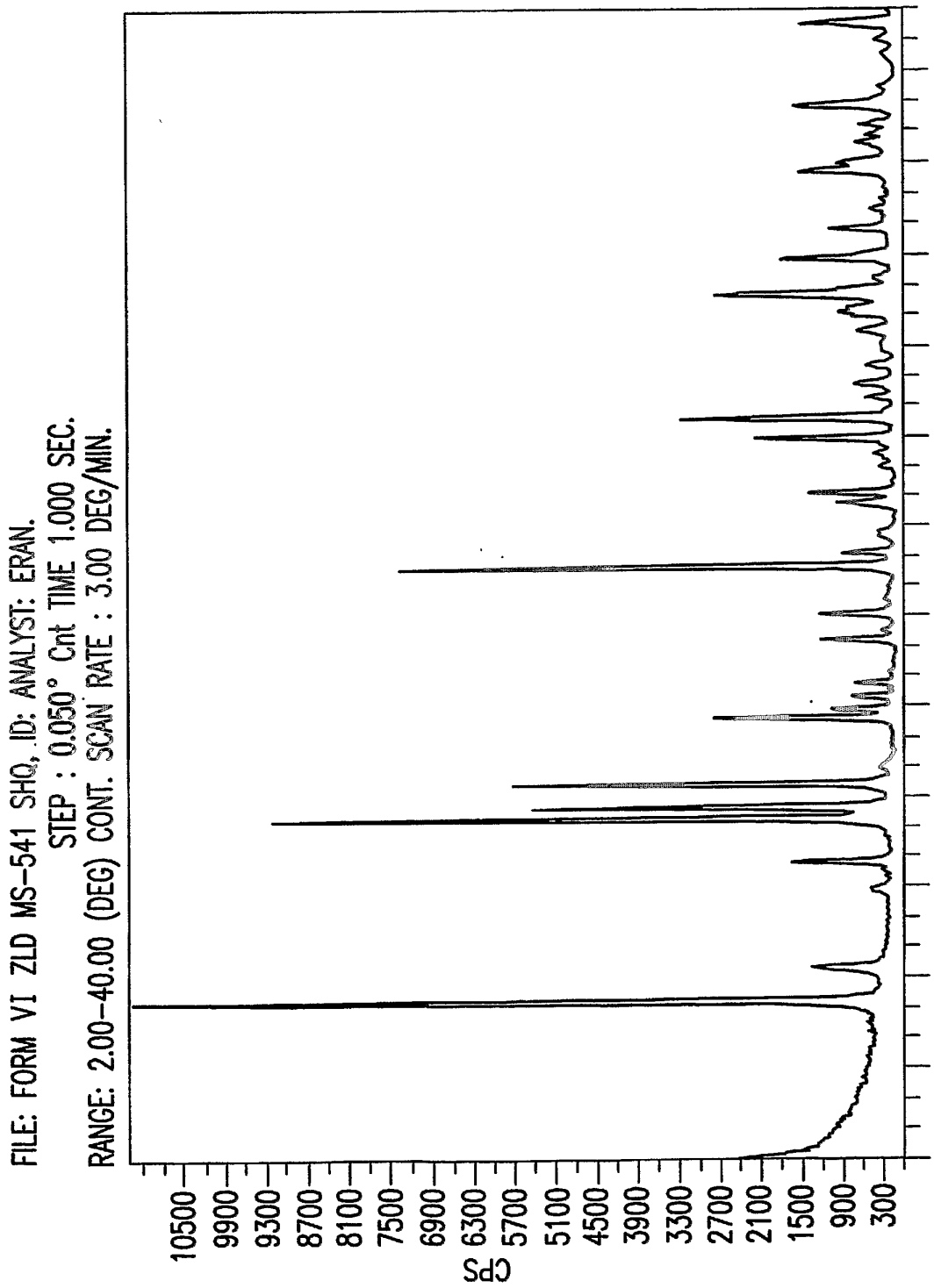


FIG.13 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM VI

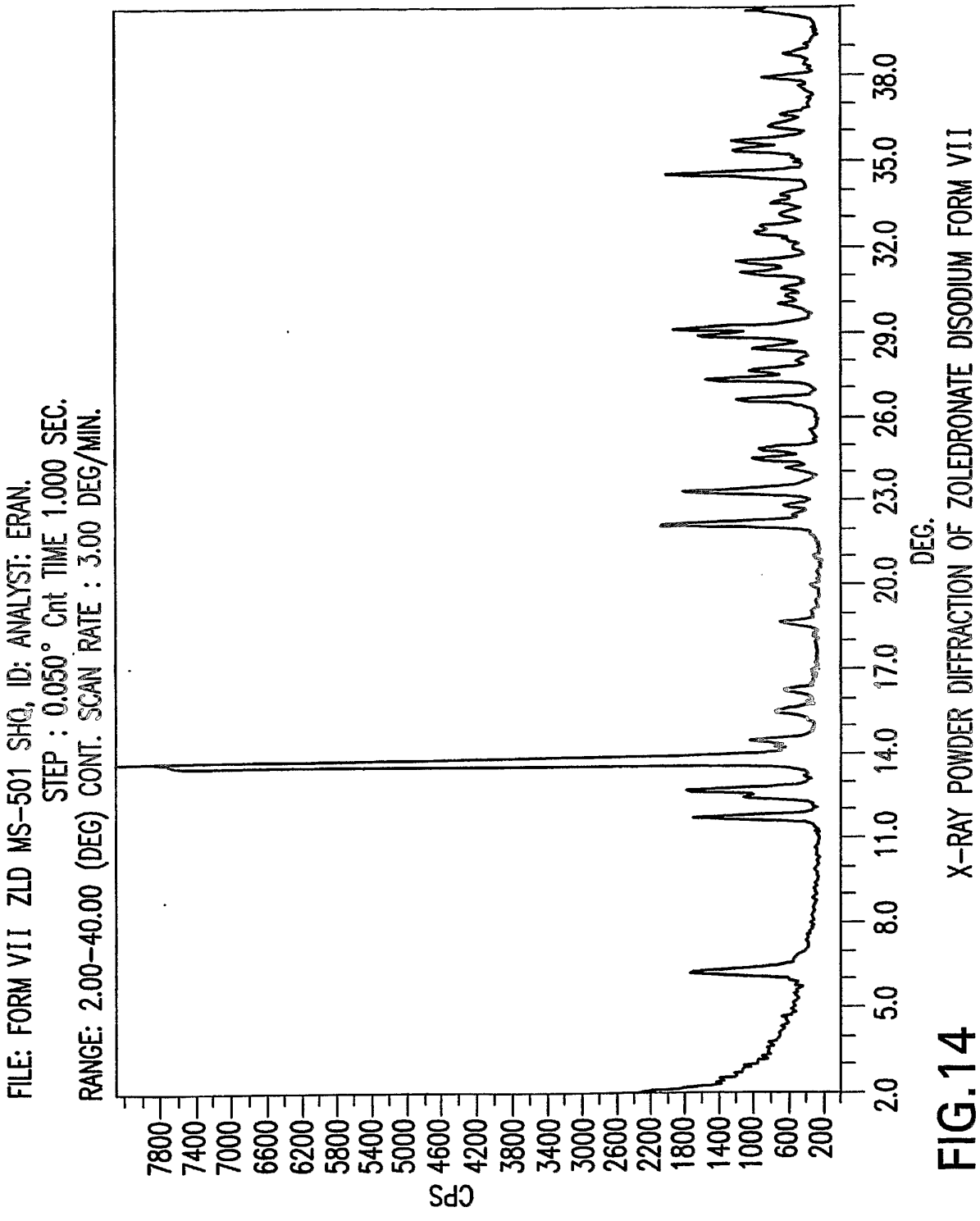


FIG.14 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM VII

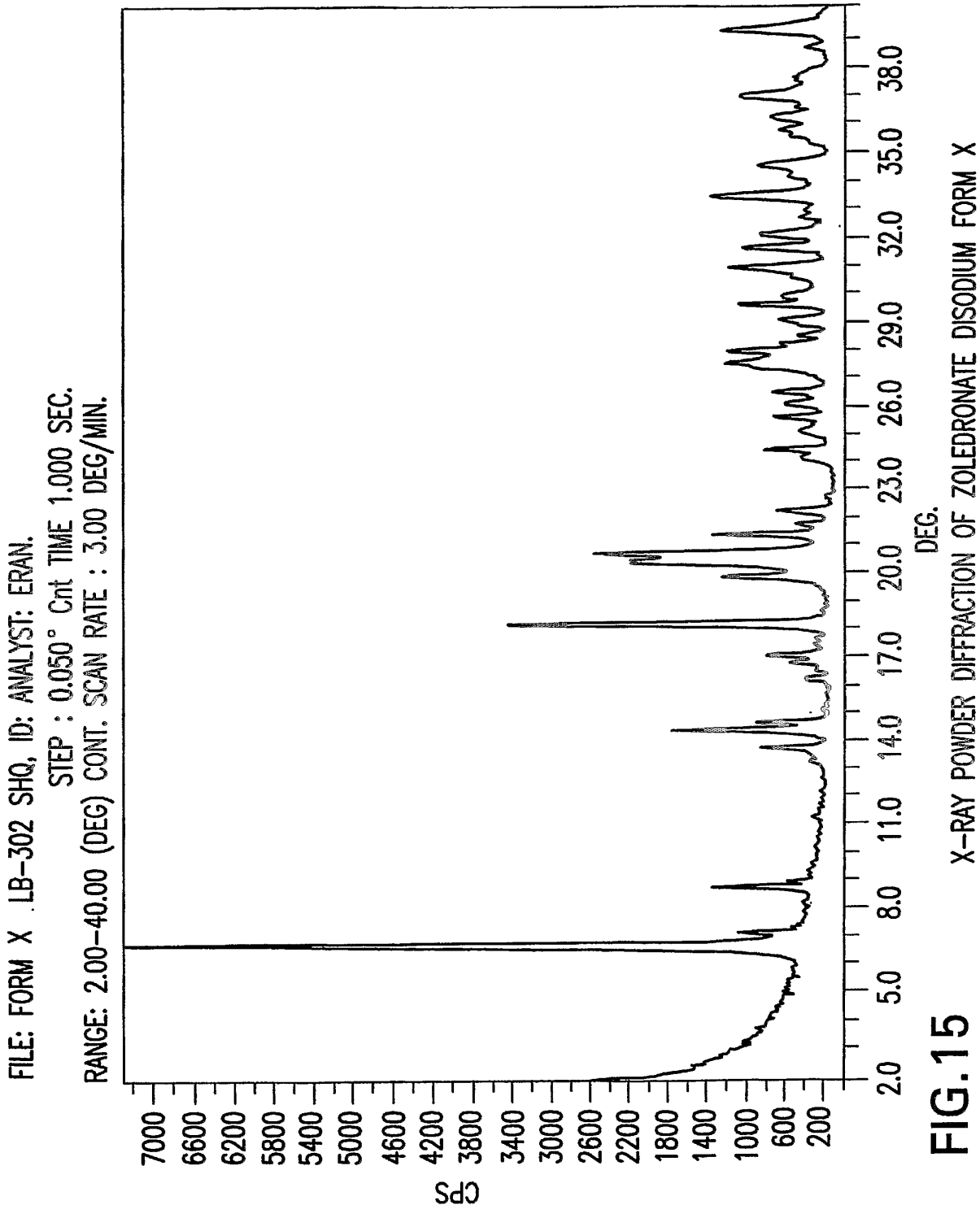


FIG.15 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM X

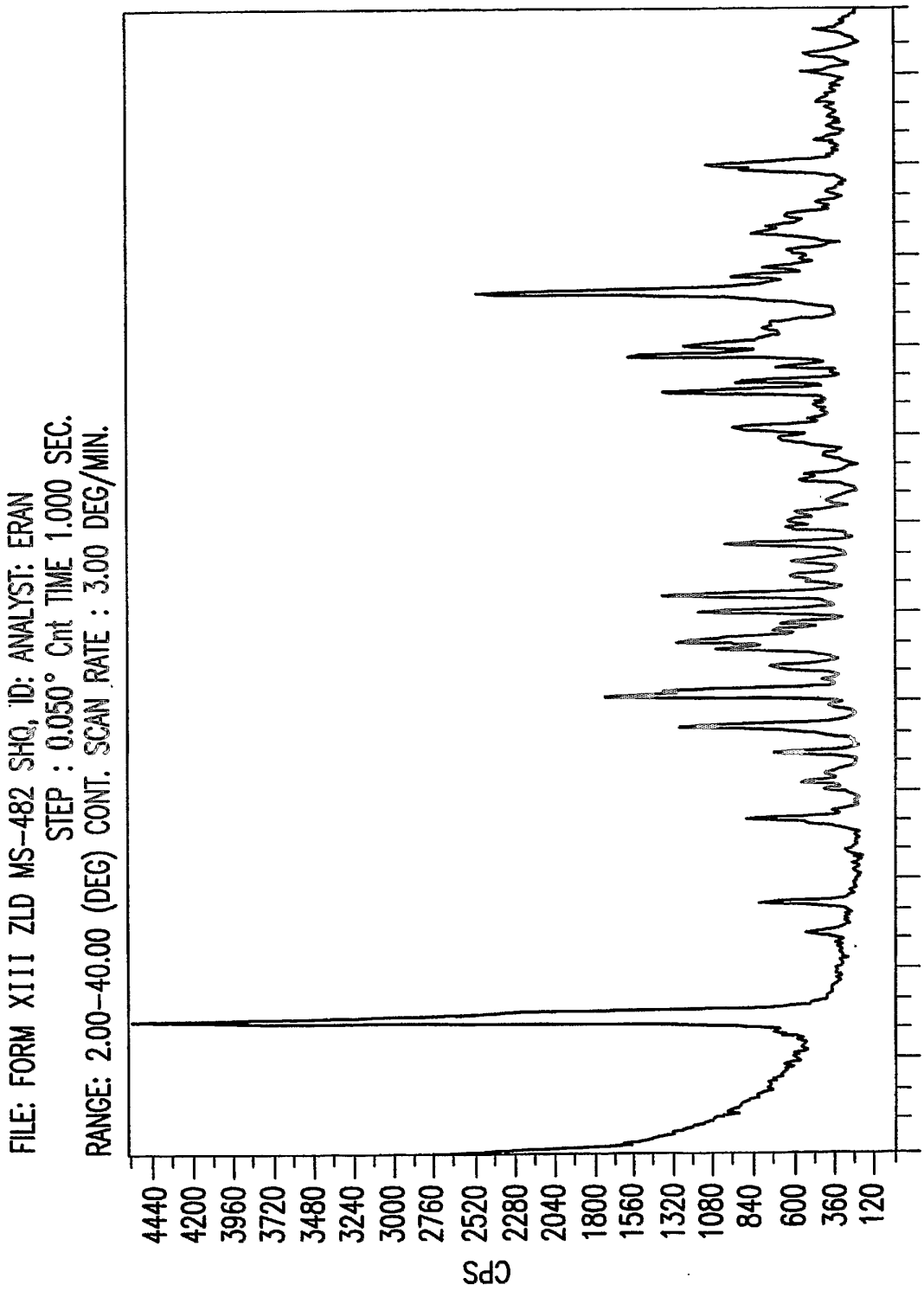


FIG.16 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIII

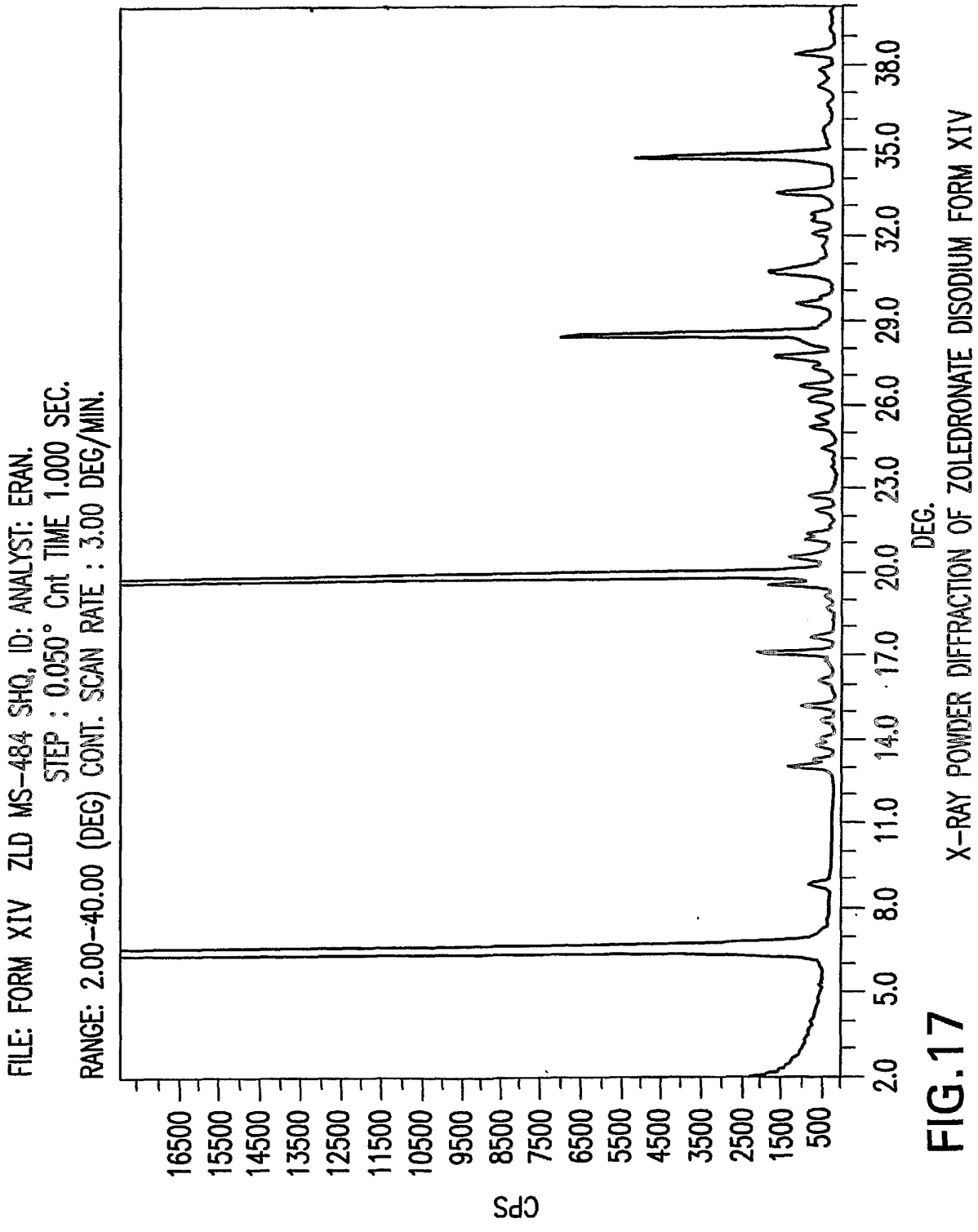


FIG.17

X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIV

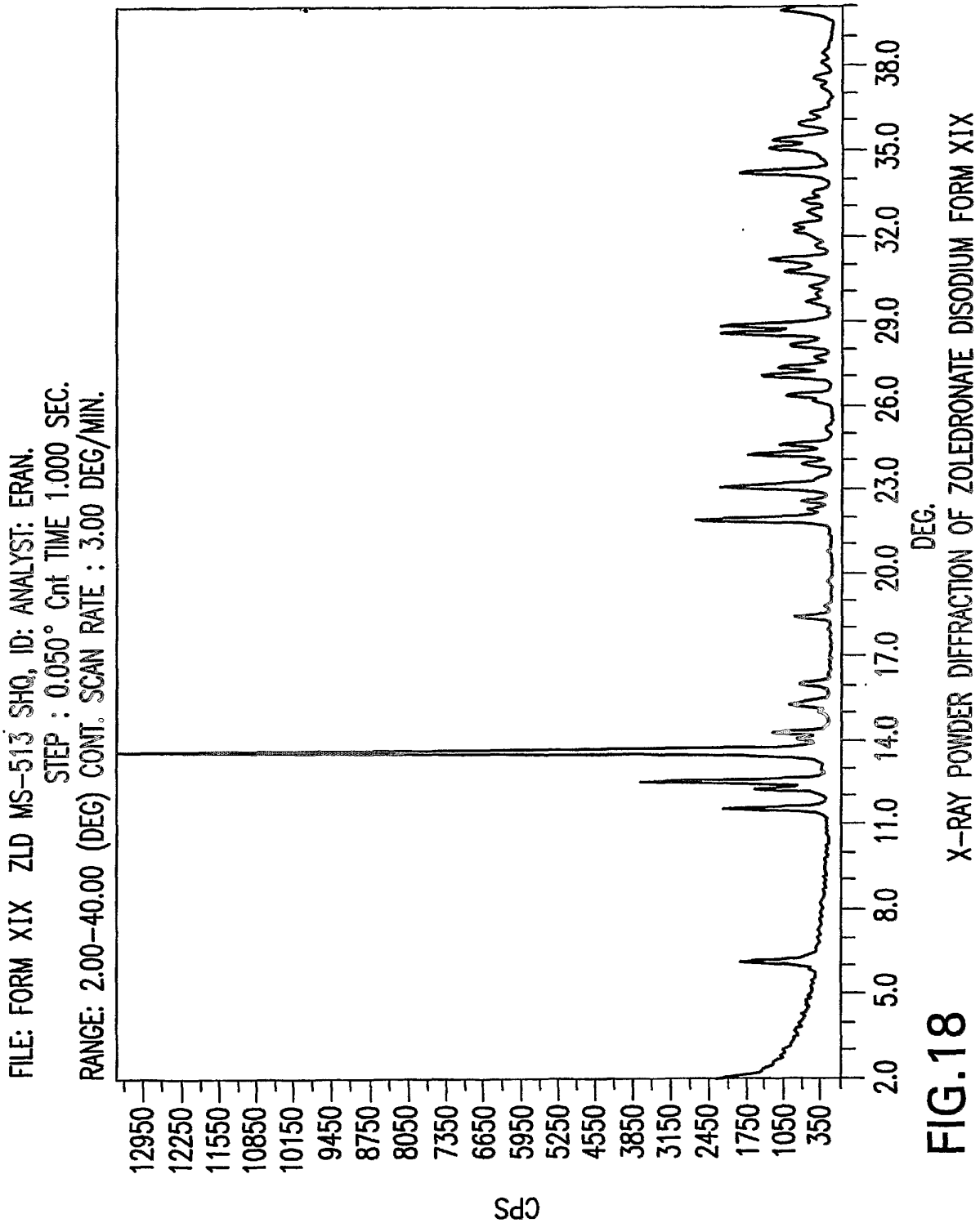


FIG.18 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIX

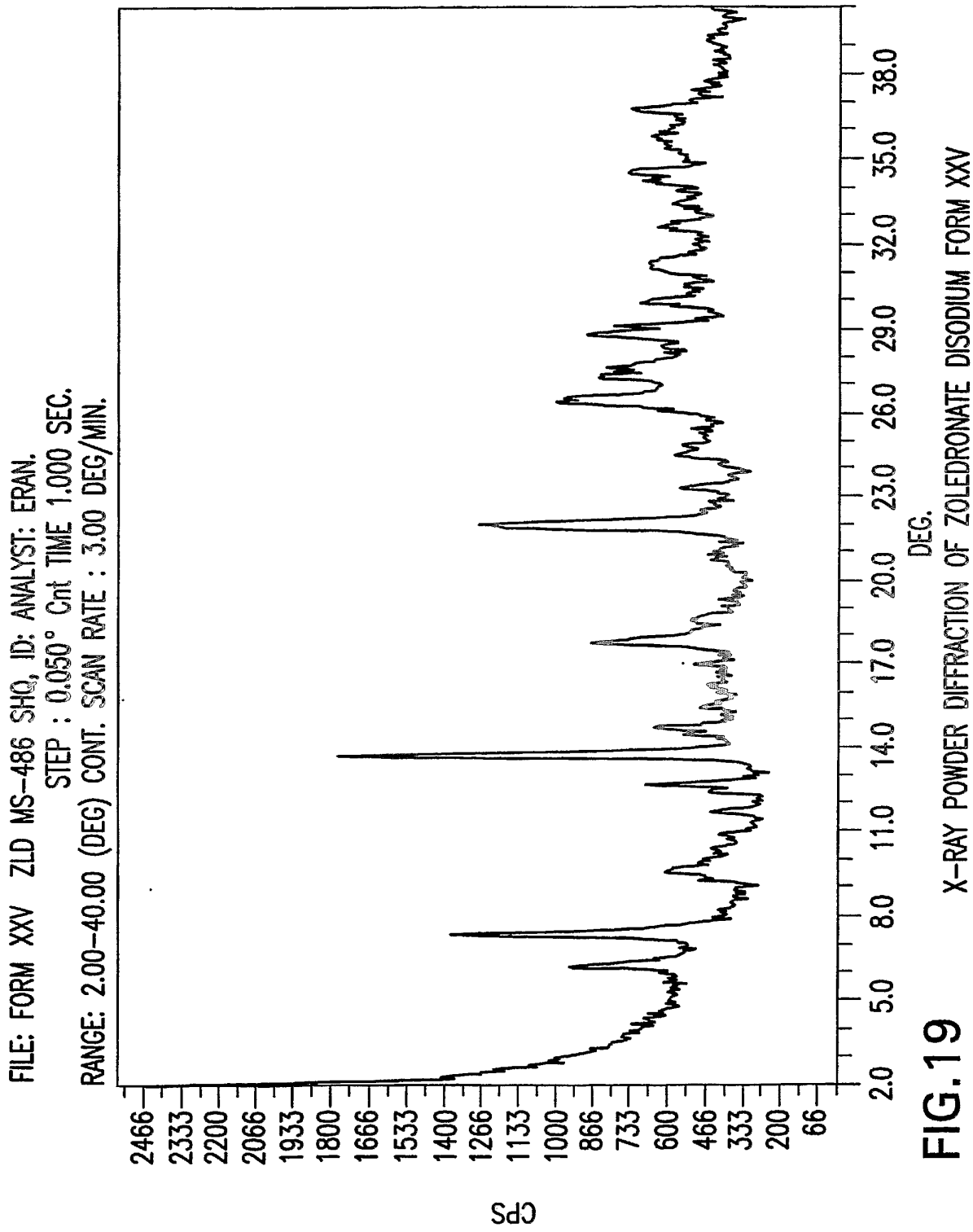


FIG.19 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XXV

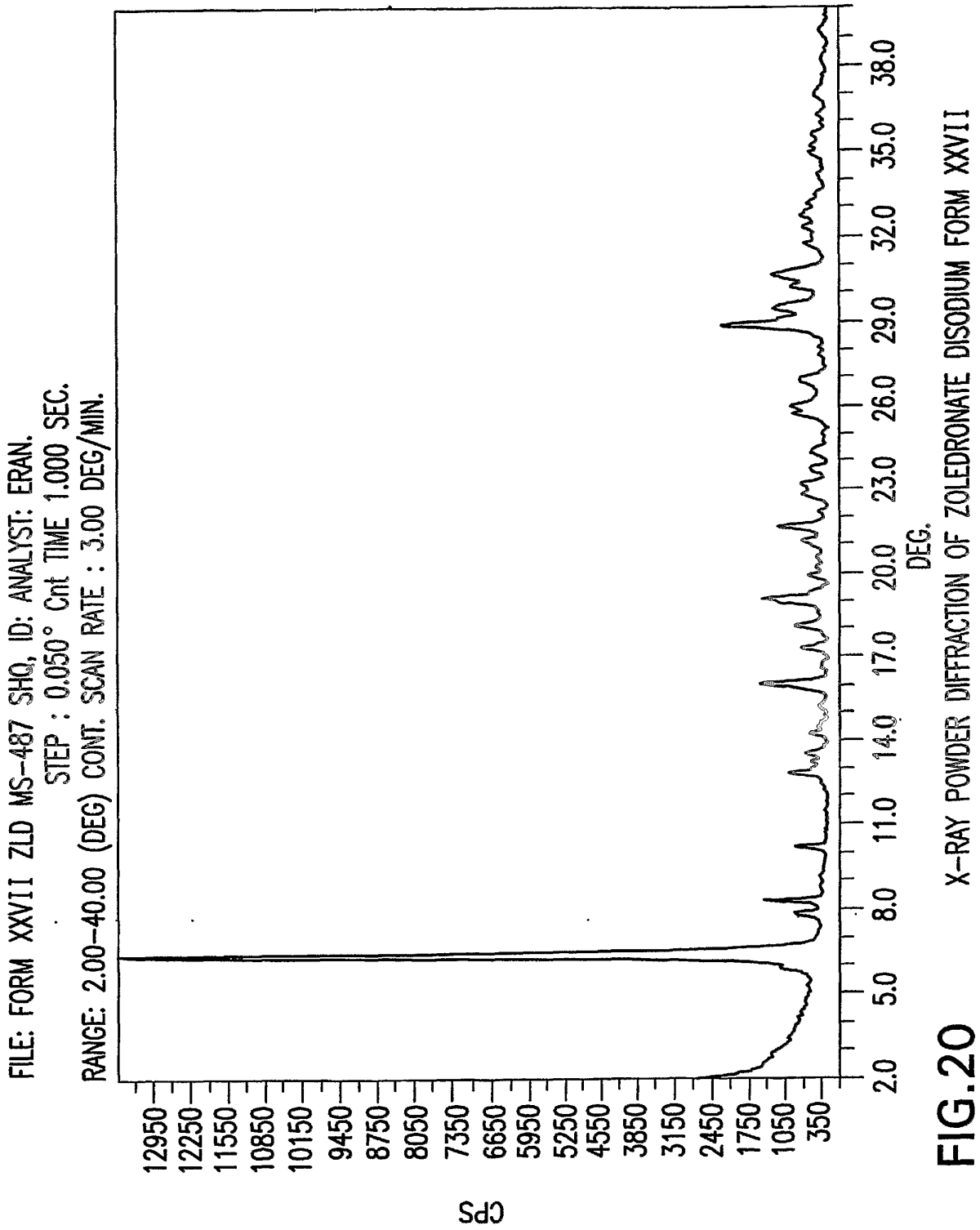


FIG.20 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XXVII

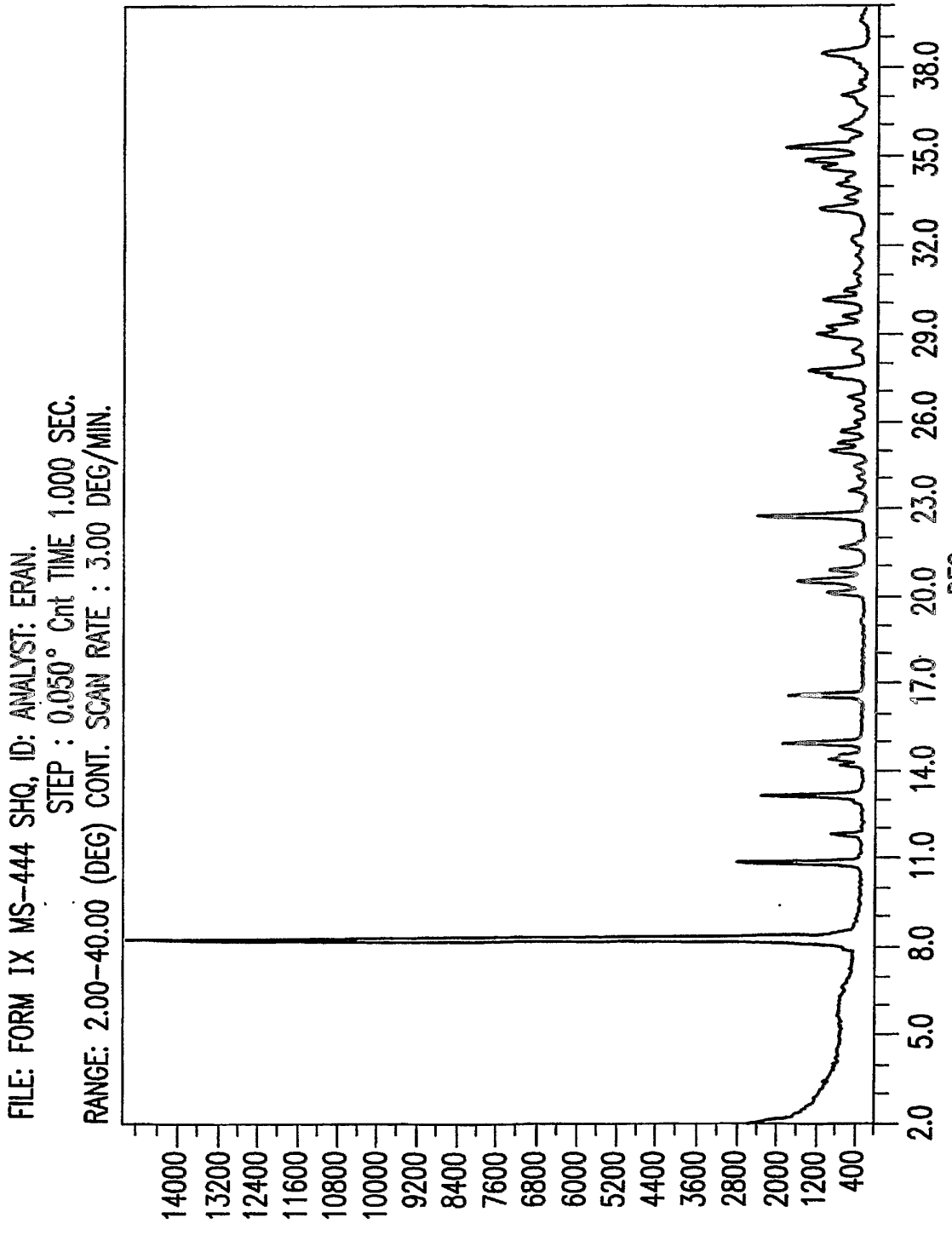


FIG.21 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM IX

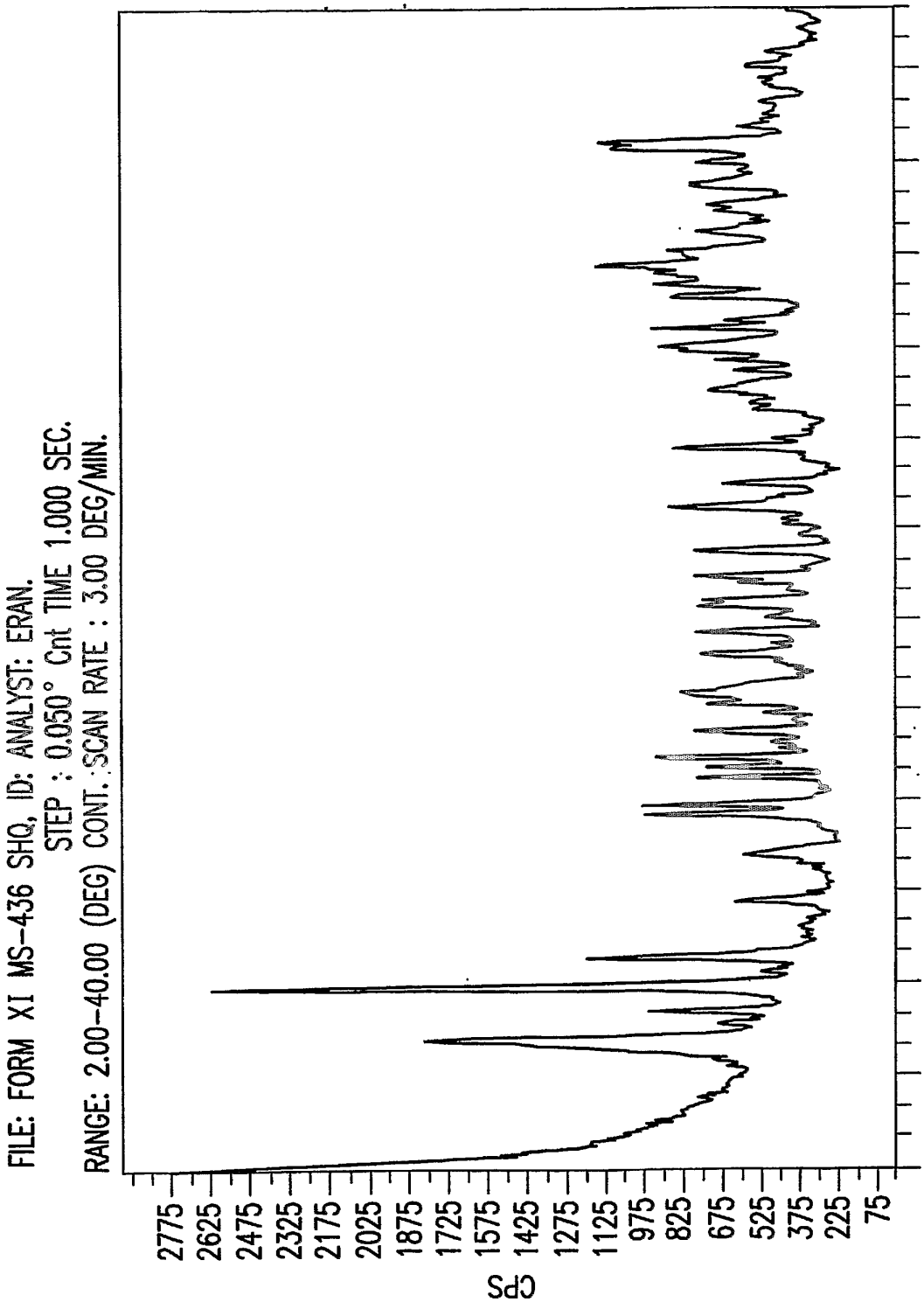


FIG.22 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XI

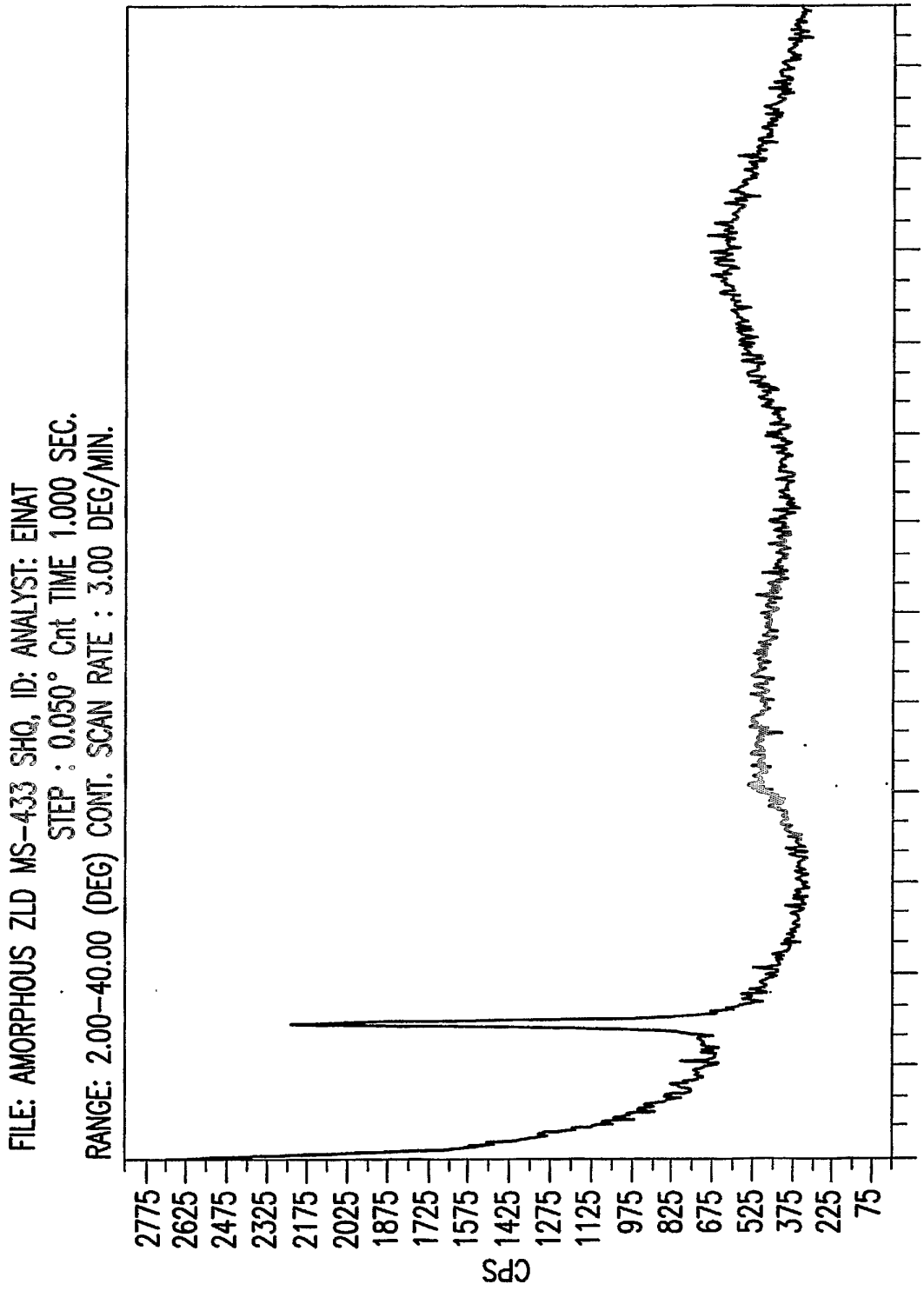
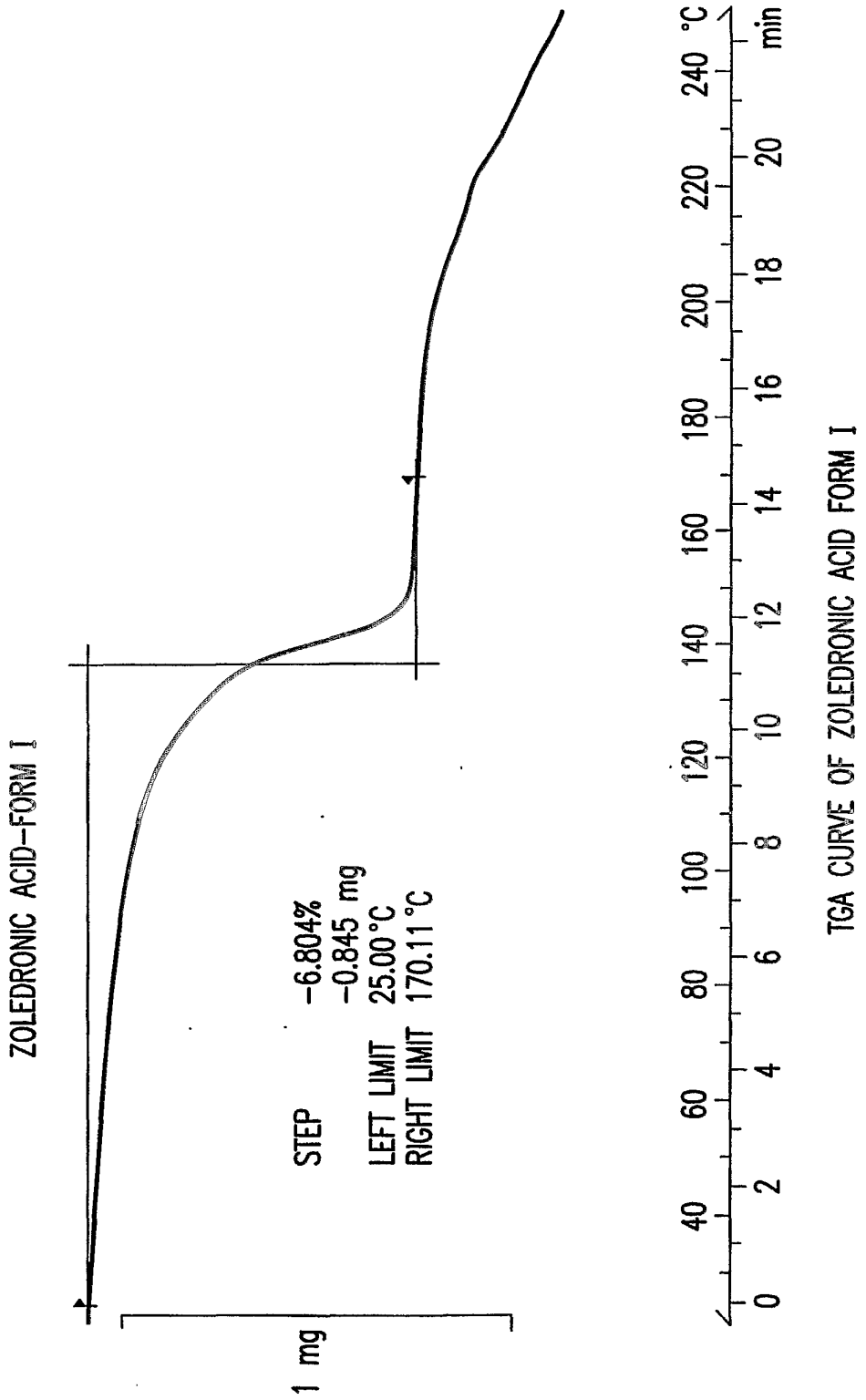
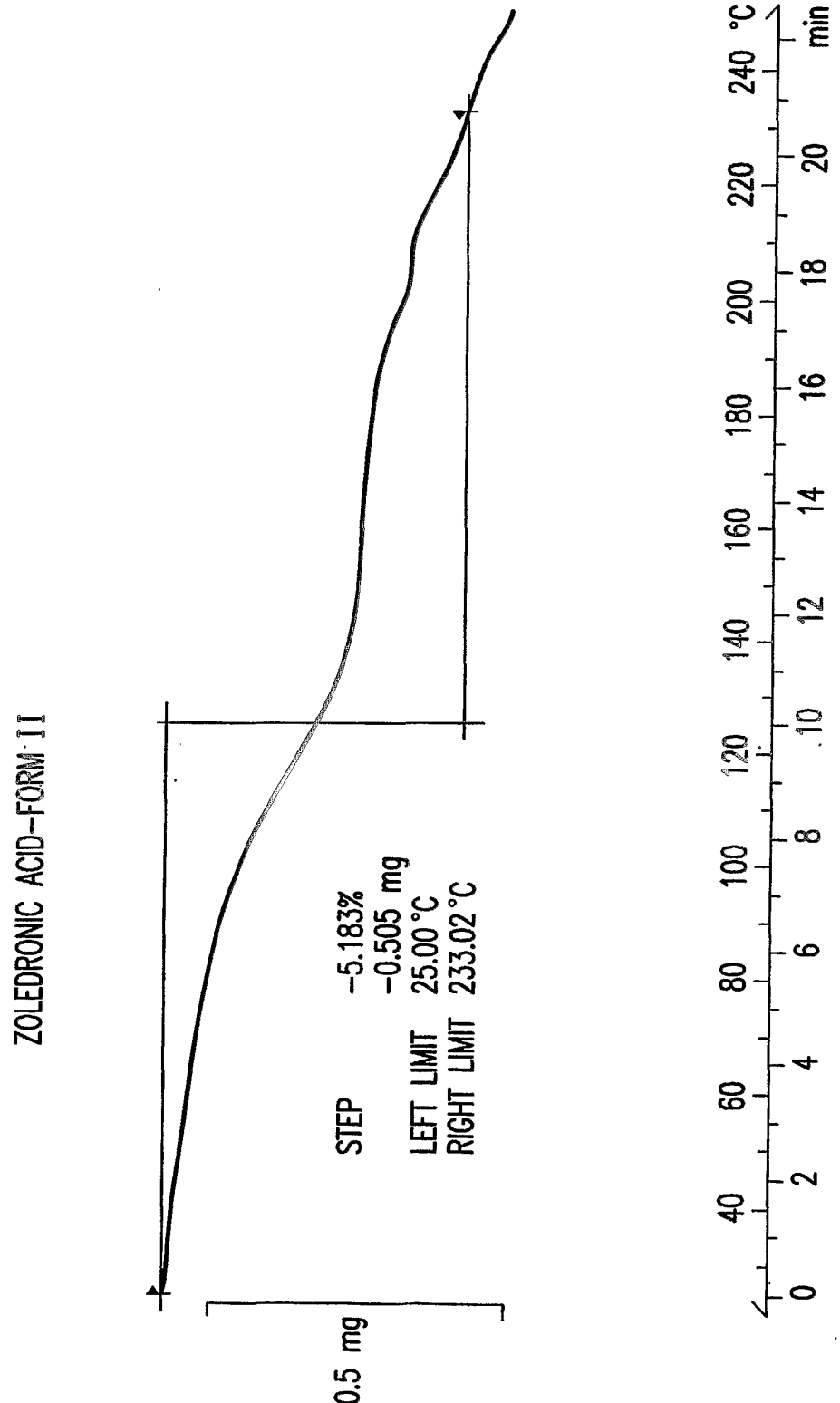


FIG.23 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE SODIUM AMORPHOUS



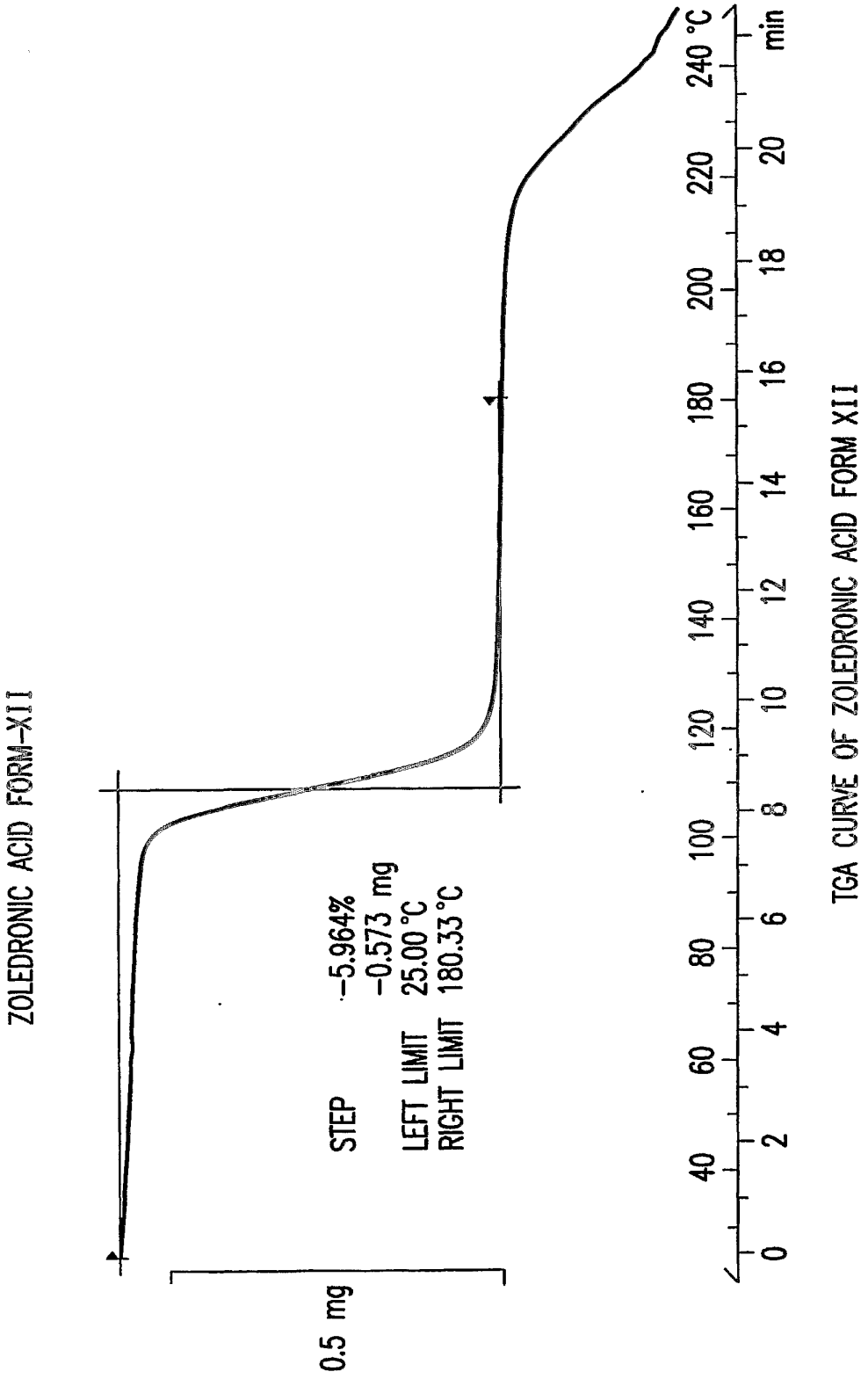
TGA CURVE OF ZOLEDRONIC ACID FORM I

FIG. 24



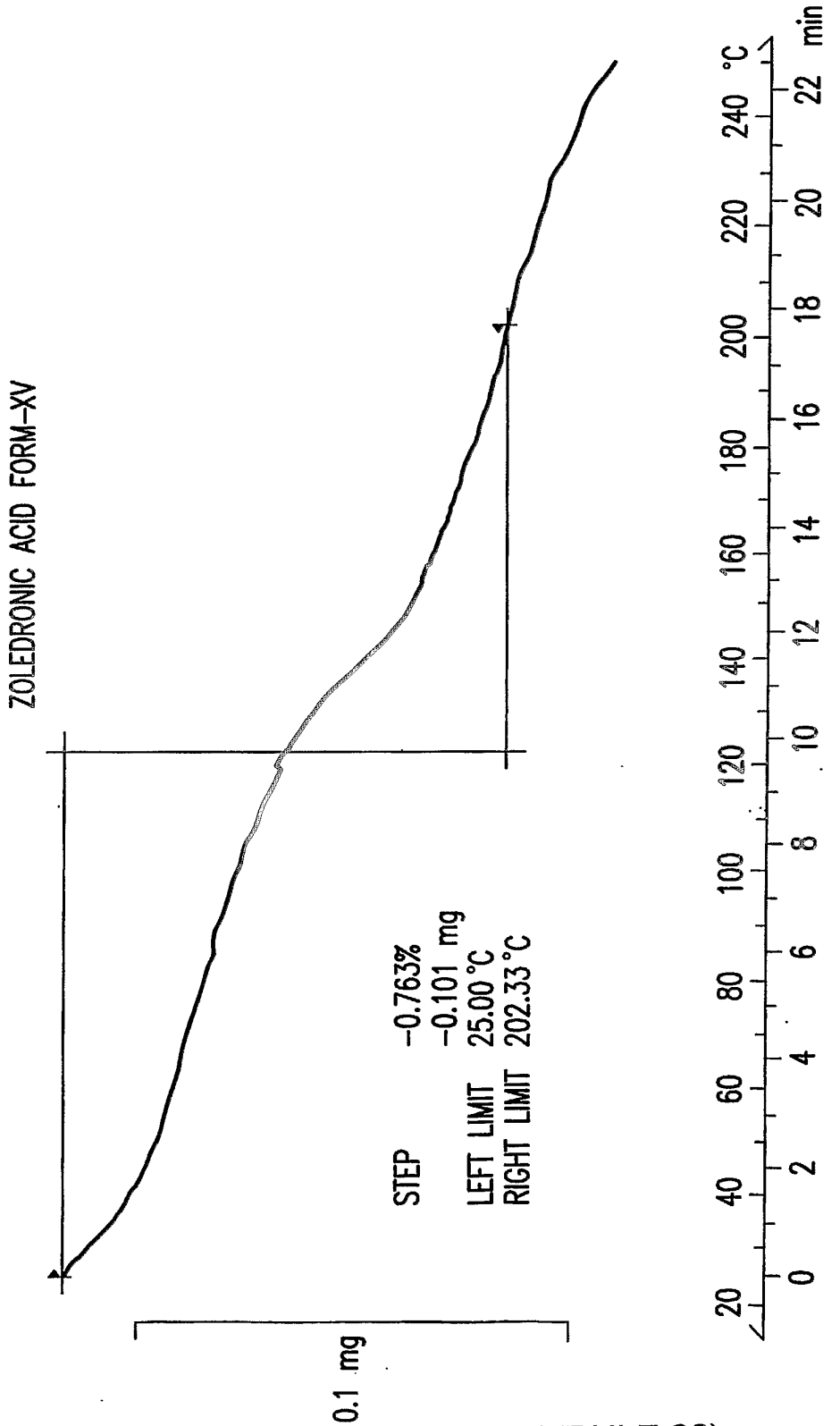
TGA CURVE OF ZOLEDRONIC ACID FORM II

FIG. 25



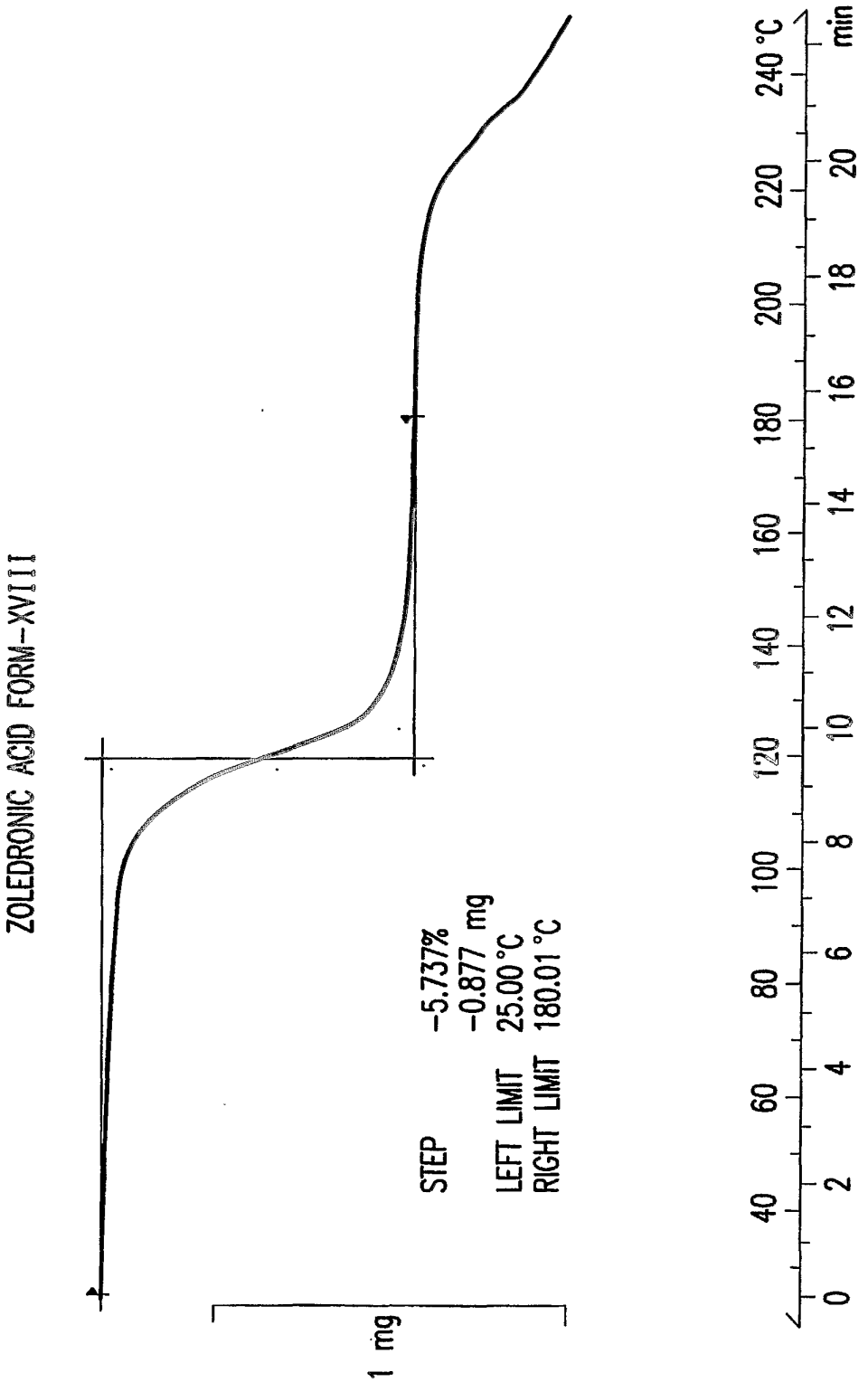
TGA CURVE OF ZOLEDRONIC ACID FORM XII

FIG. 26



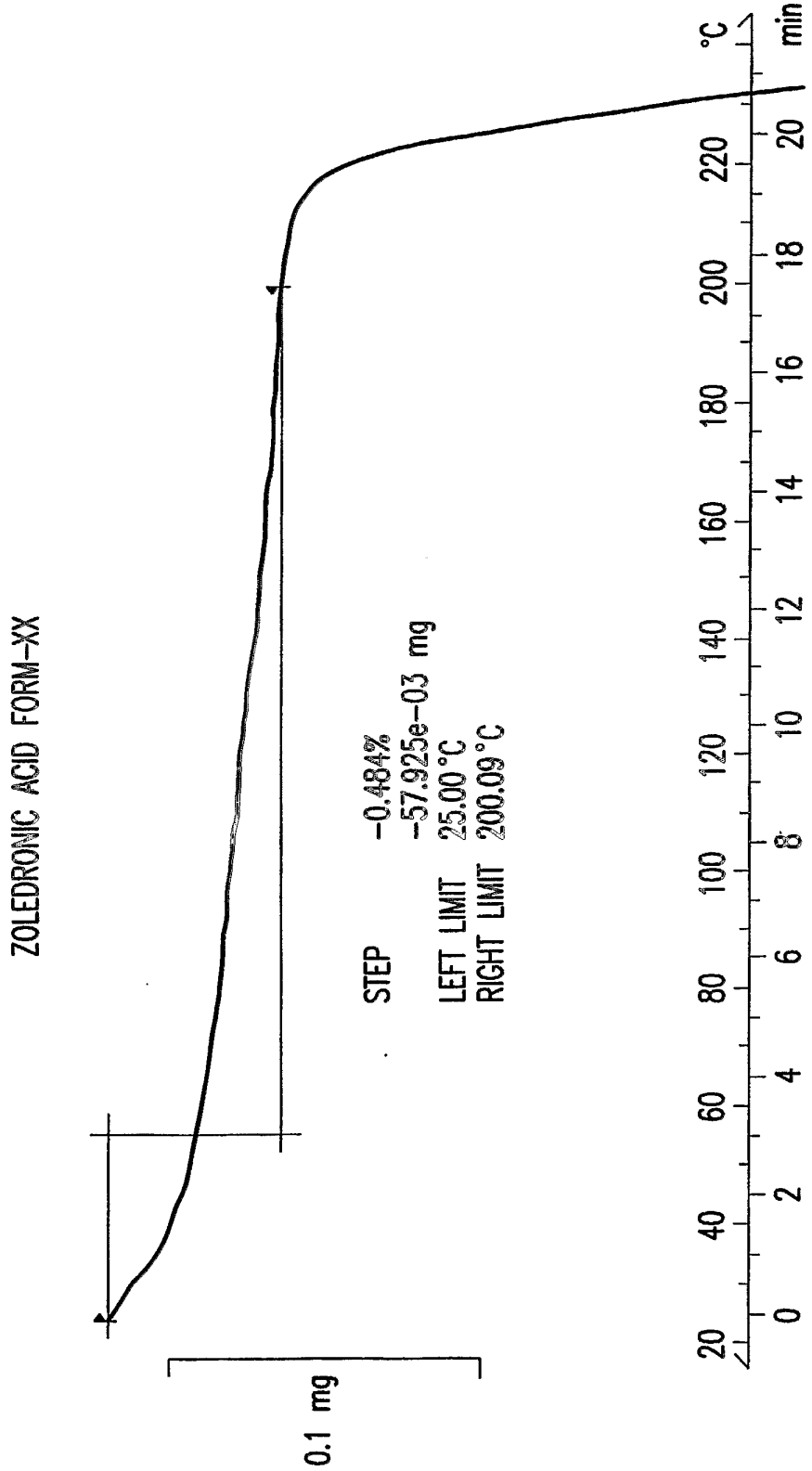
TGA CURVE OF ZOLEDRONIC ACID FORM XV

FIG.27



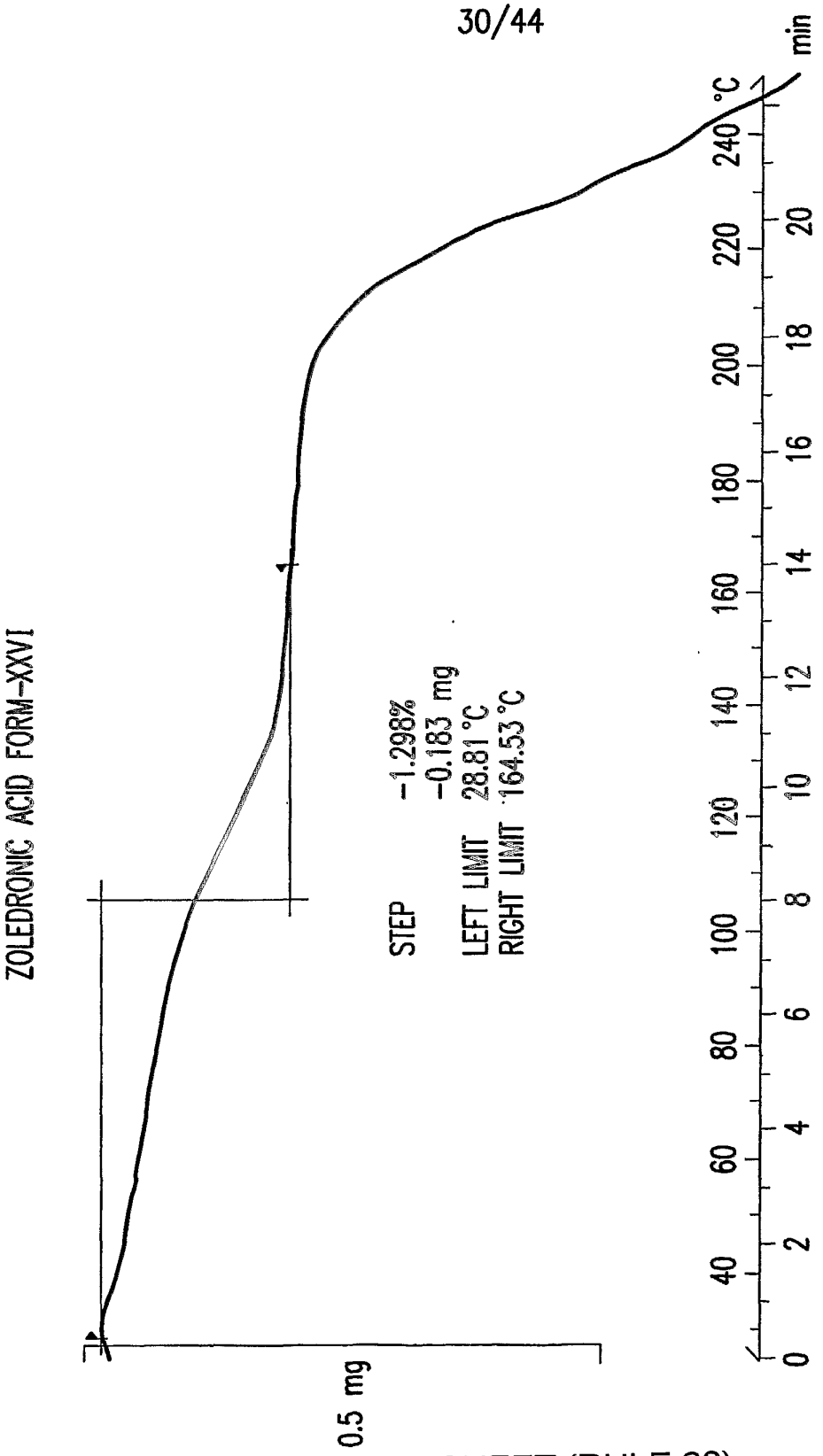
TGA CURVE OF ZOLEDRONIC ACID FORM XVIII

FIG.28



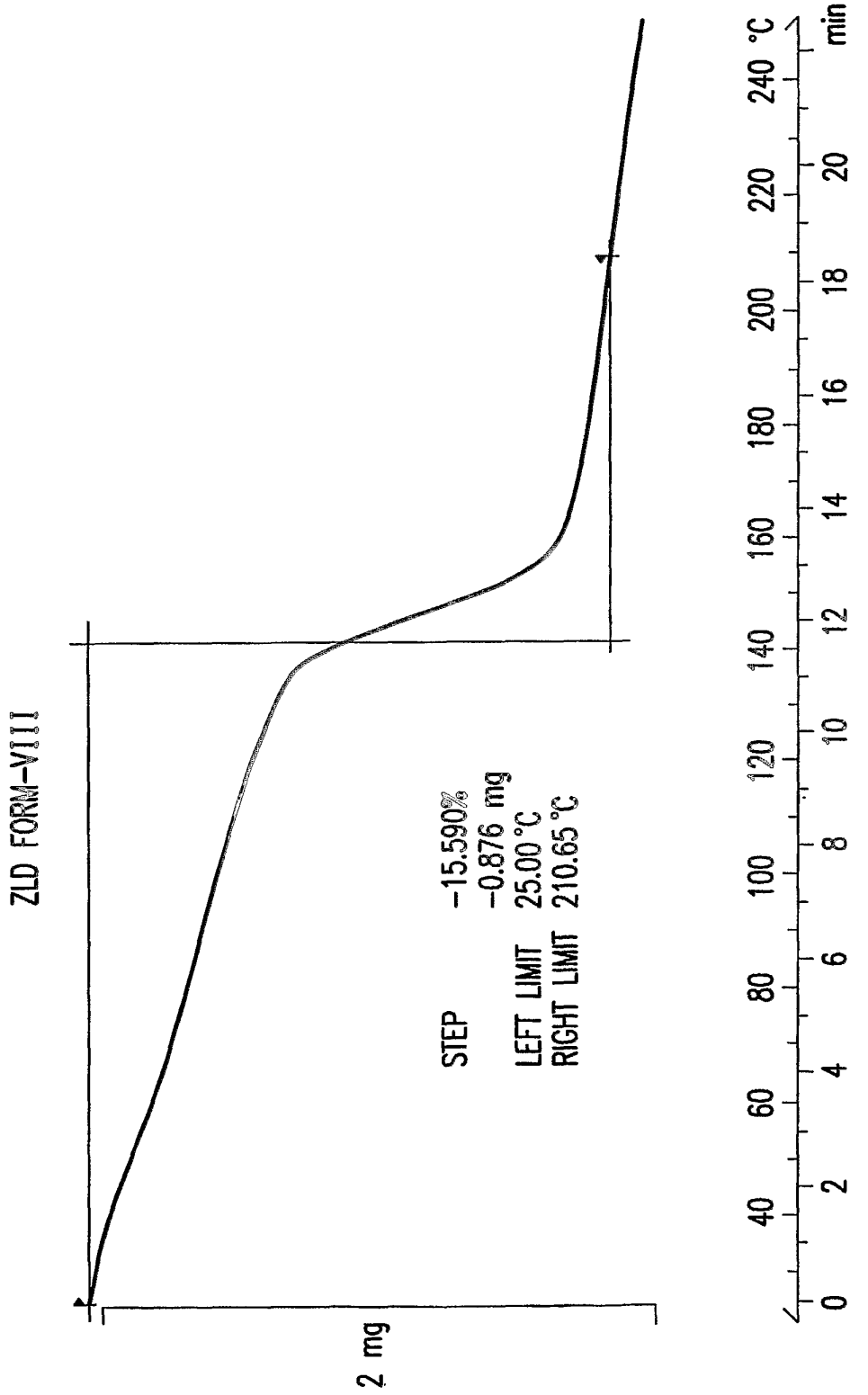
TGA CURVE OF ZOLEDRONIC ACID FORM XX

FIG.29



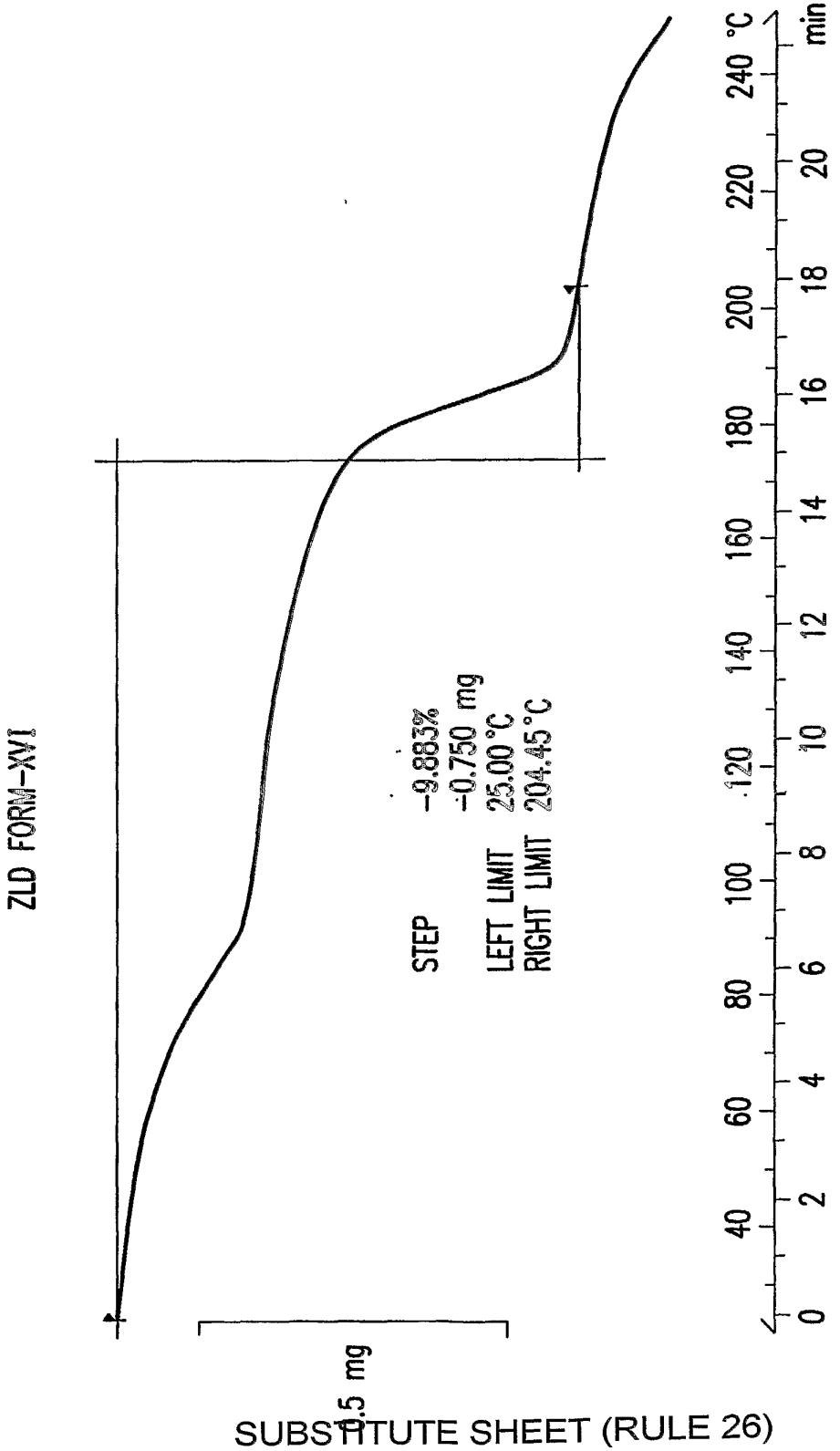
TGA CURVE OF ZOLEDRONIC ACID FORM XXVI

FIG.30



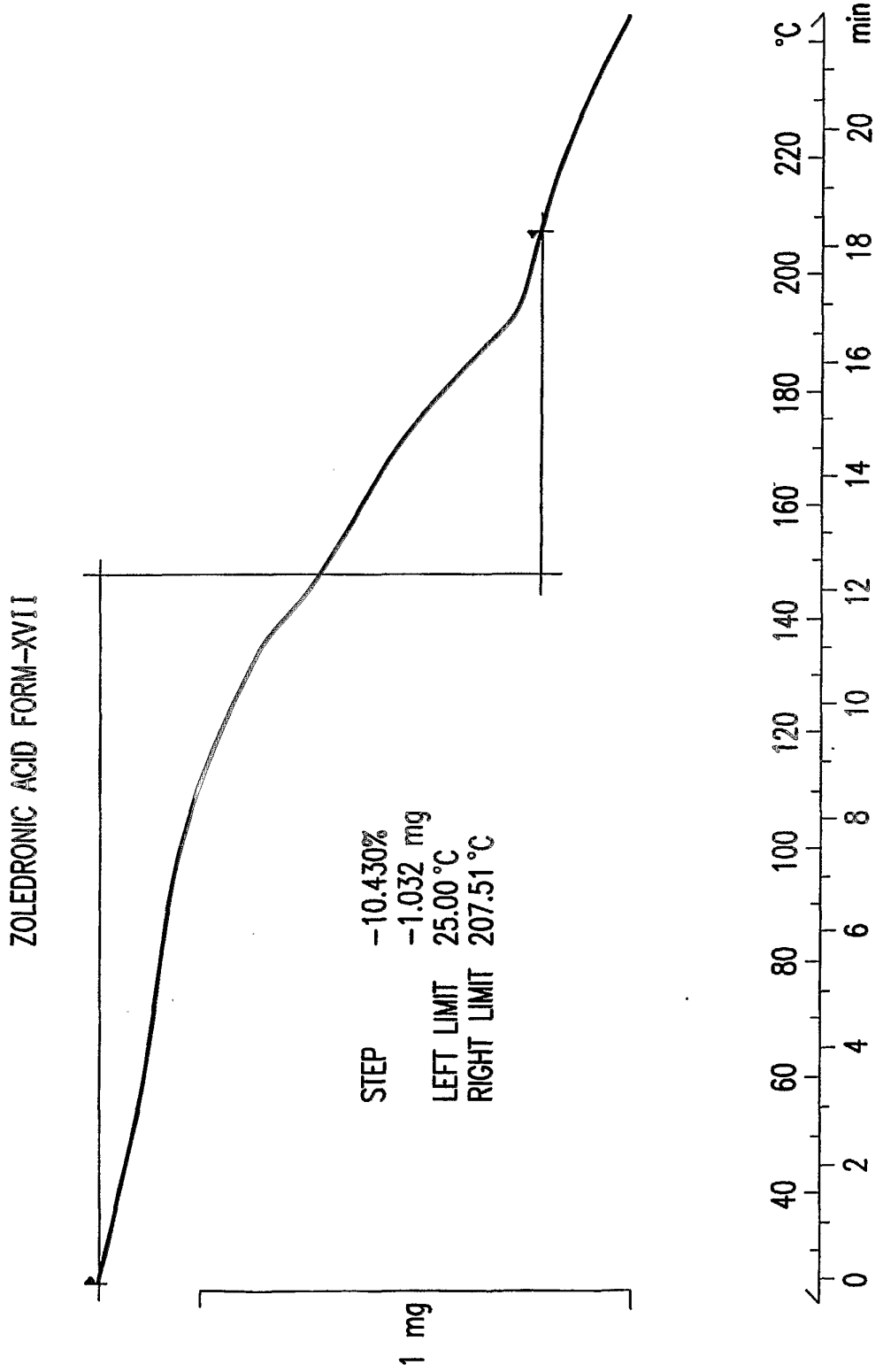
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM VIII

FIG. 31



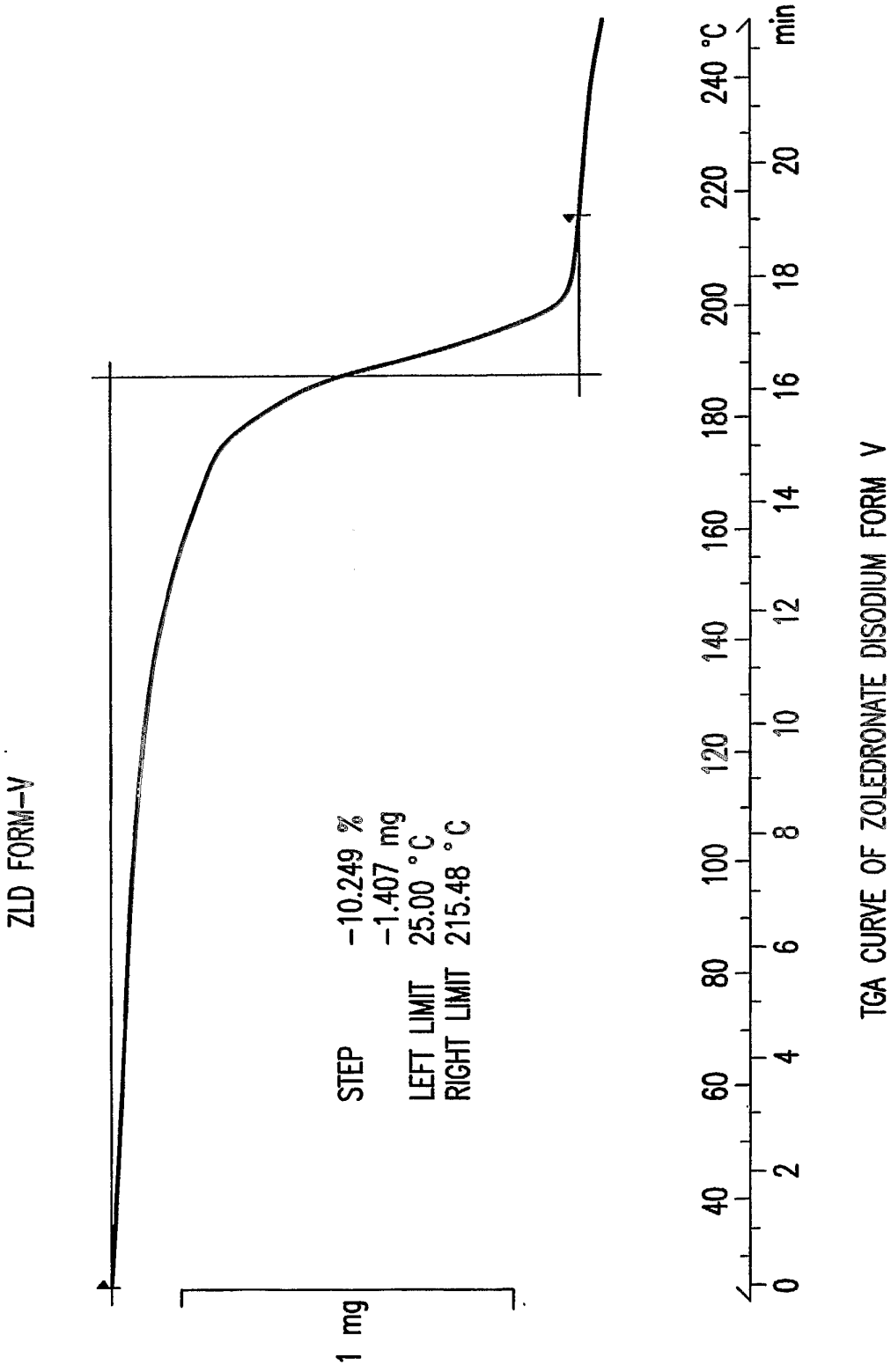
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM XVI

FIG. 32



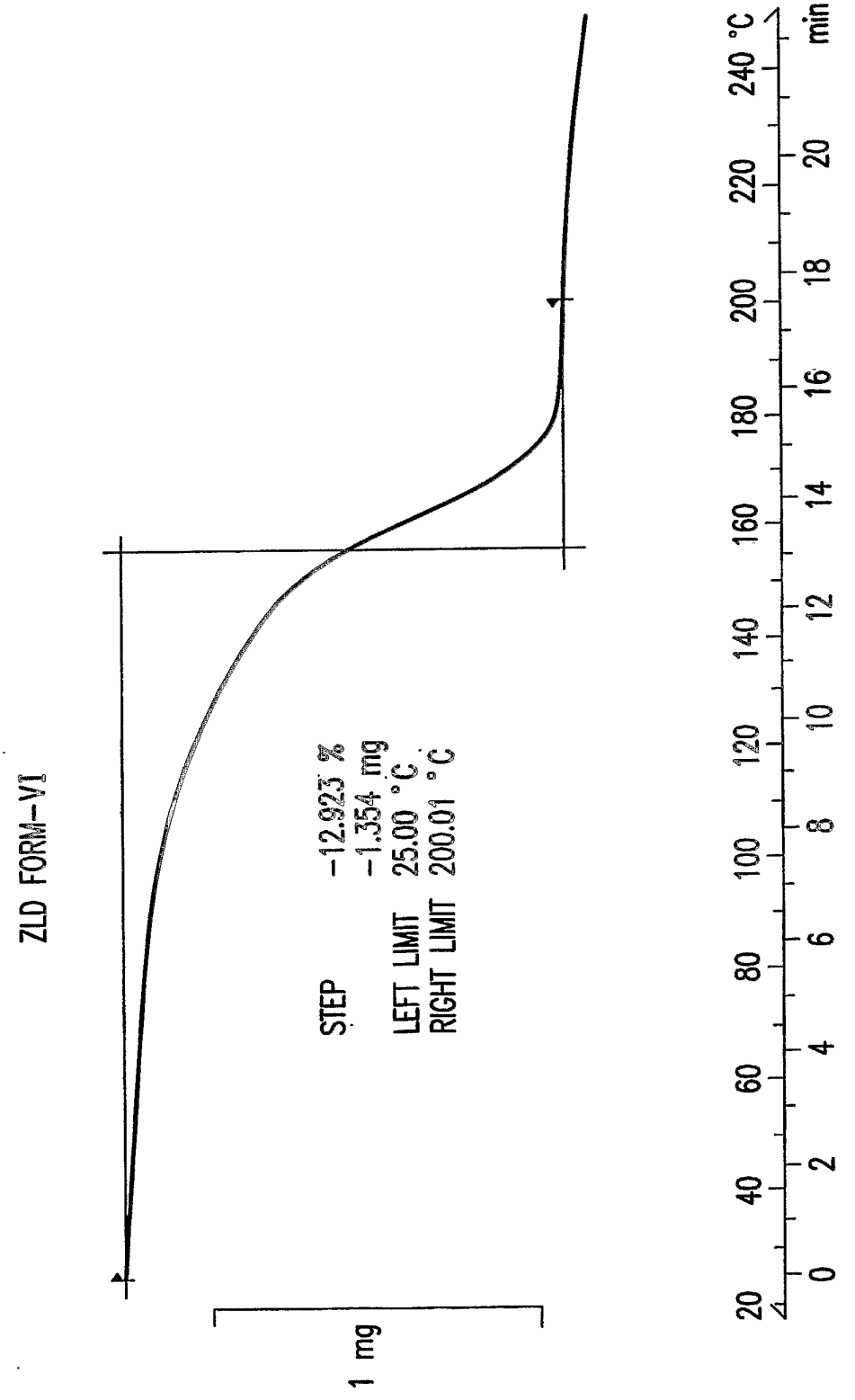
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM XVII

FIG. 33



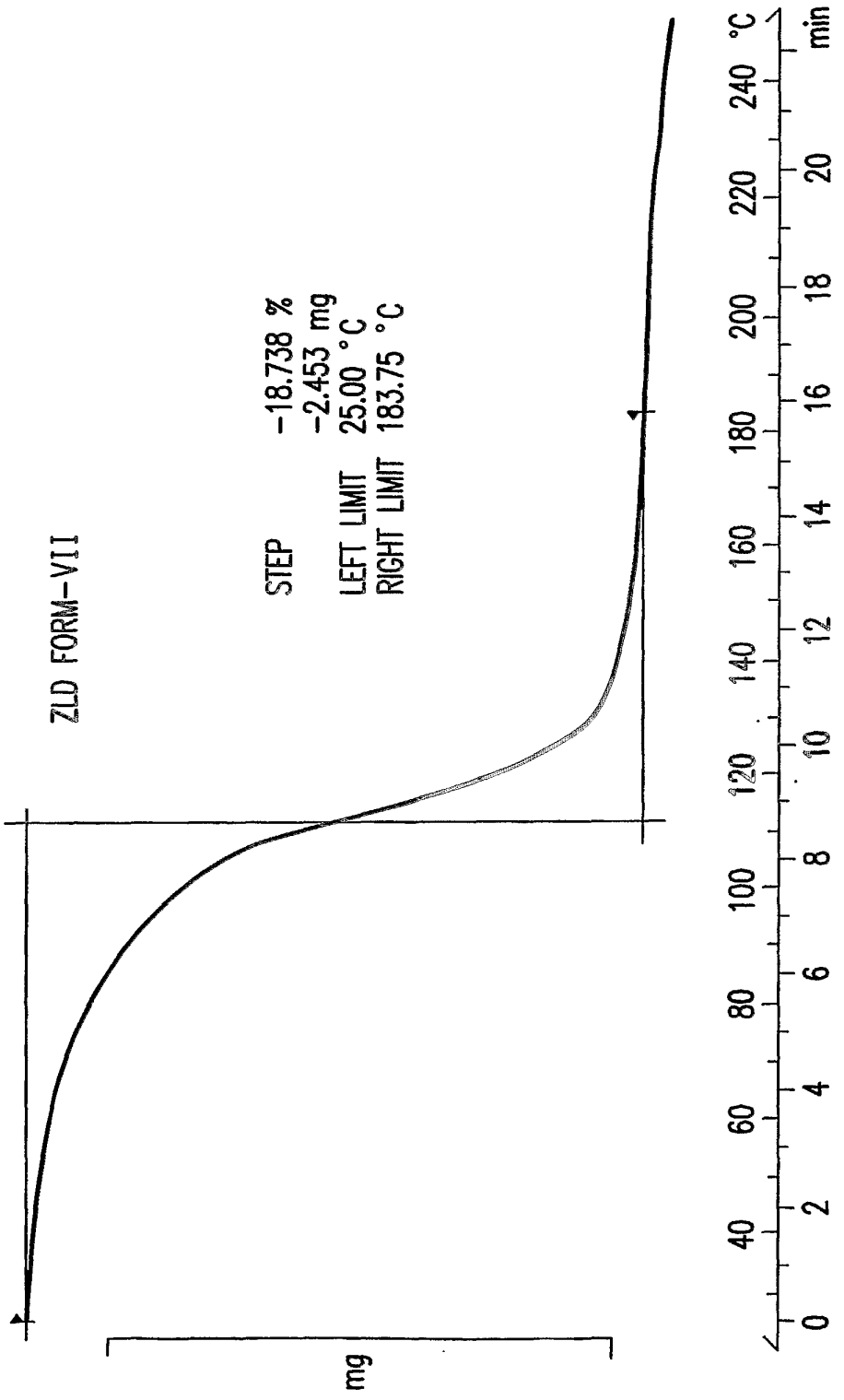
TGA CURVE OF ZOLEDRONATE DISODIUM FORM V

FIG.34



TGA CURVE OF ZOLEDRONATE DISODIUM FORM VI

FIG. 35



TGA CURVE OF ZOLEDRONATE DISODIUM FORM VII

FIG:36

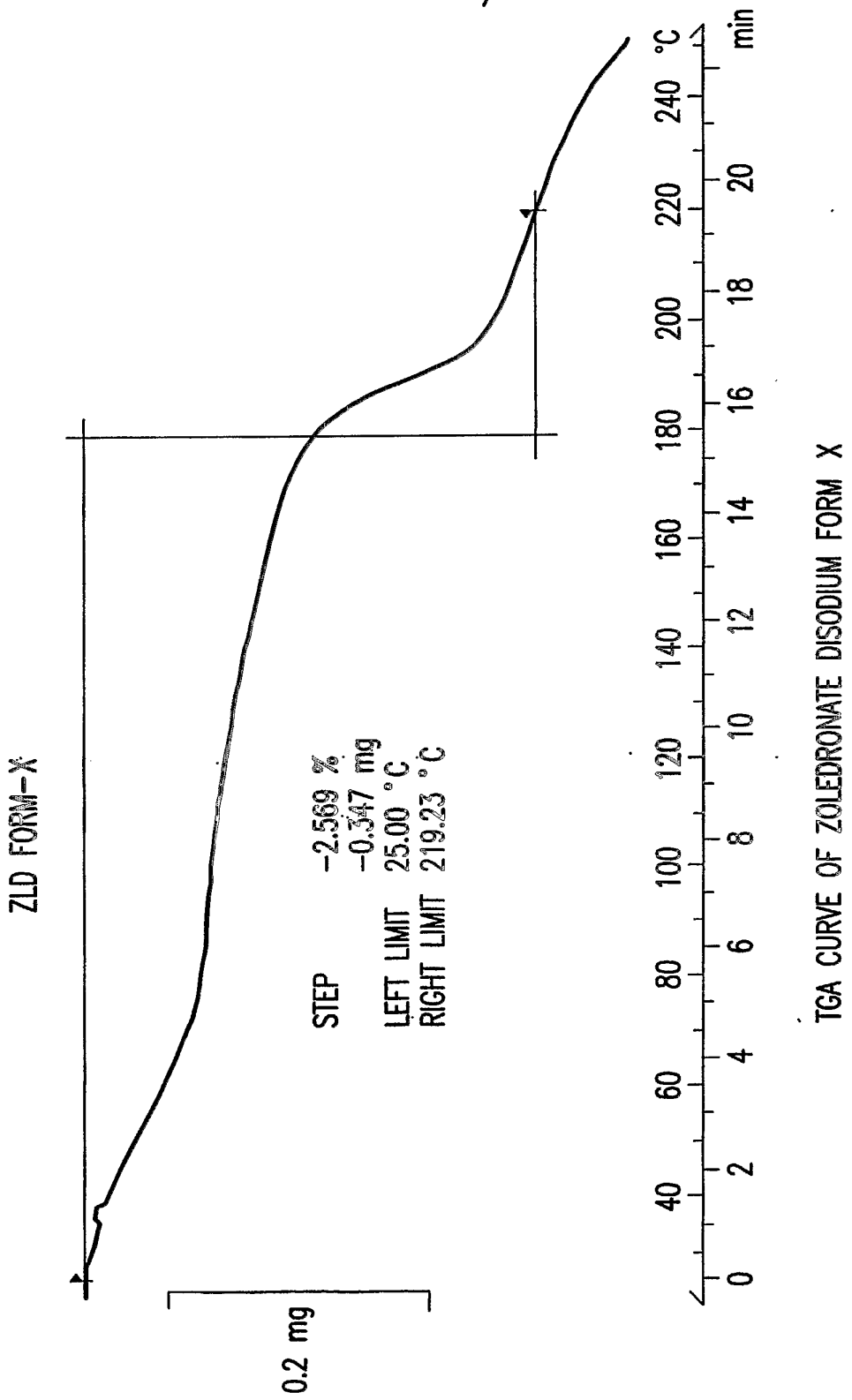
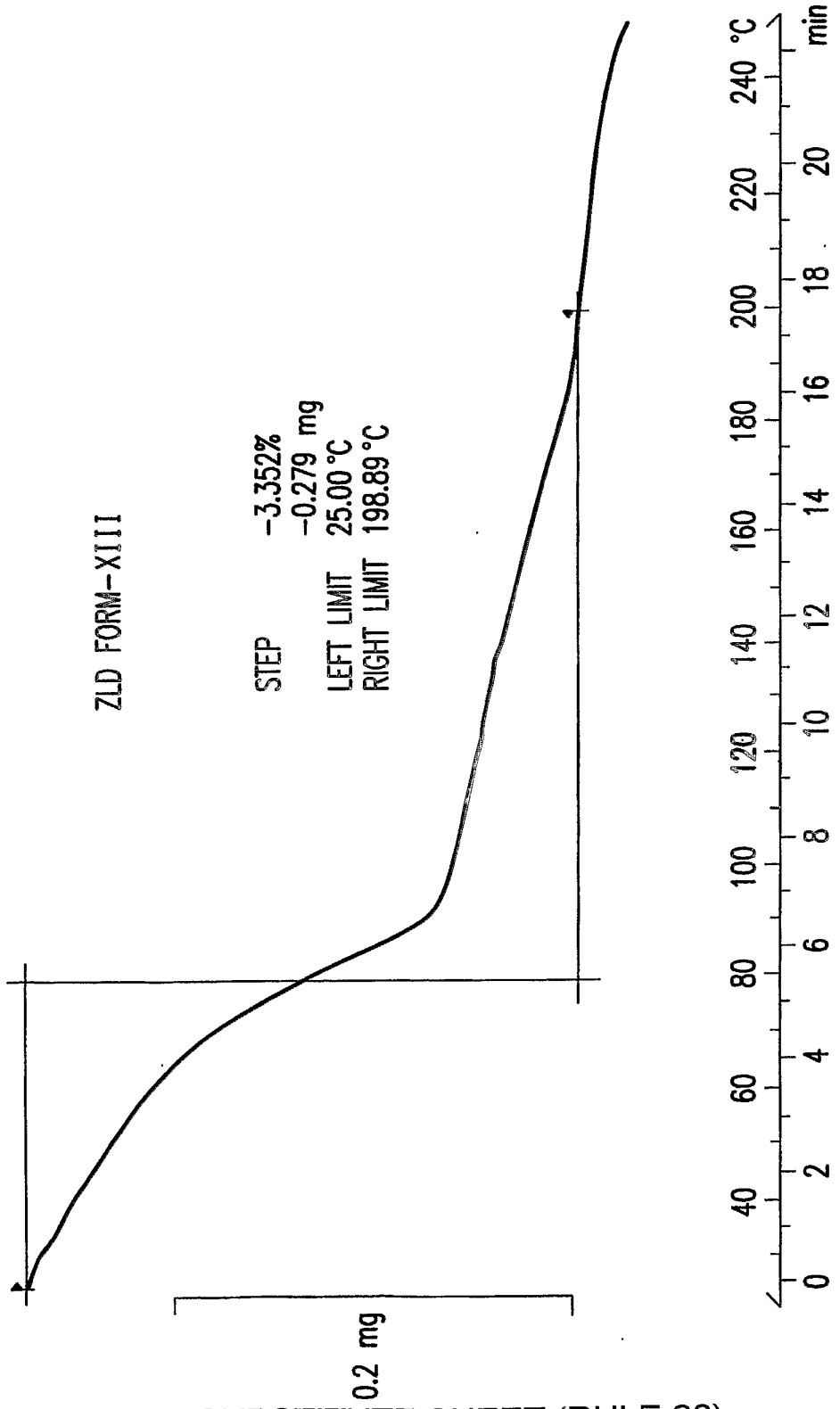
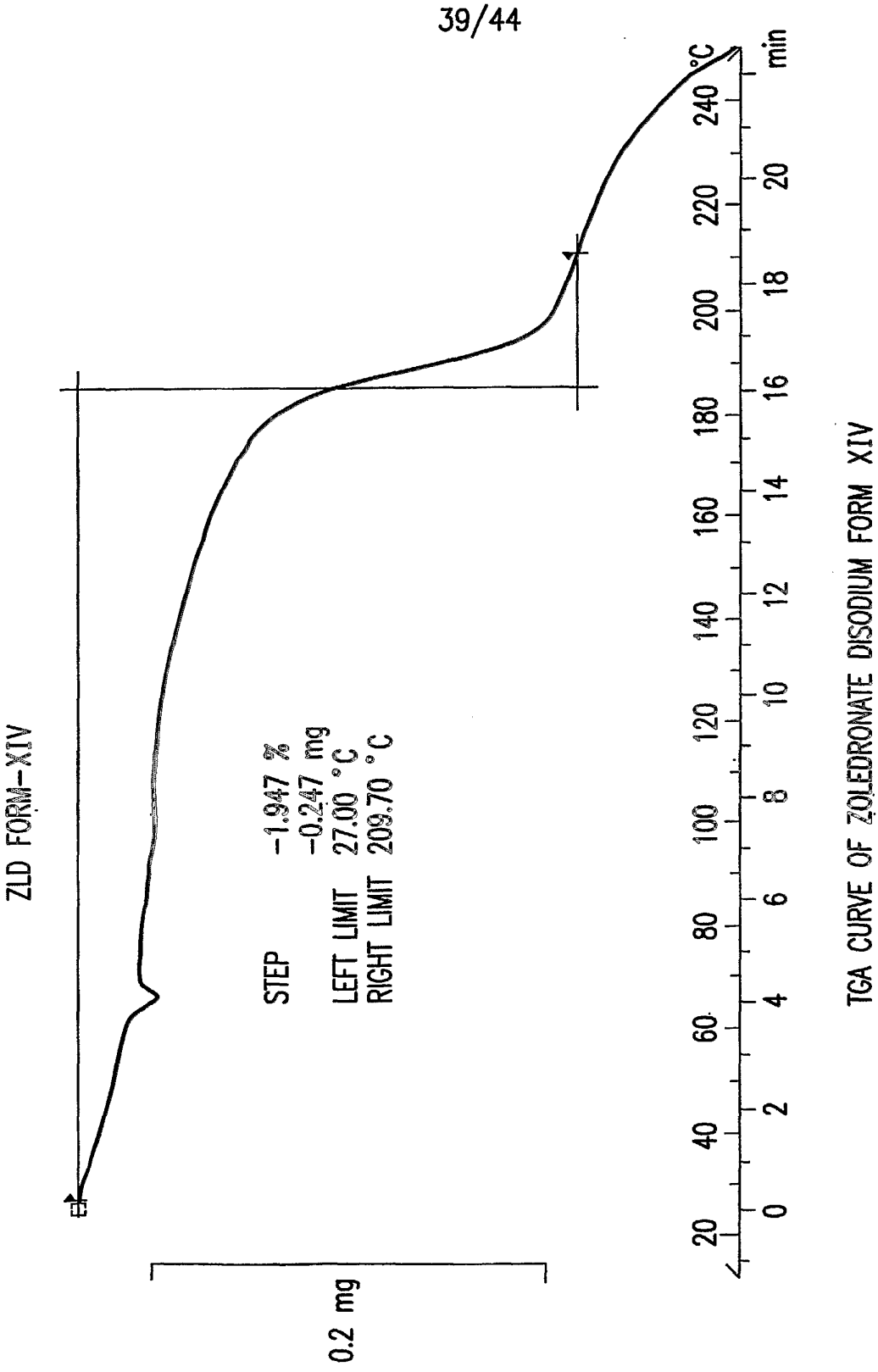

ZLD FORM-X
STEP -2.569 %
-0.347 mg
LEFT LIMIT 25.00 °C
RIGHT LIMIT 219.23 °C
0.2 mg
0 2 4 6 8 10 12 14 16 18 20 min
40 60 80 100 120 140 160 180 200 220 240 °C
TGA CURVE OF ZOLEDRONATE DISODIUM FORM X

FIG.37



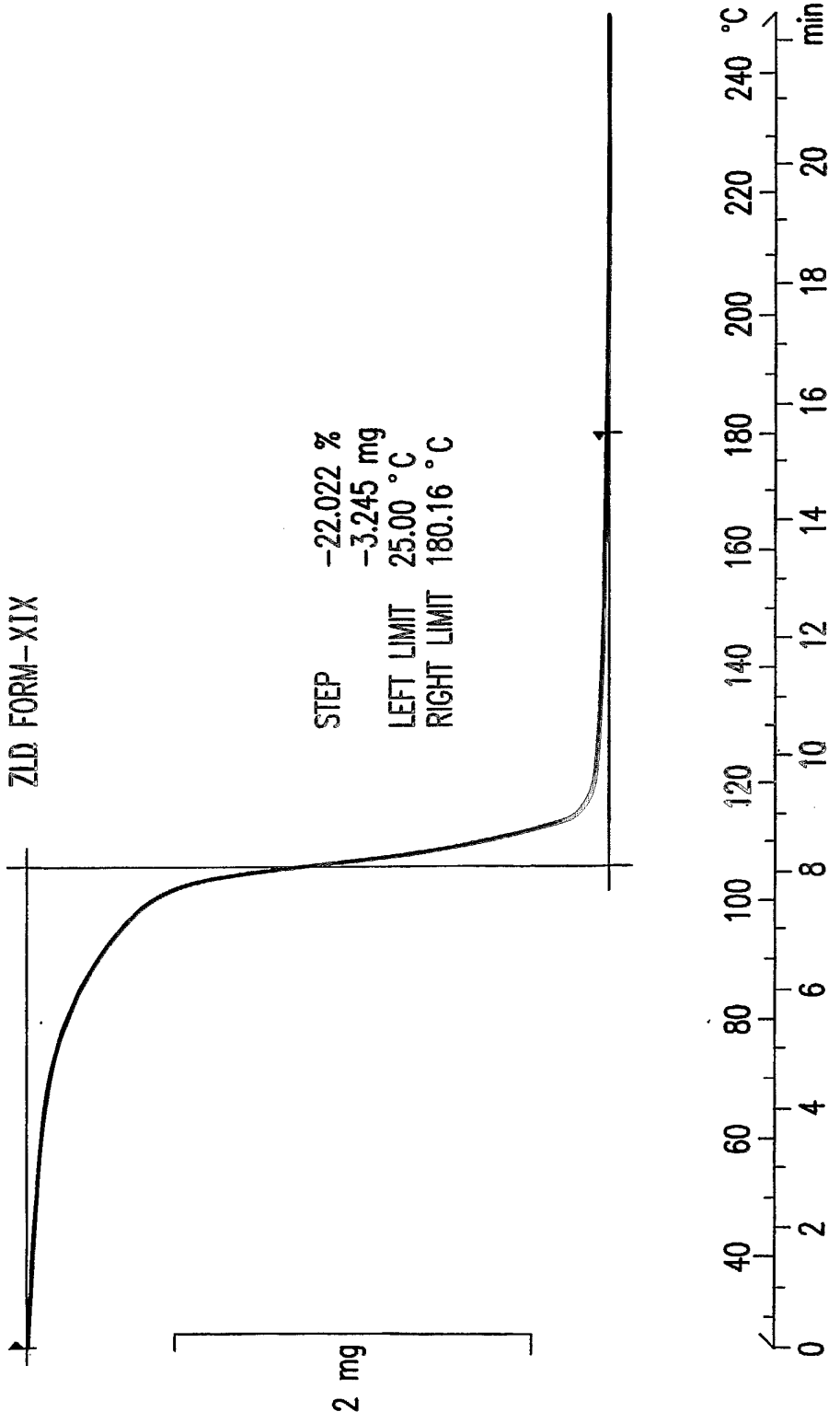
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIII

FIG.38



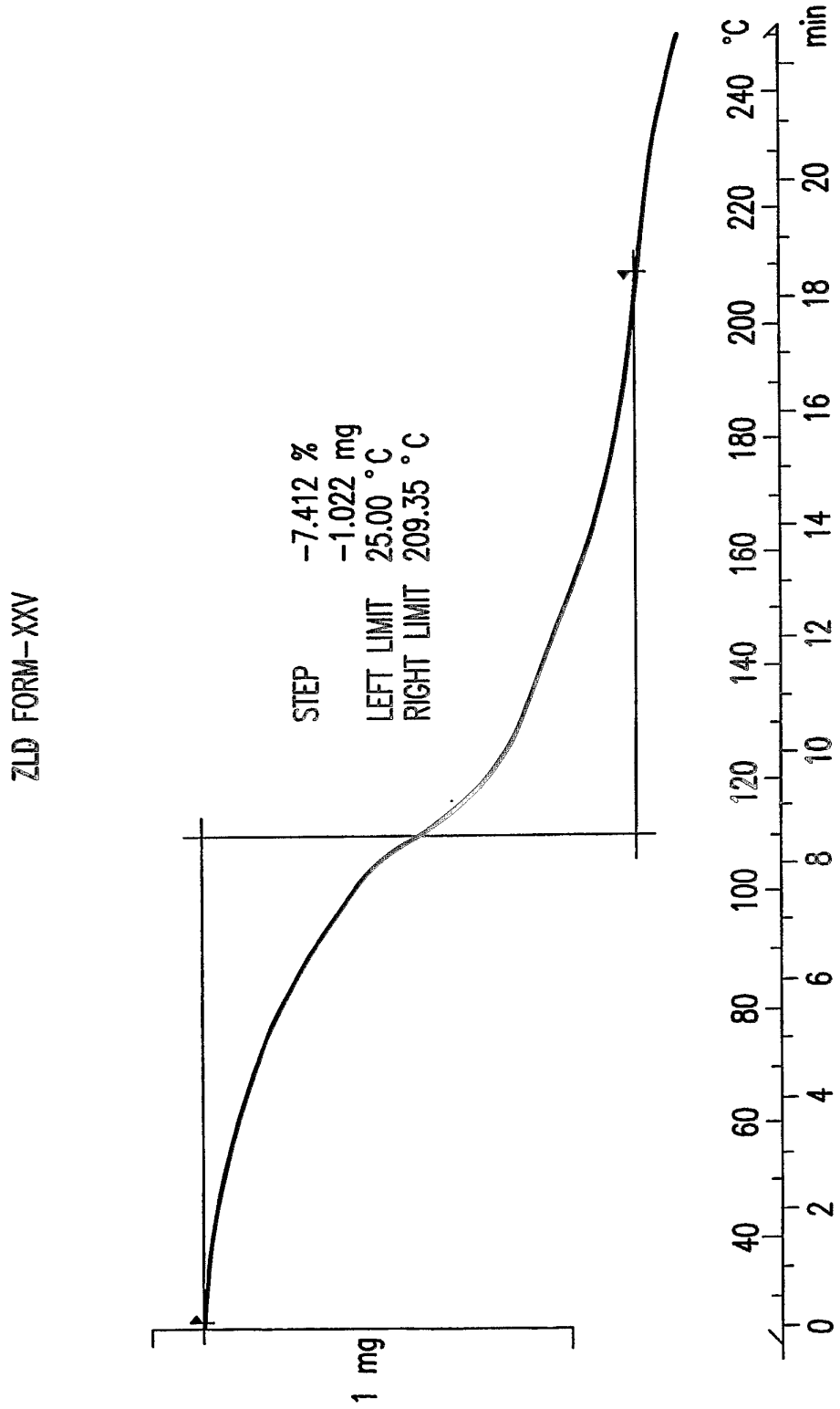
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIV

FIG.39



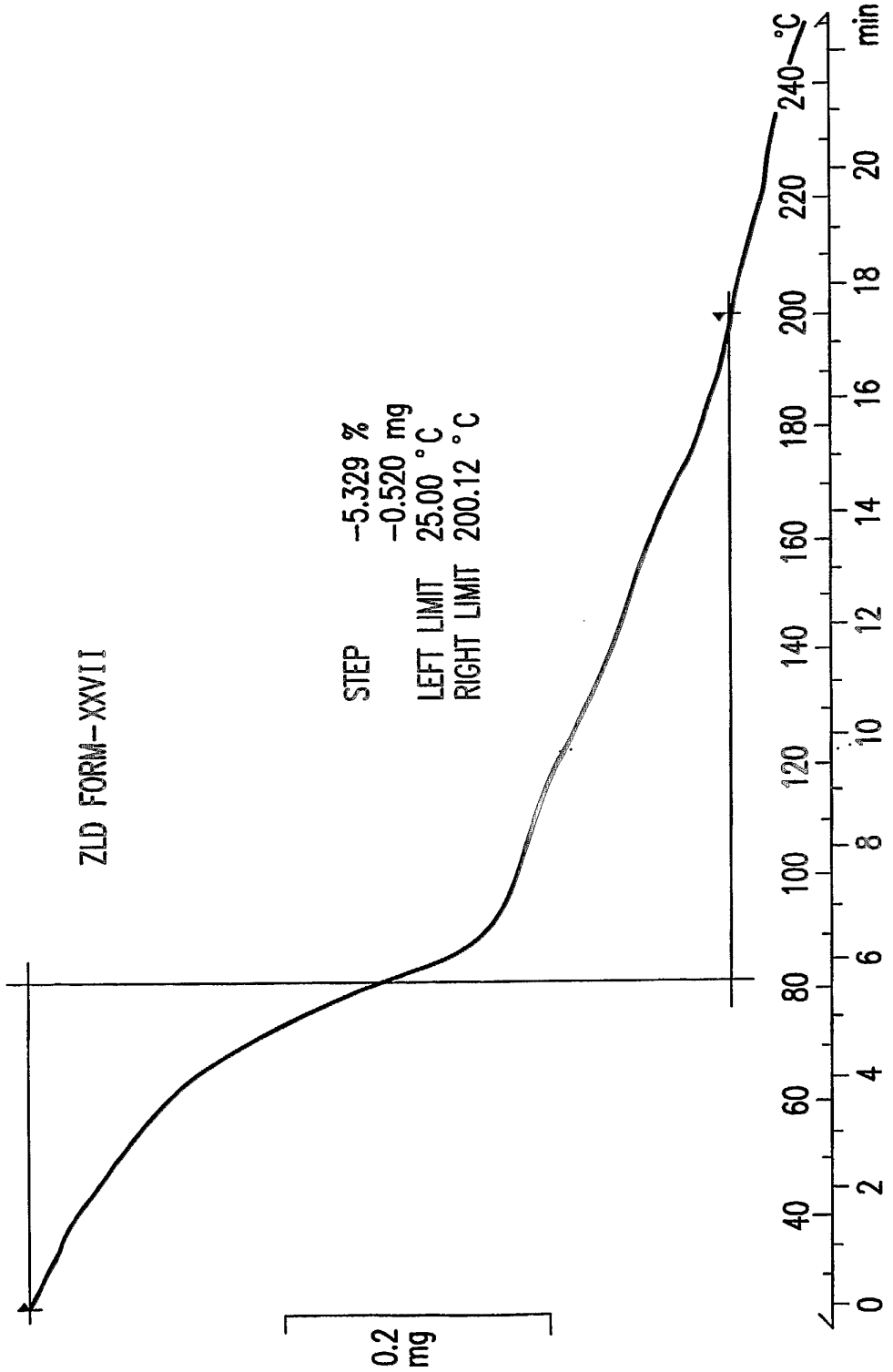
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIX

FIG.4O



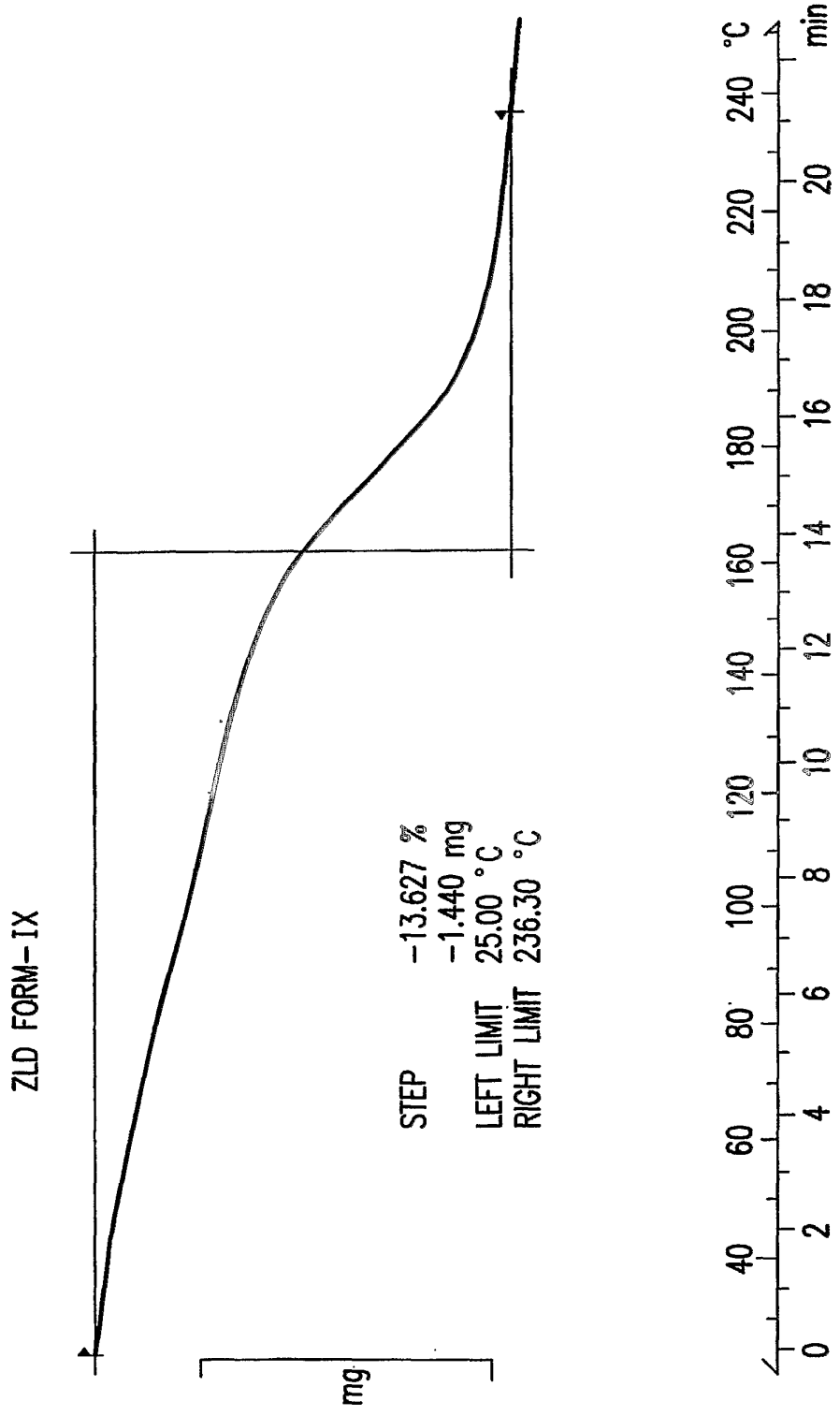
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XXV

FIG. 41



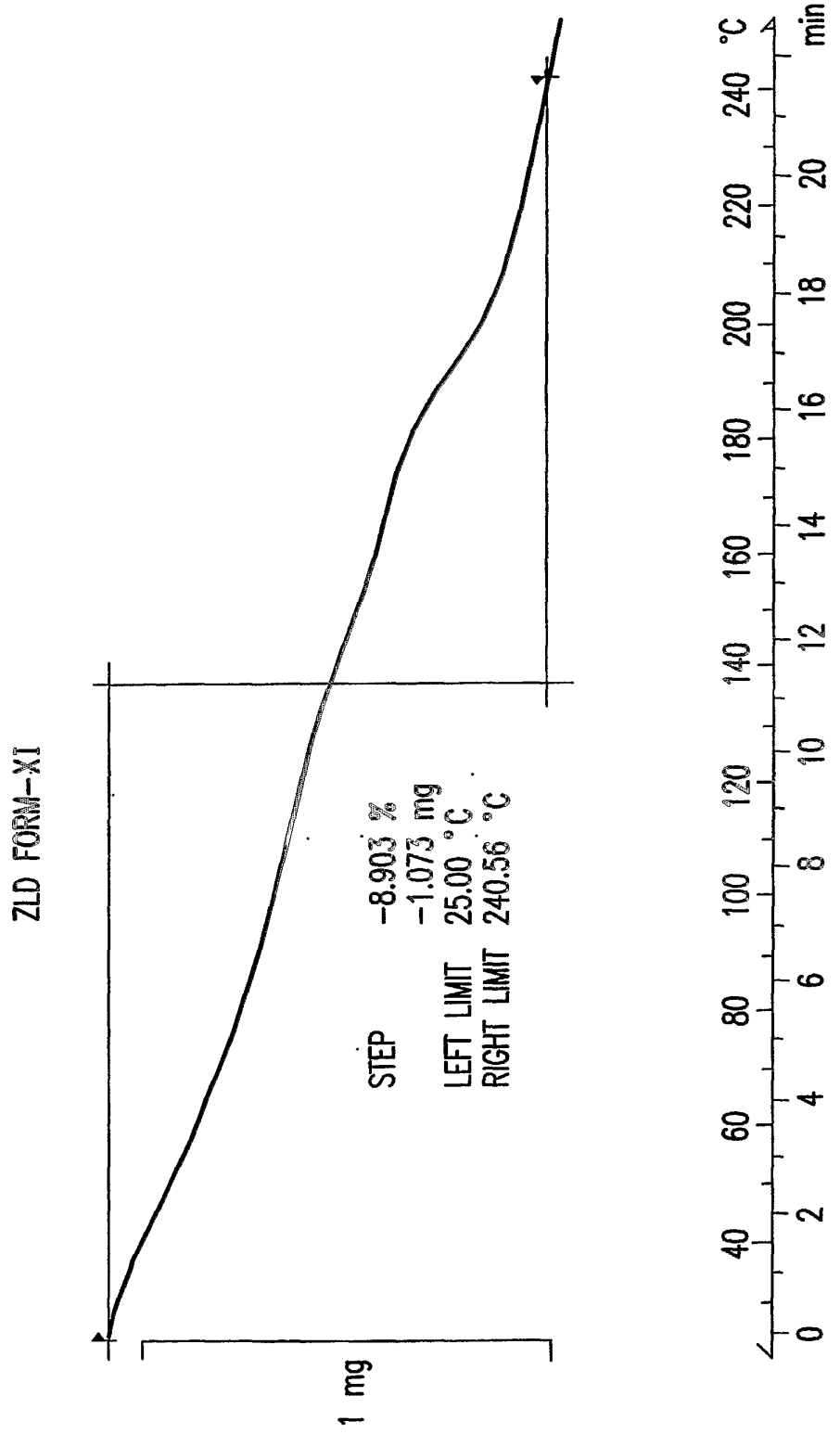
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XXVII

FIG.42



TGA CURVE OF ZOLEDRONATE DISODIUM FORM IX

FIG.43



TGA CURVE OF ZOLEDRONATE DISODIUM FORM XI

FIG. 44

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	384	((zoledronic adj acid) or zolendronate).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/07/03 14:56
L2	591067	oral	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/07/03 14:56
L3	18	1 same 2	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/07/03 14:56
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
S3	3196	(zoledronic adj acid) or zolendronate	US-PGPUB; USPAT; EPO; JPO	OR	ON	2013/11/25 17:29
S4	357	((zoledronic adj acid) or zolendronate).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:29
S5	563501	oral	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:30
S6	285	S4 and S5	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2013/11/25 17:30
S7	379	((zoledronic adj acid) or zolendronate).clm.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/25 15:13
S8	582695	oral	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/25 15:13
S9	58	S7 same3 S8	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/04/25 15:13
S10	3	"20110028435"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/07/03 12:10
S11	2	"20140051669"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2014/07/03 12:58

EAST Search History (Interference)

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7/3/2014 2:56:48 PM
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Scholarly articles for **pamidronate disodium and oral**
... , placebo-controlled studies of **pamidronate disodium** ... - Small - Cited by 328
... side effects associated with **pamidronate disodium** - Fraunfelder - Cited by 119
... of the bisphosphonate **pamidronate disodium** in urine ... - Fleisch - Cited by 62

pamidronate disodium injection, solution [pfizer ... - DailyMed
dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a8ba3ed0-7047...
Each mL of the 30 mg vial contains, 3 mg **Pamidronate Disodium**, 47 mg ... **Pamidronate disodium** (daily **oral** administration) was not carcinogenic in an 80 ...

Pamidronate Injection: MedlinePlus Drug Information
www.nlm.nih.gov/.../a601163... - United States National Library of Medicine
Pamidronate is used to treat high levels of calcium in the blood that may be caused by certain types of cancer. ... Be sure to mention any of the following: cancer chemotherapy medicationc; **oral** steroids such as ... AHPrBP **Sodium**.

Pamidronate Disodium Injection - RxList
www.rxlist.com/**pamidronate-disodium**.../warnings-precautions.ht... - RxList
When the dose calculations were adjusted to account for the limited **oral** bioavailability of **pamidronate disodium** in rats, the lowest daily dose associated with ...

Aredia (**Pamidronate Disodium**) Drug Information ... - RxList
www.rxlist.com/aredia-drug.htm - RxList
Aredia, **pamidronate disodium** (APD), is a bisphosphonate available in 30-mg or 90-mg vials for intravenous administration. Each 30-mg and 90-mg vial ...

Medac **Disodium Pamidronate** 3 mg/ml, sterile concentrate ...
www.medicines.org.uk/emc/medicine/15008/spc
Aug 8, 2014 - Each ml sterile concentrate contains 3 mg **pamidronate disodium** as .... and patients with Paget's disease of the bone, should be given **oral** ...

PAMIDRONATE DISODIUM INJECTIONPAMIDRONATE ...
www.medicineonline.com › Medical Drugs › Drugs beginning with p
Pamidronate Disodium injection is a bone resorption inhibitor available in 30 mg ... **Pamidronate disodium** (daily **oral** administration) was not carcinogenic in an ...

single-dose bioavailability study of **pamidronate disodium**
pdfs.journals.lww.com/.../A_SINGLE_DOSE_BIOAVAILABILITY_STUD...
by WF Cheung - 1994 - Cited by 2 - Related articles
comparing the relative bioavailability of **pamidronate disodium** after **oral** doses of ... Keywords: **pamidronate disodium**, postmenopausal osteoporosis women, ...

Pamidronate (Aredia) - Aetna
www.aetna.com/cpb/medical/data/600_699/0672.html - Aetna
The available evidence indicates that **oral** clodronate, IV pamidronate, and IV zoledronic acid are superior ..... J2430, Injection, **pamidronate disodium**, per 30 mg

Pamidronate Disodium for Palliative Therapy of Feline Bone ...
www.hindawi.com/journals/vmi/2014/675172/
by JM Wypij - 2014
Apr 17, 2014 - Median progression free survival was 55 days for all cats and 71 days for cats with **oral** squamous cell carcinoma. **Pamidronate** therapy ...

Behbod Darou::Products::**Pamidronate Disodium** omega
behboddarou.com/Product_**Pamidronate**.html
Ototoxicity ,manifest as tinnitus and sudden hearing loss, has been reported in 2 patients given both intravenous and **oral** **pamidronate** for pre-existing ...

Searches related to pamidronate disodium and oral

pamidronate disodium **iv**
pamidronate disodium **infusion**
pamidronate disodium **/30 mg**
pamidronate disodium **mechanism action**
pamidronate disodium **injection**

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SODIUM CLODRONATE 800MG TABLETS | **Drugs**.com
www.drugs.com › Drugs ▾
Bonefos 800mg Tablets (**sodium clodronate**) Patient Information Leaflet Read all of this leaflet carefully before you start taking this **medicine**. - Keep this leaflet.

BONEFOS CAPSULES 400MG | **Drugs**.com
www.drugs.com › Drugs ▾
80803476 Do not take **Bonefos** Capsules if: If you have very poor kidney function. If you are allergic to the active ingredient (**sodium clodronate**), or to any of ...

BONEFOS 400MG CAPSULES | **Drugs**.com
www.drugs.com › Drugs ▾
Bonefos 400mg Capsules (**sodium clodronate**) Your **medicine** is known by the above name, but will be referred to as **Bonefos** Capsules throughout this.

BONEFOS 800MG TABLETS | **Drugs**.com
www.drugs.com › Drugs ▾
(**disodium clodronate**) Patient Information Leaflet 27mm. This product is known by the above name but will usually be referred to as **Bonefos** Tablets throughout ...

Bonefos (sodium clodronate) - NetDoctor.co.uk
www.netdoctor.co.uk/cancer/**medicines**/**bonefos**.html ▾
Jan 13, 2012 - **Bonefos** tablets and capsules contain the active ingredient **sodium clodronate**, which is a type of **medicine** called a bisphosphonate. ... These will be printed on the dispensing **label** that your pharmacist has put on the packet of ...

Searching British National Formulary for **Sodium Clodronate** ...
www.bnf.org/bnf/search.htm?q=**Sodium%20Clodronate**
SODIUM CLODRONATE. British National Formulary: 6 Endocrine system > 6.6 **Drugs** ... and other **drugs** affecting bone metabolism > Bisphosphonates, **Bonefos®**. British ... Appendix 3 Cautionary and advisory **labels** for dispensed medicines.

Sodium Clodronate - Search Results - Evidence Search ...
www.evidence.nhs.uk/**medicine**/**sodium-clodronate**... ▾ NHS Evidence Search ▾
Results 1 - 20 - Treatment > Cancer **drugs** > **Sodium clodronate** (**Bonefos**, Clasteon) What. ... **sodium clodronate** 800 mg, net price 60-tab pack = £152.56. **Label**.

[PDF] **sodium clodronate** - Medicines and Healthcare products ...
www.mhra.gov.u... ▾ Medicines and Healthcare Products Regulatory Agen... ▾
Oct 5, 2011 - This is a **Prescription**-Only **Medicine** (POM) used to manage bone diseases, particularly ... Module 4: **Labelling** ... **Sodium clodronate** tablets are also indicated for the maintenance of clinically acceptable serum .... amended, claiming to be a generic medicinal product of **Bonefos** 800mg Tablets, which was.

Bonefos Tablets (supportive therapy in cancer treatment ...
www.nps.org.au/**medicines**/.../**sodium-clodronate**.../b... ▾ NPS MedicineWise ▾
Sep 9, 2014 - Developed by the **pharmaceutical** company responsible for the **medicine** in ... **sodium clodronate**, the active ingredient in **Bonefos**; any of the ... If you do not understand the instructions printed on the pharmacist **label**, ask your ...

Sodium clodronate 400mg capsules - bone metastases ...
www.**medicines**.org.uk/guides/**sodium%20clodronate**/bone%20metastases ▾
Aug 27, 2014 - The information in this **Medicine** Guide for **Sodium clodronate** varies ... Leaflet that comes with this **medicine** or on the **medicine label**. You can ...

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Etidronate Disodium Oral tablet > Yale Medical Group | Yal...
yalemedicalgroup.org/info/health.aspx?ContentTypeId=121... 1124
Jun 11, 2010 - Print. Alchemy Patient Education Sheets | **Etidronate Disodium Oral** tablet ... ETIDRONATE (e ti DROE nate) reduces calcium loss from bone.

RxMed: Pharmaceutical Information - DIDROCAL
www.rxmed.com/b.main/b2.pharmaceutical/b2.1.../DIDROCAL.html
Etidronate disodium is not metabolized. The amount of drug absorbed after an **oral** dose is approximately 3.5%. Within 24 hours, approximately half the ...

Efficacy of **oral** administration of **etidronate disodium** in ...
europepmc.org/abstract/MED/3111705
by Q S Ringenberg - 1986 - Cited by 25 - Related articles
Abstract: As part of a multicenter trial of **etidronate disodium** for control of hypercalcemia in patients with malignancies, patients achieving ...

[PDF] **Etidronate Disodium** - Santa Cruz Biotechnology
datasheets.scbt.com/sc-205687.pdf
Etidronate Disodium sc-205687 ... **Etidronate Disodium**, STATEMENT OF ... The acute **oral** LD50 in rat was determined to be 2910 mg active acid/kg bw. In.

ETIDRONATE DISODIUM - RobHolland.com
www.robholland.com/Nursing/Drug_Guide/data/.../E056.html
ETIDRONATE DISODIUM (e-ti-droe'nate) ... Enterocolitis; children, pathologic fractures; pregnancy (category B, **oral**; category C, parenteral). Safety during ...

[PDF] **Etidronate** - Medsafe
www.medsafe.govt.nz/profs/datasheet/a/ArrowEtidronatetab.pdf Medsafe
Disodium etidronate is the **disodium** salt of (1-hydroxyethylidene) diphosphonic ... **Etidronate** should be taken as a single, **oral**, daily dose at bedtime. However,.

Etidronate disodium hydrate - Sigma-Aldrich
www.sigmaaldrich.com/catalog/product/.../p5248?lang... Sigma-Aldrich
Sigma-Aldrich offers Sigma-P5248, **Etidronate disodium** hydrate for your ... **Oral** bisphosphonates: early endosseous dental implant success and crestal bone ...

Didronel PMO (**etidronate** and calcium) - NetDoctor.co.uk
www.netdoctor.co.uk/seniors-health/medicines/didronel-pmo.html
Jan 9, 2012 - Osteoporosis. **Etidronate disodium** (Didronel tablets), calcium carbonate (Cacit ... The risk may also be increased by poor **oral** hygiene, dental ...

etidronate disodium (CHEBI:4906)
www.ebi.ac.uk/chebi/searchId.do?... European Bioinformatics Institute
Feb 19, 2014 - **etidronate disodium** (CHEBI:4906) is a organic sodium salt ... for 6 to 12 mo with disodium etidronate (EHDP) in **oral** doses of 20 mg/kg/day.

Etidronate Disodium (Mylan Pharmaceuticals, Inc.)
www.rxresource.org › Drugs & Supplements
Etidronate disodium tablets, USP contain either 200 mg or 400 mg of **etidronate disodium**, the disodium salt of (1-hydroxyethylidene) diphosphonic acid, for **oral** ...

Searches related to **etidronate disodium oral**

etidronate disodium **calcium carbonate**
etidronate disodium **side effects**

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Did you mean: cellulose ***HPMC*** 603 and bioavailability

Patent US20020022056 - **Bioavailability**; core overcoated ...
www.google.com/patents/US20020022056 Google
Feb 21, 2002 - **Bioavailability**; core overcoated with hydrophilic permeable exterior ..... [0052] Mix the TRILEPTAL, **cellulose HPM 603** (binder) and AVICEL PH ...

HTML - Patent data - EPO
https://data.epo.org/publication-server/rest/v1.0/...dates/.../document.html
Jul 23, 2008 - [0003] The **bioavailability** and **bioequivalence** of a drug substance depend on ..... [0069] Mix the TRILEPTAL, **cellulose HPM 603** (binder) and a ...

[PDF] Oxacarbazepine film-coated tablets
patentimages.storage.googleapis.com/pdfs/US20030190361.pdf
by B Schlutermann - 2003 - Cited by 2 - Related articles
May 5, 2003 - With respect to, for example **bioavailability** and compliance. [0003] EP 0 646 374 ..... [0053] Mix the TRILEPTAL, **cellulose HPM 603** (binder).

Ashish Sarode | LinkedIn
www.linkedin.com/pub/ashish-sarode/21/591/635
Greater Boston Area - Post Doctoral Fellow at University of Rhode Island
Hydroxypropyl **cellulose** stabilizes amorphous solid dispersions of the poorly water ... Overcoming the low oral **bioavailability** of many drugs due to their poor .... Eudragit L-100, **HPMCAS**-LF, **HPMCAS**-MF, Pharmacoat **603**, and Kollidon VA-64 ...

9004-65-3(Hydroxypropyl methyl **cellulose** - lookchem
www.lookchem.com › Products
Also offer free database of 9004-65-3(Hydroxypropyl methyl **cellulose**) including ... **603**;Pharmacoat HPMC 615;Marpolose 90MP15000;Celacol **HPM** 5000 ...

Patent US5695782 - Double-layered oxcarbazepine tablets ...
www.google.cat/patents/US5695782
1.9 mgOuter **layerCellulose HPM 603** (hydroxypropyl methyl c. ... 1993, University Of Florida, Method of improving oral **bioavailability** of carbamazepine.

Pharmaceutical compositions - Patents - Justia
patents.justia.com › Patents
Feb 15, 2007 - The **bioavailability** and **bioequivalence** of a drug substance depend on its ..... Mix the TRILEPTAL, **cellulose HPM 603** (binder) and a portion ...

Hot melt extrusion (HME) for amorphous solid dispersions ...
www.researchgate.net/.../233989317_Hot_melt_extrusion_(H... ResearchGate
... L-100-55, Eudragit L-100, **HPMCAS**-LF, **HPMCAS**-MF, Pharmacoat **603**, and Kollidon ... by hot-melt extrusion for dissolution and **bioavailability** enhancement.

Old **603** 029 patents | Patentfish.com
www.patentfish.com/**603**-029/old
Inventions related to **603** 029, sorted with oldest patents first . ... dioxide 1 029 1, **cellulose hpm 603**, device having battery-save circuitry, 1 029 1, having battery-save circuitry, 684 ... **Bioavailability**; core overcoated with hydrophilic permeable .

Evaluation of Griseofulvin Binary and Ternary Solid ...
link.springer.com/.../10.1208%2Fs122... Springer Science+Business Media
by H Al-Obaidi - 2009 - Cited by 25 - Related articles
Dec 1, 2009 - Solid dispersions of griseofulvin and hydroxypropyl **methylcellulose** acetate succinate (**HPMCAS**) were prepared using the spray drying ...

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Oral clodronate for adjuvant treatment of operable breast ...
www.ncbi.nlm.nih.gov/... National Center for Biotechnology Information
by AH Paterson - 2012 - Cited by 49 - Related articles
Jun 14, 2012 - **Oral clodronate** for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a ...

SODIUM **CLODRONATE** - **ORAL** - EHEandME
https://www.eheandme.com/drug_db_monographs/5174
Drug Information: SODIUM **CLODRONATE** - **ORAL**

Abstract - Annals of Oncology - Oxford Journals
annonc.oxfordjournals.org/content/12/10/1433 Annals of Oncology
by SP Jagdev - 2001 - Cited by 93 - Related articles
Comparison of the effects of intravenous pamidronate and **oral clodronate** on symptoms and bone resorption in patients with metastatic bone disease.

Clodronate Disodium Drug Information, Professional
www.drugs.com › Drugs A to Z
In Wistar rats treated with **oral clodronate** at doses of 200, 600, and 1000 mg per kg of body weight (mg/kg) from day 6 to 19 of pregnancy, **clodronate** was not ...

Oral Sodium **Clodronate** for Nonmetastatic Prostate Cancer
www.medscape.com/viewarticle/552293_1 Medscape
Oral Sodium **Clodronate** for Nonmetastatic Prostate Cancer--Results of a Randomized Double-Blind Placebo-Controlled Trial. Malcolm D. Mason, Matthew R.

[PDF] BONEFOS® (sodium **clodronate**) - Take a look at ...
www.bayerresources.com.au/resources/uploads/pi/file9309.pdf
BONEFOS contains sodium **clodronate** which is a bone metabolism regulator. ... Five of the eleven patients treated with **oral** sodium **clodronate** (45%) achieved.

Adjuvant therapy with **oral** sodium **clodronate** in locally ...
www.thelancet.com/journals/lanonc/article/...3/abstract The Lancet
by DP Dearnaley - 2003 - Cited by 124 - Related articles
Aug 11, 2003 - Adjuvant therapy with **oral** sodium **clodronate** in locally advanced and metastatic prostate cancer: long-term overall survival results from the ...

Double-Blind Controlled Trial of **Oral Clodronate** in Patients ...
jco.ascopubs.org/content/11/1/59.full.pdf Journal of Clinical Oncology
by AH Paterson - 1993 - Cited by 596 - Related articles
double-blind, placebo-controlled trial of **oral clodronate**, 1,600 mg/d (86 patients) compared with an identical placebo (86 patients). Results: The patients in each ...

Sodium **Clodronate** - **Oral** - Health Link Alberta
https://myhealth.alberta.ca/health/medications/.../conditions.aspx?... Alberta
Sodium **clodronate** is used with other drugs to reduce the breakdown of bone caused by cancer that has spread to the bones. It is also used to treat a high level ...

Oral adjuvant **clodronate** therapy could improve overall ...
www.sciencedirect.com/science/.../S0959804913000841 ScienceDirect
by J Zhu - 2013 - Cited by 2 - Related articles
Feb 28, 2013 - **Oral** adjuvant **clodronate** therapy could improve overall survival in early breast cancer: Results from an updated systematic review and meta-...

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

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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	1	20140051669		2014-02-20	Herriot Tabuteau	

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	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

	1	FDA Commissioner Margaret A. Hamburg Statement on Prescription Opioid Abuse (April 3, 2014), available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391590.htm.	☐
	2	Garth T. Whiteside et al., DiPOA ([8-(3,3-Diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic Acid), a Novel, Systemically Available, and Peripherally Restricted Mu Opioid Agonist with Antihyperalgesic Activity: II. In Vivo Pharmacological Characterization in the Rat, 310 J. PHARMACOL. & EXP. THER. 793 (2004)).	☐
	3	Henry McQuay, Opioids in pain management, 353 LANCET 2229, Abstract and 2229 (1999).	☐

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EXAMINER SIGNATURE

Examiner Signature	/Svetlana Ivanova/	Date Considered	10/09/2014

*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.

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

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	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)	2014-08-04
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.**

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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.

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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.

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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
EAST search	4/25/2014	si
EAST search	7/3/2014	si
Google searches	10/9/2014	si
EAST search	10/9/2014	si

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

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	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								
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CLAIM		DATE								
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	119	-	-	-	-	-	-			
	120			✓	✓	✓	✓			
	121				✓	✓	✓			

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**

APPEAL BRIEF PURSUANT TO 37 CFR §1.192

Mail Stop Appeal Brief—Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

This brief is submitted with a Notice of Appeal in response to the Office Action dated October 16, 2014 ("the Office Action").

The fees required under §1.17, and any required petition for extension of time for filing this brief and fees therefore, are submitted herewith. Any additional fees that may be required are hereby authorized to be withdrawn from deposit account no. 021818.

Respectfully submitted,

Dated: January 14, 2015

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

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

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**Copies of each item in the Evidence Appendix are being submitted in a separate document.

REAL PARTY IN INTEREST

Antecip Bioventures II LLC is the assignee of record and the real party in interest in this appeal.

RELATED APPEALS, INTERFERENCES, AND TRAILS

Appeals have been or are being filed in the following related cases, all of which are before Examiner Ivanova:

— U.S. Application No. 13/894,262 (Atty No. 1958603.00009)

— U.S. Application No. 13/894,252 (Atty No. 1958603.00019)

— U.S. Application No. 13/894,274 (Atty No. 1958603.00015)

SUMMARY OF CLAIMED SUBJECT MATTER

Two independent claims and 18 dependent claims are presented on appeal.

Claim 40 is an independent claim drawn to an oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid, wherein the dosage form contains no bioavailability enhancing agents, and wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.

Claim 60 is an independent claim drawn to an oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid and an excipient, wherein the dosage form contains no bioavailability enhancing agents, and wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.

Support for the pending claims can be found in the specification as filed, for example, at least at the following:

Claim 40	Specification Support
An oral dosage form comprising	Abstract
about 30 mg to about 250 mg of zoledronic acid,	Paragraph [049]
wherein the dosage form contains no bioavailability enhancing agents, and	Abstract and paragraph [055]
wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.	Paragraphs [055]-[060]
Claim 60	**Specification Support**
An oral dosage form comprising	Abstract
about 30 mg to about 250 mg of zoledronic acid	Paragraph [049]
and an excipient,	Paragraph [072]
wherein the dosage form contains no bioavailability enhancing agents, and	Abstract and paragraph [055]
wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.	Paragraphs [055]-[060]

ARGUMENTS

I. Introduction

The claimed oral dosage forms and the claimed pharmaceutical product are useful for providing an effective amount of zoledronic acid in an oral form. According to the Office, Claims 40, 42, 44-57, 60, 61, 120, and 121 are obvious over U.S. Publication No. 2004/0063670 ("Fox") in view of Labeling of Unit Dose Packages of Drugs, Policy No. PH-04-06, Department of Pharmacy Policy, Univ. of Kentucky Hospital, Chandler Medical Center (Nov. 2009) ("Chandler"), Leonard et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid, Poster presentation at AACR-NCI-EORTC: Molecular Targets and Cancer Therapeutics October 2007 ("Leonard"), International Publication No. WO 2005/005447 ("Aronhime"), and/or L.A. Sorbera et al., *Zolendronate Disodium*, 25(3) DRUGS OF THE FUTURE 259 (2000) ("Sorbera"), and/or Fosamax® (alendronate sodium) tablets, for oral use, approved 1995, revised Feb. 2012, *available at* http://www.accessdata.fda.gov/drugsatfda_docs /label/2012/021575s017lbl.pdf ("Fosamax label") and/or Bonefos Product Monograph, Part III: Consumer Information Bonefos® clodronate disodium, pages 25-28, revised September 22, 2011, *available at* http://www.bayer.ca/files/BONEFOS-PM-ENG-PT3-22SEP2011-147998.pdf ("Bonefos monograph"). Appellant appeals this rejection.

II. Cited References

A. Fox

The Fox publication relates to the use of bisphosphonates for pain treatment. Fox discloses various dosage forms but states that "[intravenous] administration is considered to be of particular importance." Fox at para. [0072]. As for frequency of administration, Fox prefers a single dose. *See id.* at para. [0077]. Fox also discloses a number of studies intending to show an effect of bisphosphonates in rat models of inflammatory and neuropathic pain. *See id.* at Example 5.

B. Chandler

The Chandler publication outlines the policies and procedures used by the pharmacy facilities of the University of Kentucky Hospital, Chandler Medical Center. Chandler outlines the information to be included on pharmaceutical labels and how that information is to be displayed.

C. Leonard

The Leonard reference presents the results of a study of the bioavailability of zoledronic acid in bioavailability enhanced oral dosage forms of zoledronic acid as compared to intravenous zoledronic acid.

D. Aronhime

The Aronhime reference discloses polymorphs of zoledronic acid and zoledronate sodium salts, amorphous zoledronate sodium salt, and methods of making them. *See* Aronhime at Abstract.

E. Sorbera

The Sorbera reference discloses a number of studies analyzing the tolerability and efficacy of zoledronate administered intravenously.

F. Fosamax Label

The Fosamax label is a standard label providing safety and dosing information for alendronate sodium.

G. Bonefos Monograph

The Bonefos monograph is a standard label providing safety and dosing information for clodronate disodium.

III. Legal Standard for Obviousness under 35 U.S.C. §103

In order to make a *prima facie* case of obviousness, the Office must establish: (1) that there is an apparent reason to combine the known elements in the manner claimed (*KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-41 (U.S. 2007)), (2) that all elements of the claims are

taught or suggested in the prior art (*id.*; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)), and (3) that the result is predictable (*KSR*, 127 S. Ct. at 1740-41.). 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. *Id.* These factors must be considered as a whole, including those portions that teach away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP 2140.02(VI).

II. Arguments in Response to the Most Recent Office Action

A. The most recent Office Action does not "create a stronger record and reduce further issues for appeal"

The most recent action by Appellant was to file a brief on appeal on August 5, 2014. According to the most recent Office Action, "a decision was made . . . to re-open prosecution in the 13/894,244 . . . application[] in order to create a stronger record and reduce further issues for appeal." Office Action at p. 2.

Appellant respectfully disagrees that the Office Action creates a stronger record for appeal and disagrees that the Office Action reduces further issues for appeal. Appellant will show that the new references introduced—Aronhime, Sorbera, the Fosamax Label, and the Bonefos monograph—are either cumulative or weaken the Office's alleged *prima facie* case of obviousness.

Furthermore, Appellant will demonstrate that the theories of unpatentability presented in the most recent Office Action were addressed in the last brief on appeal. Finally, Appellant will demonstrate that many of the arguments made in the last brief on appeal were ignored in the most recent Office Action.

B. The combination of references does not teach or suggest an oral dosage form of zoledronic acid "wherein the bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being."

The combination of Fox, Chandler, Leonard, Aronhime, Sorbera, the Fosamax label, and the Bonefos monograph does not teach or suggest the bioavailability range recited by the

claims. In fact, the only information provided by the combination of references with respect to bioavailability is that "[a]ll bisphosphonates, including zoledronic acid, have poor oral bioavailability" (Leonard at background section[1]), and that "[t]he current marketed dosage form of zoledronic acid is given as an infusion to overcome the limitations of oral dosing of bisphosphonates" (*Id.* at p. 1, Introduction section). Leonard further states 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." *Id.* at p. 1, Introduction section (emphasis added); *see also* Leonard et al., Safety Profile of Zoledronic acid in a novel oral formulation, Poster presentation at AACR-NCI-EORTC Molecular Targets & Cancer Therapeutics Conference, p. 2 (November 2009) ("Leonard 2009") and Cullen et. al, *MER-101 A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae*, Poster presentation at AAPS, Background section (November 2007) ("Cullen"). Thus, according to Leonard, the low bioavailability of zoledronic acid prevents an oral dosage form from being effective, but Leonard has improved the bioavailability in order to "enable the development of an oral dosage form." Leonard states that "[t]he dose administered via a 20 mg tablet equals that of a 1 mg intravenous infusion." Leonard at p. 1, Conclusions section. Thus, Leonard reports a 5% bioavailability of its oral dosage form, which is well outside of the range of the claims.

What the Office has never explained is why the references suggest a bioavailability of "about 1.2% to 3% in a human being" when Leonard reports a 5% bioavailability, and states that it is this higher bioavailability that "enable[s] the development of an oral dosage form." The range of the claims is in the opposite direction to that suggested by Leonard. Therefore, the combination of references does not teach or suggest this bioavailability range, and the appealed claims are not obvious. (*Appellant points out that the arguments made in the previous two paragraphs*

[1] See also Sorbera and p. 260 ("However, all the available compounds [bisphosphonates] are poorly absorbed from the gastrointestinal tract.")

were presented in section A(8) of the previous brief entitled "Leonard teaches away from 'the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.'")

Instead of addressing the express teachings of Leonard, the Office Action incorrectly relies on inherency.

> Stated differently, as detailed below, as Fox discloses an oral dosage form, which possesses Applicant's claimed ingredient zoledronic acid (and an excipient), including in the disclosed mg, with no bioavailability enhancing agents, the mere discovery of a previously unappreciated property of it, namely, % oral bioavailability . . . this discovery by Applicant does not render the old dosage form patently new to the discoverers. Office Action at p. 4.

This passage contains several factual and legal errors. First, inherency cannot be the basis of showing that cited references teach or suggest a claim element in an obviousness rejection. *See In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.") *(Appellant points out that this legal principle was argued in the previous brief in section A(8)(a) entitled "Leonard teaches away from 'the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.'")*

Second, Fox does not actually describe any particular oral dosage form that contains zoledronic acid to a level of detail to render the bioavailability range of the appealed claims inherent. In order for a bioavailability range to be inherent, there must be an embodiment identified in Fox that would <u>always</u> have a bioavailability within the allegedly inherent range. There is no such embodiment identified in Fox. Therefore, the bioavailability range of the appealed claims is not inherent.

The Office Action also alleges that:

> [Fox] explicitly teaches in an example oral administration [*sic*] solid dosage forms, such as tablets and dragees applicable to an active ingredient of any of the bisphosphonates taught, and their method of specific making with any of the bisphosphonates taught,

and with a specific illustration with disodium pamidronate ([0081], [0087-8]). Office Action at p. 5.

As shown by Leonard, there are "tablets and dragees" containing zoledronic acid that have a bioavailability of 5%, which is outside of the range recited by the appealed claims. Therefore the range of the claims is not inherent in this disclosure.

Immediately following this quote, page 6 of the Office Action contains a reproduction of paragraphs [0086]-[0087] of Fox, and the table following those paragraphs. This section is reproduced below, except that it is formatted for easier reading.

[0086] In the following Examples the term "active ingredient" is to be understood as being any one of the bisphosphonic acid derivatives mentioned above as being useful according to the present invention.

EXAMPLES

Example 1

[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	52.7 mg
(Avicel ® PH 105)	
	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

Appellant first points out that, because this dosage form does not contain zoledronic acid, this dosage form does not have any inherent bioavailability for zoledronic acid. Therefore, the range of the claims cannot be inherent. (*Appellant highlighted this dosage form in the previous brief in section A (5) entitled "The European Medicines Agency and Novartis teach away from an "oral dosage form comprising…zoledronic acid."*)

Furthermore, this dosage form contains polyethylene glycol, which is well known in the art to be a bioavailability enhancing agent. Thus, the dosage form is not unenhanced, and any allegedly inherent bioavailability of this dosage form is irrelevant to the pending claims.

The following quotations from the prior art show that polyethylene glycol can be a bioavailability enhancing agent.

> A mean 2-fold increase in plasma concentrations (Table I) occurred when PEG 400 was co-administered with fexofenadine. U.S. Patent No. 6,451,815, col. 10, lines 64.
>
> A mean 2-fold increase in plasma concentrations [AUC(0-24h) values calculated from the concentrations shown in Table IV] occurred when PEG 1000 was co-administered with fexofenadine. *Id.* at col. 13, lines 1-4.
>
> The bioavailability of ranitidine in male subjects is improved by the administration of low dose – 1% PEG 400. Diane A.I. Ashiru-Oredope et al., *The effect of polyoxyethylene polymers on the transport of ranitidine in Caco-2 cell monolayers*, 409 INT'L J PHARM. 164, 167 (2011).
>
> "From the results presented it can be concluded that – when formulating a drug with a low aqueous solubility – microcrystalline cellulose pellets loaded with polyethylene glycol 400 yielded a higher bioavailability compared to pellets without PEG 400." Chris Vervaet et al., *Bioavailability of hydrochlorothiazide from pellets, made by extrusion/*

spheronisation, containing polyethylene glycol 400 as a dissolution enhancer, 14(11) PHARM. RESEARCH 1644, 1646 (1997).

"However, solid dispersions with PEG enhance bioavailability but slightly reduce their gastric ulceration." Ramadan et al., 9(1) BULL. PHARM. SCI. ASSIUT UNIV. 30, 30 (1986).

Finally, the Supreme Court has emphasized the importance of an "apparent reason to combine" elements of the prior art:

> Often, it will be necessary for [the Patent Office] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *KSR*, 127 S. Ct. at 1740-1741 (emphasis added).

The Office Action alleges that the bioavailability range of the claims is inherent to a dosage form that does not contain bioavailability enhancing agents.[2] But the Office Action has not provided an apparent reason to combine zoledronic acid with an unenhanced oral dosage form. The Office Action relies upon the following assertion:

> Most important, Leonard is significant in that it provides direct further evidence from other art that the oral dosage form of Fox is enabled. Leonard explicitly teaches an oral dosage form of zoledronic acid which is well tolerated and has no serious side effects associated with its administration, and which is with proprietary penetration enhancers (i.e. bioavailability enhancing agents), which improved the absorption of the drug in small intestine. Office Action at p. 11 (emphasis added).

Thus, the alleged enablement of Fox's oral dosage forms is provided by a dosage form containing a bioavailability enhancing agent. Leonard explicitly states that improved bioavailability of zoledronic acid "enable[d] the development of an oral dosage form." Leonard at p. 1, Introduction section (emphasis added). If, as the Office Action and Leonard assert, the oral dosage form of zoledronic acid is enabled by the bioavailability enhancing agent, there is

[2] As explained in section A(8)(a) below, the bioavailability range recited in the appealed claims is not inherent to a dosage form that contains no bioavailability enhancing agents.

no apparent reason to use an oral dosage form that contains no bioavailability enhancing agent. Since there is no apparent reason to use an oral dosage form that contains no bioavailability enhancing agent, there is no apparent reason to use the bioavailability range in the appealed claims. (*Appellant points out that the arguments made in this paragraph are similar to arguments presented in section A(8) of the previous brief entitled "Leonard teaches away from 'the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.'"*)

For at least these reasons, the combination of cited references does not teach or suggest the bioavailability range recited in the appealed claims, and the claims are not *prima facie* obvious.

B. Leonard and Sorbera teach away from an unenhanced oral dosage form of zoledronic acid

As explained above, Leonard reports a 5% bioavailability for MER-101, and states that it is the higher bioavailability of MER-101 that "enable[s] the development of an oral dosage form." Sorbera reinforces statements made by Leonard and at least seven other references (*explained in sections A(1)-(7) of the previous brief*) that show that oral zoledronic acid is unlikely to work without bioavailability enhancing agents. Like the other references, Sorbera states that "all the available compounds [bisphosphonates] are poorly absorbed from the gastrointestinal tract." Sorbera at p. 260.

Sorbera further provides data showing that oral zoledronic acid has greatly inferior potency in at least one animal model, as compared to subcutaneous and intravenous zoledronic acid. The Office Action alleges that "Sorbera similarly discloses zoledronate sodium, its method of making, and its clinical utility in the treatment of tumor-induced hypercalcemia." Office Action at p. 8. However, Sorbera only shows the clinical utility of <u>intravenous</u> zoledronate in the treatment of tumor induced hypercalcemia. Sorbera at p. 266, Box 9. In fact, Sorbera strongly suggests that oral zoledronic acid is unlikely to be useful in treating hypercalcemia in human beings. For example, Sorbera provides data showing that for reducing hypercalcemia in rats, oral zoledronic acid was over three orders of magnitude less potent than intravenous and

subcutaneous zoledronic acid. *Id.* at p. 260 (see quote below). The significantly lower potency of oral zoledronic acid reported in Sorbera is depicted in Figures A and B below.

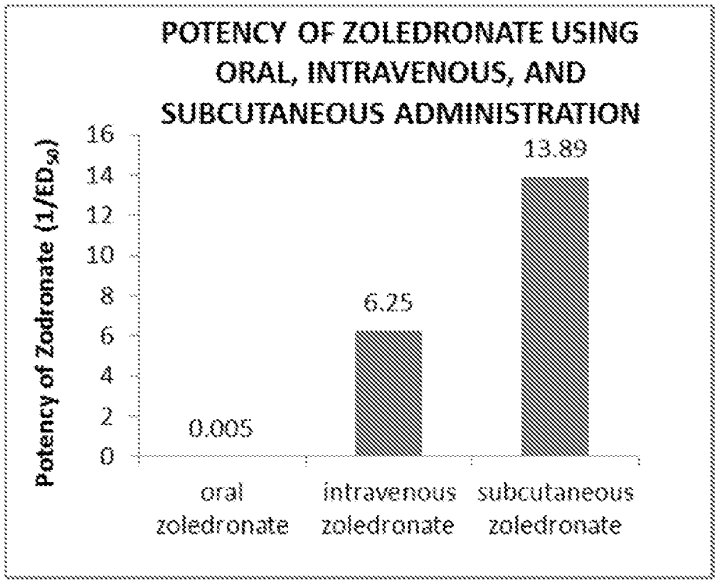

Figure A. Data from potency values reported in Sorbera.

Figure A shows that the potency of oral zoledronic acid is over 1000 times lower than that of intravenous zoledronic acid, and the potency of oral zoledronic acid is over 2000 times lower than that of subcutaneous zoledronic acid. Based on this result, a person of ordinary skill in the art would have expected that, for example, 277 mg/kg of zoledronic acid would need to be given orally to a rat in order to obtain less than three hours of pain relief as reported for the 0.1 mg/kg subcutaneous dose administered in example 5, paragraph [0102] of Fox. Sorbera states that "zoledronate (0.02 and 0.04 mg/kg) administered as a short-time infusion effectively treated patients with tumor-induced hypercalcemia and were well-tolerated…" *Id.* at p. 266, Box 9. Based upon the result shown in Figure A, oral doses of 25 mg/kg (e.g. 1500 mg for a 60 kg patient) and 50 mg/kg (e.g. 3000 mg for a 60 kg patient) would have been expected in order to achieve the same result. These doses are too high to be considered reasonable for human

administration when bisphosphonates were known for gastrointestinal toxicity. See Conte et al., *Safety of intravenous and oral bisphosphonates and compliance with dosing regimens,* 9(4) ONCOLOGIST 28, 29 (2004), and section A(1) of the previous brief. This demonstrates that a person of ordinary skill in the art would not have considered an oral dosage form of zoledronic acid to be feasible in the methods disclosed in Fox or Sorbera.

Furthermore, as illustrated in Figure B below, the data in Sorbera shows that the relative potency of oral zoledronic acid is over 6 times less than the relative potency of oral pamidronic acid. This demonstrates that an oral dosage form of pamidronate would be expected to be a far better candidate for oral administration than an oral dosage form of zoledronate. Thus, even though Fox includes an oral dosage form containing pamidronate, a person of ordinary skill in the art would not have expected oral zoledronic acid to be effective.

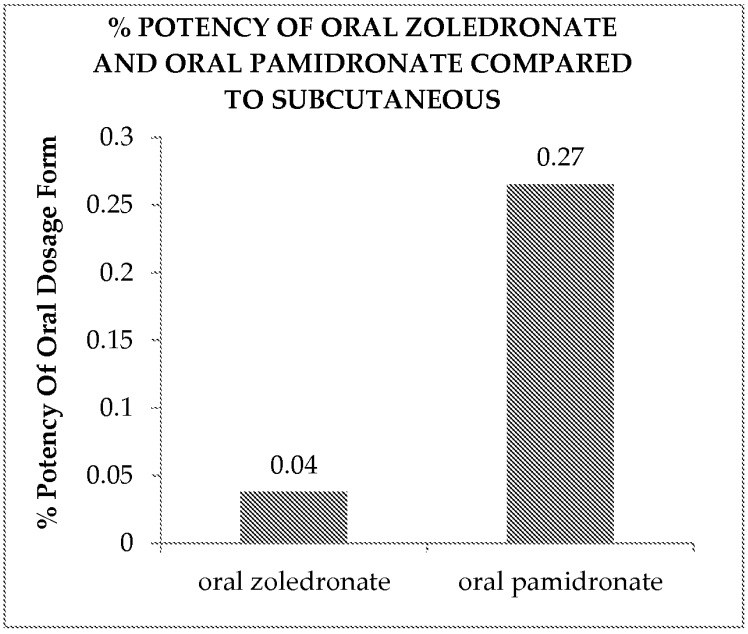

Figure B. Relative potencies for oral zoledronate and oral pamidronate based upon data reported in Sorbera

In Figure B, the percent potency of oral zoledronate is the potency of oral zoledronate divided by the potency of subcutaneous zoledronate (and multiplied by 100). Similarly, the percent potency of oral pamidronate is the potency of oral pamidronate divided by the potency of subcutaneous pamidronate (and multiplied by 100).

The data from Figures A and B were derived from the following passage from Sorbera, in which the bolded and underlined values in the quote were used to obtain the values in Figure A.

> An ED_{50} value for zoledronate to reduce hypercalcemia in 1,25-$(OH)_2D_3$-treated thyroparathyroidectomized rats *in vivo* of **0.072** ± 0.018 **μg/kg s.c.** was reported, which was 850 times more potent than values obtained for pamidronate (**61** ± 7.5 **μg/kg s.c.**). Zoledronate treatment resulted in dose-dependent inhibition of 1,25-$(OH)_2D_3$-induced hypercalcemia with maximum effects (100%) observed with a dose of 1.4 μg/kg. Zoledronate showed a low oral bioavailability when administered orally for 4 days in the same model but remained 120-fold more potent than pamidronate (ED_{50} = **0.19** ± 0.06 vs. **23** ± 2.9 **mg/kg p.o.**). Following i.v. administration, zoledronate was 690 times more active than pamidronate (ED_{50} = **0.16** vs. **110** **μg/kg i.v.**) (5). *Id.* at p. 260 (emphasis added).

Furthermore, at least twelve human clinical studies described in Sorbera were done using intravenous administration of zoledronic acid, and no clinical studies described in Sorbera used oral administration of zoledronic acid. *Id.* at pp. 261-67, esp. Boxes 1-12.

Thus, the low bioavailability of oral zoledronic acid reported in Leonard and Sorbera, and even lower relative potency of oral zoledronic acid reported in Sorbera teach away from an unenhanced oral dosage form of zoledronic acid. For at least this reason, the appealed claims are not *prima facie* obvious.

The Office Action argues:

> Most important, Aronhime and/or Sorbera render Fox alone fully enabled for an oral dosage of zoledronic acid as both the base compound (the diacid), as well as for its pharmaceutically acceptable salts thereof, and are thus only employed as cumulative in their nature. Office Action at p. 8.

First, Appellant does not agree that adding references to a rejection that are "cumulative in their nature" justifies reopening prosecution after filing a brief on appeal. Second, Aronhime and Sorbera contain no experiments showing that an unenhanced oral dosage form containing zoledronic acid is enabled. Additionally, it was known in the art that the inventors of the Fox reference failed to develop an oral dosage form of zoledronic acid.

A person of ordinary skill in the art would have known that Novartis is the assignee of the patent application that published as the Fox reference (*see* Fox, Correspondence Address) and that, according to the European Medicines Agency, Novartis developed its intravenous product "[d]ue to the poor absorption of zoledronic acid after oral administration." European Medicines Agency Scientific Assessment Report-Aclasta® (zoledronic acid, Novartis) Injection, p. 2 (Mar. 4, 2006) ("EMA Scientific Assessment"). Thus, a person of ordinary skill in the art would have known that the inventors of the Fox publication (which never issued as a patent) or their colleagues, failed to develop an oral dosage form of zoledronic acid. (*This argument was made in section A(5) of the previous brief, entitled "The European Medicines Agency and Novartis teach away from an "oral dosage form comprising…zoledronic acid."*)

Furthermore, Leonard and at least six other references (*explained in sections A(1)-(7) of the previous brief*) teach that oral zoledronic acid is unlikely to work without bioavailability enhancing agents.

The Office Action alleges that, because pamidronate, alendronate and clodronate are commercially available oral dosage forms, this shows that unenhanced zoledronic acid should also be effective as an oral dosage form. Office Action at pp. 13-15. But, as explained above, others have tried and failed to prepare a therapeutically effective unenhanced dosage form containing zoledronic acid.

C. Arguments ignored in the most recent Office Action

The Office Action failed to address the sections listed below from the previous brief on appeal (identified by section numbers as they appear in the brief).

C. *The favorable bioavailability results achieved using an oral dosage form were unexpected*

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

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

(3) The Total Pain Relief of a claimed dosage form was unexpected as compared to morphine

(4) The Total Pain Relief of a claimed dosage form was unexpected as compared to Fox

(5) The Total Pain Relief of a dosage form of the claimed method was unexpected as compared to an oral dosage form of Fox

(6) The results of an oral dosage form of the claims in a CRPS rat study were unexpected as compared to Fox

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

D. *The unexpected results when compared to morphine satisfy a long-felt need*

V. Arguments from Previous Brief on Appeal

The appealed claims are not *prima facie* obvious at least because the prior art as a whole teaches away from the claims, the references do not teach or suggest all of the claim elements, the result is not predictable, the claimed oral dosage form and pharmaceutical product exhibit unexpected results, and because the claimed oral dosage form and pharmaceutical product satisfy a long-felt need.

A. The prior art as a whole teaches away from the claims

"When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, 127 S. Ct. at 1740. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1381 (Fed. Cir. 2007). Moreover,

> "Teaching away" does not require that the prior art foresaw the specific invention that was later made, and warned against taking that path. It is indeed of interest if the prior art warned against the very modification made by the patentee, but it is not the sole basis on which a trier of fact could find that the prior art led away from the direction taken by the patentee. *Spectralytics, Inc. v. Cordis Corp.*, 649 F.3d 1336, 1343 (Fed. Cir. 2011).

(1) <u>The prior art teaches away from oral bisphosphonates</u>

It was generally believed in the art at the time of filing the present application that oral zoledronic acid had significant disadvantages, as compared to intravenous administration, that would make its use unsuitable for treatment of medical conditions.

For example, one paper states:

> Although daily oral bisphosphonate therapy can be administered at home and may seem more convenient than i.v. administration for the patient, <u>oral bisphosphonate therapy appears to be less effective and may not be any more convenient than monthly infusions</u> [16–18]. <u>Oral bisphosphonates are less effective</u> for the treatment of HCM [hypercalcemia of malignancy] (i.e., less rapid

> and sustained normalization of serum calcium) and appear to have limited activity in patients with bone metastases compared with i.v. therapy [16, 17] (reviewed by Coleman [19]). Furthermore, the oral administration of bisphosphonates is limited by poor bioavailability (<5%) and gastrointestinal (GI) toxicities (primarily esophagitis and diarrhea) [16, 18, 20]. Because of poor GI tolerability, compliance with oral bisphosphonate therapy is also an issue, and many patients require dose adjustments or discontinue therapy as a result, which can adversely affect efficacy. Therefore, in line with the updated ASCO guidelines on bisphosphonate therapy in breast cancer and multiple myeloma [2], as well as consensus guidelines and recommendations for bisphosphonate therapy in prostate cancer [21–23] and lung cancer [24], most physicians prefer i.v. bisphosphonates for the treatment of malignant bone disease, wherein strict compliance with the regimen is critical to achieve maximum therapeutic benefit. Conte et al., *Safety of intravenous and oral bisphosphonates and compliance with dosing regimens*, 9(4) ONCOLOGIST 28, 29 (2004) (emphasis added) ("Conte").

Thus, this reference explicitly states that oral bisphosphonates are less effective than intravenous administration for at least one condition and appear to be less effective in general. The reference also mentions poor bioavailability, gastrointestinal toxicity, problems with compliance for bisphosphonates, and that physicians prefer intravenous bisphosphonates. These problems with respect to bisphosphonates are also mentioned in other references. For example, Reid states that "[oral bisphosphonates] 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 . . . ." Ian R. Reid, et al., *Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density*, 346(9) N ENGL J MED 653, 653 (2002).

(2) The prior art also ties problems with oral bisphosphonates to zoledronic acid

Not only are problems with oral bisphosphonates in general emphasized in the prior art, but a number of references specifically state that zoledronic acid suffers from these problems as well. For example, Leonard, which was cited by the Office in the most recent rejection, states that "[t]he current marketed dosage form of zoledronic acid is given as an infusion to overcome

the limitations of oral dosing of bisphosphonates, including low bioavailability, gastric irritation, and gastric reflux." Leonard at p. 1, Introduction section.

Cullen, which was cited in a related application, states:

> All 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. Cullen, Background section.

Similarly, another Leonard reference, also cited in a related application, states:

> All 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. Leonard 2009, Background section.

And still another reference states:

> The low oral bioavailability of zoledronic acid, which is <1% of the oral dose, can be attributed to poor permeability in the gastrointestinal (GI) tract. It was also noted that insoluble metal complexes were formed in the upper intestines, most commonly with calcium. Zoledronic acid has also been shown to cause severe GI irritation both in the stomach and in the intestines. In some cases the irritation was so severe that medical treatment was required. U.S. Publication No. 2012/0190647 at para. [0006] (emphasis added).

In addition, the following passage from the prior art demonstrates that those of skill in the art believed that the low oral absorption of zoledronic acid precluded development of an oral dosage form at the time of filing: "Due to the poor absorption of zoledronic acid after oral administration the pharmaceutical development was aimed at developing a parenteral formulation." EMA Scientific Assessment, p. 2.

In fact, a comparison between intravenous zoledronic acid and oral risedronate (another bisphosphonate) concluded that the intravenous formulation was superior to the oral

formulation for a number a reasons. Johann D. Ringe, *Development of Clinical Utility of Zoledronic Acid and Patient Considerations in the Treatment of Osteoporosis*, 4 J. PATIENT PREFERENCE & ADHERENCE 231, 238 (2010) ("Ringe") (citing D. M. Reid, et al., *Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicenter, double-blind, double-dummy, randomized controlled trial*, 373 LANCET 1253 (2009)). The intravenous formulation demonstrated superior bone mass density increase at 12 months compared to the oral formulation. Ringe at p. 238. The intravenous formulation significantly decreased levels of β-CTx and PINP compared to the oral formulation. *Id.* Additionally, 84% of all patients in the study preferred annual intravenous administration over daily oral pills. *Id.*

These passages illustrate that a significant number of prior art references clearly teach away from using an oral dosage form.

(3) Patients and physicians preferred intravenous zoledronic acid to oral bisphosphonates

Ringe states that intravenous zoledronic acid was developed to improve compliance over oral bisphosphonates:

> Currently, bisphosphonates are the mainstay of treatment for osteoporosis though long-term persistence and adherence to bisphosphonates, especially those taken orally, remain low. This medication noncompliance has serious consequences on osteoporotic patients as it is associated with a significantly higher fracture risk. Intravenous (IV) zoledronic acid (ZOL), [was] developed to increase compliance by overcoming the frequent and burdensome dosing requirements of oral bisphosphonates . . . . *Id.* at Abstract.

Ringe further explains that most patients prefer intravenous zoledronic acid to oral alendronate.

> A once-yearly IV ZOL [zoledronic acid] has been preferred by a majority of trial outpatients in 2 separate trials, who switched to ZOL from weekly oral ALN [alendronate]. McClung et al reported that 79% of patients preferred an annual infusion of ZOL vs weekly oral ALN. Similarly, Saag et al reported that a majority of patients (66%) preferred for annual ZOL vs weekly ALN. Moreover, patients who cannot tolerate or do not prefer oral dosing may opt for yearly IV

> infusion of ZOL. Intravenous regimens may also be particularly advantageous for elderly patients residing in long-term care facilities or those with impairments affecting self management of medication. *Id.* at p. 241 (internal citations omitted).

(4) The efficacy of intravenous zoledronic acid for treating medical conditions is far better established than for oral zoledronic acid.

The prior art contains a number of studies that demonstrate the clinical efficacy of intravenous zoledronic acid in a variety of conditions. For example, Ringe describes a number of human clinical trials demonstrating the efficacy of zoledronic acid in osteoporosis (*id.* at pp. 234-36), hip fractures (*id.* at p. 234), Paget's disease (*id.* at p. 236), breast cancer (*id.*), multiple myeloma (*id.*), prostate cancer (*id.*), and other conditions. According to Ringe "[t]his article traces the development of ZOL's [zoledronic acid's] clinical utility and evaluates its patient preference by collating data from all major clinical trials, studying the efficacy and safety of ZOL in the treatment of osteoporosis and other benign bone disorders." *Id.* at Abstract (emphasis added). All of the clinical trials reported by Ringe were intravenous, and none were oral. Furthermore, none of the cited references include any clinical trials that demonstrate the effectiveness of oral zoledronic acid for the treatment of any particular condition.

Thus, the weight of the prior art evidence would have led a person of ordinary skill in the art toward intravenous zoledronic acid—the commercially available dosage form with a well established history of clinical efficacy—and not oral zoledronic acid, for which significantly less experimental evidence existed related to effectiveness for any medical condition. Therefore, the weight of the prior art evidence teaches away from the claims.

(5) The European Medicines Agency and Novartis teach away from an "oral dosage form comprising…zoledronic acid"

The European Medicines Agency (EMA) and Novartis Pharmaceuticals teach away from the claim element "an oral dosage form comprising…zoledronic acid" because, according to the EMA, Novartis developed zoledronic acid as an intravenous formulation because of the low

oral bioavailability of zoledronic acid. The EMA's scientific assessment of Novartis' intravenous zoledronic acid product states the following:

> Due to the poor absorption of zoledronic acid after oral administration the pharmaceutical development was aimed at developing a parenteral formulation. EMA Scientific Assessment at p. 2.

Thus, according to the EMA and Novartis, the low oral bioavailability of zoledronic acid prevented development of an oral dosage form. Thus, the EMA and Novartis teach away from this claim element.

The Final Office Action states that "Fox expressly teaches an oral dosage form . . . ." Final Office Action issued July 15, 2014, p. 5 ("Final Office Action"). Fox states the following with respect to various routes of administration of bisphosphonates.

> 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).
>
> 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.
>
> The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, hormonal status (e.g. post-menopausal) and bone mineral density as appropriate. Most preferably, however, the bisphosphonate is administered intravenously. Fox at para. [0071]-[0073].

Appellant points out that these passages refer to "pharmaceutical compositions" or "bisphosphonate," and do not specify zoledronic acid. A person of ordinary skill in the art would have known that, for example, "alendronate…, risedronate…, and ibandronate are oral bisphosphonate," but that "zoledronic acid…[is] available as an IV formulation…" Ringe at p. 232. Furthermore, Fox describes an example of an oral dosage form of pamidronate (Fox at

para. [0087]-[0088], Example 1), but contains no example of an oral dosage form of zoledronic acid.

A person of ordinary skill in the art would further know that Novartis is the assignee of the patent application that published as the Fox reference (*see* Fox, Correspondence Address) and that, according to the European Medicines Agency, Novartis developed its intravenous product "[d]ue to the poor absorption of zoledronic acid after oral administration." EMA Scientific Assessment, p. 2 (Mar. 4, 2006). Thus, a person of ordinary skill in the art would have known that the inventors of the Fox publication (which never issued as a patent) failed to develop an oral dosage form of zoledronic acid. Based upon this, a person of ordinary skill in the art would have understood references to oral bisphosphonate as referring to alendronate, risedronate, ibandronate, or other bisphosphonates that are actually administered orally, but would not have expected an oral zoledronic acid to be feasible based upon the disclosure of Fox. Thus, in view of the prior art as a whole, Fox does not suggest oral zoledronic acid.

(6) Leonard, the EMA, and Novartis, teach away from a "dosage form contain[ing] no bioavailability enhancing agents"

Leonard teaches away from the claim element "the dosage form contains no bioavailability enhancing agents" because, according to Leonard, a bioavailability enhancing agent is necessary for an oral dosage form containing zoledronic acid to be effective.

As explained above, Leonard asserts that "[t]he current marketed dosage form of zoledronic acid is given as an infusion to overcome the limitations of oral dosing of bisphosphonates, including low bioavailability, gastric irritation, and gastric reflux." Leonard at p. 1, Introduction section (emphasis added). The EMA's statement that Novartis developed its intravenous product "[d]ue to the poor absorption of zoledronic acid after oral administration" (EMA Scientific Assessment, p. 2 (Mar. 4, 2006)) further supports Leonard's assertion.

Leonard further states 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." Leonard at p. 1, Introduction section (emphasis added); *see also* Leonard 2009 at p. 2 and Cullen at p. 2, Background section. Thus, according to Leonard, the low bioavailability of zoledronic acid prevents an oral dosage form from being effective, but Leonard has improved the bioavailability enough to "enable the development of an oral dosage form." Based on this, a person of ordinary skill in the art would not have believed that an oral dosage form that "contains no bioavailability enhancing agents" would be effective. Thus, Leonard, in the context of teachings by the EMA and Novartis, teaches away from this claim element.

(7) Use of an oral zoledronic acid was unpredictable prior to the development of the claimed dosage form

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S. Ct. at 1739. It follows that the combination of familiar elements according to known methods is not obvious when it does not yield predictable results. As explained above, the inventors of the Fox publication failed to develop an oral dosage form containing zoledronic acid. Furthermore, there is no document on the record that shows that the inventors of the Fox publication ever published any results demonstrating a therapeutic effect of an oral dosage form comprising zoledronic acid. This clearly establishes that Fox does not predictably lead to a therapeutically effective oral dosage form of zoledronic acid.

The lack of FDA approval for the oral dosage form of zoledronic acid further demonstrates that the use of an oral dosage form of zoledronic acid is unpredictable. Appellant points out that failure of 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." *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (citations present in published opinion).

There is currently no oral dosage form of zoledronic acid available in the United States, or anywhere else in the world. According to the Orange Book, there are 19 zoledronic acid products available in the United States, all of them are intravenous, and none are oral. Orange Book listings from "OB_Rx" table for query on "zoledronic acid" performed on Feb. 28, 2014. "[T]he Orange Book…identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) . . . ." Orange Book Preface (emphasis added). Thus, the lack of a listing of oral zoledronic acid in the Orange Book demonstrates that oral zoledronic acid is not approved by the FDA.

The prior art strongly suggests that the reason that no oral zoledronic acid is approved by the FDA is due to failure of the oral dosage form. As pointed out above, the European Medicines Agency has stated that "due to the poor absorption of zoledronic acid after oral administration the pharmaceutical development was aimed at developing a parenteral formulation." EMA Scientific Assessment at p. 2. Furthermore, Leonard states that "[t]he current marketed dosage form of zoledronic acid is given as an intravenous infusion to overcome the issues with oral dosing of bisphosphonates." Leonard at p. 1, Introduction section. Additionally, Cullen states that "[t]he current marketed dosage form of zoledronic acid is given as an intravenous infusion to overcome the issues with oral dosing of bisphosphonates . . . ." Cullen at p. 2, Background section. Thus, despite apparent attempts to develop an oral zoledronic acid, the fact that oral zoledronic acid is not approved by the FDA is significant evidence of the nonobviousness of the claimed method.

In summary, there were multiple reasons that 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, several references cited by the Office describe significant problems associated

with oral zoledronic acid. Second, for at least some conditions, oral bisphosphonates are less effective than intravenous bisphosphonates. Third, several references establish that intravenous zoledronic acid was developed and used because of failure of oral zoledronic acid. Fourth, all nineteen zoledronic acid products available in the U.S. are intravenous, and none are oral. Fifth, the oral zoledronic acid allegedly referred to in Fox has not been approved by the FDA. Therefore, the prior art as a whole teaches away from "[a]n oral dosage form comprising…zoledronic acid, wherein the dosage form contains no bioavailability enhancing agents."

(8) Leonard teaches away from "the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being"

Leonard teaches away from the claim element "the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being" because Leonard implies that a bioavailability of about 5% or higher would be needed for effective oral dosing.

As explained above, Leonard alleges that "[t]he current marketed dosage form of zoledronic acid is given as an infusion to overcome the limitations of oral dosing of bisphosphonates, including low bioavailability, gastric irritation, and gastric reflux." Leonard at p. 1, Introduction section (emphasis added). Thus, Leonard asserts that low bioavailability prevents oral zoledronic acid from being effective. Leonard further states 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." Leonard at p. 1, Introduction section, emphasis added; *see also* Leonard 2009 at p. 2 and Cullen at p. 2, Background section. Thus, according to Leonard, MER-101 has a bioavailability sufficiently high enough to "enable the development of an oral dosage form."

Leonard states that "[t]he dose administered via a 20 mg tablet equals that of a 1 mg intravenous infusion." Leonard at p. 1, Conclusions section. Leonard reports a 5% bioavailability of its oral dosage form and makes it clear that an even higher bioavailability

would have been desirable. Leonard tested a 10 mg tablet as well as a 20 mg tablet (Leonard at p. 1, data summary section), undoubtedly hoping that 10% bioavailability would be achievable. Based on this and on assertions by Leonard and other references that low bioavailability of zoledronic acid limits its effectiveness, a person of ordinary skill in the art would be motivated to prepare a dosage form with a bioavailability of 5% or higher. Because Leonard's dosage form is reported to have a bioavailability of 5%, the potential effectiveness of a dosage form having a lower bioavailability would have been uncertain. Thus, Leonard would have clearly pointed a person of ordinary skill in the art to a bioavailability of at least 5%, and Leonard teaches away from a dosage form that has an oral bioavailability that "is about 1.2% to about 3% in a human being."

The Office alleges that a formulation of Fox "will inherently possess the bioavailability…of Applicant's claims." Final Office Action at p. 4. However, inherency cannot be the basis of showing that cited references teach or suggest a claim element in an obviousness rejection. *See In re Rijckaert*, 9 F.3d at 1534 ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.")

Furthermore,

> [t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (internal quotations and citations omitted).

The extrinsic evidence makes it clear that the bioavailability range of the claims is not necessarily present. As shown in Table 1, the C_{max} (maximum plasma concentration of zoledronic acid) of dosage forms encompassed by, but not taught or suggested by, Fox can vary significantly even without bioavailability enhancing agents. For example, even when the C_{max} is

dose-adjusted to 5 mg/kg, the dosage form identified as "Tablet Acid" has a C_{max} that is twice that of the dosage forms identified as "Fox" and "Fox-enteric coated."

According to U.S. Publication No. 2011/0028435 ("Hanna"), the oral bioavailability of zoledronic acid is "approximately 1%." Hanna at para. [0007]. Thus, it is possible that the zoledronic acid in the dosage forms identified as "Fox" and "Fox-enteric coated" have an oral bioavailability that is about 1%. By contrast, consistent with the signficantly higher C_{max} in Table 2, the dosage form identified as "Tablet Acid" could have a bioavailability within the range of the claims. Thus, it cannot be said that the bioavailability range is "necessarily present" in the disclosure of Fox. For at least this reason, this claim element is not inherent in Fox.

Dosage form	Description	C_{max}	Relevant disclosure of Fox
Fox	5 mg/kg zoledronic acid[3] in the form of zoledronic acid monohydrate[4] in a gelatin capsule[5]	110.73 ng/mL [6]	"Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin."[7]
Fox Enteric-Coated	5 mg/kg zoledronic acid[8] in the form of zoledronic acid monohydrate in an enteric coated gelatin capsule[9]	109.37 ng/mL [10]	"Other orally administrable pharmaceutical preparations are dry-filled capsules made of gelatin."[11] "Dragee cores are provided with suitable coatings that may be resistant to gastric juices."[12]
Tablet Acid	3 tablets of 50 mg zoledronic acid plus excipients for 6-10 kg dogs[13] (average 19 mg/kg) Free of bioavailability enhancing agents[14]	846 ng/mL [15] Scaled to 5 mg/kg by multiplying by 5/19 to obtain a scaled C_{max} of **222 ng/mL**	

Table 1

Table 1 demonstrates that "Fox" and "Fox Enteric-Coated" are within the description provided by Fox. The composition of these dosage forms, as compared to the relevant disclosure of Fox, is shown in Table 1 below. The C_{max} values are shown in Table 1 with a reference to where the values are found in the relevant document. The C_{max} values for the "Tablet Acid" were scaled down because a larger amount of zoledronic acid was given to the dogs receiving those dosage forms. The dosage forms labeled "Fox" and "Fox Enteric-Coated"

[3]Hanna at para. [0133] and [0147]
[4]*Id.* at Table 3, Leg #2.
[5] *Id.* at para. [0147].
[6] *Id.* at Table 3, Leg #2 at 0.5 hours.
[7] Fox at para. [0082].
[8] Hanna at para. [0147]
[9] *Id.* at para. [0148].
[10] *Id.* at Table 4, Leg #7, p. 15, at 2 hours.
[11] Fox at para. [0082].
[12] *Id.* at para. [0081].
[13] U.S. Publication No. 2014/0051669 at para. [0142] ("Tabuteau").
[14] *Id.* at para. [0113]. As is clear from this paragraph, a salt form is not a bioavailability enhancing agent.
[15] *Id.* at Table 1, Group 2 at 0.5 hours.

are described in Hanna. The dosage form labeled "Tablet Acid" is described in U.S. Publication No. 2014/0051669 ("Tabuteau"), a related application filed by Appellant. Thus, Table 1 clearly shows that the bioavailability range of the claims is not necessarily present in dosage forms within the description provided by Fox. For at least this reason, the rejected claims are not obvious.

Furthermore, the Office stated that "[t]hat the C_{max} shows some differences therefore may simply reflect different ingredients . . . ." Final Office Action at p. 2. If the C_{max} or the bioavailability depends upon the ingredients within the scope of Fox, it cannot be said that the range recited in the claims is necessarily present. Therefore, the element is not inherent, and the claims are not obvious.

B. The cited references do not teach or suggest every limitation of the claims

"Obviousness requires a suggestion of all limitations of a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The Office has not established that the cited references teach or suggest the element "[a]n oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid" as recited in the appealed claims.

(1) <u>The cited references do not teach or suggest "about 30 mg to about 250 mg of zoledronic acid"</u>

The Office alleges that "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." Appellant first notes that the claim actually recites the range "about 30 mg to about 250 mg," and not "about 30 mg to about 400 mg." This line of reasoning is a classic example of the Office substituting a rigid application of some legal principle for actually considering what the prior art as a whole teaches or suggests. The implication of the statement above is that the Office is taking the position that "a prior art reference that discloses a range encompassing a somewhat narrower claimed range

is sufficient to establish a prima facie case of obviousness," (*In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003)), and because the range of the claims allegedly falls within the range of Fox, the reference suggests the range.

However, the courts have never intended such a bright line rule to be a substitute for looking at all of the available facts of a particular situation. The Supreme Court stated:"[W]hen a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs." *KSR*, 127 S. Ct. at 1741. The facts of the present case clearly show that the prior art does not suggest the range of the rejected claims.

A person of ordinary skill in the art, upon reading the disclosure in Fox referred to above, would also have noticed the following aspects of Fox. First, Fox only actually tested zoledronic acid in amounts of 0.003-0.1 mg/kg, administered *subcutaneously*. Fox at paras. [0102] and [0108]. Second, Fox further states that "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." *Id.* at para. [0078]. Thus, the range that Fox identifies for treatment of humans is less than that of the claims, and the preferred range is even further from the claims.

More importantly, a person of ordinary skill in the art would have been aware that typical use of zoledronic acid is well outside of the range of the appealed claim. For example, the highest dosage of zoledronic acid reported in one comprehensive review is "4 mg via 15-minute IV infusion, every 3-4 weeks" (Ringe at p. 236), and for some indications, such as prevention of fractures in patients who have had hip fractures, the dosage reported is "5 mg . . . once-yearly" (*id.* at p. 234). Furthermore, the Zometa label states that in clinical trials, 8 mg IV zoledronic acid was found to be toxic: "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." Zometa product label, section 14.2, second paragraph.

Furthermore, Leonard reports that its "20 mg tablet equals that of a 1 mg intravenous infusion." Leonard at p. 1, Conclusions section. Because Leonard also tested a 10 mg tablet (Leonard at p. 1, Data Summary section), the authors of Leonard were undoubtedly hoping that a dosage form containing less than 20 mg of zoledronic acid could be used. This is consistent with the knowledge in the art that, as explained above, bisphosphonates have oral toxicity. For at least these reasons, a person of ordinary skill in the art would have been motivated to further reduce, rather than increase, the amount of zoledronic acid administered orally. Thus, the prior art as a whole would suggest seeking a dosage form that has even less than 20 mg of zoledronic acid, which is a trend in the opposite direction of the range of the appealed claims.

(2) The cited references do not teach or suggest "about 30 mg to about 50 mg of zoledronic acid"

For similar reasons, the cited references do not teach or suggest "about 30 mg to about 50 mg" as recited in claim 42. Therefore, this claim is not *prima facie* obvious.

(3) The cited references do not teach or suggest "about 10 mg to about 50 mg of zoledronic acid"

For similar reasons, the cited references do not teach or suggest "about 10 mg to about 50 mg" as recited in claim 45. Therefore, this claim is not *prima facie* obvious.

C. The favorable bioavailability results achieved using an oral dosage form were unexpected

The claims are not obvious at least because an oral dosage form made in accordance with the present specification has an unexpectedly high C_{max} (peak plasma concentration of zoledronic acid) as compared to some dosage forms of Fox. "Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness." MPEP 2145 (citing *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)). There is nothing in Fox, or any of the cited references, that would suggest to a person of ordinary skill in the art that any oral

dosage form that is free of bioavailability enhancing agents would have a significantly higher C_{max} than any of Fox's oral dosage forms.

Figure 1 illustrates that a dosage form made in accordance with the specification (labeled "Tablet Acid") clearly has an unexpectedly higher C_{max} (about twice) than two dosage forms of Fox.[16] Therefore, the claimed dosage form is not obvious over Fox.

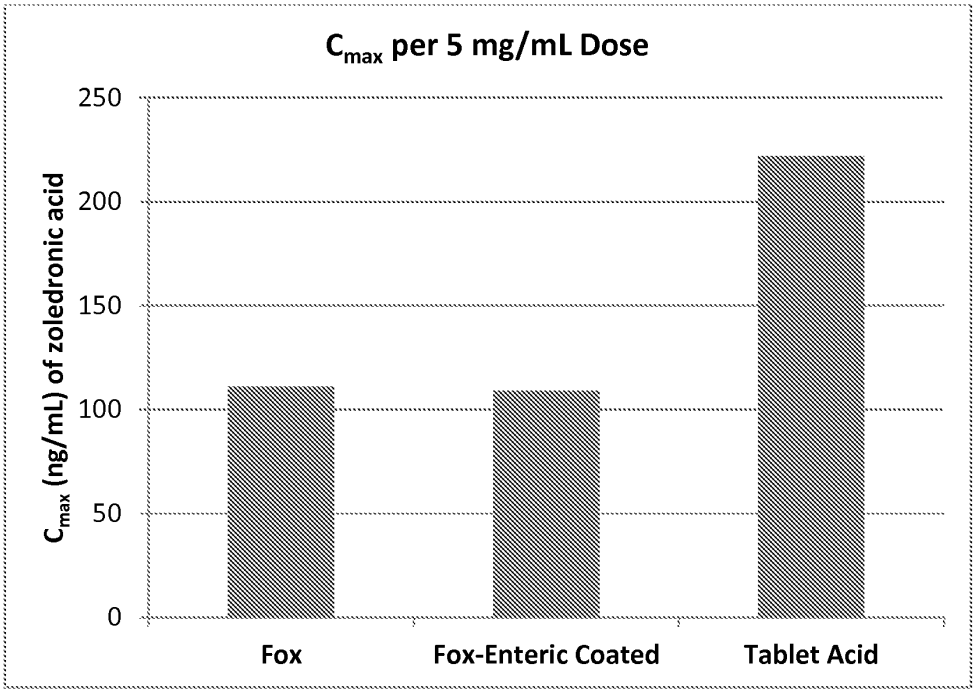

Figure 1

The dosage forms of Figure 1 are those described in Table 1 above.

The Office alleges that:

> The issue with the data presented by Applicant is how can there possibly be a showing of unexpected results when all tablets compared fall within the scope of Applicant's claims? ***Specifically, with reference to the names given on***

[16] Appellant merely asserts that these dosage forms fall within the broad disclosure of Fox. Appellant does not admit that these dosage forms, or any others, are anticipated or obvious over the disclosure of Fox.

> ***Applicant's chart (Response at p.6) Fox, Fox enteric-coated and Tablet Acid are all oral dosage forms of comprising about 30 mg to about 250 mg of zoledronic acid, wherein the dosage form contain no bioavailability enhancing agents.*** Final Office Action at p. 2 (emphasis present in Office Action).

Appellant respectfully points out that all dosage forms compared do not fall within the scope of Applicant's claims. Specifically, not all of the dosage forms have an "oral bioavailability of zoledronic acid" of "about 1.2% to about 3% in a human being." The two dosage forms with the lower C_{max} values (110.73 ng/mL and 109.37 ng/mL) do not have an oral bioavailability within the range of the claims. By contrast, the third dosage form, with a scaled C_{max} value of 222 ng/mL, could have an oral bioavailability within the range of the claims. According to Hanna, zoledronic acid has an oral bioavailability of "approximately 1%." Thus, based upon C_{max}, "Fox" and "Fox-Enteric Coated" would have an oral bioavailability of about 1% or less, while "Tablet Acid" would fall within the range of the claims. This shows that the dosage form prepared by Appellant, notwithstanding the fact that it does not have any bioavailability enhancing agent, has a bioavailability that is unexpectedly greater than other unenhanced dosage forms that are within the broad disclosure of Fox.

The Office further alleges "[t]hat the C_{max} shows some differences therefore may simply reflect different ingredients (e.g. gel for the Fox tablets, versus the ingredients of paragraph [142] for Applicant) different fasting state of the animals (e.g. fed versus fasting), different weight of the animals, etc. Final Office Action at pp. 2-3.

Appellant has adjusted the data in Table 2 and Figure 1 to reflect C_{max} scaled to 5 mg/kg. So the difference in C_{max} does not reflect a difference in weight of the animals. Furthermore, in both experiments the animals were fasted (Hanna at para. [0125]; Tabuteau at para. [0142]), so the C_{max} does not reflect a difference in fasting state of the animals. Thus, the only remaining difference is the "different ingredients." There is nothing in any of the cited references that suggests that dosage forms having "different ingredients" that are not bioavailability enhancing

agents should result in significantly different C_{max} values. Therefore, this result is unexpected, and the claims are not obvious.

The Office further states that "[n]one of Applicant's data is based upon direct comparison, it is only comparing results from different sources." Final Office Action at p. 3. However, there does not appear to be any significant difference between the experiments carried out in Hanna and those carried out in Tabuteau that would justify a belief that the experiments could not be directly compared.

The description of the determination of C_{max} in Hanna is as follows:

> After initial administration of zoledronic acid or its complexes, blood (approx. 2.5 mL per sample) was withdrawn from each of 5 animals in Group A (IV administration) at 15 time points: Pre-dose (0), 2, 5, 10, 15, 30, 45 min, 1, 1.5, 2, 4, 6, 8, 24 and 48 hrs and at 13 time points for Group B (oral administration): Pre-dose (0), 5, 10, 15, 30, 45 min, 1, 1.5, 2, 4, 6, 8, and 24 hrs. Blood samples were placed without the use of an anticoagulant and allowed to sit at room temperature for approximately 30 minutes. Samples were then centrifuged at a temperature of 4° C, at a speed of 13,000 rpm, for 5 minutes. Serum was collected and split into two aliquots and stored frozen (-80° C) till analysis. Samples were thawed on the day of analysis and processed using analytical procedures for zoledronic acid containing an LC/MS/MS analysis method. Hanna at para. [0152].

By comparison, the determination of C_{max} in Tabuteau does not appear to be different in any way that would affect the results obtained.

> Serial blood samples were collected from each animal by venipuncture of the jugular vein at various points after dosing for measurement of plasma concentrations of zoledronic acid. Blood samples were collected into chilled tubes containing K2EDTA as the anticoagulant. Samples were then centrifuged at approximately 3000 rpm at +4°C for 10 minutes for plasma derivation. Plasma concentrations of zoledronic acid were measured using an LC/MS/MS method. Tabuteau at para. [0143].

Therefore, the results obtained are in fact unexpected, and the appealed claims are not obvious.

(1) 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. 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 paragraph [090] 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." Specification at para. [085]. As stated at paragraph 6 of the Declaration of Herriot Tabuteau submitted in U.S. Application No. 13/894,252 on March 28, 2014, "zoledronic acid 54 mg/m^2 (or 9 mg/kg), divided in three equal daily [18 mg/m^2] doses, was tolerated." Thus, for this group of rats, oral zoledronic acid was unexpectedly proven to be safe and effective in a rat model of inflammatory pain.

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

Because 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 provided extended pain relief that continued for days.

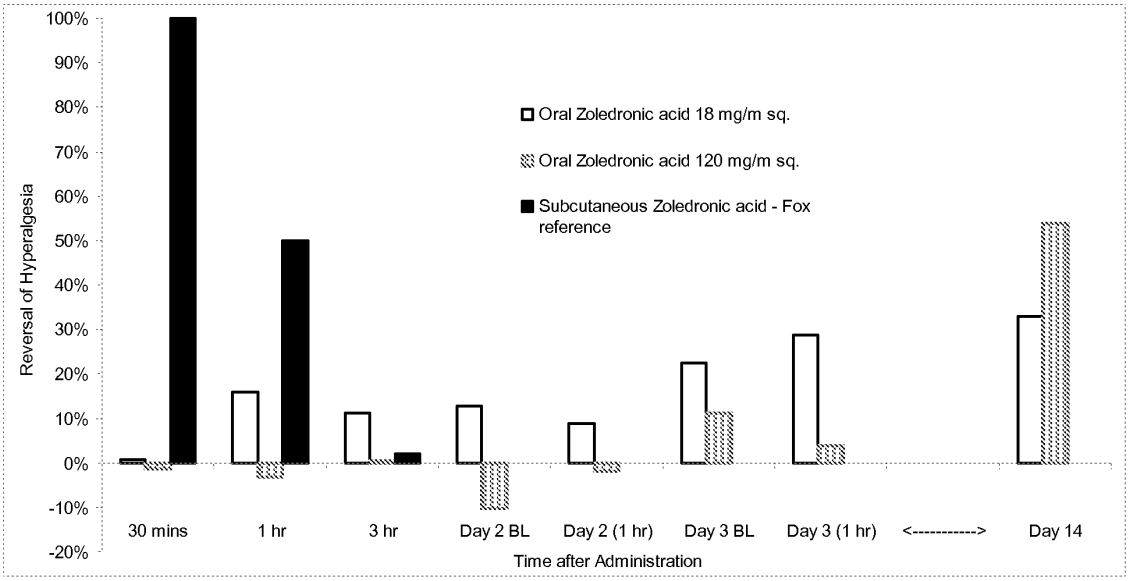

Figure 2

Figure 2 is a compilation of the data from Examples 1 and 2 of the specification and the Fox reference.[17] This figure clearly demonstrates that at the 18 mg/m^2 dosage 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).[18] Therefore, the rejected claims are also not obvious because of these unexpected results, and the rejection should be withdrawn.

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[17] 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 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 at para. [0102].

[18] 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.

(3) The Total Pain Relief of a claimed dosage form was unexpected as compared to morphine

The 24-hour Total Pain Relief (TOTPAR) observed in the rat inflammatory pain model of Example 1 of the specification is unexpectedly greater than that observed for morphine in the same rat model of inflammatory pain. As shown in Figure 3 below, with oral zoledronic acid, TOTPAR increased on consecutive dosing days, and on day 3 unexpectedly surpassed the value for morphine.

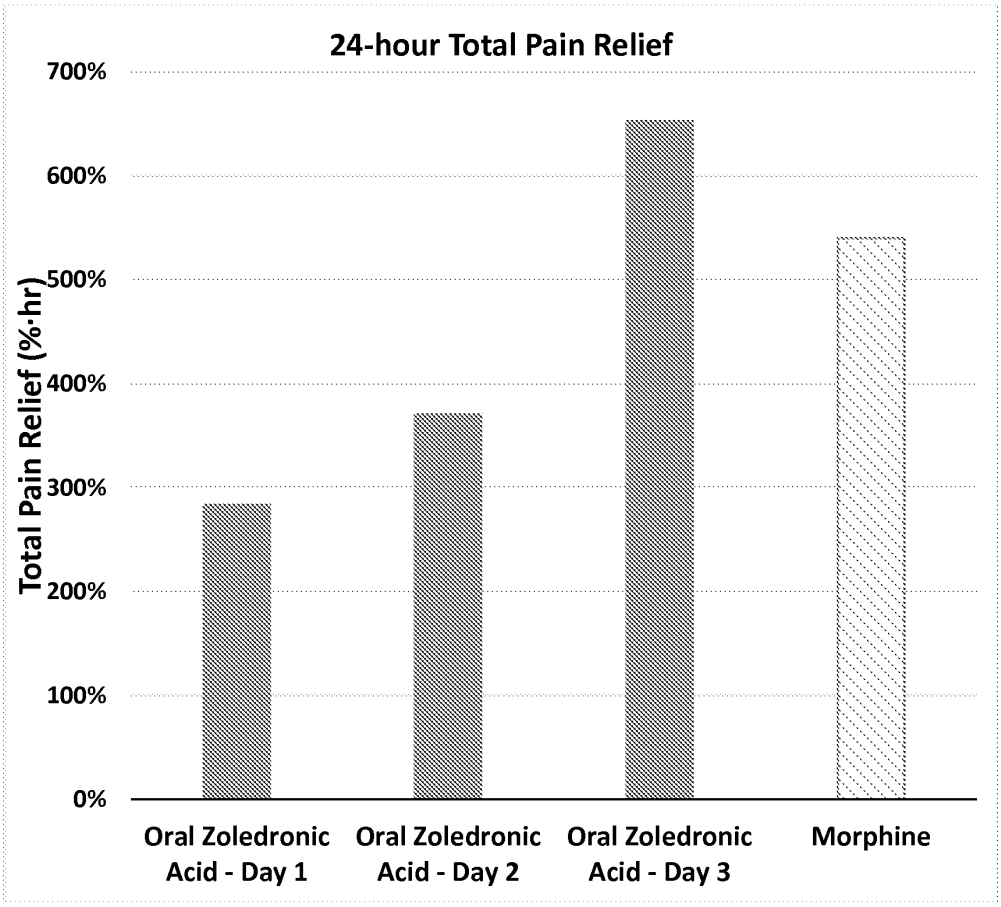

Figure 3

"Opioids are our most powerful analgesics," and "[m]orphine is the standard opioid agonist against which others are judged." Henry McQuay, *Opioids in pain management*, 353

LANCET 2229, Abstract and 2229 (1999). In addition, several prior art references indicate that oral bisphosphonates were believed to be less effective than intravenous bisphosphonates at the time of filing. Therefore it was unexpected that oral zoledronic acid could provide similar or greater TOTPAR than morphine in the rat inflammatory pain model.

As explained at paragraph 6 of the Declaration of Herriot Tabuteau submitted in U.S. Application. No. 13/894,262 on June 6, 2014., TOTPAR for the 24 hours following drug administration was calculated as the area under the pain relief versus time curve, as described in U.S. Publication No. 2014/0107210, using the linear trapezoidal rule. TOTPAR values were quantified as %·hr, or the product of reversal of hyperalgesia (%) and time (hr). Values for morphine are calculated based on results reported in Whiteside. *Id.* at para. 7 (citing Garth T. Whiteside et al., *DiPOA ([8-(3,3-Diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic Acid), a Novel, Systemically Available, and Peripherally Restricted Mu Opioid Agonist with Antihyperalgesic Activity: II. In Vivo Pharmacological Characterization in the Rat*, 310 J. PHARMACOL. & EXP. THER. 793 (2004)).

(4) The Total Pain Relief of a claimed dosage form was unexpected as compared to Fox

As shown in Figure 4 below, the average 24-hour TOTPAR observed in the rat inflammatory pain model of Example 1 of the specification is unexpectedly greater than the TOTPAR calculated based on the results reported in Fox for the same rat model of inflammatory pain.

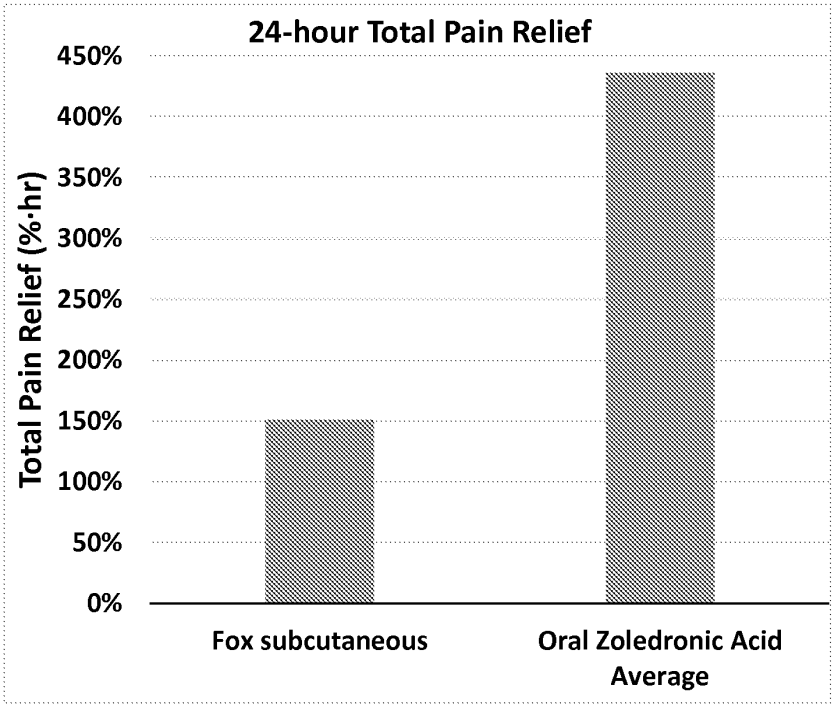

Figure 4

As previously discussed, Fox contains no suggestion that oral administration of zoledronic acid is materially different than subcutaneous administration in terms of pain relief or any other therapeutic effect. Therefore it was unexpected that oral administration could provide greater TOTPAR than subcutaneous administration.

(5) The Total Pain Relief of a dosage form of the claimed method was unexpected as compared to an oral dosage form of Fox

As shown in Figure 5 below, the average dose-normalized 24-hour TOTPAR for days 1-3, observed in the rat inflammatory pain model of Example 1 of the specification is unexpectedly greater than what would be expected for an oral dosage form of Fox based upon the results described in Fox for the same rat model of inflammatory pain.

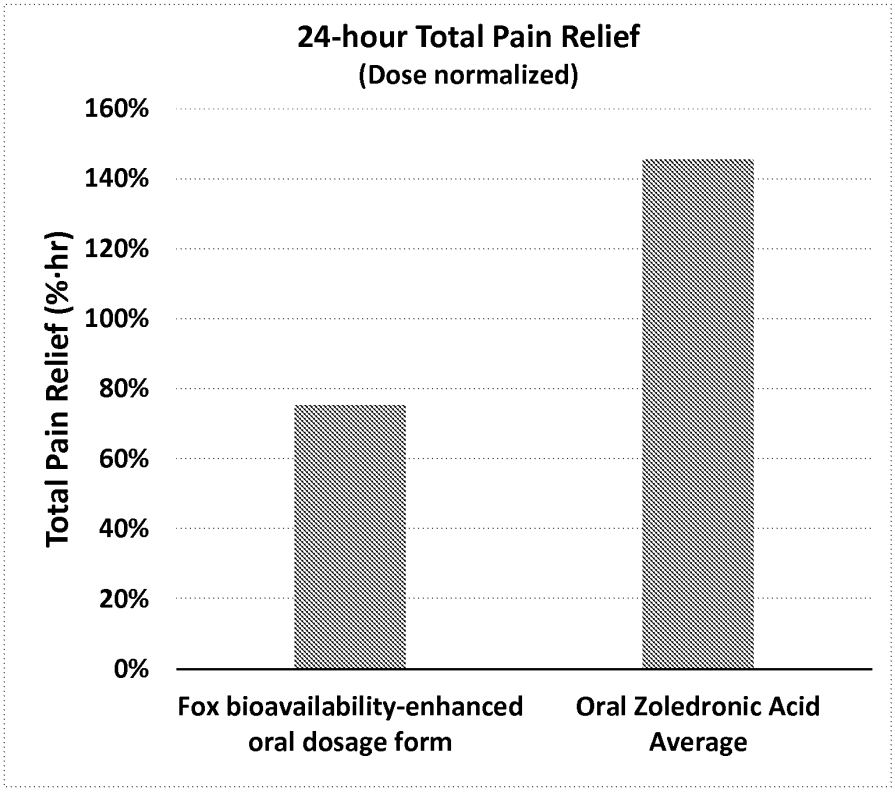

Figure 5

The dose normalized TOTPAR was arrived at by dividing the observed TOTPAR by oral doses expressed in mg/kg. As explained in the Final Office Action, Leonard "teaches that for oral tablets of zoledronic acid, the dose administered via a 20 mg tablet is equivalent to 1 mg intravenous infusion . . . ." Final Office Action at p. 7. Thus, for a bioavailability enhanced dosage form, the subcutaneous dose reported in Fox of 0.1 mg/kg is multiplied by 20 to obtain the oral dose that would have been expected.[19] As a result, the 0.1 mg/kg subcutaneous dose

[19]As explained previously, 0.1 mg/kg administered subcutaneously in a rat is equivalent to 5 mg administered intravenously to a person. Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, FDA, p. 19 (July 2005). The FDA recommended reference body weight for a human being is 60 kg, so this corresponds to 0.083 mg/kg. *Id.* In this case, the value of TOTPAR for Fox would be 90 %·hr, which is still much lower than the TOTPAR from Example 1.

reported in Fox is equivalent to 2 mg/kg for a bioavailability enhanced dosage form. The dose in Example 1 of the specification is 3 mg/kg.

Figure 5 illustrates that the TOTPAR of an embodiment of the claimed invention is significantly higher than what would be expected from Fox. An unenhanced dosage form applied to Fox's results would require an even larger oral dose, which would further increase the difference between Fox and the claimed invention. Therefore, the claimed invention is not obvious because it unexpectedly provides a significantly greater TOTPAR as compared to what would have been expected from oral administration according to Fox.

(6) The results of an oral dosage form of the claims in a CRPS rat study were unexpected as compared to Fox

Additionally, an oral dosage form of the rejected claims performed significantly better in a CRPS rat study than what would have been expected based upon the studies presented in Fox. According to Sebastin (cited in a related application), "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." S.J. Sebastin, *Complex Regional Pain Syndrome*, 44(2) INDIAN J. PLAST. SURG. 298, 298 (2011) (emphasis added). 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. 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, 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 due to problems with oral zoledronic acid such as low oral bioavailability.

Thus, it is surprising that, as shown in Figure 6 below, the pain relieving effect after oral administration in the rat model of CRPS is significantly higher than the pain relieving effect reported after subcutaneous 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.

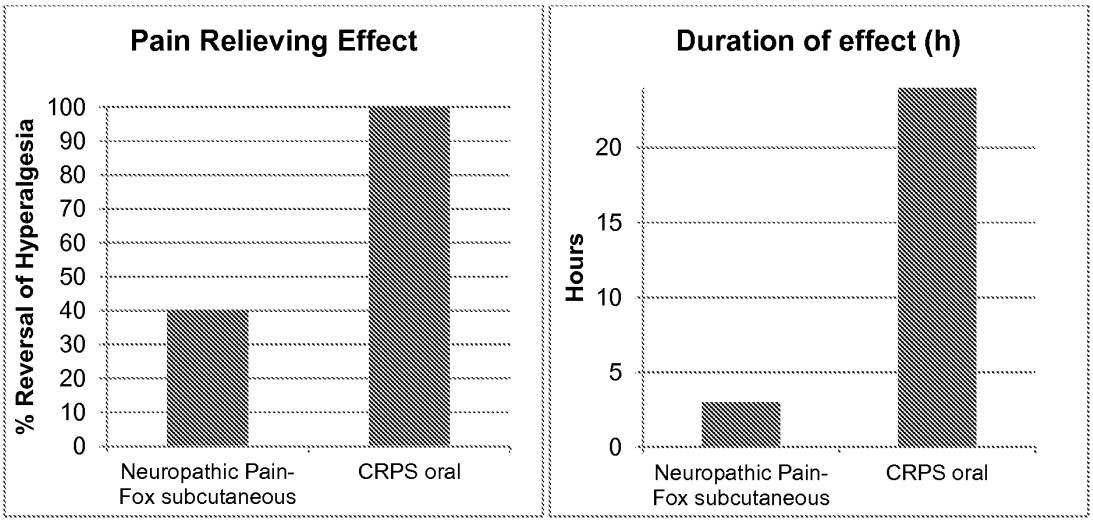

Figure 6

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. Declaration of Herriot Tabuteau at para. 24 submitted in U.S. Application No. 13/894,274 on March 10, 2014 ("the '274 Declaration).

(7) 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.

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 . . . ." Specification at para. [085]. 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." '274 Declaration, Exhibit 3. As explained in paragraph [0109] 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.

D. The unexpected results when compared to morphine satisfy a long-felt need

In addition to the reasons given above, the claimed oral dosage forms are not obvious because they satisfy a long-felt need for orally administered non-opioid pain medications. MPEP 716.04. "Secondary considerations [such as long-felt but unsolved needs and failure of others] 'can be the most probative evidence of non-obviousness in the record, and enables the . . . court to avert the trap of hindsight" (*Crocs, Inc. v. Int'l Trade Com'n*, 598 F.3d 1294, 1310 (Fed. Cir. 2010) (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 960 (Fed. Cir. 1986))) and may often establish that an invention appearing to have been obvious in light of the prior art was not" (*Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)). "The claimed invention must satisfy a long-felt need which was recognized, persistent, and not solved by others."

As explained in the Examiner Interview of May 29, 2014, there has existed and continues to exist an urgent need for orally administered non-opioid pain medications. FDA Commissioner Margaret A. Hamburg has stated, "Tragically, the most recent data shows that more than 16,000 lives are lost each year due to opioid-related overdoses. In fact, drug overdose deaths, driven largely by prescription drug overdose deaths, are now the leading cause of injury death in the United States – surpassing motor vehicle crashes…" FDA

Commissioner Margaret A. Hamburg Statement on Prescription Opioid Abuse (April 3, 2014), *available at* www.fda.gov/NewsEvents /Newsroom/PressAnnouncements/ucm391590.htm.

Hamburg further explained that this has been a long-felt need since at least 2001. For example, she stated that "[s]ince 2001 the FDA has taken a number of actions designed to help address prescription opioid abuse and to encourage the development of new drug treatments for pain . . . and to advance the development of new non-opioid medications to treat pain with the goal of bringing new non- or less abusable products to the market." *Id.* It is well known that many the prescription opioids that are abused are administered orally.

The fact that zoledronic acid provided more TOTPAR on day three than morphine demonstrates that zoledronic acid could satisfy this long felt need and could be a viable alternative to orally administered opioid pain medications.

The above evidence establishes that (1) there was a long-felt need that was recognized by the FDA as early as 2001, (2) the need has been continuous since 2001, and (3) the need clearly has not been solved by others as the FDA commissioner's comments were issued only three months ago. Accordingly, this long-felt need and the fact that zoledronic acid can satisfy this long-felt need serves as "probative evidence of non-obviousness in the record, and enables the [board] to avert the trap of hindsight [bias]." *Crocs*, 598 F.3d at 1310.

CONCLUSION

For at least the reasons given above, the claimed method is not obvious over the art of record. Therefore, Appellant submits that the claims are patentable and respectfully requests that the Board reverse the obviousness rejection.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 021818.

CLAIMS APPENDIX

1.-39. (Canceled)

40. An oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid, wherein the dosage form contains no bioavailability enhancing agents, and wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.

41. (Canceled)

42. The oral dosage form of claim 40, wherein the oral dosage form contains about 30 mg to about 50 mg of zoledronic acid.

43. (Canceled)

44. A pharmaceutical product comprising more than one unit of the 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. 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. The pharmaceutical product of claim 44, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about 40 mg to about 600 mg of zoledronic acid of zoledronic acid to be administered in about 1 month.

47. The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form to be administered in about 3 months.

48. The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form to be administered in about 6 months.

49. The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form to be administered in about 1 year.

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

51. The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form to be administered within a period of about 1 month.

52. The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form to be administered in about 2 months.

53. The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form be administered in about 3 months.

54. The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form to be administered in about 6 months.

55. The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form to be administered in about 1 year.

56. 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. The oral dosage form of claim 40, wherein the zoledronic acid is in the form of a sodium salt.

58.-59. (Canceled)

60. An oral dosage form comprising about 30 mg to about 250 mg of zoledronic acid and an excipient, wherein the dosage form contains no bioavailability enhancing agents, and wherein the oral bioavailability of zoledronic acid in the dosage form is about 1.2% to about 3% in a human being.

61. 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. The oral dosage form of claim 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. 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.

EVIDENCE APPENDIX

1. U.S. Publication No. 2004/0063670 ("Fox").
2. Labeling of Unit Dose Packages of Drugs, Policy No. PH-04-06, Department of Pharmacy Policy, Univ. of Kentucky Hospital, Chandler Medical Center (Nov. 2009) ("Chandler").
3. Leonard et al., MER-101 Tablets: A Pilot Bioavailability Study of a Novel Oral Formulation of Zoledronic Acid, Poster presentation at AACR-NCI-EORTC: Molecular Targets and Cancer Therapeutics October 2007 ("Leonard").
4. International Publication No. WO 2005/005447 ("Aronhime").
5. L.A. Sorbera et al., *Zolendronate Disodium*, 25(3) DRUGS OF THE FUTURE 259 (2000) ("Sorbera").
6. Fosamax® (alendronate sodium) tablets, for oral use, approved 1995, revised Feb. 2012, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021575s017lbl.pdf ("Fosamax label")
7. Bonefos Product Monograph, Part III: Consumer Information Bonefos® clodronate disodium, pages 25-28, revised September 22, 2011, *available at* http://www.bayer.ca/files/BONEFOS-PM-ENG-PT3-22SEP2011-147998.pdf ("Bonefos monograph")
8. Leonard et al., Safety Profile of Zoledronic acid in a novel oral formulation, Poster presentation at AACR-NCI-EORTC Molecular Targets & Cancer Therapeutics Conference, Background section (November 2009) ("Leonard 2009").
9. Cullen et. al, MER-101 A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae, Poster presentation at AAPS (November 2007) ("Cullen").
10. U.S. Patent No. 6,451,815.
11. Diane A.I. Ashiru-Oredope et al., *The effect of polyoxyethylene polymers on the transport of ranitidine in Caco-2 cell monolayers*, 409 INT'L J PHARM. 164, 167 (2011).
12. Chris Vervaet et al., *Bioavailability of hydrochlorothiazide from pellets, made by extrusion/spheronisation, containing polyethylene glycol 400 as a dissolution enhancer*, 14(11) PHARM. RESEARCH 1644, 1646 (1997).
13. Ramadan et al., 9(1) BULL. PHARM. SCI. ASSIUT UNIV. 30, 30 (1986).
14. European Medicines Agency Scientific Assessment Report-Aclasta® (zoledronic acid, Novartis) Injection (Mar. 4, 2006) ("EMA Scientific Assessment").
15. Conte et al., *Safety of intravenous and oral bisphosphonates and compliance with dosing regimens*, 9(4) OCOLOGIST 28 (2004) ("Conte").
16. Ian R. Reid, et al., *Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density*, 346(9) N ENGL J MED 653 (2002) ("Reid").

17. U.S. Publication No. 2012/0190647.

18. Johann D. Ringe, *Development of Clinical Utility of Zoledronic Acid and Patient Considerations in the Treatment of Osteoporosis*, 4 J. PATIENT PREFERENCE & ADHERENCE 231 (2010) ("Ringe").

19. Orange Book listings from "OB_Rx" table for query on "zoledronic acid" performed on Feb. 28, 2014.

20. Orange Book Preface.

21. U.S. Publication No. 2011/0028435 ("Hanna").

22. U.S. Publication No. 2014/0051669 ("Tabuteau").

23. Zometa product label (2012).

24. Declaration of Herriot Tabuteau submitted in U.S. Application No. 13/894,252 on March 28, 2014.

25. Henry McQuay, *Opioids in pain management*, 353 LANCET 2229 (1999).

26. Declaration of Herriot Tabuteau submitted in U.S. Application. No. 13/894,262 on June 6, 2014.

27. U.S. Publication No. 2014/0107210.

28. Garth T. Whiteside et al., *DiPOA ([8-(3,3-Diphenyl-propyl)-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]dec-3-yl]-acetic Acid), a Novel, Systemically Available, and Peripherally Restricted Mu Opioid Agonist with Antihyperalgesic Activity: II. In Vivo Pharmacological Characterization in the Rat*, 310 J. PHARMACOL. & EXP. THER. 793 (2004).

29. Guidance for Industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, FDA, p. 19 (July 2005), *available at* http://www.fda.gov/downloads/Drugs/ Guidance/UCM078932.pdf ("FDA's Guidance").

30. S.J. Sebastin, *Complex Regional Pain Syndrome*, 44(2) INDIAN J. PLAST. SURG. 298 (2011).

31. Declaration of Herriot Tabuteau submitted in U.S. Application No. 13/894,274 on March 10, 2014 ("the '274 Declaration).

32. FDA Commissioner Margaret A. Hamburg Statement on Prescription Opioid Abuse (April 3, 2014), *available at* www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm 391590.htm.

1. U.S. Publication No. 2004/0063670 ("Fox").

US 20040063670A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0063670 A1

Fox et al. (43) Pub. Date: Apr. 1, 2004

(54) USE OF BISPHOSPHONATES FOR PAIN TREATMENT

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(57) ABSTRACT

A method for the treatment of pain, in particular antinociceptive or anti-allodynic treatment of pain, in a patient in need of such treatment, e.g. a patient with osteoporosis or osteopenia, a tumour patient or a patient suffering from an inflammatory disease, which comprises administering an effective amount of a bisphosphonate, e.g. zoledronic acid or salts or hydrates thereof, to the patient.

USE OF BISPHOSPHONATES FOR PAIN TREATMENT

[0001] This invention relates to pharmaceutical compositions and uses, in particular to pharmaceutical compositions comprising bisphosphonates and to new therapeutic uses of bisphosphonates.

[0002] Bisphosphonates are widely used to inhibit osteoclast activity in a variety of both benign and malignant diseases which involve excessive or inappropriate bone resorption. These pyrophosphate analogs not only reduce the occurrence of skeletal related events but they also provide patients with clinical benefit and improve survival. Bisphosphonates are able to prevent bone resorption in vivo; the therapeutic efficacy of bisphosphonates has been demonstrated in the treatment of osteoporosis, osteopenia, Paget's disease of bone, tumour-induced hypercalcemia (TIH) and, more recently, bone metastases (BM) and multiple myeloma (MM) (for review see Fleisch H 1997 Bisphosphonates clinical. In Bisphosphonates in Bone Disease. From the Laboratory to the Patient. Eds: The Parthenon Publishing Group, New York/London pp 68-163). The mechanisms by which bisphosphonates inhibit bone resorption are still not completely understood and seem to vary according to the bisphosphonates studied. Bisphosphonates have been shown to bind strongly to the hydroxyapatite crystals of bone, to reduce bone turn-over and resorption, to decrease the levels of hydroxyproline or alkaline phosphatase in the blood, and in addition to inhibit the formation, recruitment, activation and the activity, of osteoclasts. Recently farnesyl diphosphate synthase, an enzyme of the mevalonate pathway of cholesterol biosynthesis, has been identified as the molecular target of nitrogen-containing bisphosphonates (reviewed in Rogers M J, Gordon S, Benford H L, Coxon F P, Luckman S P, Monkkonen J, Frith J C. 2000. Cellular and molecular mechanisms of action of bisphosphonates. Cancer 88(suppl):2961-2978)

[0003] Bone pain resulting from structural damage, periosteal irritation, and nerve entrapment is the most common complication of both benign and metastatic bone disease, and presents a significant problem in both hospital and community practice (Coleman, 1997, Cancer 80; 1588-1594).

[0004] MM is a plasma-cell malignancy characterized by the proliferation and the accumulation of malignant plasma cells within the bone marrow. The main clinical consequences are lytic bone lesions associated with pathologic fractures and bone pain. These lesions result from an excessive bone resorption, frequently leading to hypercalcemia. Bisphosphonates have been introduced for the long-term treatment of MM in combination with conventional chemotherapy. It has been shown recently that bisphosphonates such as clodronate and pamidronate can reduce the occurrence of skeletal related events such as lytic bone lesions and pathologic fractures and can relieve associated bone pain and improve the quality of life of patients (Laktinen et al. Lancet 1992, 340, 1049-1052; McCloskey et al. B. J. Haematol., 1998, 100, 317-325; and Berenson et al. N. Eng. J. Med. 1996, Vol. 334, No. 8, 488-493). Similar effects have been reported in breast cancer patients treated with bisphosphonates (Hortobagyi G N, Theriault R L, Porter L, Blayney D, Lipton A, Sinoff C, Wheeler H, Simeone J F, Seaman J, Knight R D. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group., N Engl J Med. 1996;335:1785-91; Kanis J A, Powles T, Paterson A H G, McCloskey E V, Ashley S. Clodronate decreases the frequency of skeletal metastases in women with breast cancer. Bone 1996; 19: 663-7.)

[0005] It has now been found surprisingly that certain bisphosphonates exert profound and apparently direct palliative effects on pain in in vivo animal models. For example, zoledronic acid has been found to reverse mechanical hyperalgesia in rat models of chronic inflammatory and neuropathic pain, with a fast onset of action and efficacy of up to about 100%. Additionally zoledronic acid has been found to reduce mechanical allodynia and reduce hind limb sparing in a rat model of bone cancer pain. These results indicate that zoledronic acid and similar bisphosphonates may have direct, fast acting, anti-nociceptive and anti-allodynic activity on pain.

[0006] Accordingly the present invention provides a method for the treatment of pain in a patient in need of such treatment, which comprises administering an effective amount of a bisphosphonate to the patient.

[0007] The invention further provides use of a bisphosphonate in the preparation of a medicament for the treatment of pain.

[0008] The invention yet further provides use of a bisphosphonate to treat pain associated with diseases or pathological conditions in mammals.

[0009] The present invention is particularly applicable to the palliative treatment of pain, i.e. the direct relief of pain in addition to the relief of pain as the result of amelioration of the underlying disease or medical condition, which is the cause of the pain. Thus, advantageously the invention provides methods and uses for the direct analgesic or acute treatment of pain.

[0010] Preferably the invention is used for the direct treatment of pain in diseases and medical conditions in which bisphosphonates are used to inhibit osteoclast activity. For example, the invention may be used for direct treatment of pain in diseases and conditions which involve excessive or inappropriate bone loss e.g. as the result of inappropriate osteoclast activity. Examples of such diseases and conditions include benign diseases and conditions such as osteoporosis of various genesis, Pagets disease, osteoarthritis, RA, periodontal disease; and especially malignant diseases such as MM and TIH and BM associated with various cancers, e.g. cancer of the breast, prostate, lung, kidney, ovary, or osteosarcoma. Generally the invention may be used to treat pain in other circumstances where bisphosphonates are used and pain is encountered, e.g. when bisphosphonates are use in bone fracture healing, osteonecrosis or treatment of prosthesis loosening.

[0011] The uses and methods of the present invention represent an improvement to existing therapy of malignant diseases in which bisphosphonates are used to prevent or inhibit development of bone metastases or excessive bone resorption, and also for the therapy of inflammatory diseases such as rheumatoid arthritis and osteoarthritis, as well as for all forms of osteoporosis and osteopenia.

[0012] Thus in the present description the terms "treatment" or "treat" refer to both prophylactic or preventative treatment as well as curative or palliative treatment of pain, in particular anti-nociceptive and anti-allodynic treatment of pain, especially treatment of bone pain

[0013] Thus in particular embodiments the invention provides:

[0014] a method for the treatment of bone pain in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient;

[0015] use of a bisphosphonate in the preparation of a medicament for the treatment of bone pain; or

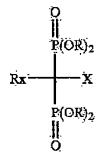
[0016] use of a bisphosphonate as an agent for treatment of bone pain.

[0017] The bisphosphonates used in the present invention are typically those which relieve pain, in particular those which have an anti-nociceptive or anti-allodynic, and preferably rapid onset, activity on pain.

[0018] Thus, for example, suitable bisphosphonates for use in the invention may include the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxyethidene-bisphosphonic acid, e.g. etidronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (=BM 21.0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid, e.g. zoledronic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid), e.g. tiludronate; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. FR 78844 (Fujisawa); 5-benzoyl-3,4dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid, e.g. YM 529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), e.g. clodronate.

[0019] Preferably the bisphosphonates for use in the invention are the nitrogen containing bisphosphonates. For the purposes of the present descxription a nitrogen containing bisphosphonate is a compound which in addition to the characteristic geminal bisphosphate (P—C—P) moiety comprises a nitrogen containing side chain, e.g. a compound of formula I

I



[0020] wherein

[0021] X is hydrogen, hydroxyl, amino, alkanoyl,or an amino group substituted by C_1-C_4 alkyl or alkanoyl;

[0022] R is hydrogen or C_1-C_4 alkyl and

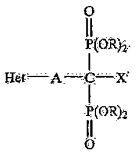
[0023] Rx is a side chain which contains an optionally substituted amino group, or a nitrogen containing heterocycle (including aromatic nitrogen-containing heterocycles),

[0024] and pharmaceutically acceptable salts thereof or any hydrate thereof.

[0025] Particularly preferred nitorogen containing bisphosphonates are those having side chains containing nitrogen-containing heterocycles, most especially containing aromatic nitrogen-containing heterocycles.

[0026] Thus in one embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula I'

I'



[0027] wherein

[0028] Het is an imidazole, oxazole, isoxazole, oxadiazole, thiazole, thiadiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole or benzimidazole radical, which is optionally substituted by alkyl, alkoxy, halogen, hydroxyl carboxyl an amino group optionally substituted by alkyl or alkanoyl radicals or a benzyl radical optionally substituted by alkyl, nitro, amino or aminoalkyl;

[0029] A is a straight-chained or branched, saturated or unsaturated hydrocarbon moiety containing from 1 to 8 carbon atoms;

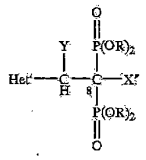
[0030] X is a hydrogen atom, optionally substituted by alkanoyl, or an amino group optionally substituted by alkyl or alkanoyl radicals, and

[0031] R is a hydrogen atom or a C_1-C_4 alkyl radical,

[0032] and the pharmacologically acceptable salts thereof.

[0033] In a further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula II

II



[0034] wherein

[0035] Het' is a substituted or unsubstituted heteroaromatic five-membered ring selected from the group consisting of imidazolyl, imidazolinyl, isoxazolyl, oxazolyl, oxazolinyl, thiazolyl, thiazolinyl, triazolyl, oxadiazolyl and thiadiazolyl wherein said ring can be partly hydrogenated and wherein said substituents are selected from at least one of the group consisting of C_1-C_4 alkyl, C_1-C_4 alkoxy, phenyl, cyclohexyl, cyclohexylmethyl halogen and amino and wherein two adjacent alkyl substituents of Het can together form a second ring;

[0036] Y is hydrogen or C_1-C_4 alkyl;

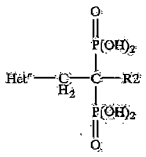
[0037] X' is hydrogen, hydroxyl amino, or an amino group substituted by C_1-C_4alkyl, and

[0038] R is hydrogen or C_1-C_4 alkyl;

[0039] as well as the pharmacologically acceptable salts and isomers thereof.

[0040] In a yet further embodiment a particularly preferred bisphosphonate for use in the invention comprises a compound of Formula III

III



[0041] wherein

[0042] Het' is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, by lower alkoxy, bx phenyl which may in turn be mnon- or disubstituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, and

[0043] R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, lower radicals having up to and including 7 C-atoms,

[0044] or a pharmacologically acceptable salt thereof.

[0045] Examples of particularly preferred bisphophonates for use in the invention are:

[0046] 2-(1-Methylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

[0047] 2-(1-Benzylimidazol-2-yl)-1-hydroxyethane-1,1-diphosphonic acid;

[0048] 2-(1-Methylimidazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

[0049] 1-Amino-2-(1-methylimidazol-4-yl)ethane-1,1-diphosphonic acid;

[0050] 1-Amino-2-(1-benzylimidazol-4-yl)ethane-1,1-diphosphonic acid;

[0051] 2-(1-Methylimidazol-2-yl)ethane-1,1-diphosphonic acid;

[0052] 2-(1-Benzylimidazol-2-yl)ethane-1,1-diphosphonic acid;

[0053] 2-(Imidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid;

[0054] 2-(Imidazol-1-yl)ethane-1,1-diphosphonic acid;

[0055] 2-(4H-1,2,4-triazol-4-yl)-1-hydroxyethane-1,1-diphosphonic acid;

[0056] 2-(Thiazol-2-yl)ethane-1,1-diphosphonic acid;

[0057] 2-(Imidazol-2-yl)ethane-1,1-diphosphonic acid;

[0058] 2-(2-Methylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

[0059] 2-(2-Phenylimidazol-4(5)-yl)ethane-1,1-diphosphonic acid;

[0060] 2-(4,5-Dimethylimidazol-1-yl)-1-hydroxyethane-1,1-diphosphonic acid, and

[0061] 2-(2-Methylimidazol-4(5)-yl)-1-hydroxyethane-1,1-diphosphonic acid,

[0062] and pharmacologically acceptable salts thereof.

[0063] The most preferred bisphosphonate for use in the invention is 2-(imidazol-1yl)-1-hydroxyethane-1,1-diphosphonic acid (zoledronic acid) or a pharmacologically acceptable salt thereof or any hydrate thereof.

[0064] Pharmacologically acceptable salts are preferably salts with bases, conveniently metal salts derived from groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, including alkali metal salts, e.g. potassium and especially sodium salts, or alkaline earth metal salts, preferably calcium or magnesium salts, and also ammonium salts with ammonia or organic amines.

[0065] Especially preferred pharmaceutically acceptable salts are those where one, two, three or four, in particular one or two, of the acidic hydrogens of the bisphosphonic acid are replaced by a pharmaceutically acceptable cation, in particular sodium, potassium or ammonium, in first instance sodium.

[0066] A very preferred group of pharmaceutically acceptable salts is characterized by having one acidic hydrogen and one pharmaceutically acceptable cation, especially sodium, in each of the phosphonic acid groups.

[0067] All the bisphosphonic acid derivatives mentioned above are well known from the literature. This includes their manufacture (see e.g. EP-A-513760, pp. 13-48). For example, 3-amino-1-hydroxypropane-1,1-diphosphonic acid is prepared as described e.g. in U.S. Pat. No. 3,962,432 as well as the disodium salt as in U.S. Pat. Nos. 4,639,338 and 4,711,880, and 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid is prepared as described e.g. in U.S. Pat. No. 4,939,130. See also U.S. Pat. Nos. 4,777,163 and 4,687,767.

[0068] The bisphosphonates (hereinafter referred to as the Agents of the Invention) may be used in the form of an isomer or of a mixture of isomers where appropriate, typically as optical isomers such as enantiomers or diastereoisomers or geometric isomers, typically cis-trans isomers. The optical isomers are obtained in the form of the pure antipodes and/or as racemates.

[0069] The Agents of the Invention can also be used in the form of their hydrates or include other solvents used for their crystallisation.

[0070] The Agents of the Invention (the bisphosphonates) are preferably used in the form of pharmaceutical compositions that contain a therapeutically effective amount of active ingredient optionally together with or in admixture with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers which are suitable for administration.

[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.

[0073] The particular mode of administration and the dosage may be selected by the attending physician taking into account the particulars of the patient, especially age, weight, life style, activity level, hormonal status (e.g. post-menopausal) and bone mineral density as appropriate. Most preferably, however, the bisphosphonate is administered intravenously.

[0074] The dosage of the Agents of the Invention may depend on various factors, such as effectiveness and duration of action of the active ingredient, mode of administration, warm-blooded species, and/or sex, age, weight and individual condition of the warm-blooded animal.

[0075] Normally the dosage is such that a single dose of the bisphosphonate active ingredient from 0.002-20.0 mg/kg, especially 0.01-10.0 mg/kg, is administered to a warm-blooded animal weighing approximately 75 kg. If desired, this dose may also be taken in several, optionally equal, partial doses.

[0076] "mg/kg" means mg drug per kg body weight of the mammal—including man—to be treated.

[0077] The dose mentioned above—either administered as a single dose (which is preferred) or in several partial doses—may be repeated, for example once daily, once weekly, once every month, once every three months, once every six months or once a year. In other words, the pharmaceutical compositions may be administered in regimens ranging from continuous daily therapy to intermittent cyclical therapy.

[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.

[0079] Formulations in single dose unit form contain preferably from about 1% to about 90%, and formulations not in single dose unit form contain preferably from about 0.1% to about 20%, of the active ingredient. Single dose unit forms such as capsules, tablets or dragees contain e.g. from about 1 mg to about 500 mg of the active ingredient.

[0080] Pharmaceutical preparations for enteral and parenteral administration are, for example, those in dosage unit forms, such as dragees, tablets or capsules and also ampoules. They are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes.

[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 dragee 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.

[0083] Parenteral formulations are especially injectable fluids that are effective in various manners, such as intra-arterially, intramuscularly, intraperitoneally, intranasally, intradermally, subcutaneously or preferably intravenously. Such fluids are preferably isotonic aqueous solutions or suspensions which can be prepared before use, for example from lyophilised preparations which contain the active ingredient alone or together with a pharmaceutically acceptable carrier. The pharmaceutical preparations may be sterilised and/or contain adjuncts, for example preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

[0084] Suitable formulations for transdermal application include an effective amount of the active ingredient with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the active ingredient of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[0085] The following Examples illustrate the invention described hereinbefore.

[0086] In the following Examples the term "active ingredient" is to be understood as being any one of the bisphosphonic acid derivatives mentioned above as being useful according to the present invention.

EXAMPLES

Example 1

[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 Höfliger and Karg.

Example 2

[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.

Example 4

[0093] Ampoule containing active ingredient, for instance disodium pamidronate pentahydrate dissolved in water. The solution (concentration 3 mg/ml) is for i.v. infusion after dilution.

Composition:	
active ingredient (≙ 5.0 mg of anhydrous active ingredient)	19.73 mg
mannitol	250 mg
water for injection	5 mL

Example 5

The Effect of Bisphosphonates in Rat Models of Inflammatory and Neuropathic Pain

[0094] Methods

[0095] Inflammatory hyperalgesia

[0096] Mechanical hyperalgesia was examined in a rat model of inflammatory pain. Paw withdrawal thresholds to an increasing pressure stimulus were measured by the Randal-Selitto technique using an analgesymeter (Ugo Basile, Milan), in naive animals prior to an intraplantar injection of complete Freund's complete adjuvant (FCA) into the left hind paw. 24 h later paw withdrawal thresholds were measured again prior to (predose) and then from 10 min to 6 h following drug or vehicle administration. Reversal of hyperalgesia in the ipsilateral paw was calculated according to the formula:

$$\%\ \text{reversal} = \frac{\text{postdose threshold} - \text{predose threshold}}{\text{naive threshold} - \text{predose threshold}} \times 100$$

[0097] Neuropathic hyperalgesia

[0098] Mechanical hyperalgesia was examined in a rat model of neuropathic pain induced by partial ligation of the left sciatic nerve. Approximately 14 days following surgery mechanical withdrawal thresholds of both the ligated (ipsilateral) and non-ligated (contralateral) paw were measured prior to (predose) and then from 10 min to 6 h following drug or vehicle administration. Reversal of hyperalgesia at each time point was calculated according to the formula:

$$\%\ \text{reversal} = \frac{\text{ipsilateral threshold postdose} - \text{ipsilateral threshold predose}}{\text{contralateral threshold predose} - \text{ipsilateral threshold predose}} \times 100$$

[0099] All experiments were carried out using groups of 6 animals. Stock concentrations of drugs were dissolved in distilled water and subsequent dilutions were made in 0.9% saline for subcutaneous administration in a volume of 4 $mlkg^{-1}$. All drugs were made up in plastic vials and kept in the dark.

[0100] Statistical analysis was carried out on withdrawal threshold readings (g) using ANOVA with repeated measures followed by Tukey's HSD test. Efficacy refers to the maximal reversal of hyperalgesia observed at the doses used.

[0101] Results

[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.

[0103] 2. Pamidronate (0.03-1 $mgkg^{-1}$ s.c.) and Clodronate (0.3-10 $mgkg^{-1}$ s.c.) were both ineffective in reversing inflammatory mechanical hyperalgesia, but rather produced slight reductions of paw withdrawal thresholds at the highest doses tested.

[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.

[0105] 4. Pamidronate (0.03-1 $mgkg^{-1}$ s.c.) was only weakly active in the model of neuropathic pain, producing a maximal 20% reversal of hyperalgesia, whilst Clodronate (0.3-10 $mgkg^{-1}$ s.c.) was inactive. Both drugs again produced some reductions in contraleral paw withdrawal thresholds.

[0106] 5. These data show that Zoledronate reverses mechanical hyperalgesia in models of chronic inflammatory and neuropathic pain in the rat.

Example 6

[0107] The Effect of Bisphosphonates in a Rat Model of Bone Cancer Pain

[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.

1. A method for the treatment of pain in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient.

2. Use of a bisphosphonate in the preparation of a medicament for the treatment of pain.

3. Use of a bisphosphonate to treat pain associated with diseases or pathological conditions in mammals.

4. A method for the anti-nociceptive or anti-allodynic treatment of pain in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient;

use of a bisphosphonate in the preparation of a medicament for the anti-nociceptive or anti-allodynic treatment of pain; or

use of a bisphosphonate as an anti-nociceptive or anti-allodynic agent.

5. A method for the treatment of bone pain in a patient in need of such treatment which comprises administering an effective amount of a bisphosphonate to the patient;

use of a bisphosphonate in the preparation of a medicament for the treatment of bone pain; or

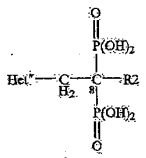
use of a bisphosphonate as an agent for treatment of bone pain.

6. A method according to claim 1 or a use according to claim 2 or 3 for the treatment of pain associated with osteoporosis, rheumatoid arthritis, osteoarthritis and tumour formation, e.g. tumour growth, invasion or metastasis.

7. A method according to claim 1 or a use according to claim 2 or 3, in which the bisphosphonate is selected from the following compounds or a pharmaceutically acceptable salt thereof, or any hydrate thereof: 3-amino-1-hydroxypropane-1,1-diphosphonic acid (pamidronic acid), e.g. pamidronate (APD); 3-(N,N-dimethylamino)1-hydroxypropane--1,1-diphosphonic acid, e.g. dimethyl-APD; 4-amino-1-hydroxybutane-1,1-diphosphonic acid (alendronic acid), e.g. alendronate; 1-hydroxy-ethidene-bisphosphonic acid, e.g. etidronate; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid, ibandronic acid, e.g. ibandronate; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid, e.g. amino-hexyl-BP; 3-(N-methyl-N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid, e.g. methyl-pentyl-APD (=BM 21,0955); 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid), e.g. risedronate, including N-methyl pyridinium salts thereof, for example N-methyl pyridinium iodides such as NE-10244 or NE-10446; 1-(4chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid), e.g. tiludronate; 3-[N-(2-phenylthioethyl)-N-methylamino]-1-hydroxy-propane-1,1-diphosphonic acid; 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid, e.g. EB 1053 (Leo); 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid, e.g. PR 78844 (Fujisawa); 5-benzoyl-3,4dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester, e.g. U-81581 (Upjohn); 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane--1,1-diphosphonic acid, e.g. YM 529; and 1,1-dichloromethane-1,1-diphosphonic acid (clodronic acid), e.g. clodronate.

8. A method according to claim 1 or a use according to claim 2 or 3, in which the bisphosphonate is a compound of Formula III

III.



wherein

Het" is an imidazolyl, 2H-1,2,3-, 1H-1,2,4- or 4H-1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl or thiadiazolyl radical which is unsubstituted or C-mono- or di-substituted by lower alkyl, by lower alkoxy, bx phenyl which may in turn be mnon- or disubstituted by lower alkyl, lower alkoxy and/or halogen, by hydroxy, by di-lower alkylamino, by lower alkylthio and/or by halogen and is N-substituted at a substitutable N-atom by lower alkyl or by phenyl-lower alkyl which may in turn be mono- or di-substituted in the phenyl moiety by lower alkyl, lower alkoxy and/or halogen, and

R_2 is hydrogen, hydroxy, amino, lower alkylthio or halogen, lower radicals having up to and including 7 C-atoms,

or a pharmacologically acceptable salt thereof.

9. A method according to claim 1 or a use according to claim 2 or 3, in which the bisphosphonate is zoledronic acid, or a pharmaceutically acceptable salt thereof, or any hydrate thereof.

10. All novel compounds, processes, methods and uses substantially as hereinbefore described with particular reference to the Examples.

* * * * *

2. Labeling of Unit Dose Packages of Drugs, Policy No. PH-04-06, Department of Pharmacy Policy, Univ. of Kentucky Hospital, Chandler Medical Center (Nov. 2009) ("Chandler").

SUBJECT: Labeling of Unit Dose Packages of Drugs

SEE ALSO: Pharmacy Policy P-04-7, Expiration dating and labeling

PURPOSE: The following guidelines should be used for labeling of unit dose packages of oral solids, oral liquids, and injectable syringe dosage forms. Labels should not be written by hand, unless emergency situations warrant.

INFORMATION:

Name
The generic (nonproprietary) name, strength and dosage form should be the most prominent part of the package label. It is NOT necessary to include the brand (proprietary) name.

Dosage Form
Special characteristics of the dosage form should be a part of the label (e.g. extended release). Medication packages should be labeled as to the route of administration if other than oral (e.g. topical use)

Strength
Strength should be stated in accordance with terminology in the American Hospital Formulary Service. The metric system should be used, with dosage forms formulated to provide the rounded off figures in the USP table of approximate equivalents and expressed in the smallest whole number. Micrograms should be used through 999, then milligrams through 999, then grams. Thus,

- 300mg (not 5gr, nor 325mg, nor 0.3gm)
- 60mg (not 1gr, nor 0.6gm, nor 64.5mg. nor 65mg)
- 400mcg (not 1/150gr, nor 0.4mg. nor 0.0004gm)

For milliliters, use ml instead of cc (cubic centimeters) as "cc "is not an approved abbreviation.

Strength of Dose and Total Contents Delivered
The total contents and total dose of the package should be indicated. Thus,

- A unit dose package containing a 600mg dose as two 300mg tablets should be a labeled "600mg (2 x 300mg)".

- A 500mg dose of a liquid or injections containing 100mg/mL should be labeled "delivers 500mg per 5ml".

Special Notes
Special notes such as conditions of storage (e.g. refrigerate), preparation (e.g. shake well), and administration (e.g. not to be chewed) that are not obvious from the dosage form designation are to be included on the label.

Labeling of multi-release rate drugs should include the trade name of the drug the generic equivalent is mimicking, and the drug's marketed schedule frequency (e.g. 12hr, or 24hr)

Beyond-Use Date (UK Packaged Products)
The beyond-use date is the date after which a product must not be used by the patient is placed on the label by the dispenser to limit the patient's use of the medication. Beyond-Use dates should appear on all packages prepared by the University of Kentucky Hospital Pharmacy. Beyond-Use date for nonsterile solid and liquid dosage forms packaged in single unit and unit dose containers shall be one year or less, unless the stability data or manufacturer's labeling or manufacturer's product indicates otherwise. The date should be assigned according to the USP guidelines or the manufacturer's expiration date, whichever is less. If the drug must be reconstituted, the expiration time shall be that of the final product at refrigerated temperature.

- Oral solids — 12 months (unless product expires before the 12 month date)
- Oral liquids — 12 months (unless product expires before the 12 month date)
- Reconstituted liquids — See manufacturer's labeling
- Sterile products — See P-04-7 policy

For very short dated products, i.e., less than four days, the date and time should be noted together.

Control Number for Bulk Packaging Only:
The UK hospital Pharmacy Control Number shall appear on the label which provides a means of complete product identification and packaging history of batch products.

This number consists of six digits: the first two digits represent the month, the third digit the year the product was manufactured and/or packaged. The remaining digits represent the product batch number.

Month	Date	Year	Count for Day
05	21	00	01

Plus area descriptor: M=manufacturing area; P=pediatric satellite; IV=IV room.

The control number 05210001 represents the first product batch prepared on May 21, 2000.

Examples

- Oral solid:
  Sodium Bicarbonate tablet
  648mg
  UK: M063001001

- Oral Liquid:
  Phenytoin Suspension 50mg/ml
  Delivers 125mg per 5ml
  Shake well; Store at Room Temp
  UK: M022801001

- Reconstituted Oral Liquid:
  Ampicillin Suspension 50mg/ml
  Delivers 125mg per 2.5ml
  Shake well; refrigerate
  Exp: 7-20-01

(14-day expiration is based on reconstitution and storage at refrigerated temperature.)

Approved:_____ Authorized:_____

Rebecca Reagan, PharmD
Associate Director, Pharmacy Services

John Armitstead, MS, RPh
Director, Pharmacy Services

3. Leonard et al., MER-101 Tablets: A Pilot Bioavailability Study of a Novel Oral Formulation of Zoledronic Acid, Poster presentation at AACR-NCI-EORTC: Molecular Targets and Cancer Therapeutics October 2007 ("Leonard").

MER-101: A Pilot Bioavailability Study of a Novel Oral Formulation of Zoledronic Acid

Thomas W. Leonard, Catherine McHugh, Bozena Adamczyk, Angela Walsh

AACR-NCI-EORTC: Molecular Targets and Cancer Therapeutics October 2007

Introduction

The purpose of the study was to compare the absorption of two strengths of an investigational oral dosage form of MER-101, a tablet form of zoledronic acid, to the parenteral reference product, commercially available zoledronic acid intravenous infusion, (Zometa® Injection, Novartis). MER-101 was developed by Mermon Pharmaceuticals using GIPET™ I technology to improve the oral bioavailability of zoledronic acid and thereby enable the development of an oral dosage form. GIPET™ I is based on proprietary penetration enhancers which improve the absorption of such drugs in the small intestine. There is no chemical modification to the active drug. The enhancer system is comprised of food based material which is on the US GRAS list. These are important factors in reducing regulatory requirements and the time to market. GIPET™ technology is equally applicable to small molecules, macromolecules and biologics, and is broadly applicable over a wide range of marketed and emerging products.

Zoledronic acid is a bisphosphonate used in the treatment of bone metastases. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone. The 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.

Experimental Procedures

The study was a single dose, three way crossover bioequivalence study in 13 postmenopausal female subjects with osteoporosis. There was a washout period of at least 7 days between dosing days. Cumulative urinary excretion of zoledronic acid over a 48-hour period was used as the basis for the pharmacokinetic analysis. Eleven subjects successfully completed all treatment periods of the study and were included in the final analysis.

The treatments administered during the clinical trial were: MER-101 10mg and 20mg Enteric Coated Tablets and Zometa® Injection 1mg, administered as a 15 minute infusion in 100ml of normal saline. The treatments were well tolerated in all cases.

Data Summary

The MER-101 20mg tablet had a mean 48-hour urinary excretion of zoledronic acid approximately 44% greater than the MER-101 10mg tablet. The MER-101 20mg tablet had a mean zoledronic acid excretion that was similar to the Zometa® 1mg Injection (0.514mg and 0.541mg respectively).

Conclusions

A tablet dosage form of zoledronic acid has been successfully developed which will allow once weekly treatment of patients. The dose administered via a 20mg tablet equals that of a 1mg intravenous infusion. MER-101 was well tolerated and there were no serious adverse events associated with its administration.

STUDY OBJECTIVE

To compare the absorption from two strengths, 10mg and 20mg MER-101 enteric coated tablets to the parenteral reference product, commercially-available zoledronic acid intravenous infusion, (Zometa® Injection, Novartis).

STUDY DESIGN

- Single-dose, three-way crossover bioavailability.
- 7 day washout between each of the three periods.
- 12 postmenopausal women with osteoporosis (13 enrolled).
- Mean age 60.4 years, range 49 to 69.
- Mean height 63.9 inches.
- Mean weight 182.1 pounds.

Treatments were administered:

- After an overnight fast.
- With a full glass of water.
- Patients remained fasted and upright for 4 hours post-dose.

Treatment arms:

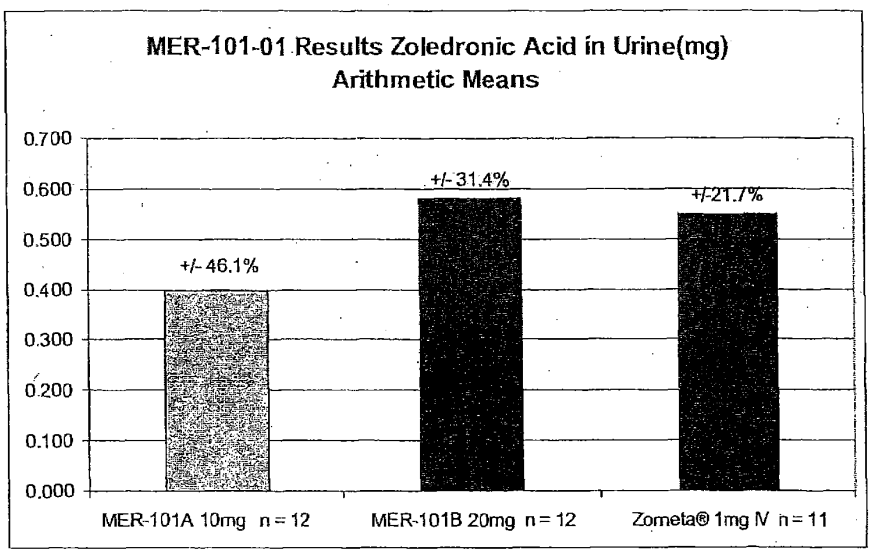
- MER-101A enteric coated tablet (10mg zoledronic acid).
- MER-101B enteric coated tablet (20mg zoledronic acid).
- Zometa® Injection 1mg 15 minute infusion in 100mL normal saline.

Pharmacokinetic samples:

- Cumulative urinary excretion of zoledronic acid.
- Urine collections pre-dose and 0-12, 12-24, 24-36, and 36-48 hours post-dose.
- All urine output from each patient was collected and measured.
- Urine assay HPLC with tandem mass spectrometry (LOQ of zoledronic acid urinary assay 4.99ng/mL; assay range 4.99-4989.60ng/mL).

RESULTS (contd.)

TABLE 2	Ratio for Cumulative Excretion Values	
Test Item	Least Square Mean Ratio (90% CI)	Ln Transformed Ratio (90% CI)
MER-101A / Zometa®	0.723 (0.42 - 1.02)	0.661 (0.48 - 0.91)
MER-101B / Zometa®	1.060 (0.76 - 1.36)	0.949 (0.69 - 1.31)
MER-101B / MER-101A	1.466 (1.06 - 1.87)	1.436 (1.05 - 1.96)



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(54) Title: ZOLEDRONIC ACID CRYSTAL FORMS, ZOLEDRONATE SODIUM SALT CRYSTAL FORMS, AMORPHOUS ZOLEDRONATE SODIUM SALT, AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The invention relates to polymorphs of zoledronic acid and zolidronate sodium salts, amorphous zoledronate sodium salts, processes for making the polymorphs and amorphous zoledronate sodium salt and pharmaceutical compositions containing the polymorphs and amorphous zoledronate sodium salt

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ZOLEDRONIC ACID CRYSTAL FORMS, ZOLEDRONATE SODIUM SALT CRYSTAL FORMS, AMORPHOUS ZOLEDRONATE SODIUM SALT, AND PROCESSES FOR THEIR PREPARATION

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. provisional application Serial No. 60/484,876, filed July 3, 2003, the contents of all of which is incorporated herein.

FIELD OF THE INVENTION

The invention relates to polymorphs of zoledronic acid and zoledronate sodium salts, amorphous zoledronate sodium salt, processes for making the polymorphs and amorphous zoledronate sodium salt and pharmaceutical compositions containing the polymorphs and amorphous zoledronate sodium salt.

BACKGROUND OF THE INVENTION

Zoledronic acid is a bisphosphonic acid, which is an inhibitor of osteoclastic bone resorption. Zoledronic acid, designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid is marketed in the U.S. under the name Zometa® (zoledronic acid for injection). Zometa® is available in vials as a sterile powder for reconstitution for intravenous infusion. The prescribing information for Zometa® states that each vial of Zometa® contains 4.264 mg of zoledronic acid monohydrate (corresponding to 4 mg zoledronic acid on an anhydrous basis).

U.S. patent 4,939,130 discloses a method for making substituted alkanediphosphonic acids. Example 10 describes a method for making zoledronic acid. In this example, at the end of the reaction, the product, which is recrystallized from water, has a melting point of 239°C with decomposition. However, repetition of the procedure described in Example 10 (which requires stirring under reflux imidazol-1-ylacetic acid hydrochloride and phosphoric acid in chlorobenzene) did not lead to zoledronic acid;

instead, the starting material was collected at the end of the reaction. Moreover, the last step of crystallization could not be repeated exactly since the detailed experimental parameters are not given (different cooling regimes, for instance, can produce different polymorphs when crystallized in the same solvent).

In the paper *Drugs of the future* 2000, 25(3): 259-268 the following forms of Zoledronate are listed:

1) Zoledronic acid disodium salt tetrahydrate CAS No. 165800-07-7

2) Zoledronic acid magnesium salt CAS No. 157432-59-2

3) Zoledronic acid zinc salt CAS No. 157432-58-1

4) Zoledronic acid disodium salt anhydrous CAS No. 131654-46-1

5) Zoledronic acid anhydrous CAS No. 118072-93-8

6) Zoledronic acid monohydrate CAS No. 165800-06-6

It is also disclosed in the paper that the free acid has a melting point of 239°C with decomposition, and the disodium salt dihydrate has a melting point of 291-293°C with decomposition. However, the paper does not describe any procedure to obtain the forms mentioned therein, nor does it give any additional data by which they can be identified. Moreover, there is nothing in the literature that discloses polymorphs or different crystal forms of zoledronic acid.

The solid state physical properties of a compound can be influenced by controlling the conditions under which the compounds are obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are determined by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. The polymorphic form may give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others. A particular polymorphic form may also give rise to distinct spectroscopic properties that may be detectable by powder X-ray diffraction (PXRD), solid state ^{13}C NMR spectrometry and infrared spectrometry.

The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. The invention provides for new polymorphic forms of zoledronic acid and zoledronate sodium, and for amorphous zoledronate sodium.

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 is a representative PXRD pattern of zoledronic acid Form I.

Fig. 2 is a representative DSC curve of zoledronic acid Form I.

Fig. 3 is a representative PXRD pattern of zoledronic acid Form II.

Fig. 4 is a representative PXRD pattern of zoledronic acid Form XII.

Fig. 5 is a representative PXRD pattern of zoledronic acid Form XV.

Fig. 6 is a representative PXRD pattern of zoledronic acid Form XVIII.

Fig. 7 is a representative PXRD pattern of zoledronic acid Form XX.

Fig. 8 is a representative PXRD pattern of zoledronic acid Form XXVI.

Fig. 9 is a representative PXRD pattern of zoledronate monohydrate Form VIII.

Fig. 10 is a representative PXRD pattern of zoledronate monosodium Form XVI.

Fig. 11 is a representative PXRD pattern of zoledronate monosodium Form XVII.

Fig. 12 is a representative PXRD pattern of zoledronate disodium Form V.

Fig. 13 is a representative PXRD pattern of zoledronate disodium Form VI.

Fig. 14 is a representative PXRD pattern of zoledronate disodium Form VII.

Fig. 15 is a representative PXRD pattern of zoledronate disodium Form X.

Fig. 16 is a representative PXRD pattern of zoledronate disodium Form XIII.
Fig. 17 is a representative PXRD pattern of zoledronate disodium Form XIV.
Fig. 18 is a representative PXRD pattern of zoledronate disodium Form XIX.
Fig. 19 is a representative PXRD pattern of zoledronate disodium Form XXV.
Fig. 20 is a representative PXRD pattern of zoledronate disodium Form XXVII.
Fig. 21 is a representative PXRD pattern of zoledronate disodium Form IX.
Fig. 22 is a representative PXRD pattern of zoledronate disodium Form XI.
Fig. 23 is a representative PXRD pattern of zoledronate sodium amorphous.
Fig. 24 is a representative TGA curve of zoledronic acid Form I.
Fig. 25 is a representative TGA curve of zoledronic acid Form II.
Fig. 26 is a representative TGA curve of zoledronic acid Form XII.
Fig. 27 is a representative TGA curve of zoledronic acid Form XV.
Fig. 28 is a representative TGA curve of zoledronic acid Form XVIII.
Fig. 29 is a representative TGA curve of zoledronic acid Form XX.
Fig. 30 is a representative TGA curve of zoledronic acid Form XXVI.
Fig. 31 is a representative TGA curve of zoledronate monosodium Form VIII.
Fig. 32 is a representative TGA curve of zoledronate monosodium Form XVI.
Fig. 33 is a representative TGA curve of zoledronate monosodium Form XVII.
Fig. 34 is a representative TGA curve of zoledronate disodium Form V.
Fig. 35 is a representative TGA curve of zoledronate disodium Form VI.
Fig. 36 is a representative TGA curve of zoledronate disodium Form VII.
Fig. 37 is a representative TGA curve of zoledronate disodium Form X.
Fig. 38 is a representative TGA curve of zoledronate disodium Form XIII.
Fig. 39 is a representative TGA curve of zoledronate disodium Form XIV.
Fig. 40 is a representative TGA curve of zoledronate disodium Form XIX.
Fig. 41 is a representative TGA curve of zoledronate disodium Form XXV.
Fig. 42 is a representative TGA curve of zoledronate disodium Form XXVII.
Fig. 43 is a representative TGA curve of zoledronate disodium Form IX.
Fig. 44 is a representative TGA curve of zoledronate disodium Form XI.

SUMMARY OF THE INVENTION

The invention relates to polymorphs of zoledronic acid and zoledronate sodium salts, amorphous zoledronate sodium salt, processes for making the polymorphs and

amorphous zoledronate sodium salt and pharmaceutical compositions containing the polymorphs and amorphous zoledronate sodium salt. The invention can be understood by reference to the following numbered embodiments.

1. Crystalline solid zoledronic acid (Form I) characterized by a powder X-ray diffraction pattern having peaks at 12.1, 12.8, 15.7, and 18.9 ± 0.2 °2θ.
2. The crystalline solid zoledronic acid of embodiment 1 further characterized by a powder XRD pattern with peaks at 20.9, 21.3, 21.8, 22.2, 25.8, 27.6, 29.2, 32.5, and 32.9 ±0.2 °2θ.
3. The crystalline solid zoledronic acid of embodiment 1, which contains less than about 5% of other polymorphic forms of zoledronic acid.
4. The crystalline solid zoledronic acid of embodiment 1, of which no more than about 5% transforms to zoledronic acid Form II upon exposure to 100% relative humidity (RH) for 7 days.
5. The crystalline solid zoledronic acid of embodiment 4, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 100% relative humidity (RH) for 7 days.
6. The crystalline solid zoledronic acid of embodiment 1, which, upon exposure to 100% relative humidity (RH) for 7 days, absorbs less than about 0.2% water.
7. The crystalline solid zoledronic acid of embodiment 1, which, upon exposure to 100% relative humidity (RH) for 7 days, retains its X-ray diffraction pattern substantially as shown in figure no.1.
8. The crystalline solid zoledronic acid of embodiment 1, of which no more than about 5% transforms to zoledronic acid form II upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
9. The crystalline solid zoledronic acid of embodiment 8, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
10. The crystalline solid zoledronic acid of embodiment 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, absorbs less than about 0.2% water.

11. The crystalline solid zoledronic acid of embodiment 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, retains its X-ray diffraction pattern substantially as shown in figure no.1.

12. A pharmaceutical composition comprising the crystalline zoledronic acid of any of embodiments 1-11.

13. The crystalline solid zoledronic acid of embodiment 1, which is a monohydrate.

14. Crystalline solid zoledronic acid (Form II) characterized by a powder X-ray diffraction pattern having peaks at 14.6, 15.4, 19.1, 22.9, and 23.9 ± 0.2 °2θ.

15. The crystalline zoledronic acid of embodiment 14, further characterized by a powder X-ray diffraction pattern with peaks at 20.8, 21.7, 25.1, 26.7, 29.5, 29.9, and ±0.2 °2θ.

16. The crystalline solid zoledronic acid of embodiment 14, which is a monohydrate.

17. Crystalline solid zoledronic acid (Form XII) characterized by a powder X-ray pattern having peaks at 9.0, 13.9, 14.8, 21.5, 24.7, and 29.8 ± 0.2 °2θ.

18. The crystalline zoledronic acid of embodiment 17, further characterized by a powder X-ray diffraction pattern with peaks at 17.0, 20.6, 20.8, 22.4, 25.8, 27.7, 28.4, 28.7, 29.1, 30.8, 3.19, 32.3, and 32.9 ±0.2 °2θ.

19. The crystalline solid zoledronic acid of embodiment 17, which is a monohydrate.

20. Crystalline solid zoledronic acid (Form XV) characterized by a powder X-ray diffraction pattern having peaks at 10.1, 17.3, 19.3, and 23.2 ± 0.2 °2θ.

21. The crystalline zoledronic acid of embodiment 20, further characterized by a powder X-ray diffraction pattern with peaks at 14.5, 16.7, 18.1, 24.5, 25.1, 25.7, 28.5, 29.1, 29.6, and 30.4 ±0.2 °2θ.

22. The crystalline solid zoledronic acid of embodiment 20, which is anhydrous.

23. Crystalline solid zoledronic acid (Form XVIII) characterized by a powder X-ray diffraction pattern having peaks at 10.7, 13.0, 16.4, 17.4, and 28.5 ± 0.2 °2θ.

24. The crystalline zoledronic acid of embodiment 23, further characterized by a powder X-ray diffraction pattern with peaks at 13.3, 18.1, 19.3, 21.3, 23.7, 25.9, 31.5, and 34.5 ±0.2 °2θ.

25. The crystalline solid zoledronic acid of embodiment 23, which is a monohydrate.

26. Crystalline solid zoledronic acid (Form XX) characterized by a powder X-ray diffraction pattern having peaks at 12.2, 19.3, 20.2, 21.3, 25.1, and 27.25 ± 0.2 °2θ.

27. The crystalline zoledronic acid of embodiment 26, further characterized by a powder X-ray diffraction pattern with peaks at 11.4, 14.9, 15.5, 17.2, 18.2 and 30.5 ±0.2 °2θ.

28. The crystalline solid zoledronic acid of embodiment 26, which is anhydrous.

29. Crystalline solid zoledronic acid (Form XXVI) characterized by a powder X-ray diffraction pattern having peaks at 9.8, 14.5, 17.1, 17.6, and 18.3 ± 0.2 °2θ.

30. The crystalline zoledronic acid of embodiment 29, further characterized by a powder X-ray diffraction pattern with peaks at 18.8, 19.7, 21.4, 25.7, 26.6, and 28.1 ±0.2 °2θ.

31. The crystalline solid zoledronic acid of embodiment 29, which is anhydrous.

32. A pharmaceutical composition comprising the crystalline solid zoledronic acid of any of embodiments 12-31.

33. Crystalline solid zoledronate monosodium.

34. Crystalline solid zoledronate monosodium hydrate.

35. The crystalline solid zoledronate monosodium of embodiment 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 15.5, 18.6, 23.6, and 26.8 ± 0.2 °2θ (Form VIII).

36. The crystalline solid zoledronate monosodium of embodiment 35, further characterized by a powder X-ray diffraction pattern with peaks at 11.8, 17.6, 20.1, 24.7, 25.0, 28.4, 31.7, and 32.8 ± 0.2 °2θ.

37. The crystalline solid zoledronate monosodium of embodiment 35, which is a trihydrate.

38. The crystalline solid zoledronate monosodium of embodiment 33, characterized by a powder X-ray diffraction pattern having peaks at 7.3, 8.8, 14.7, 21.8, and 29.6 ± 0.2 °2θ (form XVI).

39. The crystalline solid zoledronate monosodium of embodiment 38, further characterized by a powder X-ray diffraction pattern with peaks at 13.8, 16.8, 20.4, 21.4, 24.4, 25.6, 27.5, 28.2, and 31.7 ± 0.2 °2θ.

40. The crystalline solid zoledronate monosodium of embodiment 38, which is a dihydrate.

41. The crystalline solid zoledronate monosodium of embodiment 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 9.0, 14.5, 21.4, 24.5, and 29.2 ± 0.2 °2θ (Form XVII).

42. The crystalline solid zoledronate monosodium of embodiment 41, further characterized by a powder X-ray diffraction pattern with peaks at 13.9, 15.5, 16.8, 18.6, 22.3, 23.6, 26.7, 27.7, and 32.3 ± 0.2 °2θ.

43. The crystalline solid zoledronate monosodium of embodiment 41, which is a dihydrate.

44. Crystalline solid zoledronate disodium.

45. Crystalline solid zoledronate disodium hydrate.

46. Crystalline solid zoledronate disodium anhydrous.

47. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having at 11.3, 14.8, 15.5, 17.4, and 19.9 ± 0.2 °2θ (Form V).

48. The crystalline solid zoledronate disodium of embodiment 47, further characterized by a powder X-ray diffraction pattern with peaks at 18.0, 18.9, 19.7, 22.7, 25.0, 26.7, 30.9, and 34.5 ± 0.2 °2θ.

49. The crystalline solid zoledronate disodium of embodiment 47, which is a dihydrate.

50. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 7.2, 13.3, 13.7, 14.5, and 21.7 ± 0.2 °2θ (Form VI).

51. The crystalline solid zoledronate disodium of embodiment 50, further characterized by a powder X-ray diffraction pattern with peaks at 8.2, 16.6, 16.9, 17.3, 25.9, 26.6, 30.7, 31.9, and 32.9± 0.2 °2θ.

52. The crystalline solid zoledronate disodium of embodiment 50, which is a trihydrate.

53. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 6.2 11.6, 12.6, 13.7 ± 0.2 °2θ (Form VII).

54. The crystalline solid zoledronate disodium of embodiment 53, further characterized by a powder X-ray diffraction pattern with peaks at 22.0, 23.2, 26.4, 27.1, 28.6, 28.8, 34.2± 0.2 °2θ.

55. The crystalline solid zoledronate disodium of embodiment 53, which is a tetrahydrate.

56. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 6.7, 14.4, 18.2, 20.4, and 20.7 ± 0.2 °2θ (Form X).

57. The crystalline solid zoledronate disodium of embodiment 56, further characterized by a powder X-ray diffraction pattern with peaks at 8.8, 13.7, 17.0, 19.8, 21.3, 24.4, 27.5, 27.9, 30.9, and 33.4± 0.2 °2θ.

58. The crystalline solid zoledronate disodium of embodiment 56, which is a hemihydrate.

59. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 6.5, 13.0, 16.1, 17.2, and 30.7 ± 0.2 °2θ (Form XIII).

60. The crystalline solid zoledronate disodium of embodiment 59, further characterized by a powder X-ray diffraction pattern with peaks at 10.2, 19.0, 20.0, 20.6, 22.3, 27.4, 28.6, 28.9, and 34.8± 0.2 °2θ.

61. The crystalline solid zoledronate disodium of embodiment 59, which is a hemihydrate.

62. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 6.6, 19.9, 28.5, and 34.8 ± 0.2 °2θ (Form XIV).

63. The crystalline solid zoledronate disodium of embodiment 62, further characterized by a powder X-ray diffraction pattern with peaks at 13.0, 15.1, 17.1, 20.5, 27.7, 29.6, 30.7, and 33.5± 0.2 °2θ.

64. The crystalline solid zoledronate disodium of embodiment 62, which is anhydrous.

65. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 11.6, 12.5, 13.7, 22.0, and 23.1 ± 0.2 °2θ (Form XIX).

66. The crystalline solid zoledronate disodium of embodiment 65, further characterized by a powder X-ray diffraction pattern with peaks at 6.2, 14.3, 15.3, 16.0, 18.5, 24.3, and 28.6 ± 0.2 °2θ.

67. The crystalline solid zoledronate disodium of embodiment 65, which is a pentahydrate.

68. The crystalline solid zoledronate disodium of embodiment 44, characterized by a powder X-ray diffraction pattern having peaks at 7.4, 13.7, 17.6, and 21.9 ± 0.2 °2θ (Form XXV).

69. The crystalline solid zoledronate disodium of embodiment 68, further characterized by a powder X-ray diffraction pattern with peaks at 6.3, 9.5, 12.6, 14.6, 26.2, 27.1, and 28.6 ± 0.2 °2θ.

70. The crystalline solid zoledronate disodium of embodiment 68, which is a sesquihydrate.

71. The crystalline solid zoledronate disodium of embodiment 44, which is a monohydrate characterized by a powder X-ray diffraction pattern having peaks at 6.4, 8.2, 16.0, 17.4, 19.0, and 28.8 ± 0.2 °2θ (Form XXVII).

72. The crystalline solid zoledronate disodium of embodiment 71, further characterized by a powder X-ray diffraction pattern with peaks at 7.7, 10.2, 17.2, 18.1, 21.6, 25.7, and 25.9 ± 0.2 °2θ.

73. The crystalline solid zoledronate disodium of embodiment 71, which is a monohydrate.

74. Crystalline solid zoledronate trisodium.

75. The crystalline solid zoledronate trisodium of embodiment 74, characterized by a powder X-ray diffraction pattern having peaks at 8.3, 10.9, 15.0, 16.6, and 22.8 ± 0.2 °2θ (Form IX).

76. The crystalline solid zoledronate trisodium of embodiment 75, further characterized by a powder X-ray diffraction pattern with peaks at 13.1, 20.2, 20.6, 20.9, 25.0, 27.8, and 29.0 ± 0.2 °2θ.

77. The crystalline solid zoledronate trisodium of embodiment 75, which is a trihydrate.

78. The crystalline solid zoledronate trisodium of embodiment 74, characterized by a powder X-ray diffraction pattern having peaks at 6.2, 7.9, 8.8, 10.6, and 12.2 ± 0.2 °2θ (Form XI).

79. The crystalline solid zoledronate trisodium of embodiment 78, further characterized by a powder X-ray diffraction pattern with peaks at 15.0, 15.4, 17.5, 18.8, 19.6, 20.5, 22.3, 23.7, 25.7, 29.6, and 31.7 0.2 °2θ.

80. The crystalline solid zoledronate trisodium of embodiment 78, which is a dihydrate.

81. A process for preparing a solid crystalline zoledronate sodium salt comprising:

a) dissolving zoledronic acid in water to form a solution;

b) adding a base, preferably sodium hydroxide, to the solution; and

c) cooling the solution, optionally with the addition of an organic solvent such as isopropyl alcohol, to precipitate crystalline zoledronate sodium.

82. The process of embodiment 81, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

83. The process of embodiment 82, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

84. The process of embodiment 81, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

85. The process of embodiment 84, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

86. The process of embodiment 81, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

87. The process of embodiment 86, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

88. A process for preparing a crystalline solid zoledronate sodium salt comprising:

a) suspending zoledronic acid in a mixture of alcohol/water, preferably at reflux temperature

b) adding to the suspension of a) a solution of a base, preferably sodium hydroxide, in an equivalent mixture of alcohol/water as that used in the suspension of a), to form a reaction mixture; and

c) stirring the reaction mixture for a time sufficient to precipitate a crystalline solid zoledronate sodium salt.

89. The process of embodiment 88, wherein the reaction mixture is stirred at reflux for about 10 to about 20 hours, preferably about 14-16.

90. The process of embodiment 88, wherein the volume ratio of alcohol/water to zoledronic acid in a) and b) is 6-14 volumes, preferably 10 voumes.

91. The process of embodiment 88, wherein the alcohol in a) and b) is selected from the group consisting of methanol, ethanol, isopropanol and dimethylformamide.

92. The process of embodiment 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:1.

93. The process of embodiment 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:2.

94. The process of embodiment 88, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:1.1.

95. The process of embodiment 92, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

96. The process of embodiment 95, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

97. The process of embodiment 93 or embodiment 94, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

98. The process of embodiment 97, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

99. The process of embodiment 0, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:2.1.

100. The process of embodiment 99, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

101. The process of embodiment 100, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

102. A process for preparing a solid crystalline zoledronate sodium salt comprising:

a) dissolving a crystal form of zoledronate sodium in water, preferably at reflux, to form a solution; and

b) cooling the solution to precipitate a crystal form of zoledronate sodium which is different from the starting form in a).

103. The process of embodiment 102, wherein the water is added in an amount of between 20-30 volumes, preferably 25 volumes, per volume of zoledronate sodium.

104. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:

a) adding a solution of a base in an 80%/20% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/ethanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably 14-16 hours; and

c) precipitating zoledronate monosodium Form VIII.

105. The process of embodiment 104, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

106. The process of embodiment 104, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14, preferably 10.

107. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:

a) adding a solution of a base in an 80%/20% v/v mixture of water/methanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/methanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably 14-16 hours; and

c) precipitating zoledronate monosodium Form VIII.

108. The process of embodiment 107, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

109. The process of embodiment 107, wherein the volume ratio of water/methanol to zoledronic acid form I in the suspension and the solution is between 6-14, preferably 10.

110. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:

a) adding a solution of a base in an 60%/40% v/v mixture of water/isopropanol to a suspension of zoledronic acid form I in an 60%/40% v/v mixture of water/isopropanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably14-16 hours; and

c) precipitating zoledronate monosodium Form VIII.

111. The process of embodiment 110, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

112. The process of embodiment 110, wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14, preferably 10.

113. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably14-16 hours; and

c) precipitating zoledronate monosodium Form XVI.

114. The process of embodiment 113, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

115. The process of embodiment 113, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14, preferably 10.

116. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/isopropanol to a suspension of zoledronic acid Form I in a 50%/50% v/v mixture of water/isopropanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably 14-16 hours; and

c) precipitating zoledronate monosodium Form XVI.

117. The process of embodiment 116, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

118. The process of embodiment 116, wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14, preferably 10.

119. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/methanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature, preferably reflux temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours, preferably 14-16 hours; and

c) precipitating zoledronate monosodium Form XVI.

120. The process of embodiment 119, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

121. The process of embodiment 119, wherein the volume ratio of water/methanol to zoledronic acid form I in the solution is between 6-14, preferably 10, and the volume ratio of water/ethanol in the suspension is between 6-14, preferably 10.

122. A process for preparing solid crystalline zoledronate sodium Form XVII comprising:

a) dissolving zoledronic acid Form I in water to form a solution;

b) adding a base, preferably sodium hydroxide, to the solution; and

c) cooling the solution, optionally with the addition of an organic solvent, to precipitate crystalline zoledronate sodium Form XVII.

123. A pharmaceutical composition comprising the crystalline solid zoledronate monosodium of any of embodiments 35-43.

124. A pharmaceutical composition comprising the crystalline solid zoledronate disodium of any of embodiments 47-73.

125. A pharmaceutical composition comprising the crystalline solid zoledronate trisodium of any of embodiments 75-80.

126. Amorphous monosodium zoledronate.

127. Amorphous disodium zoledronate.

128. Amorphous trisodium zoledronate.

129. A pharmaceutical composition comprising the amorphous solid zoledronate of any of embodiments 126, 127 and 128.

130. A process for preparing zoledronate amorphous sodium comprising: treating zoledronic acid and a base, preferably sodium hydroxide, in water at room temperature and precipitating zoledronate amorphous sodium.

131. The process of embodiment 130, wherein the ratio of acid:base is 1:1.1.

132. The process of embodiment 130, wherein the ratio of acid:base is 1:2.1.

DETAILED DESCRIPTION OF THE INVENTION

Powder X-ray diffraction ("PXRD") analysis was performed on a Scintag X-Ray powder diffractometer model X'TRA equipped with a solid state detector. Copper radiation of 1.5418 Å was used. A round aluminium sample holder with round zero background quartz plate, with a cavity of 25 mm diameter and 0.5 mm depth, was used.

Loss on drying ("LOD") was measured by Thermal Gravimetric Analysis ("TGA") using a Mettler TG50. The sample size was about 9-15 mg. The samples were scanned at a rate of 10°C/min from 25°C to 250°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard alumina crucibles covered by lids with one hole were used.

DSC analysis was done using a Mettler 821 Star^e. The weight of the samples was about 3 mg. The samples were scanned at a rate of 10°C/min from 30°C to 300°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard 40 ml aluminum crucibles covered by lids with three holes were used.

Applicants have discovered that different crystal forms of Zoledronic acid may be obtained. Different forms of the zoledronic acid may have improved properties with regards to dissolution (since the dosage form is for injection, the material needs to be reconstituted in water, faster dissolution rate would mean faster reconstitution). The recrystallization of Zoledronic acid leads to a material with a purity of at least 99.5% area by HPLC.

The novel forms of zoledronic acid are hydrated. The level of water in Zoledronic acid is estimated by TGA the (thermogravimetric analysis) weight loss.

Zoledronic acid can be found in the anhydrous state (weight loss up to 2%), monohydrate (weight loss 5-8%), sesquihydrate (weight loss 9-11%).

A typical DSC scan of zoledronic acid shows an endothermic peak below about 160-170°C due mainly to water desorption, and a subsequent endotherm at about 200°C concomitant to an exotherm reaction (see fig.2). From this DSC scan there is no clear detection of a melting point.

Zoledronic Acid Form I

In a first aspect, the invention provides a novel crystalline solid form of Zoledronic acid that has been denominated Form I. Zoledronic acid Form I identified by its PXRD pattern, a representative example of which is provided in the diffractoram of Fig. 1. Particular characteristic peaks occur at 12.1, 12.8, 15.7, and 18.9 ±0.2 °2θ. Additional peaks occur at 20.9, 21.3, 21.8, 22.2, 25.8, 27.6, 29.2, 32.5, and 32.9 ±0.2 °2θ. The hydration level of Zoledronic acid Form I is indicated by a LOD of 5% to 8% (monohydrate) on heating from about 25-220°C.

Zoledronic acid Form I is substantially free of Zoledronic acid Form II. In addition, Zoledronic acid Form I is substantially free of other polymorphic forms of Zoledronic acid. Substantially free means less than about 5%. A suitable method for detecting other phases and mixtures of polymorphs is the X-Ray powder diffraction method (see "Polymorphism in molecular crystals", Joel Bernstein, Oxford Science Publications, or "Polymorphism in pharmaceutical solids" edited by Harry G.Brittain).

Zoledronic acid Form I is physically stable and does not substantially transform to any other crystal form when exposed to 100% relative humidity (RH) or less, for one week, or stored at 40°C and 75% RH for 3 months. After exposure to 100% RH or less, for one week, there is no significant gain of moisture in Form I (not significant means that it absorbs less than about 0.2% water). "Substantially transforms to any other crystal form" means that more than about 5% of the crystal form converts or rearranges to Form II or any other crystal form.

Accordingly in one embodiment, the invention provides a pharmaceutical composition comprising zoledronic acid Form I substantially free of other polymorphic forms of zoledronic acid and at least one pharmaceutically acceptable excipient. Preferably the pharmaceutical composition is in the form of an oral solid dosage form.

In another embodiment, the invention provides a pharmaceutical composition comprising zoledronic acid Form I, which is physically stable and does not substantially transform to any other crystal form when stored at 40°C and 75%RH for 3 months, and at least one pharmaceutically acceptable excipient. Preferably the pharmaceutical composition is in the form of an oral solid dosage form.

The novel crystal forms of Zoledronic acid preferably have a particle size distribution such that 100 % of the particles have a size below 100 microns, preferably below 50 microns.

Accordingly, another aspect of the invention is a pharmaceutical composition comprising a novel crystal form of zoledronic acid, which has a particle size distribution such that 100 % is below 100 microns, preferably below 50 microns, and at least one pharmaceutically acceptable excipient.

Zoledronic acid Form I can be prepared by a phosphorylation reaction of 1-Imidazoleacetic acid (IAA) in the presence of Phosphorous acid and Phosphorous oxychloride in a diluent, such as, Toluene, Chlorobenzene, PEG-400 and Silicon oil. Phosphorous oxychloride is added to a mixture of Phosphorous acid and IAA at 75°C-80°C. The reaction mixture is then stirred at 80°C-100°C, preferably at 80°C for 1-34 hours, preferably 5-25 hours. Then water is added at 80°C-100°C and the aqueous phase is separated. Hydrolysis occurs in about 10-20 hrs, preferably 14-16 hours. At the end of hydrolysis, a solvent like ethanol or acetone may be added to obtain a precipitate of ZLD-Ac after stirring at 5°C for 1-6 hours, preferably 2.5-4 hours.

Zoledronic Acid Form II

In a second aspect, the invention provides a novel crystalline solid form of Zoledronic acid that has been denominated Form II. Zoledronic acid Form II can be identified by its PXRD pattern, a representative example of which is provided in the diffractogram of Fig. 3. Particular characteristic peaks occur at 14.6, 15.4, 19.1, 22.9, and 23.9 ±0.2 °2θ. Additional peaks occur at 20.8, 21.7, 25.1, 26.7, 29.5, 29.9, and ±0.2 °2θ. The hydration level of Zoledronic acid Form II is indicated by a LOD of about 5% (monohydrate) on heating from about 25-220°C.

Form II can be prepared by a phosphorylation reaction of 1-Imidazoleacetic acid (IAA, 1eq.) in the presence of Phosphorous acid (2eq.) and Phosphorous oxychloride (3.7eq.) in silicon oil as a diluent. Phosphorous oxychloride is added to a mixture of phosphorous acid and IAA at 75°C. The reaction mixture is then heated to 80°C for about 27 hours. Then water is added at 80°C and the aqueous phase is separated. Hydrolysis usually occurs within about 10-20 hrs, preferably 14-16 hours. At the end of hydrolysis, ethanol is added to obtain a precipitate of ZLD-Ac after stirring at 5°C for 1-6 hours, preferably 2.5-4 hours.

Zoledronic acid Form II can also be prepared by treating Zoledronic acid form I in Toluene, preferably at reflux temperature, for a duration of 5-20 hours, most preferably 10-16 hours.

Zoledronic Acid Form XII

In a third aspect, the invention provides a novel crystalline solid form of Zoledronic acid that has been denominated Form XII. Zoledronic acid Form XII can be idenfitied by its PXRD pattern, a representative example of which is provided in the diffractogram of Fig. 4. Particular characteristic peaks occur at 9.0, 13.9, 14.8, 21.5, 24.7, and 29.8 ±0.2 °2θ. Additional peaks occur at 17.0, 20.6, 20.8, 22.4, 25.8, 27.7, 28.4, 28.7, 29.1, 30.8, 3.19, 32.3, and 32.9 ±0.2 °2θ. The hydration level of Zoledronic acid form XII is indicated by a LOD of about 6-10%, preferably 6% (monohydrate) on heating from about 25-220°C.

Zoledronic acid Form XII can be prepared by treating Zoledronic acid form XVIII in water at reflux temperature, the diluent/solid ratio being 10-30 volumes, preferably 24-26 volumes, and cooling the solution to room temperature or less.

Zoledronic Form XII can be also be prepared by stirring Form I in acetic acid.

Zoledronic Acid Form XV

In a fourth aspect, the invention provides a novel crystalline solid form of Zoledronic acid denominated Form XV. Zoledronic acid Form XV can be identified by its PXRD pattern, a representative example of which is provided in Fig. 5. Particular characteristic peaks occur at 10.1, 17.3, 19.3, and 23.2 ±0.2 °2θ. Additional peaks occur at 14.5, 16.7, 18.1, 24.5, 25.1, 25.7, 28.5, 29.1, 29.6, and 30.4 ±0.2 °2θ. The TGA of form XV shows a LOD of 1 % (anhydrous) within the temperature range 25-220°C.

Zoledronic acid Form XV can be prepared by treating any form of Zoledronic acid (preferably form I) and sodium hydroxide (1:1 mole ratio) in absolute ethanol (10 volumes per grams of ZLD-Ac) at reflux temperature for a duration of 5-20 hours, most preferably 10-16 hours.

Zoledronic acid Form XV can also be prepared by treating any form of Zoledronic acid (preferably form I or form XII) and sodium hydroxide (1:1 mole ratio) in methanol

(10 volumes per grams of ZLD-Ac) at reflux temperature for a duration of 5-20 hours, most preferably 10-16 hours.

Zoledronic Acid Form XVIII

In a fifth aspect, the invention provides a novel crystalline solid form of Zoledronic acid denominated Form XVIII. Zoledronic acid Form XVIII can be identified by its PXRD pattern, a representative example of which is provided in Fig. 6. Particular characteristic peaks occur at 10.7, 13.0, 16.4, 17.4, and 28.5 ±0.2 °2θ. Additional peaks occur at 13.3, 18.1, 19.3, 21.3, 23.7, 25.9, 31.5, and 34.5 ±0.2 °2θ. The TGA weight loss curve of Zoledronic acid form XVIII shows a LOD between 0.3% and about 6%, preferably 6% (monohydrate) within the temperature range 25-220°C.

Zoledronic acid Form XVIII can be prepared by a reaction of 1-Imidazoleacetic acid, Phosphorous acid and Silicon oil. Phosphorous oxychloride is added to the reaction mixture at 80°C and the reaction mixture is stirred at this temperature for 22 hours. The aqueous phase is separated after addition of water and heated to reflux temperature for a 16 hours. Then absolute ethanol is added and the solution is kept at reflux temperature for 2 hours. Then the solution is cooled gradually to 25°C to obtain a precipitate of ZLD-Ac.

Zoledronic acid Form XVIII can be also prepared by treating Zoledronic acid form I in methanol, 1-butanol, MTBE, acetonitrile, methanol/water 1:1 or ethanol water 1:1 (10 volumes per grams of ZLD-Ac), at room temperature or reflux temperature, for a duration of 5-20 hours, most preferably 10-16 hours.

Zoledronic Acid Form XX

In a sixth aspect, the invention provides a novel crystalline solid form of Zoledronic acid denominated Form XX. Zoledronic acid Form XX can be identified by its PXRD pattern, a representative example of which is provided in Fig. 7. Particular characteristic peaks occur at 12.2, 19.3, 20.2, 21.3, 25.1, and 27.2 ±0.2 °2θ. Additional peaks occur at 11.4, 14.9, 15.5, 17.2, 18.2, and 30.5 ±0.2 °2θ. The TGA weight loss curve of Zoledronic acid form XX shows a LOD of about 0.5% (anhydrous) within the temperature range 25-220°C.

Zoledronic acid Form XX can be prepared by treating Zoledronic acid form I in ethanol, (preferably absolute), 1-propanol, 2-propanol (IPA), preferably at reflux

temperature, the diluent/solid ratio being 15-25 volumes, preferably 10 volumes, for a duration of 5-20 hours, most preferably 10-16 hours.

Zoledronic Acid Form XXVI

In a seventh aspect, the invention provides a novel crystalline solid form of Zoledronic acid, denominated Form XXVI. Zoledronic acid Form XXVI can be identified by its PXRD pattern, a representative example of which is provided in Fig. 8. Particular characteristic peaks occur at 9.8, 14.5, 17.1, 17.6, and 18.3 ±0.2 °2θ. Additional peaks occur at 18.8, 19.7, 21.4, 25.7, 26.6, and 28.1 ±0.2 °2θ. The TGA weight loss curve of Zoledronic acid form XXVI shows typically a LOD of about 1.3% (anhydrous) within the temperature range 25-220°C.

Zoledronic acid Form XXVI can be prepared by treating Zoledronic acid form I in 2-butanol, preferably at reflux temperature. The diluent/solid ratio being 15-25 volumes, preferably 10 volumes, for a duration of 5-20 hours, most preferably 10-16 hours.

Crystal forms of Zoledronic acid sodium salt

In addition, it was also discovered that Zoledronic acid sodium salt in a crystalline form could be obtained. Use of salts in drugs is very diffused, due to the improved physico-chemical properties over the free acid or free base, mainly solubility or crystallinity properties. The crystalline state of a drug, in general, has an advantage over the amorphous state in that the physical (and chemical) properties are fully controlled and reproduced, and the capability of a material to crystallize in a solid form makes this material feasible for pharmaceutical uses. Hence, the novel crystalline Zoledronate sodium salt may have improved solubility. In addition, it was found that the sodium salts obtained have a purity of at least 99.9% area by HPLC.
Surprisingly, it was also discovered that Zoledronate sodium salt can crystallize in different crystal forms.

The level of sodium is measured by methods known in the art, like atomic absorption.

Zoledronate sodium can be found in a monosodium salt, disodium salt, trisodium salt, each of them in various hydration states. The Zoledronate monosodium salt has a

sodium content in the range of 6-8% w/w. Zoledronate disodium has a sodium content in the range of 11-13% w/w, and Zoledronate trisodium has a sodium content in the range of 17-19% w/w.

The level of water in Zoledronate sodium is estimated by TGA (thermogravimetric analysis) weight loss. The Zoledronate sodium salt can be anhydrous (weight loss up to 2%), a hemihydrate (weight loss 3-4% w/w), a monohydrate (weight loss 5-6%), a sesquihydrate (weight loss 7-8%), a dihydrate (weight loss 9-12% w/w), a trihydrate (13-16% weight loss), or a tetrahydrate (weight loss 17-19% w/w).

In general, sodium salts of Zoledronic acid may be prepared by treating Zoledronic acid with a base, preferably NaOH, in organic solvents, like lower alcohols or DMF, and water in different proportions relative to the organic solvent. The reaction is preferably carried out at reflux temperature. In these procedures a solution of a base in a mixture of alcohol/water is added to a suspension of Zoledronic acid in an equivalent mixture of alcohol/water at reflux temperature. The volume ratio of diluent/Zoledronic acid is 6-14, preferably 10 volumes. The reaction mixture is stirred at reflux temperature for 10-20 hours, preferably 14-16 hours. The reaction mixture can be cooled to room temperature or less, and filtered, or filtered at higher temperatures.

Alternatively, sodium salts of Zoledronic acid may be prepared by dissolving Zoledronic acid in water, adding a base, preferably NaOH, and precipitating it by cooling, optionally with the aid of an organic solvent such as isopropol alcohol.

Alternatively, sodium salts of Zoledronic acid may be recrystallized by treating the sodium salt of Zoledronic acid in water (20-30 volumes, preferably 25 volumes) at reflux temperature and then cooling the solution to less than room temperature to obtain a precipitate of ZLD-Na.

Zoledronate Monosodium Crystal Forms

Zoledronate monosodium can be found in crystal **Form VIII**, characterized by typical PXRD peaks at 8.2, 15.5, 18.6, 23.6, 26.8 deg. 2-theta, and additional peaks at 11.8, 17.6, 20.1, 24.7, 25.0, 28.4, 31.7, 32.8 deg. 2-theta. The TGA of form VIII shows a weight loss of 15-16% (trihydrate) within the temperature range 25-220°C.

Zoledronate monosodium can be found in crystal **form XVI**, characterized by typical XRD peaks at 7.3, 8.8, 14.7, 21.8, 29.6 deg. 2-theta, and additional peaks at 13.8,

16.8, 20.4, 21.4, 24.4, 25.6, 27.5, 28.2, 31.7 deg. 2-theta. The TGA curve of form XVI shows a weight loss of 9-10 % (dihydrate) within the temperature range 25-220°C.

Zoledronate monosodium can be found in crystal **form XVII**, characterized by typical XRD peaks at 8.2, 9.0, 14.5, 21.4, 24.5, 29.2 deg 2-theta, and additional peaks at 13.9, 15.5, 16.8, 18.6, 22.3, 23.6, 26.7, 27.7, 32.3 deg. 2-theta. The TGA of form XVII shows a weight loss of about 10% (dihydrate) within the temperature range 25-220°C.

Zoledronate monosodium **form VIII** may be prepared by dissolving Zoledronic acid in water, adding NaOH in pellets or in aquous solution (40%). IPA may be added to improve the yield of crystallization. This solution is cooled to get form VIII.

Zoledronate monosodium **form VIII** may be also obtained by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:1) in water /ethanol 80%:20% v/v, water /methanol 80%:20% v/v, water /isopropanol 80%:20% v/v or 60%:40% v/v.

Zoledronate monosodium **form XVI** may be obtained by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:1) in water /ethanol 50%:50% v/v or water /isopropanol 50%:50% v/v, or water /methanol 50%:50% v/v.

Zoledronate monosodium **form XVII** may be obtained by dissolving Zoledronic acid in water, adding NaOH in aqueous solution (29%) drop-wise (ratio of acid/base 1:0.7)

Zoledronate Disodium Crystal Forms

Zoledronate disodium can be found in **form V**, characterized by typical peaks at 11.3, 14.8, 15.5, 17.4, 19.9 deg. 2-theta, and additional peaks at 18.0, 18.9, 19.7, 22.7, 25.0, 26.7, 30.9, 34.5 deg. 2-theta. The TGA curve of form V shows a weight loss of about 10-11% (dihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form V** may be prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water /ethanol ratios between 20%-50% v/v water in ethanol, water /methanol ratios between 40%-50% v/v water in methanol, water /IPA ratios between 40%-50% v/v water in IPA.

Zoledronate disodium **form V** may also be prepared by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base1:2) in water /ethanol ratios

between 20%-50% v/v water in ethanol, water /methanol 50%:50% v/v water in methanol, water /isopropanol ratios between 20%-50% v/v water in IPA.

Zoledronate disodium **form V** may also be prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water /ethanol ratios between 20%-50% v/v water in ethanol, water /methanol ratios between 40%-50% v/v water in methanol, water /IPA ratios between 40%-50% v/v water in IPA.

Zoledronate disodium can be found in **form VI**, characterized by typical peaks at 7.2, 13.3, 13.7, 14.5, 21.7 deg. 2-theta, and additional peaks at 8.2, 16.6, 16.9, 17.3, 25.9, 26.6, 30.7, 31.9, 32.9 deg. 2-theta. The TGA curve of form VI shows a weight loss of 13-16% (trihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form VI** may be prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water /ethanol or water/methanol 60% v/v water in ethanol or methanol, or water/ isopropanol 80% v/v water in IPA.

Zoledronate disodium **form VI** may also be obtained also by recrystallizing Zoledronate disodium, preferably form XIX, in water.

Zoledronate disodium can be found in **form VII**, characterized by typical peaks at 6.2 11.6, 12.6, 13.7 deg. 2-theta, and additional peaks at 22.0, 23.2, 26.4, 27.1, 28.6, 28.8, 34.2 deg. 2-theta. The TGA curve of form VII shows a weight loss of 17-19 % within the temperature range 25-220°C (tetrahydrate). Less crystalline form VII is found with water content of 7-10% within the temperature range 25-220°C.

Zoledronate sodium **form VII** may be obtained by dissolving Zoledronic acid in water, adding a base, preferaby NaOH (aqueous solution or pearls) until the pH of 5.5-7.5, preferably 5.7-7.0. The solution is cooled and optionally an organic solvent (preferably isopropanol) is added. Optionally the solution may be concentrated to obtain the solid material. The mixture may be further stirred for a period of 1-5 hours, preferably 2 hours.

Zoledronate disodium **form VII** may be also prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water /ethanol or water/methanol or water/isopropanol 80%:20% v/v of water in the alcohol.

Zoledronate disodium **form VII** may be also prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water/ isopropanol 60%:40% v/v water in IPA.

Zoledronate disodium **form VII** may be also prepared by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:2) in water/ ethanol 80%:20% v/v water in ethanol.

Zoledronate disodium can be found in **form X**, characterized by typical peaks at 6.7, 14.4, 18.2, 20.4, 20.7 deg. 2-theta, and additional peaks at 8.8, 13.7, 17.0, 19.8, 21.3, 24.4, 27.5, 27.9, 30.9, 33.4 deg. 2-theta. The TGA curve of form X shows a weight loss of about 3 % (hemihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form X** may be obtained by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1.1) in water/ isopropanol 20%:80% v/v water in IPA.

Zoledronate disodium can be found in **form XIII**, characterized by typical peaks at 6.5, 13.0, 16.1, 17.2, 30.7 deg. 2-theta, and additional peaks at 10.2, 19.0, 20.0, 20.6, 22.3, 27.4, 28.6, 28.9, 34.8 deg. 2-theta. The TGA curve of form XIII shows a weight loss of about 3% (hemihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form XIII** may be obtained by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:2) in water/ ethanol 5%:95% v/v water in ethanol.

Zoledronate disodium can be found in **form XIV**, characterized by typical peaks at 6.6, 19.9, 28.5, 34.8 deg. 2-theta, and additional peaks at 13.0, 15.1, 17.1, 20.5, 27.7, 29.6, 30.7, 33.5 deg. 2-theta. The TGA curve of form XIV shows a weight loss of 1-2% (anhydrous) within the temperature range 25-220°C.

Zoledronate disodium **form XIV** may be obtained by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:2) in water/methanol 20%:80% v/v water in methanol.

Zoledronate disodium **form XIV** may be also obtained by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1) in water/DMF 20%:80% v/v water in DMF.

Zoledronate disodium can be found in **form XIX**, characterized by typical X-Ray peaks at 11.6, 12.5, 13.7, 22.0, 23.1 deg. 2-theta, and additional peaks at 6.2, 14.3, 15.3,

16.0, 18.5, 24.3, 28.6 deg. 2-theta. The TGA curve of form XIX shows a weight loss of about 22% (pentahydrate) within the temperature range 25-220°C.

Zoledronate disodium **form XIX** may be obtained by treating Zoledronate disodium, preferably form VII, in water and precipitating the material, preferably by cooling.

Zoledronate disodium **form XIX** may be also obtained by dissolving Zoledronic acid in water, adding a base, preferably NaOH (aqueous solution or pearls) (ratio of acid/base 1:2), in reflux..

Zoledronate disodium can be found in **form XXV**, characterized by typical peaks at 7.4, 13.7, 17.6, 21.9 deg. 2-theta, and additional peaks at 6.3, 9.5, 12.6, 14.6, 26.2, 27.1, 28.6 deg. 2-theta. The TGA curve of form XXV shows a weight loss of 7-8% (sesquihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form XXV** may be obtained by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:2) in water/methanol 80%:20% v/v water in methanol.

Zoledronate disodium can be found in **form XXVII**, characterized by typical peaks at 6.4, 8.2, 16.0, 17.4, 19.0, 28.8 deg. 2-theta, and additional peaks at 7.7, 10.2, 17.2, 18.1, 21.6, 25.7, 25.9 deg. 2-theta. The TGA curve of form XXVII shows a weight loss of about 5-6% (monohydrate) within the temperature range 25-220°C.

Zoledronate disodium **form XXVII** may be prepared by treating Zoledronic acid, preferably form I, and sodium hydroxide (ratio of acid/base 1:2) in water /methanol 5%:95% v/v water in methanol and by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:1) in water/ methanol 20%:80% v/v water in methanol.

Zoledronate Trisodium Crystal Forms

Zoledronate trisodium can be found in **form IX**, characterized by typical peaks at 8.3, 10.9, 15.0, 16.6, 22.8 deg. 2-theta, and additional peaks at 13.1, 20.2, 20.6, 20.9, 25.0, 27.8, 29.0 deg. 2-theta. The TGA curve of form IX shows a weight loss of about 13-14% (trihydrate) within the temperature range 25-220°C.

Zoledronate trisodium **form IX** may be prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:2.1) in water /ethanol or water/methanol or water/isopropanol in ratios between 20%-80% v/v of water in the alcohol.

Zoledronate trisodium can be found in **form XI**, characterized by typical peaks at 6.2, 7.9, 8.8, 10.6, 12.2 deg. 2-theta, and additional peaks at 15.0, 15.4, 17.5, 18.8, 19.6, 20.5, 22.3, 23.7, 25.7, 29.6, 31.7 deg. 2-theta. The TGA curve of form XI shows a weight loss of about 9% (dihydrate) within the temperature range 25-220°C.

Zoledronate disodium **form XI** may be prepared by treating Zoledronic acid, preferably form XII, and sodium hydroxide (ratio of acid/base 1:2.1) in water /ethanol or water /methanol 5%:95% v/v of water in ethanol or methanol.

Zoledronate sodium amorphous

Zoledronate sodium amorphous is prepared by treating Zoledronic acid and sodium hydroxide (ratio of acid/base 1:1.1 or 1:2.1 or 1:3.1) in water at room temperature, and precipitating the material by concentrating the solution by any means known in the art like evaporation of the solvent. Evaporation may be done using a vacuum.

Examples

CRYSTAL FORMS OF ZOLEDRONIC ACID (ZLD-Ac)

Preparation of ZLD-Ac crystal form I

General procedure for the preparation of ZLD-Ac crystal form **I** starting from 1-Imidazoleacetic acid (IAA), Phosphorous acid (H_3PO_3) and Phosphorous oxychloride ($POCl_3$) (Examples 1-9, see Table 1):

A cylindrical reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, is loaded with 1-Imidazoleacetic acid (IAA), Phosphorous acid and a diluent (Toluene/ Chlorobenzene/ PEG-400/ Silicon oil). The obtained suspension is heated to 75°C-80°C and Phosphorous oxychloride is added drop-wise. The reaction mixture is then heated to 75°C-100°C for 1-34 hours. Then water is

added at 80°C-100°C. The mixture is stirred vigorously for about 15 minutes. [In some cases, when Silicon oil is used as a diluent, there is a need to add Toluene in order to improve the separation between the oily phase and the aqueous phase]. Then the phases are separated. The aqueous phase is put in a clean reactor and heated to 95°C-100°C for 13.5-19 hours. Then it is cooled to 5°C and absolute Ethanol is added to obtain a precipitate after stirring at 5°C for 2.5-4 hours [In some cases a precipitate of Zoledronic acid is obtained without adding absolute Ethanol as an anti-solvent]. The white product is then filtered, washed with absolute Ethanol and dried in a vacuum oven at 50°C for 17-24 hours to obtain Zoledronic acid crystal form **I** (LOD by TGA=6.3%-9.3%).

Table 1: Preparation of ZLD-Ac crystal form I starting from IAA, H_3PO_3 and $POCl_3$

Example	Raw material (grams of IAA)	Ratio of reactants (equivalents) IAA/H_3PO_3/$POCl_3$	Diluent/ volumes per grams of IAA	Temp. of reaction	Time of reaction	Amount of water for the hydrolysis step	Addition of Toluene to improve phases separation	Time of hydrolysis step	Amount of abs.EtOH/ Acetone for the precipitation of ZLD-Ac	LOD by TGA	Yield (grams of ZLD-Ac)
1	IAA·HCl (5.4g)	1/3.6/4.5	Silicon oil/ 6.5vol.	80°C	24hrs	45ml	50ml	19hrs	90ml(EtOH)	9.1 %	79% (7.8g)
2	IAA·HCl (4.9g)	1/3.7/3.7	Chloro-benzene/ 8.8vol.	100°C	1hr	50ml	-	15.5hrs	50ml(EtOH)	-	- (8.2g)
3	IAA·HCl (4.9g)	1/3/3	PEG-400/ 5.5vol.	75°C	2hrs	27ml	27ml	13.5hrs	100ml(Acetone)	-	- (1.1g)
4	IAA·HCl (4.9g)	1/3/3.75	Silicon oil/ 5.5vol.	80°C	22hrs	54ml	54ml	19hrs	54ml(EtOH)	6.8 %	76% (6.7g)
5	IAA·HCl (4.9g)	1/3.7/3.7	Toluene/ 8.8vol.	100°C	3hrs	44ml	-	16hrs	200ml(EtOH)	9.3 %	69% (6.2g)
6	IAA·HCl (5.9g)	1/2/3	Silicon oil/ 5.5vol.	80°C	23hrs	33ml	-	16hrs	200ml(EtOH)	7.9 %	38% (4.0g)
7	IAA·HCl	1/4/4	Silicon oil/ 5.5vol.	80°C	11hrs	33ml	33ml	16hrs	33ml(EtOH)	9.3 %	74% (8.2g)

	(6.0g)										
8 MS-427	IAA (12.0g)	1/3/3.75	Silicon oil/ 6.0vol.	80°C	17hrs	72ml	-	16hrs	-	7.7 %	72% (20.0g)
9	IAA (70g)	1/3/3.75	Silicon oil/ 7.0vol.	80°C	34hrs	490ml	490ml	16hrs	490ml(EtOH) (addition of EtOH at reflux temp.)	6.3 %	59% (95.1g) Purity by HPLC 98.3% *

- ZLD HPLC method:
  Column: Phenomenex Phenyl-Hexyl 5um, 250x4.6mm
  Mobile phase: 40mM Octansulfonic acid sodium salt in 1% $HClO_4$, 0.2% H_3PO_4 : Methanol (85:15)
  Detection: 220nm

Stability was measured versus the presence of Form II.

The stability data for example 4 in the table above is:

Example No.	Time Interval (months)	Results				
4			25°C, 60% RH	40°C, 75% RH	55°C	2-8°C
ZLD-Ac	0	I	I	I	I	I
	1M			I	I	
	2M			I	I	
	3M			I	I	
	6M		I	I	I	I
	9M					
	12M					

TGA analysis

Example No.	Time Interval (months)	Results				
4			25°C, 60% RH	40°C, 75% RH	55°C	2-8°C
ZLD-Ac	0					
	1M					
	2M			6.3	6.3	
	3M			6.2	6.2	
	6M		6.5	6.5	6.5	6.4
	9M					
	12M					

Example 10:

Sodium hydroxide (pearls, 91.1g) was added to a suspension of Zoledronic acid crystal form XII (200.0g) in water (2000ml) at room temperature (pH=14) to obtain a clear solution. Then the pH of the solution was adjusted to pH 1 by addition of 32% aqueous HCl (300ml). The solution was then cooled gradually to 5°C and the white precipitate was filtered, washed with cold water (2x150ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 161.7g (84%) of Zoledronic acid crystal form I (LOD by TGA=6.7%). Purity by HPLC 99.9%.

Preparation of ZLD-Ac crystal form II

Example 11:

A 250ml three-necked flask equipped with a mechanical stirrer, a reflux condenser and a dropping funnel, was loaded with 1-Imidazoleacetic acid hydrochloride (4.9g, 0.03mole), phosphorous acid (4.9g, 0.06mole) and Silicon oil (Merck) (27ml). The suspension was heated to 75°C and phosphorous oxychloride (10.5ml, 0.11mole) was added drop-wise during 30 minutes. The reaction mixture was then heated to 80°C for 27 hours. Then water (27ml) and toluene (30ml) were added at 80°C. The mixture was stirred vigorously for about 15 minutes. Then the toluene phase (containing the silicon oil) and the aqueous phase were separated. The aqueous phase was put in a clean flask and heated to 90°C for 16 hours. Then it was cooled to room temperature and absolute Ethanol (27ml) was added during the cooling process to obtain a white precipitate immediately. The mixture was stirred at 5°C for 4 hours. The white product was then filtered, washed with absolute Ethanol (2x15ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 4.9g (58%) of Zoledronic acid crystal form II (LOD by TGA=5.2%).

Example 12:

Zoledronic acid crystal form I (2.0g) was stirred in Toluene (20ml) at reflux temperature for 14 hours. Then the suspension was cooled to room temperature, filtered, washed with Toluene (1x15ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.6g of Zoledronic acid crystal form II.

Preparation of ZLD-Ac crystal form XII

Example 13:

Zoledronic acid crystal form XVIII (10.0g) was dissolved in water (260ml) at reflux temperature. The obtained solution was stirred at reflux temperature for about 20 minutes to obtain a clear solution. Then it was cooled to 75°C during 2 hours and stirred at this temperature for 1 hour. The turbid solution was further cooled to 25°C during 4.5 hours and stirred at this temperature for 1 hour. After cooling to 0°C during 2 hours and stirring at this temperature for 16 hours, the white precipitate was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 7.8g of Zoledronic acid crystal form XII.

Example 14:

Zoledronic acid crystal form I (2.0g) was stirred in Acetic acid (20ml) at room temperature for 15.5 hours. Then it was filtered, washed with Acetic acid (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 2.0g of Zoledronic acid crystal form XII.

Preparation of ZLD-Ac crystal form XV

Example 15:

A 250ml flask was loaded with Zoledronic acid form I (4.8g), Sodium hydroxide (0.7g) and absolute Ethanol (10 volumes per grams of ZLD-Ac) (48ml). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a vacuum oven at 50°C for 23 hours to give 4.9g (96%) of Zoledronate monosodium crystal form XV in a mixture with Zoledronic acid crystal form I (LOD by TGA=5.8%).

Example 16:

A 250ml flask was loaded with Zoledronic acid form I (4.8g), Sodium hydroxide (0.7g) and Methanol (10 volumes per grams of ZLD-Ac) (48ml). The reaction mixture was heated to reflux temperature for 16 hours. Then it was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x10ml) and dried in a vacuum oven at 50°C for 22 hours to give 4.8g (99%) of Zoledronate monosodium crystal form XV (LOD by TGA=0.8%). Purity by HPLC 99.9%.

Example 17:

Zoledronic acid crystal form XII (2.0g) was stirred in Methanol (20ml) at reflux temperature for 19 hours. Then the suspension was cooled to room temperature, filtered, washed with Methanol (1x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.8g of a mixture of Zoledronic acid crystal forms XV and XVIII.

Preparation of ZLD-Ac crystal form XVIII

Example 18:

A 3L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with 1-Imidazoleacetic acid (70.0g, 0.56mole), Phosphorous acid (136.7g, 1.67mole) and Silicon oil (M-350) (490ml). The suspension was heated to 80°C and Phosphorous oxychloride (194.4ml, 2.08mole) was added drop-wise during 4 hours. The reaction mixture was stirred at 80°C for 22 hours. Then water (490ml) was added slowly at 80°C. The mixture was stirred vigorously for about 30 minutes. Then the silicon oil phase and the aqueous phase were separated. The aqueous phase was put in a clean reactor and heated to 97°C for 17.5 hours. Then absolute Ethanol (490ml) was added and the solution was stirred at reflux (87°C) for 2 hours. The solution was then cooled to 70°C-72°C during about 1 hour and was kept at this temperature for 1 hour. After cooling to 25°C during 2.5 hours and stirring at this temperature for 1 hour, half of the product was filtered, washed with small amount of cold water and dried in a vacuum oven at 50°C for 20 hours to obtain 50.8g of Zoledronic acid crystal form XVIII (MS-507-crop I, LOD by TGA=1.9%). The rest of the suspension was cooled to 0°C during 2

hours and was stirred at this temperature for about 16 hours. Then the product was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 26g of Zoledronic acid crystal form **XVIII** (MS-507-crop II, LOD by TGA=1.0%). The overall yield of the process is 50% purity by HPLC 97.7%.

Example 19:

Zoledronic acid crystal form **I** (2.0g) was stirred in Methanol (20ml) at room temperature for 14.5 hours. Then it was filtered, washed with Methanol (2x10ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 1.9g of Zoledronic acid crystal form **XVIII**.

Example 20:

Zoledronic acid crystal form **I** (2.0g) was stirred in Methanol (20ml) at reflux temperature for 16 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with Methanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.7g of Zoledronic acid crystal form **XVIII**.

Example 21:

Zoledronic acid crystal form **I** (2.0g) was stirred in 1-Butanol (20ml) at reflux temperature for 15.5 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with 1-Butanol (1x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.8g of Zoledronic acid crystal form **XVIII**.

Example 22:

Zoledronic acid crystal form **I** (2.0g) was stirred in MTBE (20ml) at reflux temperature for 15 hours. Then the suspension was cooled to room temperature and the white solid was filtered, washed with MTBE (1x10ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 1.4g of Zoledronic acid crystal form **XVIII**.

Example 23:

Zoledronic acid crystal form **I** (2.0g) was stirred in Acetonitrile (20ml) at room temperature for 22 hours. Then the suspension was filtered, washed with Acetonitrile

(2x5ml) and dried in a vacuum oven at 50°C for 23 hours to obtain 2.0g of Zoledronic acid crystal form XVIII.

Example 24:

Zoledronic acid crystal form I (2.0g) was stirred in a mixture of Methanol/water (1:1 v/v) (20ml) at reflux temperature for 18 hours. Then the suspension was cooled to 0°C, filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 1.8g of Zoledronic acid crystal form XVIII.

Example 25:

Zoledronic acid crystal form I (2.0g) was stirred in a mixture of Ethanol/water (1:1 v/v) (20ml) at reflux temperature for 18 hours. Then the suspension was cooled to 0°C, filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 1.8g of Zoledronic acid crystal form XVIII.

Preparation of ZLD-Ac crystal form XX

Example 26:

Zoledronic acid crystal form I (2.0g) was stirred in absolute Ethanol (20ml) at reflux temperature for 16 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with absolute Ethanol (2x5ml) and dried in a vacuum oven at 50°C for 22.5 hours to obtain 1.9g of Zoledronic acid crystal form XX in a mixture with crystal form I.

Example 27:

Zoledronic acid crystal form I (2.0g) was stirred in 1-Propanol (20ml) at reflux temperature for 11.5 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with 1-Propanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form XX.

Example 28:

Zoledronic acid crystal form I (2.0g) was stirred in 2-Propanol (IPA) (20ml) at reflux temperature for 14 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with IPA (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form XX. Purity by HPLC 99.8%.

Preparation of ZLD-Ac crystal form XXVI

Example 29:

Zoledronic acid crystal form I (2.0g) was stirred in 2-Butanol (20ml) at reflux temperature for about 15 hours. The suspension was then cooled to room temperature and the white solid was filtered, washed with 2-Butanol (2x5ml) and dried in a vacuum oven at 50°C for 24 hours to obtain 1.9g of Zoledronic acid crystal form XXVI.

CRYSTAL FORMS OF ZOLEDRONATE MONOSODIUM (ZLD-Na)

Preparation of ZLD-Na crystal form VIII

Example 30:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. Sodium hydroxide (pearls, 1.42g) was added. A pH test of the sodium salt showed pH=4.54. The solution was cooled to 60°C and IPA (10.5ml) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 64 hours. After cooling to 5°C and stirring at this temperature for 1 hour, the white precipitate was filtered, washed with cold water (1x10ml) and dried in a vacuum oven at 50°C for 23.5 hours to obtain 7.0g of Zoledronate monosodium crystal form VIII (pH=4.32). Purity by HPLC 100.0%.

Example 31:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to 4°C

during 2 hours and was stirred at this temperature for about 64 hours to obtain a massive precipitate. The white precipitate was filtered, washed with cold water (1x10ml) and dried in a vacuum oven at 50°C for 26 hours to obtain 7.6g (64%) of Zoledronate monosodium crystal form **VIII** (LOD by TGA=15.1%).

Example 32→:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3°C and stirring at this temperature for 1.5 hour, the white precipitate was filtered, washed with Methanol (2x15ml) and dried in a vacuum oven at 50°C for 25 hours to obtain 5.8g (49%) of Zoledronate monosodium crystal form **VIII** (LOD by TGA=15.1%). The obtained Form **VIII** (2g) was recrystallized form water (34ml) to give 1.4g (72%) of Zoledronic acid crystal form **VIII** (LOD by TGA=11.3%). Purity by HPLC 100.0%.

[Remark:

Regarding the next examples: the composition of the reflux media is expressed on a volume per volume basis (abbreviated v/v). The amount of water that should be added to the reflux media is calculated according to the following formula:

(10 volumes of alcohol per grams of ZLD-Ac x 100) / X% of alcohol = Y

when Y is the total amount of alcohol and water together→

Y x (100-X)% of water / 100 = Z

when Z is the volume of water that should be added].

Example 33:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (36ml) was added drop-wise to a suspension of Zoledronic acid form I (4.8g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (202ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a

vacuum oven at 50°C for 22 hours to give 4.7g (83%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.5%). Purity by HPLC 99.9%.

Example 34:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac fprm I) (36ml) was added drop-wise to a suspension of Zoledronic acid (4.8g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (202ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x20ml) and dried in a vacuum oven at 50°C for 22 hours to give 4.7g (81%) of Zoledronate monosodium crystal form VIII (LOD by TGA=16.03%). Purity by HPLC 99.9%.

Example 35:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2x20ml) and dried in a vacuum oven at 50°C for 24 hours to give 4.7g (79%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.40%). Purity by HPLC 99.95%.

Example 36:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form I) (19ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form I) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was

then filtered, washed with IPA (1x20ml) and dried in a vacuum oven at 50^{0}C for 27 hours to give 0.6g (10%) of Zoledronate monosodium crystal form VIII (LOD by TGA=15.0%).

Preparation of ZLD-Na crystal form XVI

Example 37:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / Ethanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (14ml) was added drop-wise to a suspension of Zoledronic acid (4.8g) in a mixture of water (50% v/v) / Ethanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (81ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x20ml) and dried in a vacuum oven at 50^{0}C for 18 hours to give 5.2g (98%) of Zoledronate monosodium crystal form XVI (LOD by TGA=9.9%). Purity by HPLC 99.95%.

Example 38:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / IPA (50% v/v, 10 volumes per grams of ZLD-Ac form I) (15ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (50% v/v) / IPA (50% v/v, 10 volumes per grams of ZLD-Ac form I) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (2x20ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 5.2g (94%) of Zoledronate monosodium crystal form XVI (LOD by TGA=9.8%). Purity by HPLC 99.9%.

Example 39:

A solution of sodium hydroxide (0.7g) in a mixture of water (50% v/v) / Methanol (50% v/v, 10 volumes per grams of ZLD-Ac form I) (14ml) was added drop-wise to a suspension of Zoledronic acid form I (4.8g) in a mixture of water (50% v/v) / Ethanol

(50% v/v, 10 volumes per grams of ZLD-Ac form I) (81ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x25ml) and dried in a vacuum oven at 50°C for 25.5 hours to give 4.8g (89%) of Zoledronate monosodium crystal form XVI (LOD by TGA=11.1%). Purity by HPLC 99.9%.

Preparation of ZLD-Na crystal form XVII

Example 40:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (247ml). The suspension was heated to 94°C to obtain a clear solution. A 29% aqueous solution of Sodium hydroxide (3.45g) was added drop-wise. The solution was then cooled to room temperature and stirred at this temperature for 16 hours. After cooling to 3°C the product was isolated by filtration. Further cooling of the mother-liquid led to the formation of a white precipitate. The precipitate was filtered and dried in a vacuum oven at 50°C for 24 hours to obtain 0.6g of Zoledronate monosodium crystal form XVII (LOD by TGA=10.3%).

CRYSTAL FORMS OF ZOLEDRONATE DISODIUM (ZLD-Na_2)

Preparation of ZLD-Na_2 crystal form V

Example 41:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (10-15ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate disodium crystal form V.

Sample No.	X% H_2O	Y% EtOH	Total volume of solution (H_2O/EtOH)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	4.9g/89%	10.3%
2	40% (33ml)	60% (50ml)	83ml	5.0g/90%	10.3%
3	50% (50ml)	50% (50ml)	100ml	5.1g/91%	10.7%

Example 42:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (13-15ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (70-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate disodium crystal form V.

Sample No.	X% H_2O	Y% MeOH	Total volume of solution (H_2O/MeOH)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% (50ml)	83ml	4.7g/85%	10.0%
2	50% (50ml)	50% (50ml)	100ml	4.9g/88%	10.8%

Example 43:

A solution of sodium hydroxide (0.7g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (13-15ml) was added drop-wise to a suspension of Zoledronic acid (4.98g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form XII) (70-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V.

Sample No.	X% H_2O	Y% IPA	Total volume of solution (H_2O/IPA)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% (50ml)	83ml	4.7g	-
2	50% (50ml)	50% (50ml)	100ml	4.8g/85%	11.2%

Example 44:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (10-15ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (X% v/v) / Ethanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.9%.

Sample No.	X% H_2O	Y% EtOH	Total volume of solution (H_2O/EtOH)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	6.0g/96%	9.7%
2	50% (50ml)	50% (50ml)	100ml	6.0g/94%	10.9%

Example 45:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (15ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (X% v/v) / Methanol (Y% v/v, 10 volumes per grams of ZLD-Ac) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^0C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95%.

Sample No.	X% H_2O	Y% MeOH	Total volume of solution (H_2O/MeOH)	Yield (g/%)	LOD by TGA
1	50% (50ml)	50% (50ml)	100ml	6.0g/94%	11.1%

Example 46:

A solution of sodium hydroxide (1.4g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac form I) (10-15ml) was added drop-wise to a suspension of Zoledronic acid (5.0g) in a mixture of water (X% v/v) / IPA (Y% v/v, 10 volumes per grams of ZLD-Ac) (53-85ml) at reflux temperature. The reaction mixture was heated at

reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate disodium crystal form V. Purity by HPLC 99.95%.

Sample No.	X% H_2O	Y% IPA	Total volume of solution (H_2O/IPA)	Yield (g/%)	LOD by TGA
1	20% (13ml)	80% (50ml)	63ml	5.7g/91%	10.3%
2	50% (50ml)	50% (50ml)	100ml	5.7g/90%	10.6%

Preparation of ZLD-Na_2 crystal form VI

Example 47:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / Ethanol or Methanol (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (60% v/v) / Ethanol or Methanol (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate disodium crystal form VI.

Sample No.	X% H_2O	Y% EtOH or MeOH	Total volume of solution (H_2O/EtOH or MeOH)	Yield (g/%)	LOD by TGA
1	60% (75ml)	40% EtOH (50ml)	125ml	4.9g/86%	12.9%
2	60%	40%	125ml	4.5g/78%	13.0%

	(75ml)	MeOH (50ml)			

Example 48:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature and the solution was evaporated to dryness. The obtained solid was dried in a vacuum oven at 50°C for 5 hours to give 5.2g (78%) of Zoledronate disodium crystal form VI (LOD by TGA=15.4%).Purity by HPLC 99.9%.

Example 49:

Zoledronate disodium crystal form XIX (4.0g) was dissolved in water (10ml) at reflux temperature. After about 30 minutes at reflux temperature a precipitate was obtained. The suspension was then cooled to 0°C using an ice-bath. The solid was isolated by filtration and dried in a vacuum oven at 50°C for 17 hours to give 2.0g (50%) of Zoledronate disodium crystal form VI.

Preparation of ZLD-Na_2 crystal form VII

Example 50:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer and a reflux condenser was loaded with Zoledronic acid form I (10.0g) and water (260ml). The suspension was heated to 80°C to obtain a clear solution. Sodium hydroxide (pearls, 2.84g) was added. A pH test of the sodium salt showed pH=7.35. The solution was cooled to 60°C and IPA (10.5ml) was added. The reaction mixture was cooled to room temperature during 2 hours and was stirred at this temperature for about 16 hours. After cooling to 5°C and stirring at this temperature for 2 hours, the solution was evaporated to dryness to obtain a white solid. The obtained solid was reslurred in water (50ml) and cooled to 4°C. The product

was then isolated by filtration and dried in a vacuum oven at 50°C for 24 hours to obtain 3.2g of Zoledronate disodium crystal form **VII** (24%) (pH=7.27). Purity by HPLC 100.0%.

Example 51:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (130ml). The suspension was heated to reflux temperature to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (6.9g) was added drop-wise. The solution was then cooled to 4°C during 2 hours and was stirred at this temperature for about 1.5 hours. The solution was concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50°C for 22 hours to obtain 2.7g (22%) of Zoledronate disodium crystal form **VII** (LOD by TGA=10.7%).

Example 52:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (10.0g) and water (130ml). The suspension was heated to reflux temperature (92°C) to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (6.9g) was added drop-wise. The solution was then cooled to 25°C was stirred at this temperature for about 16 hours. The solution was then concentrated to half of its volume to obtain a precipitate. The white precipitate was filtered and dried in a vacuum oven at 50°C for 18.5 hours to obtain 2.8g (23%) of Zoledronate disodium crystal form **VII** (LOD by TGA=10.2%). Purity by HPLC 100.0%.

Example 53:

A solution of sodium hydroxide (0.7g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered,

washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate disodium crystal form VII.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	80% (200ml)	20% EtOH (50ml)	250ml	4.9g/89%	9.2%
2	80% (200ml)	20% MeOH (50ml)	250ml	4.5g/83%	7.6%
3	80% (200ml)	20% IPA (50ml)	250ml	4.7g/85%	10.3%

Example 54:

A solution of sodium hydroxide (0.7g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (60% v/v) / IPA (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (1x20ml) and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate monosodium crystal form VIII (crop I). Then the precipitate from the mother-liquid was isolated by filtration as well, and dried in a vacuum oven at 50°C for 24 hours to give 2.8g (13%) of Zoledronate disodium crystal form VII (crop II).

Example 55:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / Ethanol (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 18.5 hours. Then the reaction mixture was cooled to room temperature and the solution was evaporated to dryness to obtain 6.7g (98%) of Zoledronate disodium crystal form VII (LOD by TGA=16.8%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form X

Example 56:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / IPA (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / IPA (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with IPA (1x25ml) and dried in a vacuum oven at 50^0C for 24 hours to give 4.7g (91%) of Zoledronate disodium crystal form X (LOD by TGA=2.6%).

Preparation of ZLD-Na_2 crystal form XIII

Example 57:

A solution of sodium hydroxide (1.4g) in a mixture of water (5% v/v) / Ethanol (95% v/v, 10 volumes per grams of ZLD-Ac form I) (8ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (5% v/v) / Ethanol (95% v/v, 10 volumes per grams of ZLD-Ac) (45ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 19.5 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Ethanol (1x10ml) and dried in a vacuum oven

at 50^{0}C for 20 hours to give 4.9g (84%) of Zoledronate disodium crystal form XIII (LOD by TGA=3.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XIV

Example 58:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / DMF (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / DMF (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with DMF (2x10ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 4.8g (92%) of Zoledronate disodium crystal form XIV (LOD by TGA=1.9%).

Example 59:

A solution of sodium hydroxide (1.4g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac form I) (10ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 17 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (1x10ml) and dried in a vacuum oven at 50^{0}C for 26 hours to give 5.6g (97%) of Zoledronate disodium crystal form XIV (LOD by TGA=1.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XIX

Example 60:

Zoledronate disodium crystal form VII (1.0g) was dissolved in water (19ml) at reflux temperature. After about 30 minutes at reflux temperature a light precipitate was obtained. The suspension was then cooled to 0°C using an ice-bath and was concentrated

under vacuum to obtain a massive precipitation. The solid was isolated by filtration after further stirring at 0°C, and dried in a vacuum oven at 50°C for 27 hours to give 0.4g (40%) of Zoledronate disodium crystal form XIX.

Example 61:

A 0.5L reactor equipped with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, was loaded with Zoledronic acid form I (20.0g) and water (260ml). The suspension was heated to reflux temperature (92°C) to obtain a clear solution. A 40% aqueous solution of Sodium hydroxide (13.8g) was added drop-wise. The solution was then cooled to 25°C and was stirred at this temperature for about 16 hours. The solution was then concentrated to half of its volume to obtain a precipitate. After stirring at 0°C for 72 hours, the white precipitate was filtered and dried in a vacuum oven at 50°C for 23 hours to obtain 10.4g of Zoledronate disodium crystal form XIX.

Preparation of ZLD-Na_2 crystal form XXV

Example 62:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac form I) (38ml) was added drop-wise to a suspension of Zoledronic acid form I (5.0g) in a mixture of water (80% v/v) / Methanol (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 19 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The solution was then evaporated to dryness to obtain 6.1g (99%) of Zoledronate disodium crystal form XXV (LOD by TGA=7.4%). Purity by HPLC 99.9%.

Preparation of ZLD-Na_2 crystal form XXVII

Example 63:

A 100ml flask was loaded with Zoledronic acid form I (4.9g), Sodium hydroxide (1.4g), Methanol (50ml) and water (2.5ml) [= 5% v/v water in Methanol]. The reaction mixture was heated to reflux temperature for 21 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x75ml) and dried in a vacuum oven at 50°C

for 27.5 hours to give 5.7g (93%) of Zoledronate disodium crystal form XXVII (LOD by TGA=5.3%). Purity by HPLC 99.9%.

Example 64:

A solution of sodium hydroxide (0.7g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (4.98g) in a mixture of water (20% v/v) / Methanol (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x15ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 4.85g (90%) of Zoledronate disodium crystal form XXVII (LOD by TGA=7.5%).

CRYSTAL FORMS OF ZOLEDRONATE TRISODIUM (ZLD-Na_3)

Preparation of ZLD-Na_3 crystal form IX

Example 65:

A solution of sodium hydroxide (1.4g) in a mixture of water (20% v/v) / Ethanol or Methanol or IPA (80% v/v, 10 volumes per grams of ZLD-Ac form XII) (10ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (20% v/v) / Ethanol or Methanol or IPA (80% v/v, 10 volumes per grams of ZLD-Ac) (53ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50^{0}C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA

1	20% (13ml)	80% EtOH (50ml)	63ml	5.6g/84%	13.6%
2	20% (13ml)	80% MeOH (50ml)	63ml	5.9g/88%	13.7%
3	20% (13ml)	80% IPA (50ml)	63ml	5.6g/85%	13.5%

Example 66:

A solution of sodium hydroxide (1.4g) in a mixture of water (40% v/v) / Ethanol or Methanol or IPA (60% v/v, 10 volumes per grams of ZLD-Ac form XII) (13ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (40% v/v) / Ethanol or Methanol or IPA (60% v/v, 10 volumes per grams of ZLD-Ac) (71ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	40% (33ml)	60% EtOH (50ml)	83ml	5.7g/68%	13.9%
2	20% (33ml)	60% MeOH (50ml)	83ml	5.5g	-
3	20% (33ml)	60% IPA (50ml)	83ml	5.7g/85%	14.3%

Example 67:

A solution of sodium hydroxide (1.4g) in a mixture of water (50% v/v) / Ethanol or Methanol or IPA (50% v/v, 10 volumes per grams of ZLD-Ac form XII) (15ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (50% v/v) / Ethanol or Methanol or IPA (50% v/v, 10 volumes per grams of ZLD-Ac) (85ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	50% (50ml)	50% EtOH (50ml)	100ml	5.5g/84%	11.6%
2	50% (50ml)	50% MeOH (50ml)	100ml	5.2g/77%	14.6%
3	50% (50ml)	50% IPA (50ml)	100ml	5.3g/85%	8.6%

Example 68:

A solution of sodium hydroxide (1.4g) in a mixture of water (60% v/v) / Ethanol or Methanol or IPA (40% v/v, 10 volumes per grams of ZLD-Ac form XII) (19ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (60% v/v) / Ethanol or Methanol or IPA (40% v/v, 10 volumes per grams of ZLD-Ac) (106ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and

dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	60% (75ml)	40% EtOH (50ml)	125ml	5.1g/58%	16.8%
2	60% (75ml)	40% MeOH (50ml)	125ml	4.1g/64%	11.8%
3	60% (75ml)	40% IPA (50ml)	125ml	5.3g/79%	14.1%

Example 69:

A solution of sodium hydroxide (1.4g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac form XII) (38ml) was added drop-wise to a suspension of Zoledronic acid form XII (5.0g) in a mixture of water (80% v/v) / Ethanol or Methanol or IPA (20% v/v, 10 volumes per grams of ZLD-Ac) (212ml) at reflux temperature. The reaction mixture was heated at reflux temperature for additional 16 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed and dried in a vacuum oven at 50°C for 24 hours to give Zoledronate trisodium crystal form IX.

Sample No.	X% H_2O	Y% EtOH or MeOH or IPA	Total volume of solution (H_2O/EtOH or MeOH or IPA)	Yield (g/%)	LOD by TGA
1	80%	20%	250ml	5.7g/84%	15.1%

	(200ml)	EtOH (50ml)			
2	80% (200ml)	20% MeOH (50ml)	250ml	5.6g/86%	12.4%
3	80% (200ml)	20% IPA (50ml)	250ml	5.6g/83%	14.5%

Preparation of ZLD-Na_3 crystal form XI

Example 70:

A 250ml flask was loaded with Zoledronic acid form XII (5.0g), Sodium hydroxide (1.4g), absolute Ethanol (50ml) and water (2.5ml) [= 5% v/v water in Ethanol]. The reaction mixture was heated to reflux temperature for 20 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with absolute Ethanol (2x25ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 5.4g (86%) of Zoledronate trisodium crystal form XI (LOD by TGA=8.9%).

Example 71:

A 250ml flask was loaded with Zoledronic acid form XII (5.0g), Sodium hydroxide (1.4g), Methanol (50ml) and water (2.5ml) [= 5% v/v water in Methanol]. The reaction mixture was heated to reflux temperature for 22 hours. Then the reaction mixture was cooled to room temperature. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with Methanol (2x50ml) and dried in a vacuum oven at 50^{0}C for 24 hours to give 5.4g (84%) of Zoledronate trisodium crystal form XI in a mixture with crystal form IX (LOD by TGA=10.5%).

General procedure for the preparation of amorphous Zoledronate sodium

Example 72:

A 100ml flask was loaded with Zoledronic acid crystal form XII (2.0g), Sodium hydroxide (0.57g) and water (10ml). The reaction mixture was stirred at room

temperature to obtain a clear solution. Then the solution was concentrated under vacuum to obtain a precipitate. Further cooling was performed using an ice-bath. The precipitate was then filtered, washed with water (2x10ml) and dried in a vacuum oven at 50^0C for 24 hours to give 0.76g of amorphous Zoledronate sodium.

Summarizing tables – crystals forms of Zoledronate sodium salts

1. Preparation of Zoledronate monosodium salt:

	EtOH	MeOH	IPA
0% v/v H_2O	I (ZLD-Ac)+XV(ZLD-Ac)	XV(ZLD-Ac)	reaction
20% v/v H_2O	XII (ZLD-Ac) >IV		
50% v/v H_2O	XVI	No reaction	XVI
80% v/v H_2O	VIII>>XII (ZLD-Ac)		

- *Using ZLD-Ac (assay 100%, Form I) as a starting material*

2. Preparation of Zoledronate disodium salt:

	EtOH	MeOH	IPA
5% v/v H_2O	XIII	XXVII	No reaction
20% v/v H_2O	V	XIV	V
50% v/v H_2O	V>VI+IX	V>>IX?	V
80% v/v H_2O	VII	XXV	VI

- *Using ZLD-Ac (assay 100%, Form I) as a starting materia*

	EtOH	MeOH	IPA	DMF
20% v/v H_2O	V	V+XXVII	X	XIV
40% v/v H_2O	V	V>XII	V	=
50% v/v H_2O	V	V>VIII	V>VIII	=
60% v/v H_2O		VI+11.3	VIII (crop I) VII+8.2 (crop II)	=
80% v/v H_2O	VII	VII	VII+8.2,9.1	-
100% v/v H_2O	Amorphous			

- *Using ZLD-Ac (assay 90%, Form XII) as a starting material*

3. Preparation of Zoledronate trisodium salt:

	EtOH	MeOH	IPA
5% v/v H_2O		IX+XI	-
20% v/v H_2O	IX+IV	IX>IV+9.9	IX+6.4,6.7
40% v/v H_2O	IX	IX+V	IX+IV
50% v/v H_2O	IX+IV	IX+V>>IV	IX+IV+amorph.+7.1
60% v/v H_2O	IX+IV	IX>IV	IX
80% v/v H_2O	IX	IX	IX
100% v/v H_2O	Amorphous		

- *Using ZLD-Ac (assay 90%, Form XII) as a starting material*

What is claimed is:

1. Crystalline solid zoledronic acid (Form I) characterized by a powder X-ray diffraction pattern having peaks at 12.1, 12.8, 15.7, and 18.9 ± 0.2 °2θ.
2. The crystalline solid zoledronic acid of claim 1 further characterized by a powder X-ray diffraction pattern with peaks at 20.9, 21.3, 21.8, 22.2, 25.8, 27.6, 29.2, 32.5, and 32.9 ±0.2 °2θ.
3. The crystalline solid zoledronic acid of claim 1, which contains less than about 5% of other polymorphic forms of zoledronic acid.
4. The crystalline solid zoledronic acid of claim 1, of which no more than about 5% transforms to zoledronic acid Form II upon exposure to 100% relative humidity (RH) for 7 days.
5. The crystalline solid zoledronic acid of claim 4, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 100% relative humidity (RH) for 7 days.
6. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 100% relative humidity (RH) for 7 days, absorbs less than about 0.2% water.
7. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 100% relative humidity (RH) for 7 days, retains its X-ray diffraction pattern substantially as shown in figure no.1.
8. The crystalline solid zoledronic acid of claim 1, of which no more than about 5% transforms to zoledronic acid form II upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
9. The crystalline solid zoledronic acid of claim 8, of which no more than about 5% transforms to other polymorphic forms of zoledronic acid upon exposure to 75% relative humidity (RH) at 40°C for 3 months.
10. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, absorbs less than about 0.2% water.
11. The crystalline solid zoledronic acid of claim 1, which, upon exposure to 75% relative humidity (RH) at 40°C for 3 months, retains its X-ray diffraction pattern substantially as shown in figure no.1.
12. A pharmaceutical composition comprising the crystalline zoledronic acid of claim 1.

13. The crystalline solid zoledronic acid of claim 1, which is a monohydrate.

14. Crystalline solid zoledronic acid (Form II) characterized by a powder X-ray diffraction pattern having peaks at 14.6, 15.4, 19.1, 22.9, and 23.9 ± 0.2 °2θ.

15. The crystalline zoledronic acid of claim 14, further characterized by a powder X-ray diffraction pattern with peaks at 20.8, 21.7, 25.1, 26.7, 29.5, 29.9, and ±0.2 °2θ.

16. The crystalline solid zoledronic acid of claim 14, which is a monohydrate.

17. Crystalline solid zoledronic acid (Form XII) characterized by a powder X-ray pattern having peaks at 9.0, 13.9, 14.8, 21.5, 24.7, and 29.8 ± 0.2 °2θ.

18. The crystalline zoledronic acid of claim 17, further characterized by a powder X-ray diffraction pattern with peaks at 17.0, 20.6, 20.8, 22.4, 25.8, 27.7, 28.4, 28.7, 29.1, 30.8, 3.19, 32.3, and 32.9 ±0.2 °2θ.

19. The crystalline solid zoledronic acid of claim 17, which is a monohydrate.

20. Crystalline solid zoledronic acid (Form XV) characterized by a powder X-ray diffraction pattern having peaks at 10.1, 17.3, 19.3, and 23.2 ± 0.2 °2θ.

21. The crystalline zoledronic acid of claim 20, further characterized by a powder X-ray diffraction pattern with peaks at 14.5, 16.7, 18.1, 24.5, 25.1, 25.7, 28.5, 29.1, 29.6, and 30.4 ±0.2 °2θ.

22. The crystalline solid zoledronic acid of claim 20, which is anhydrous.

23. Crystalline solid zoledronic acid (Form XVIII) characterized by a powder X-ray diffraction pattern having peaks at 10.7, 13.0, 16.4, 17.4, and 28.5 ± 0.2 °2θ.

24. The crystalline zoledronic acid of claim 23, further characterized by a powder X-ray diffraction pattern with peaks at 13.3, 18.1, 19.3, 21.3, 23.7, 25.9, 31.5, and 34.5 ±0.2 °2θ.

25. The crystalline solid zoledronic acid of claim 23, which is a monohydrate.

26. Crystalline solid zoledronic acid (Form XX) characterized by a powder X-ray diffraction pattern having peaks at 12.2, 19.3, 20.2, 21.3, 25.1, and 27.25 ± 0.2 °2θ.

27. The crystalline zoledronic acid of claim 26, further characterized by a powder XRD pattern with peaks at 11.4, 14.9, 15.5, 17.2, 18.2 and 30.5 ±0.2 °2θ.

28. The crystalline solid zoledronic acid of claim 26, which is anhydrous.

29. Crystalline solid zoledronic acid (Form XXVI) characterized by a powder X-ray diffraction pattern having peaks at 9.8, 14.5, 17.1, 17.6, and 18.3 ± 0.2 °2θ.

30. The crystalline zoledronic acid of claim 29, further characterized by a powder X-ray diffraction pattern with peaks at 18.8, 19.7, 21.4, 25.7, 26.6, and 28.1 ±0.2 °2θ.

31. The crystalline solid zoledronic acid of claim 29, which is anhydrous.

32. A pharmaceutical composition comprising the crystalline solid zoledronic acid of claim 14.

33. Crystalline solid zoledronate monosodium.

34. Crystalline solid zoledronate monosodium hydrate.

35. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 15.5, 18.6, 23.6, and 26.8 ± 0.2 °2θ (Form VIII).

36. The crystalline solid zoledronate monosodium of claim 35, further characterized by a powder X-ray diffraction pattern with peaks at 11.8, 17.6, 20.1, 24.7, 25.0, 28.4, 31.7, and 32.8 ± 0.2 °2θ.

37. The crystalline solid zoledronate monosodium of claim 35, which is a trihydrate.

38. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 7.3, 8.8, 14.7, 21.8, and 29.6 ± 0.2 °2θ (form XVI).

39. The crystalline solid zoledronate monosodium of claim 38, further characterized by a powder X-ray diffraction pattern with peaks at 13.8, 16.8, 20.4, 21.4, 24.4, 25.6, 27.5, 28.2, and 31.7 ± 0.2 °2θ.

40. The crystalline solid zoledronate monosodium of claim 38, which is a dihydrate.

41. The crystalline solid zoledronate monosodium of claim 33, characterized by a powder X-ray diffraction pattern having peaks at 8.2, 9.0, 14.5, 21.4, 24.5, and 29.2 ± 0.2 °2θ (Form XVII).

42. The crystalline solid zoledronate monosodium of claim 41, further characterized by a powder X-ray diffraction pattern with peaks at 13.9, 15.5, 16.8, 18.6, 22.3, 23.6, 26.7, 27.7, and 32.3 ± 0.2 °2θ.

43. The crystalline solid zoledronate monosodium of claim 41, which is a dihydrate.

44. Crystalline solid zoledronate disodium.

45. Crystalline solid zoledronate disodium hydrate.

46. Crystalline solid zoledronate disodium anhydrous.

47. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having at 11.3, 14.8, 15.5, 17.4, and 19.9 ± 0.2 °2θ (Form V).

48. The crystalline solid zoledronate disodium of claim 47, further characterized by a powder X-ray diffraction pattern with peaks at 18.0, 18.9, 19.7, 22.7, 25.0, 26.7, 30.9, and 34.5 ± 0.2 °2θ.

49. The crystalline solid zoledronate disodium of claim 47, which is a dihydrate.

50. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 7.2, 13.3, 13.7, 14.5, and 21.7 ± 0.2 °2θ (Form VI).

51. The crystalline solid zoledronate disodium of claim 50, further characterized by a powder X-ray diffraction pattern with peaks at 8.2, 16.6, 16.9, 17.3, 25.9, 26.6, 30.7, 31.9, and 32.9± 0.2 °2θ.

52. The crystalline solid zoledronate disodium of claim 50, which is a trihydrate.

53. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.2 11.6, 12.6, 13.7 ± 0.2 °2θ (Form VII).

54. The crystalline solid zoledronate disodium of claim 53, further characterized by a powder X-ray diffraction pattern with peaks at 22.0, 23.2, 26.4, 27.1, 28.6, 28.8, 34.2± 0.2 °2θ.

55. The crystalline solid zoledronate disodium of claim 53, which is a tetrahydrate.

56. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.7, 14.4, 18.2, 20.4, and 20.7 ± 0.2 °2θ (Form X).

57. The crystalline solid zoledronate disodium of claim 56, further characterized by a powder X-ray diffraction pattern with peaks at 8.8, 13.7, 17.0, 19.8, 21.3, 24.4, 27.5, 27.9, 30.9, and 33.4± 0.2 °2θ.

58. The crystalline solid zoledronate disodium of claim 56, which is a hemihydrate.

59. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.5, 13.0, 16.1, 17.2, and 30.7 ± 0.2 °2θ (Form XIII).

60. The crystalline solid zoledronate disodium of claim 59, further characterized by a powder X-ray diffraction pattern with peaks at 10.2, 19.0, 20.0, 20.6, 22.3, 27.4, 28.6, 28.9, and 34.8± 0.2 °2θ.

61. The crystalline solid zoledronate disodium of claim 59, which is a hemihydrate.

62. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 6.6, 19.9, 28.5, and 34.8 ± 0.2 °2θ (Form XIV).

63. The crystalline solid zoledronate disodium of claim 62, further characterized by a powder X-ray diffraction pattern with peaks at 13.0, 15.1, 17.1, 20.5, 27.7, 29.6, 30.7, and 33.5± 0.2 °2θ.

64. The crystalline solid zoledronate disodium of claim 62, which is anhydrous.

65. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 11.6, 12.5, 13.7, 22.0, and 23.1 ± 0.2 °2θ (Form XIX).

66. The crystalline solid zoledronate disodium of claim 65, further characterized by a powder X-ray diffraction pattern with peaks at 6.2, 14.3, 15.3, 16.0, 18.5, 24.3, and 28.6 ± 0.2 °2θ.

67. The crystalline solid zoledronate disodium of claim 65, which is a pentahydrate.

68. The crystalline solid zoledronate disodium of claim 44, characterized by a powder X-ray diffraction pattern having peaks at 7.4, 13.7, 17.6, and 21.9 ± 0.2 °2θ (Form XXV).

69. The crystalline solid zoledronate disodium of claim 68, further characterized by a powder X-ray diffraction pattern with peaks at 6.3, 9.5, 12.6, 14.6, 26.2, 27.1, and 28.6 ± 0.2 °2θ.

70. The crystalline solid zoledronate disodium of claim 68, which is a sesquihydrate.

71. The crystalline solid zoledronate disodium of claim 44, which is a monohydrate characterized by a powder X-ray diffraction pattern having peaks at 6.4, 8.2, 16.0, 17.4, 19.0, and 28.8 ± 0.2 °2θ (Form XXVII).

72. The crystalline solid zoledronate disodium of claim 71, further characterized by a powder X-ray diffraction pattern with peaks at 7.7, 10.2, 17.2, 18.1, 21.6, 25.7, and 25.9 ± 0.2 °2θ.

73. The crystalline solid zoledronate disodium of claim 71, which is a monohydrate.

74. Crystalline solid zoledronate trisodium.

75. The crystalline solid zoledronate trisodium of claim 74, characterized by a powder X-ray diffraction pattern having peaks at 8.3, 10.9, 15.0, 16.6, and 22.8 ± 0.2 °2θ (Form IX).

76. The crystalline solid zoledronate trisodium of claim 75, further characterized by a powder X-ray diffraction pattern with peaks at 13.1, 20.2, 20.6, 20.9, 25.0, 27.8, and 29.0 ± 0.2 °2θ.

77. The crystalline solid zoledronate trisodium of claim 75, which is a trihydrate.

78. The crystalline solid zoledronate trisodium of claim 74, characterized by a powder X-ray diffraction pattern having peaks at 6.2, 7.9, 8.8, 10.6, and 12.2 ± 0.2 °2θ (Form XI).

79. The crystalline solid zoledronate trisodium of claim 78, further characterized by a powder X-ray diffraction pattern with peaks at 15.0, 15.4, 17.5, 18.8, 19.6, 20.5, 22.3, 23.7, 25.7, 29.6, and 31.7 0.2 °2θ.

80. The crystalline solid zoledronate trisodium of claim 78, which is a dihydrate.

81. A process for preparing a solid crystalline zoledronate sodium salt comprising:

a) dissolving zoledronic acid in water to form a solution;

b) adding a base to the solution; and

c) cooling the solution to precipitate crystalline zoledronate sodium.

82. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

83. The process of claim 82, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

84. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

85. The process of claim 84, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

86. The process of claim 81, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

87. The process of claim 86, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

88. A process for preparing a crystalline solid zoledronate sodium salt comprising:
a) suspending zoledronic acid in a mixture of alcohol/water
b) adding to the suspension of a) a solution of a base, in an equivalent mixture of alcohol/water as that used in the suspension of a), to form a reaction mixture; and
c) stirring the reaction mixture for a time sufficient to precipitate a crystalline solid zoledronate sodium salt.

89. The process of claim 88, wherein the reaction mixture is stirred at reflux for about 10 to about 20 hours.

90. The process of claim 88, wherein the volume ratio of alcohol/water to zoledronic acid in a) and b) is 6-14 volumes.

91. The process of claim 88, wherein the alcohol in a) and b) is selected from the group consisting of methanol, ethanol, isopropanol and dimethylformamide.

92. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:1.

93. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form I and the ratio of acid to base is 1:2.

94. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:1.1.

95. The process of claim 92, wherein the crystalline solid zoledronate sodium salt is the monosodium salt.

96. The process of claim 95, wherein the crystalline solid zoledronate monosodium is selected from the group consisting of Form VIII, Form XVI and Form XVII.

97. The process of claim 93 or claim 94, wherein the crystalline solid zoledronate sodium salt is the disodium salt.

98. The process of claim 97, wherein the crystalline solid zoledronate disodium is selected from the group consisting of Form V, Form VI, Form VII, Form X, Form XIII, Form XIV, Form XIX, Form XXV, and Form XXVII.

99. The process of claim 88, wherein the zoledronic acid is zoledronic acid Form XII and the ratio of acid to base is 1:2.1.

100. The process of claim 99, wherein the crystalline solid zoledronate sodium salt is the trisodium salt.

101. The process of claim 100, wherein the crystalline solid zoledronate trisodium is selected from the group consisting of Form IX and Form XI.

102. A process for preparing a solid crystalline zoledronate sodium salt comprising:
a) dissolving a crystal form of zoledronate sodium in water to form a solution; and
b) cooling the solution to precipitate a crystal form of zoledronate sodium which is different from the starting form in a).

103. The process of claim 102, wherein the water is added in an amount of between 20-30 volumes per volume of zoledronate sodium.

104. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:
a) adding a solution of a base in an 80%/20% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/ethanol at elevated temperature;
b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
c) precipitating zoledronate monosodium Form VIII.

105. The process of claim 104, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

106. The process of claim 104, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14.

107. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:
a) adding a solution of a base in an 80%/20% v/v mixture of water/methanol to a suspension of zoledronic acid form I in an 80%/20% v/v mixture of water/methanol at elevated temperature;
b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and
c) precipitating zoledronate monosodium Form VIII.

108. The process of claim 107, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

109. The process of claim 107, wherein the volume ratio of water/methanol to zoledronic acid form I in the suspension and the solution is between 6-14.

110. A process for preparing crystalline solid zoledronate monosodium Form VIII comprising:

a) adding a solution of a base in an 60%/40% v/v mixture of water/isopropanol to a suspension of zoledronic acid form I in an 60%/40% v/v mixture of water/isopropanol at elevated temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and

c) precipitating zoledronate monosodium Form VIII.

111. The process of claim 110, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

112. The process of claim 110, wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14.

113. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/ethanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and

c) precipitating zoledronate monosodium Form XVI.

114. The process of claim 113, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

115. The process of claim 113, wherein the volume ratio of water/ethanol to zoledronic acid form I in the suspension and the solution is between 6-14.

116. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/isopropanol to a suspension of zoledronic acid Form I in a 50%/50% v/v mixture of water/isopropanol at elevated temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and

c) precipitating zoledronate monosodium Form XVI.

117. The process of claim 116, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

118. The process of claim 116 wherein the volume ratio of water/isopropanol to zoledronic acid form I in the suspension and the solution is between 6-14.

119. A process for preparing crystalline solid zoledronate monosodium Form XVI comprising:

a) adding a solution of a base in a 50%/50% v/v mixture of water/methanol to a suspension of zoledronic acid form I in a 50%/50% v/v mixture of water/ethanol at elevated temperature;

b) stirring the mixture of a) at reflux temperature for about 10 to 20 hours; and

c) precipitating zoledronate monosodium Form XVI.

120. The process of claim 119, wherein the base is sodium hydroxide, which is added in an amount of a 1:1 molar ratio to the zoledronic acid.

121. The process of claim 119, wherein the volume ratio of water/methanol to zoledronic acid form I in the solution is between 6-14 and the volume ratio of water/ethanol in the suspension is between 6-14.

122. A process for preparing solid crystalline zoledronate sodium Form XVII comprising:

a) dissolving zoledronic acid Form I in water to form a solution;

b) adding a base to the solution; and

c) cooling the solution, optionally with the addition of an organic solvent, to precipitate crystalline zoledronate sodium Form XVII.

123. A pharmaceutical composition comprising the crystalline solid zoledronate monosodium of claim 33.

124. A pharmaceutical composition comprising the crystalline solid zoledronate disodium of claim 44.

125. A pharmaceutical composition comprising the crystalline solid zoledronate trisodium of claim 74.

126. Amorphous monosodium zoledronate.

127. Amorphous disodium zoledronate.

128. Amorphous trisodium zoledronate.

129. A pharmaceutical composition comprising the amorphous solid zoledronate of claim 126.

130. A process for preparing zoledronate amorphous sodium comprising:

treating zoledronic acid and a base, in water at room temperature and precipitating zoledronate amorphous sodium.

131. The process of claim 130, wherein the ratio of acid:base is 1:1.1.

132. The process of claim 130, wherein the ratio of acid:base is 1:2.1.

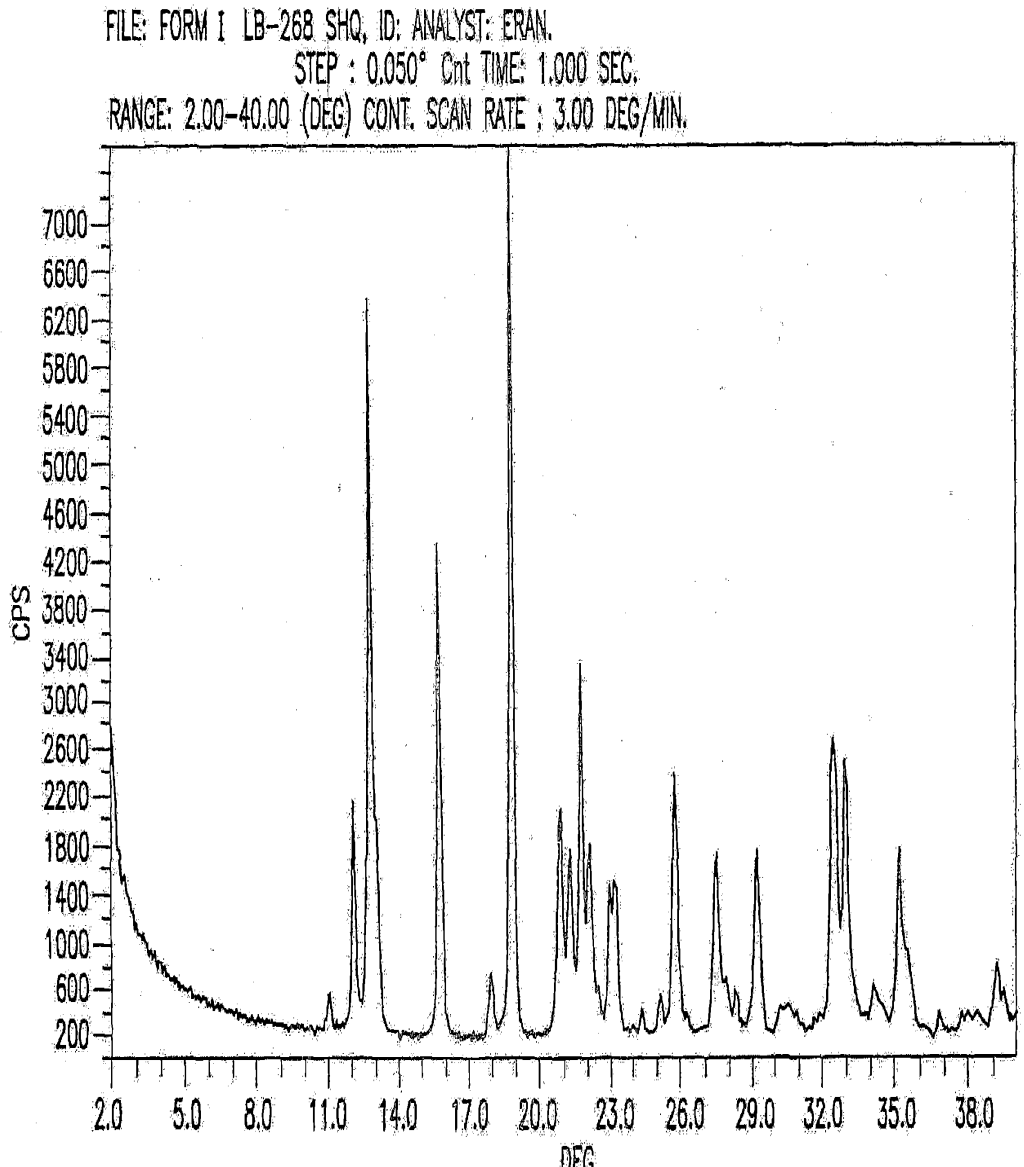
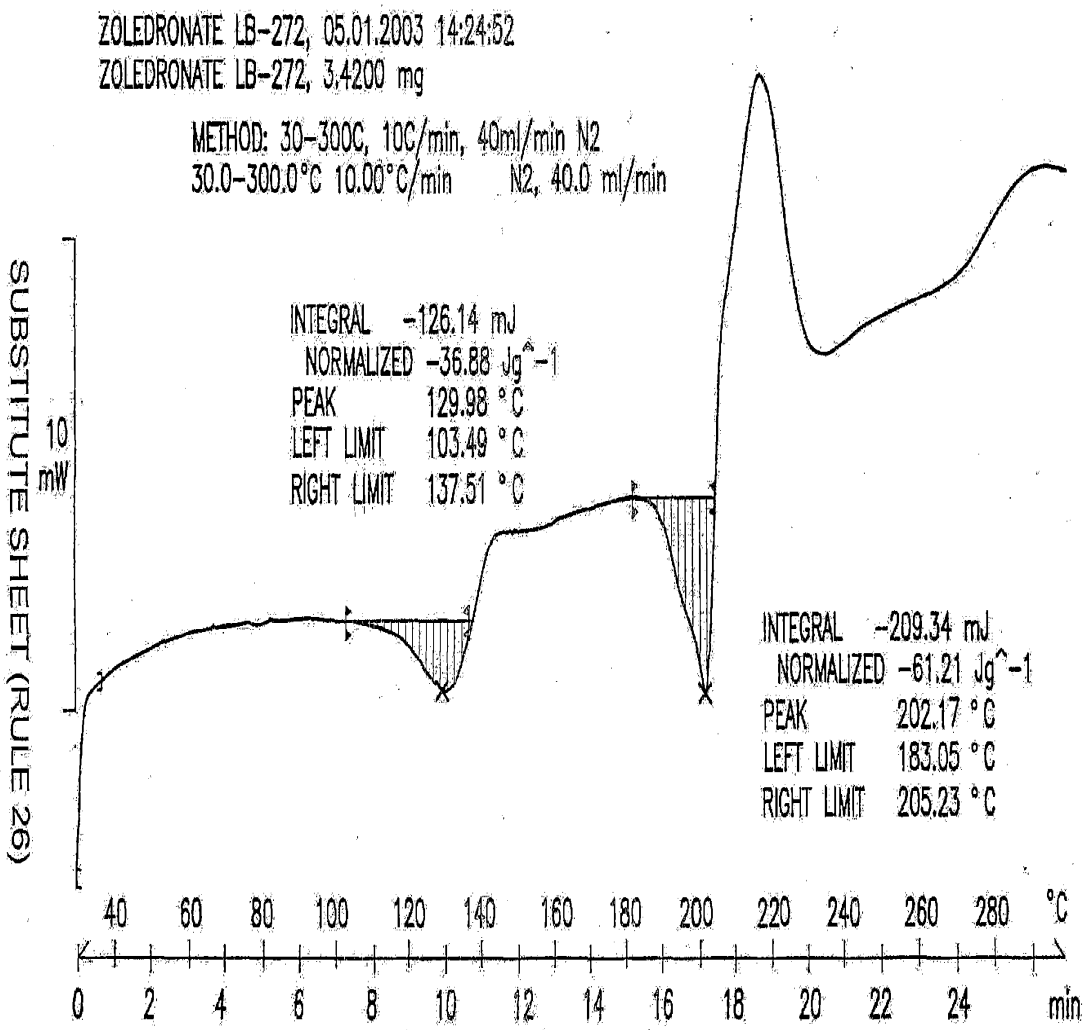


FIG.1 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM I



DSC CURVE OF ZOLEDRONIC ACID FORM I

FIG.2

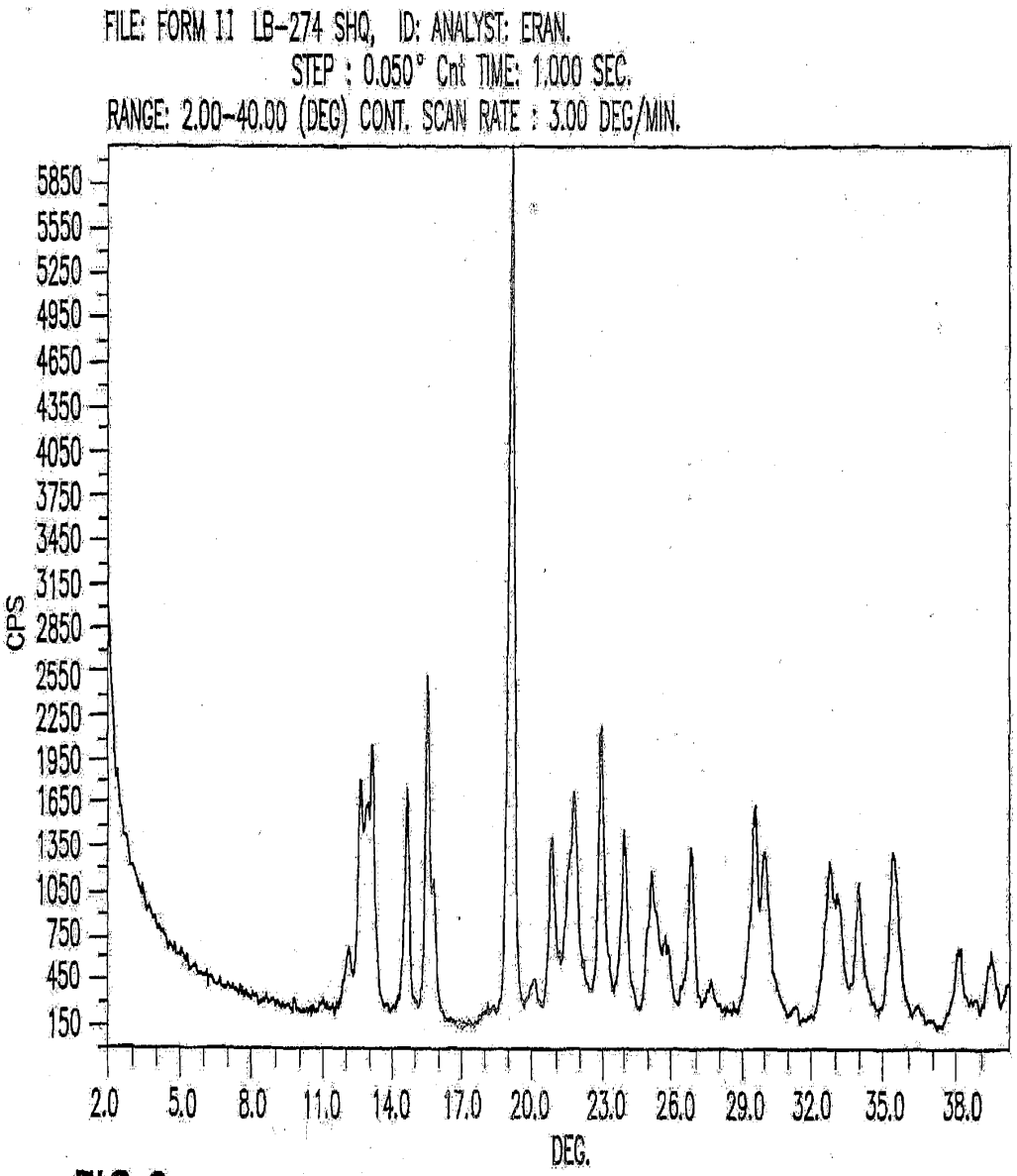


FIG.3 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM II

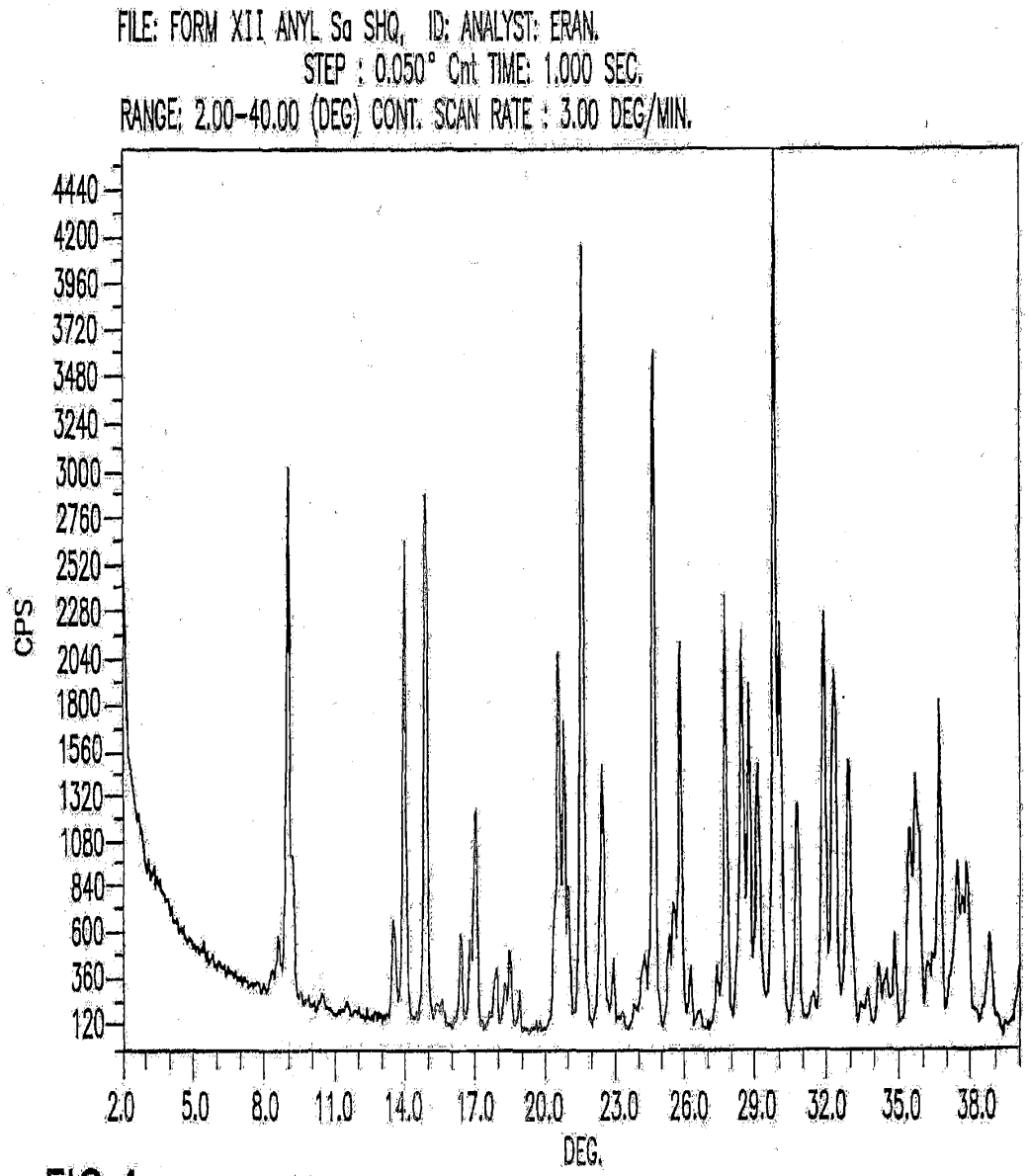


FIG.4 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XII

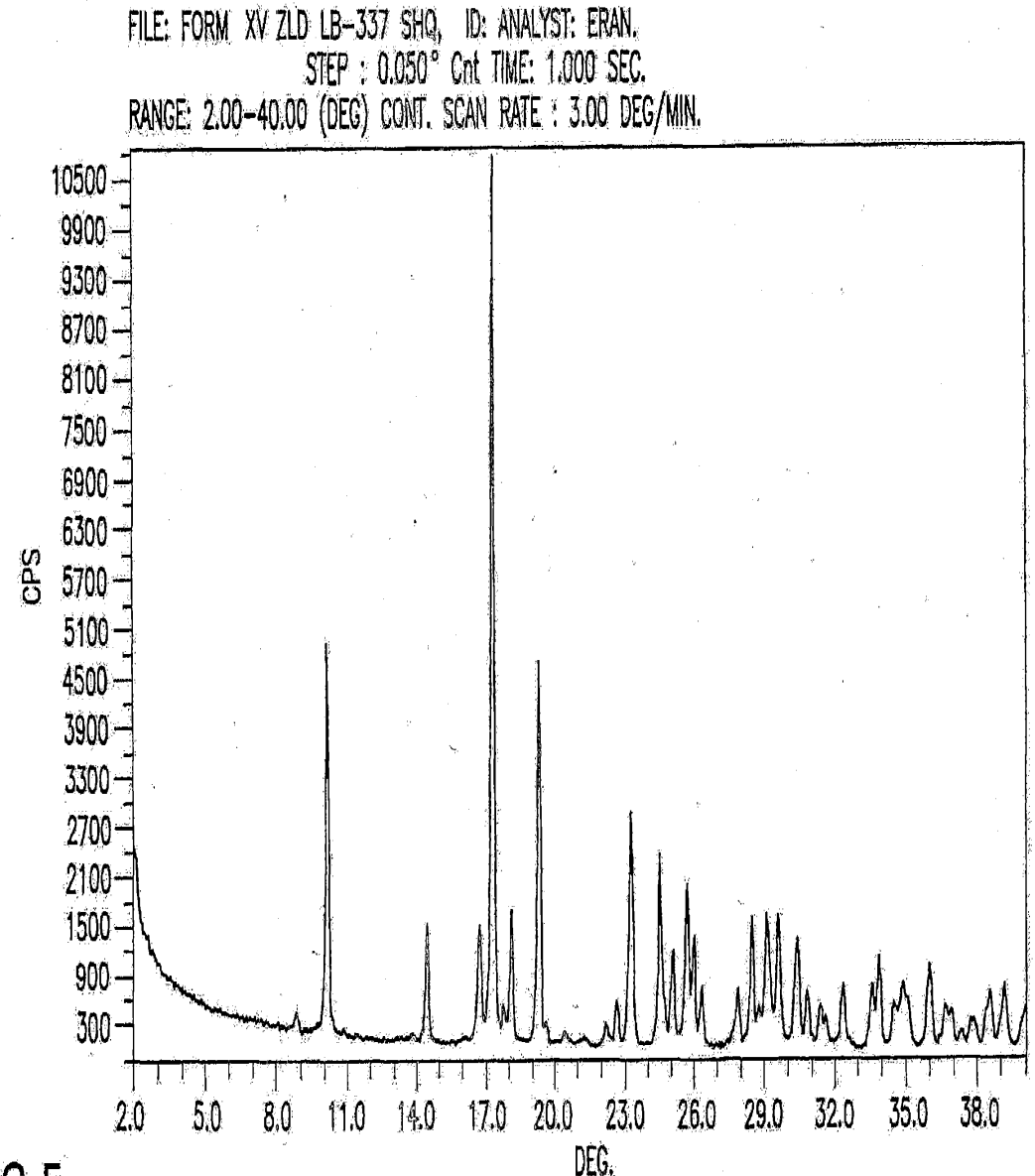


FIG.5

X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XV

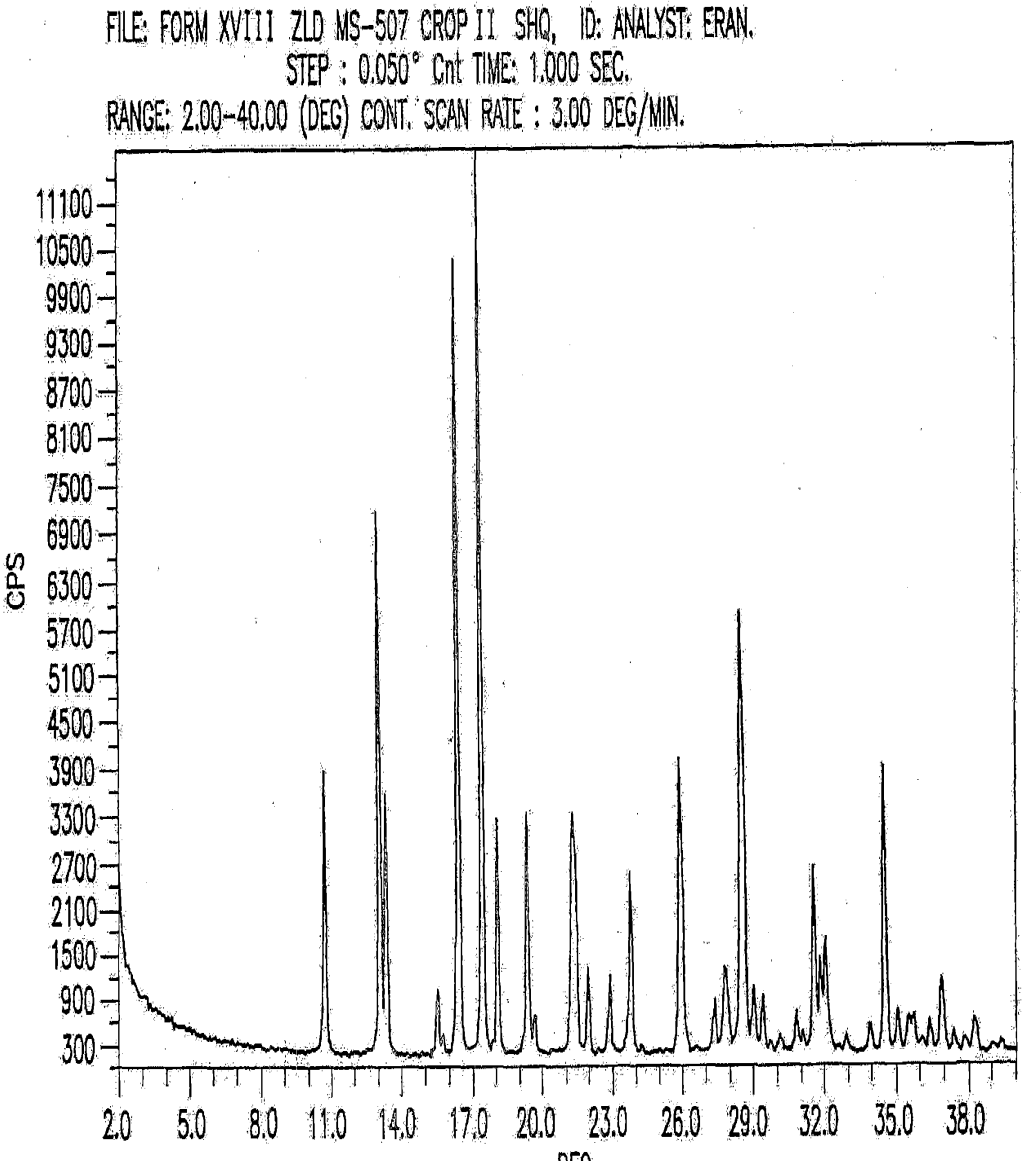


FIG.6

X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XVIII

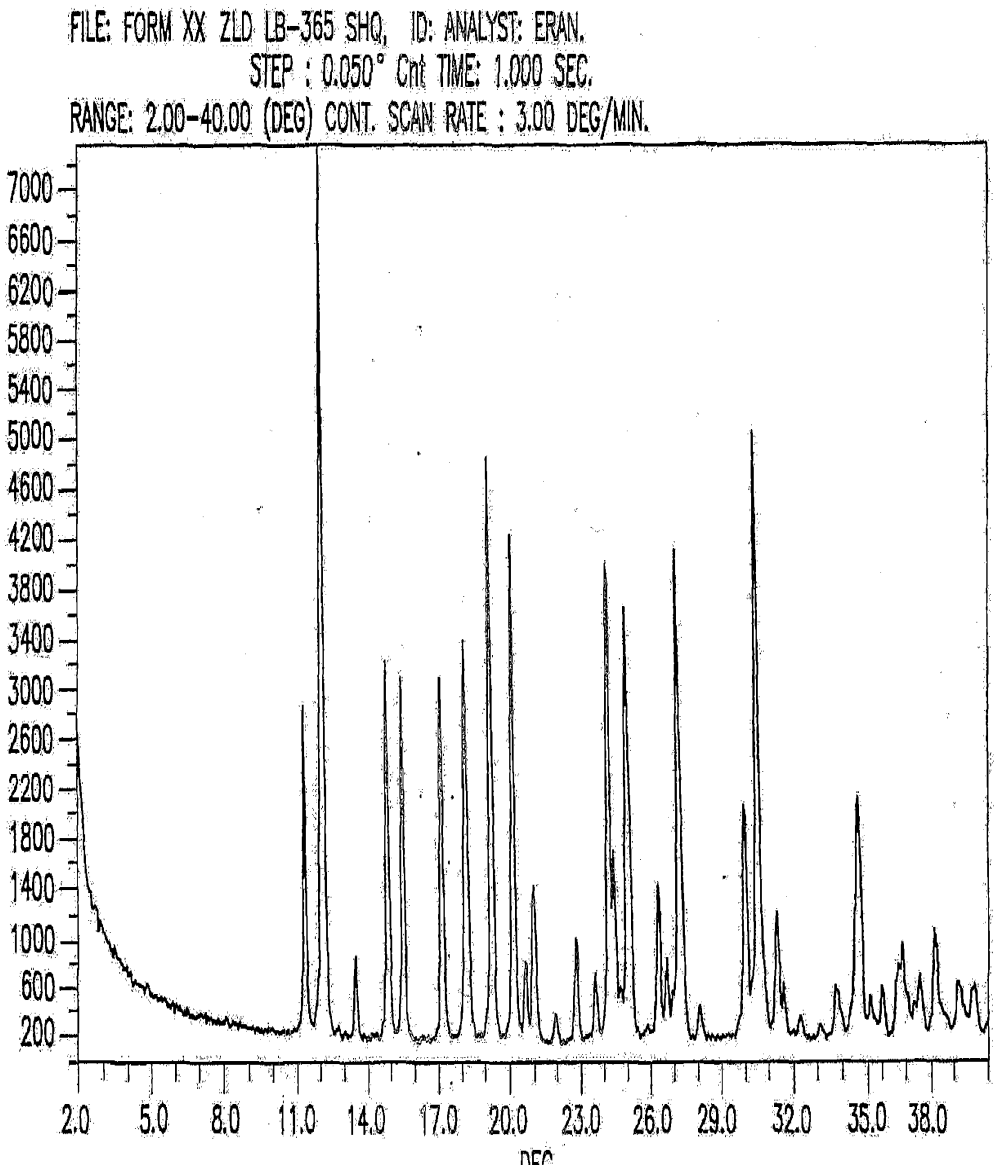


FIG.7 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XX

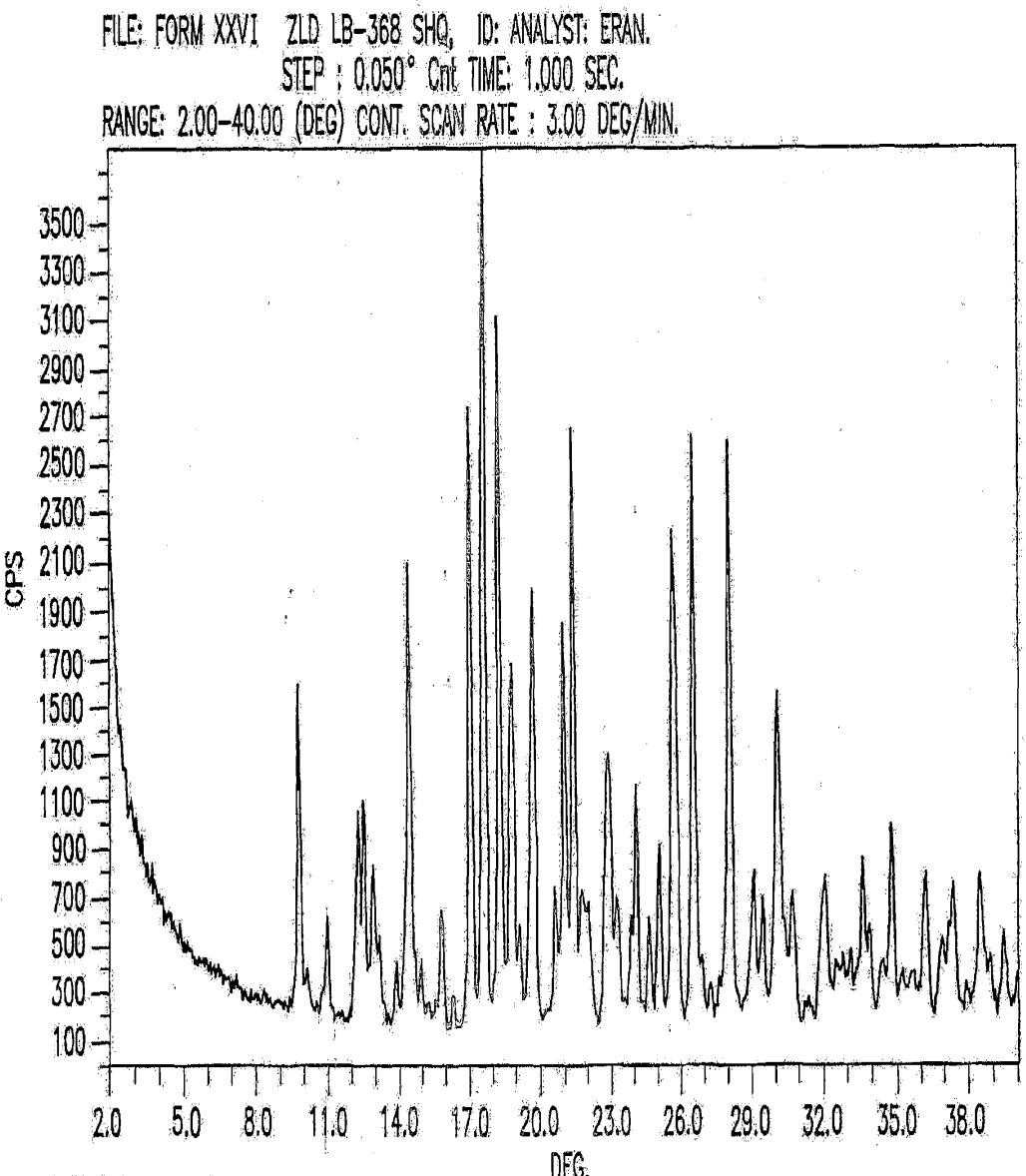


FIG.8 X-RAY POWDER DIFFRACTION OF ZOLEDRONIC ACID FORM XXVI

SUBSTITUTE SHEET (RULE 26)

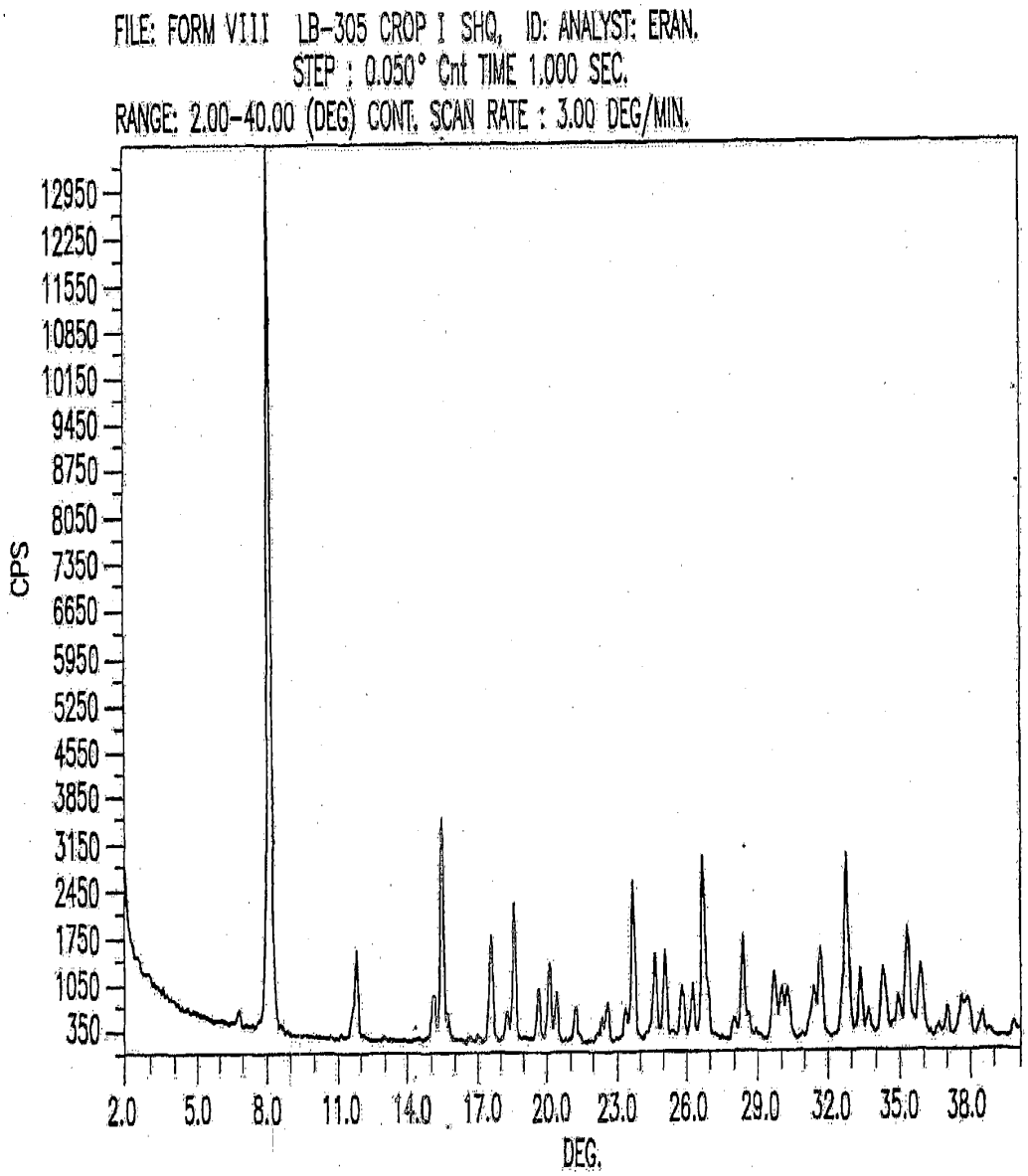


FIG.9 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM VIII

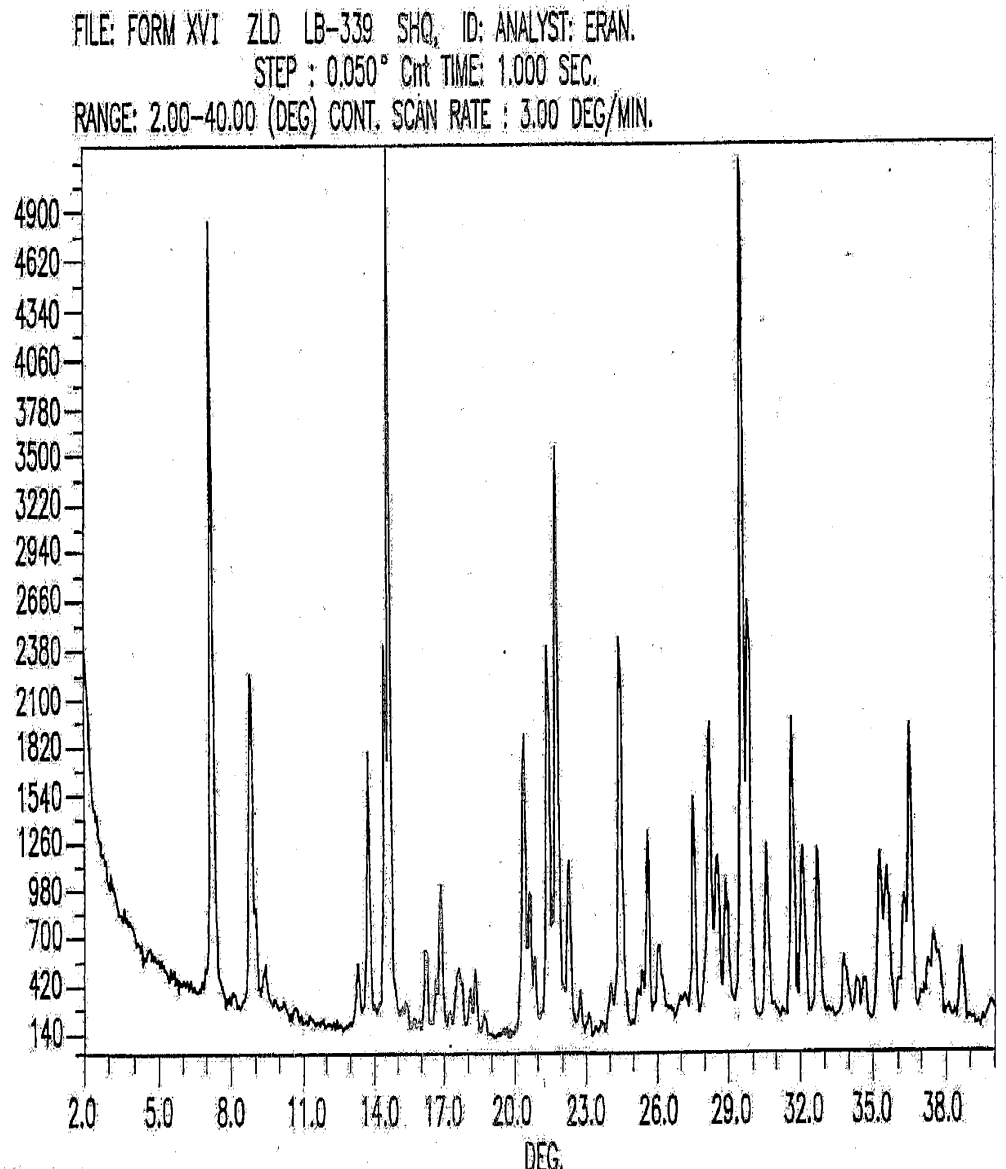


FIG.10 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM XVI

SUBSTITUTE SHEET (RULE 26)

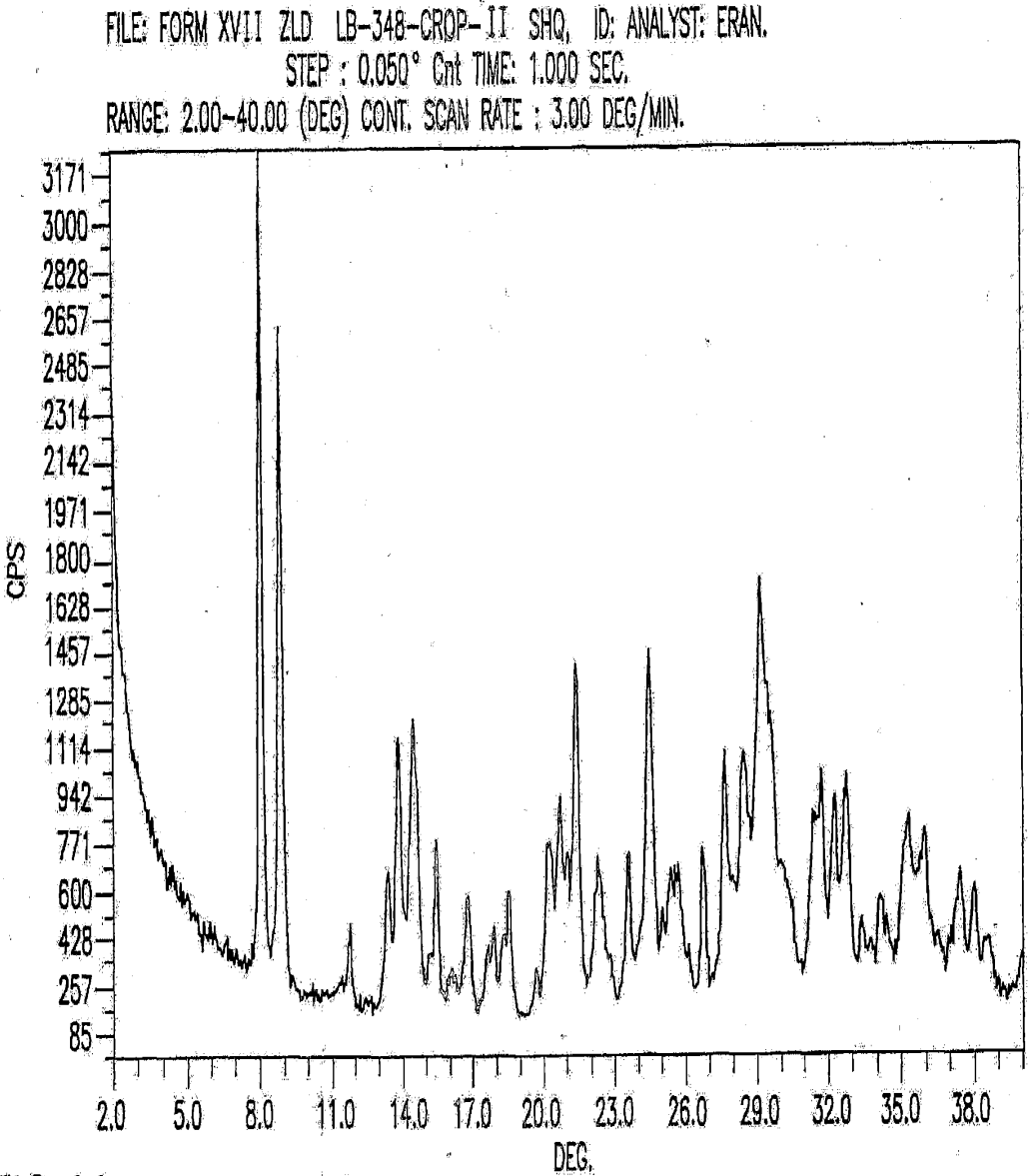


FIG.11 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE MONOSODIUM FORM XVII

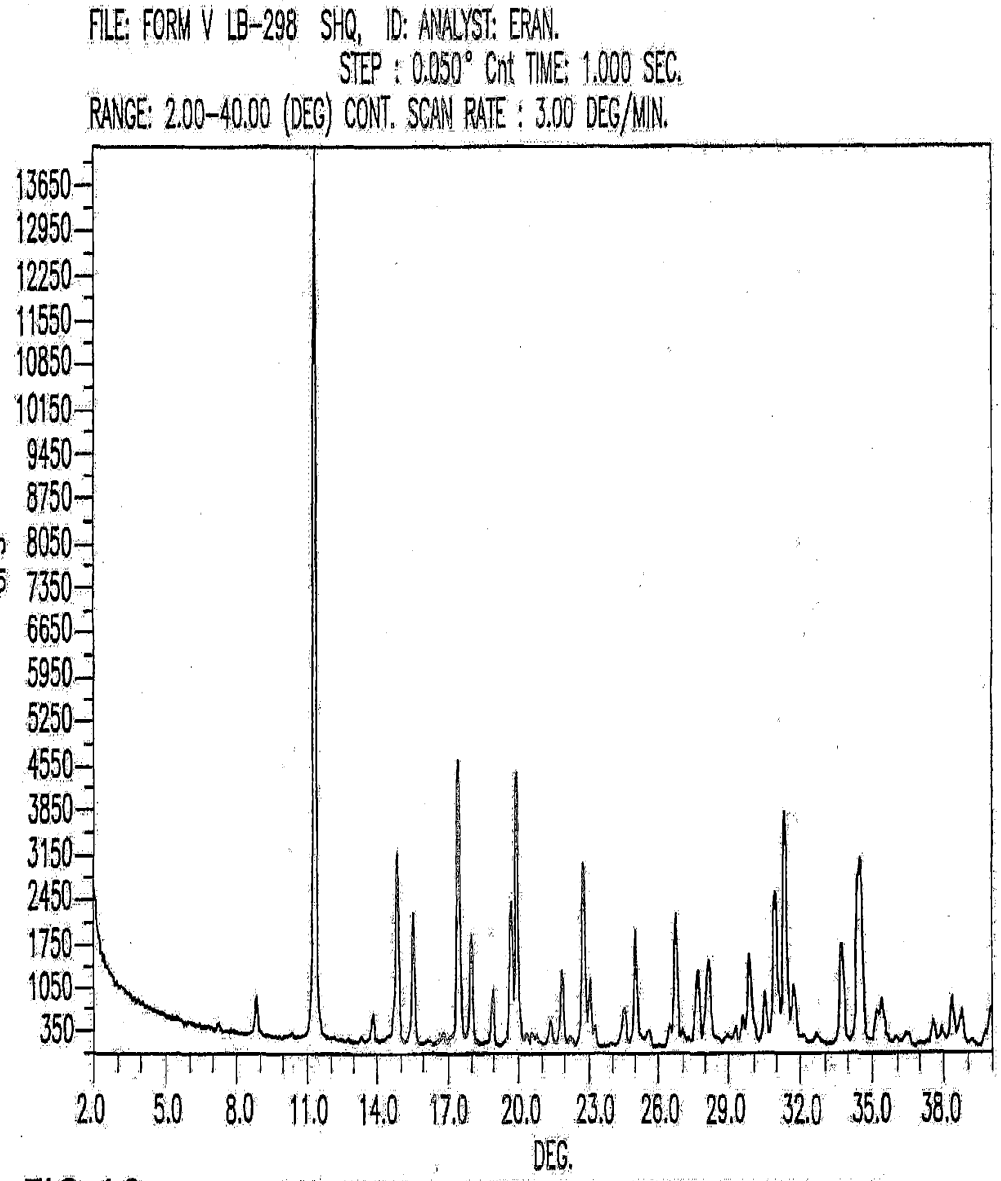


FIG.12 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM V

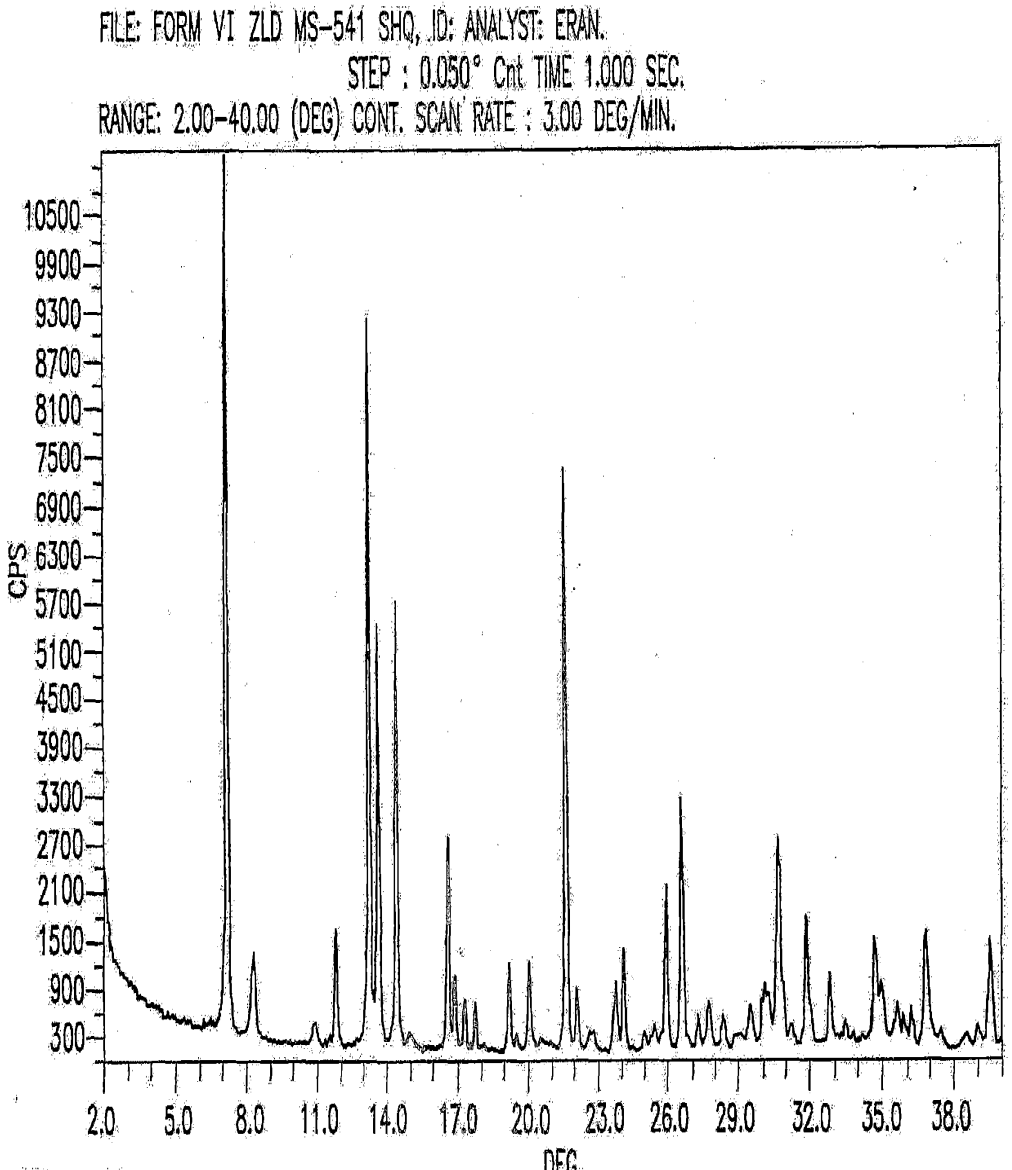


FIG.13 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM VI

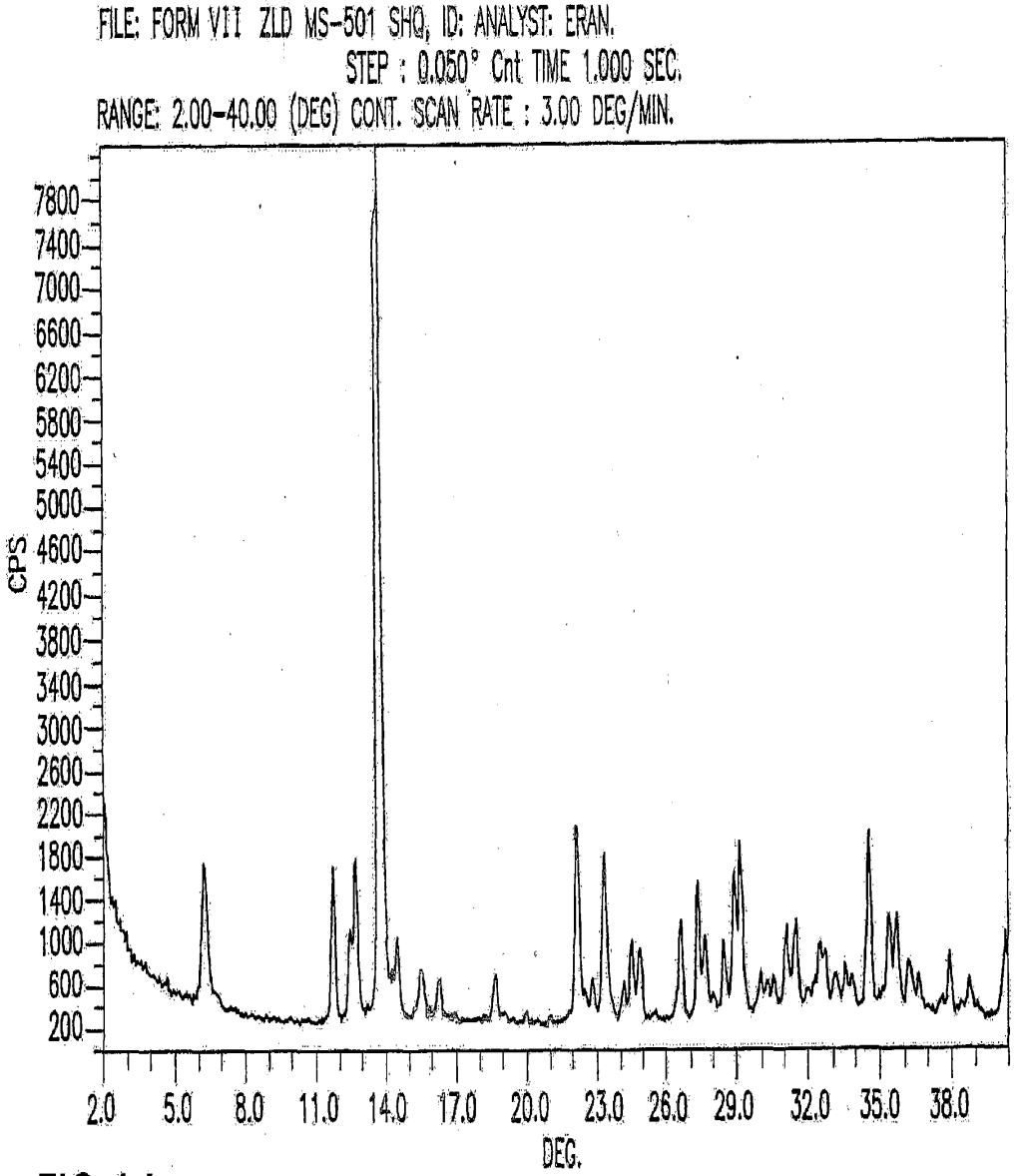


FIG.14 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM VII

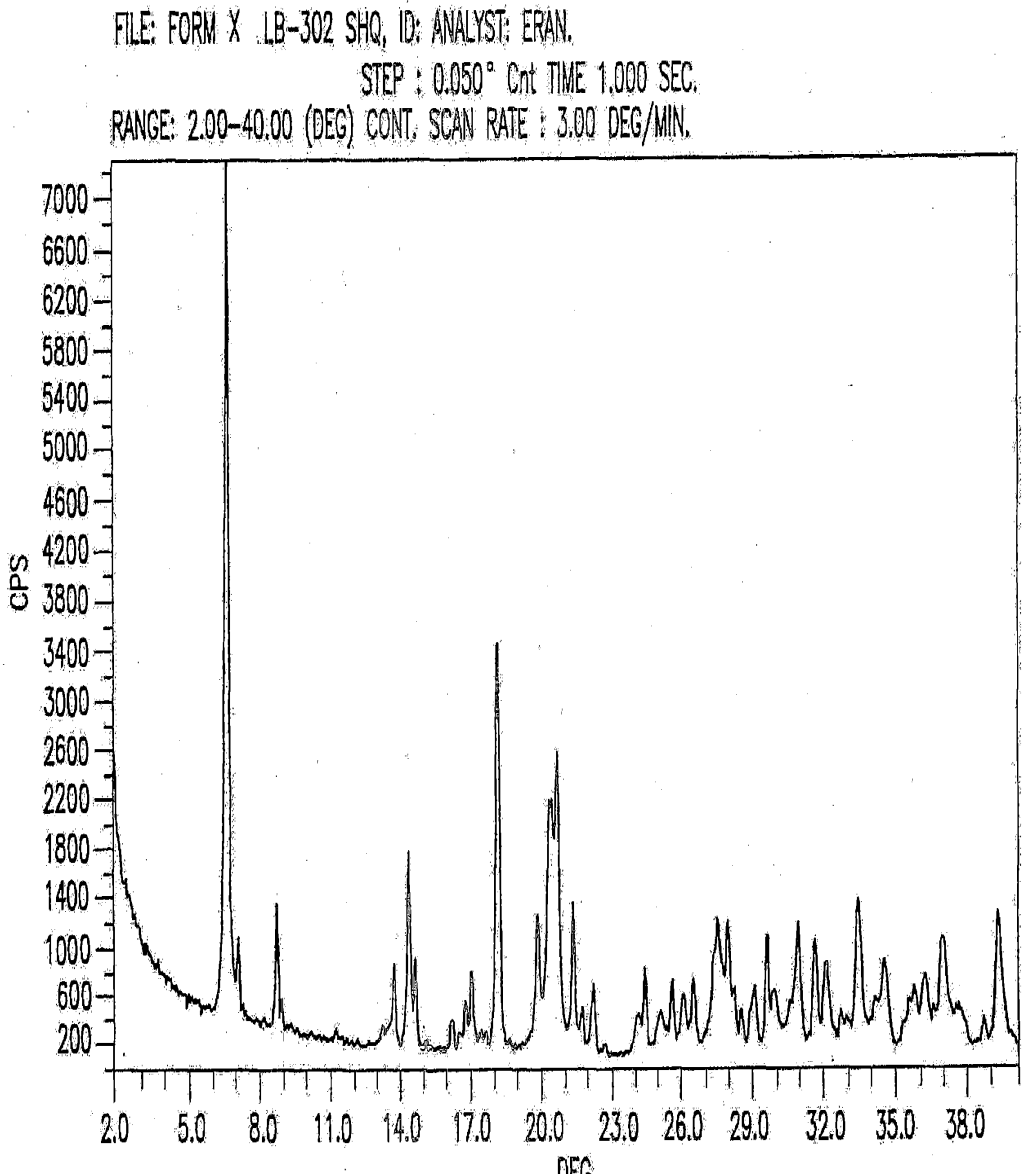


FIG.15 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM X

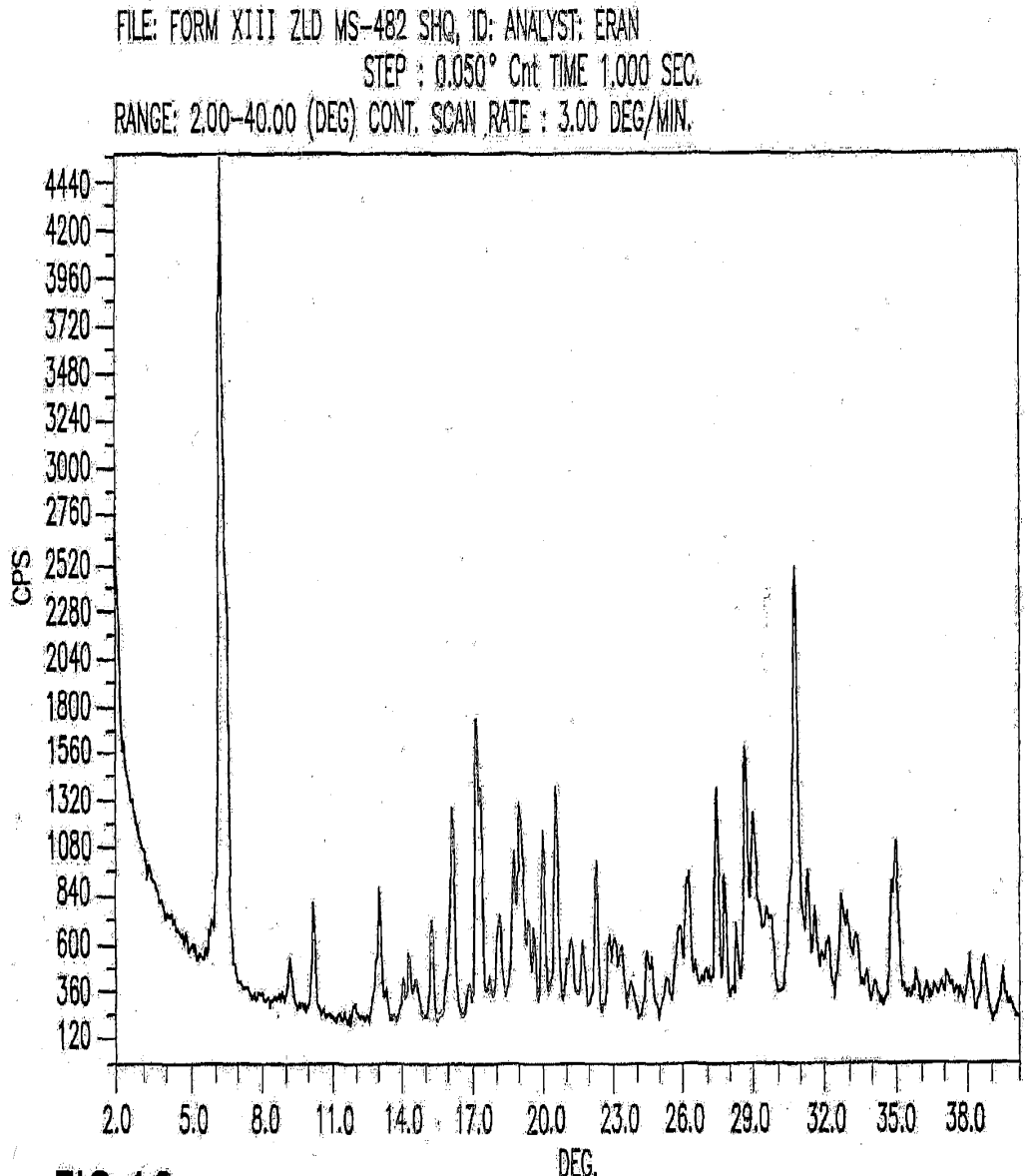


FIG.16 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIII

SUBSTITUTE SHEET (RULE 26)

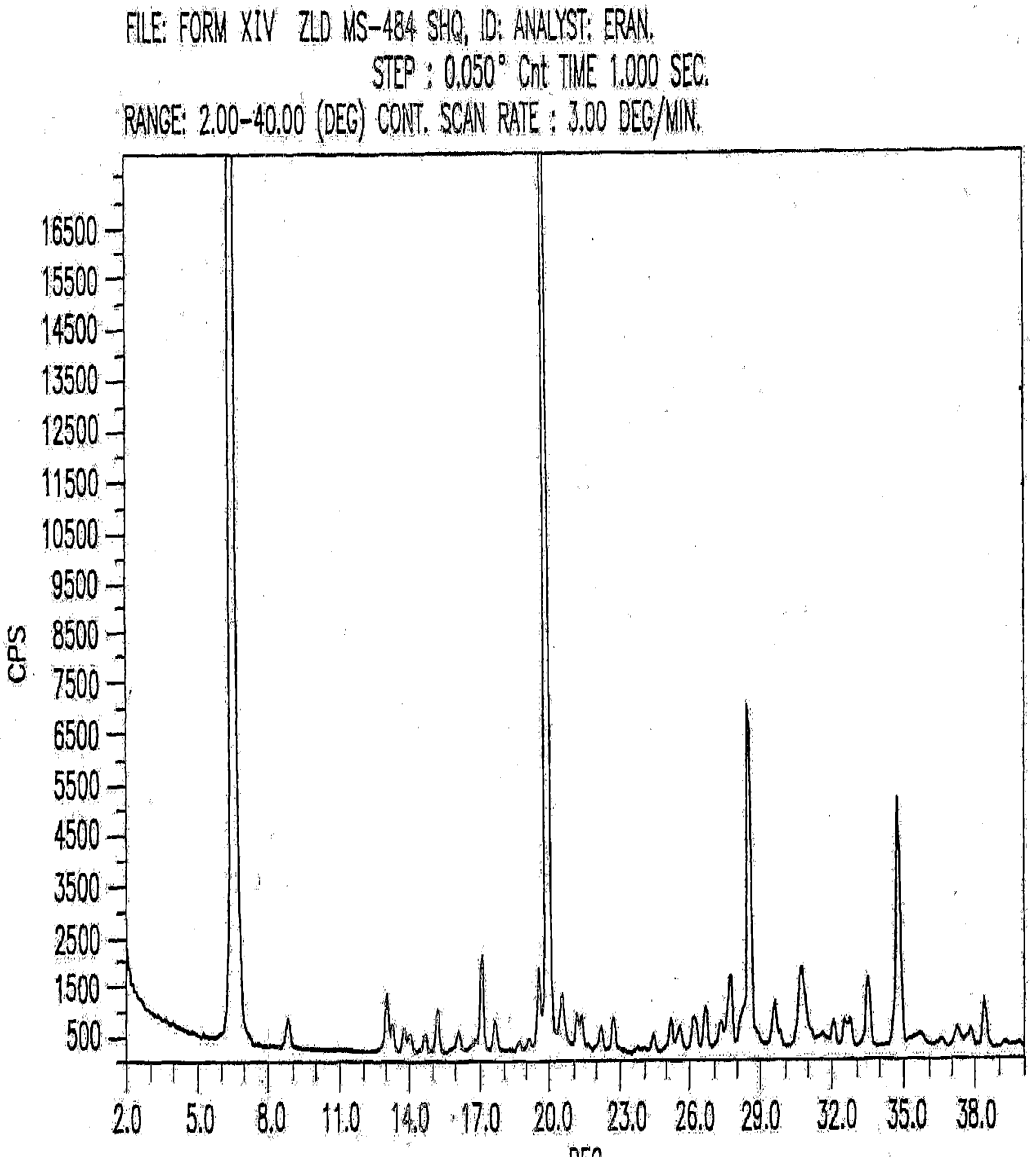


FIG.17 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIV

SUBSTITUTE SHEET (RULE 26)

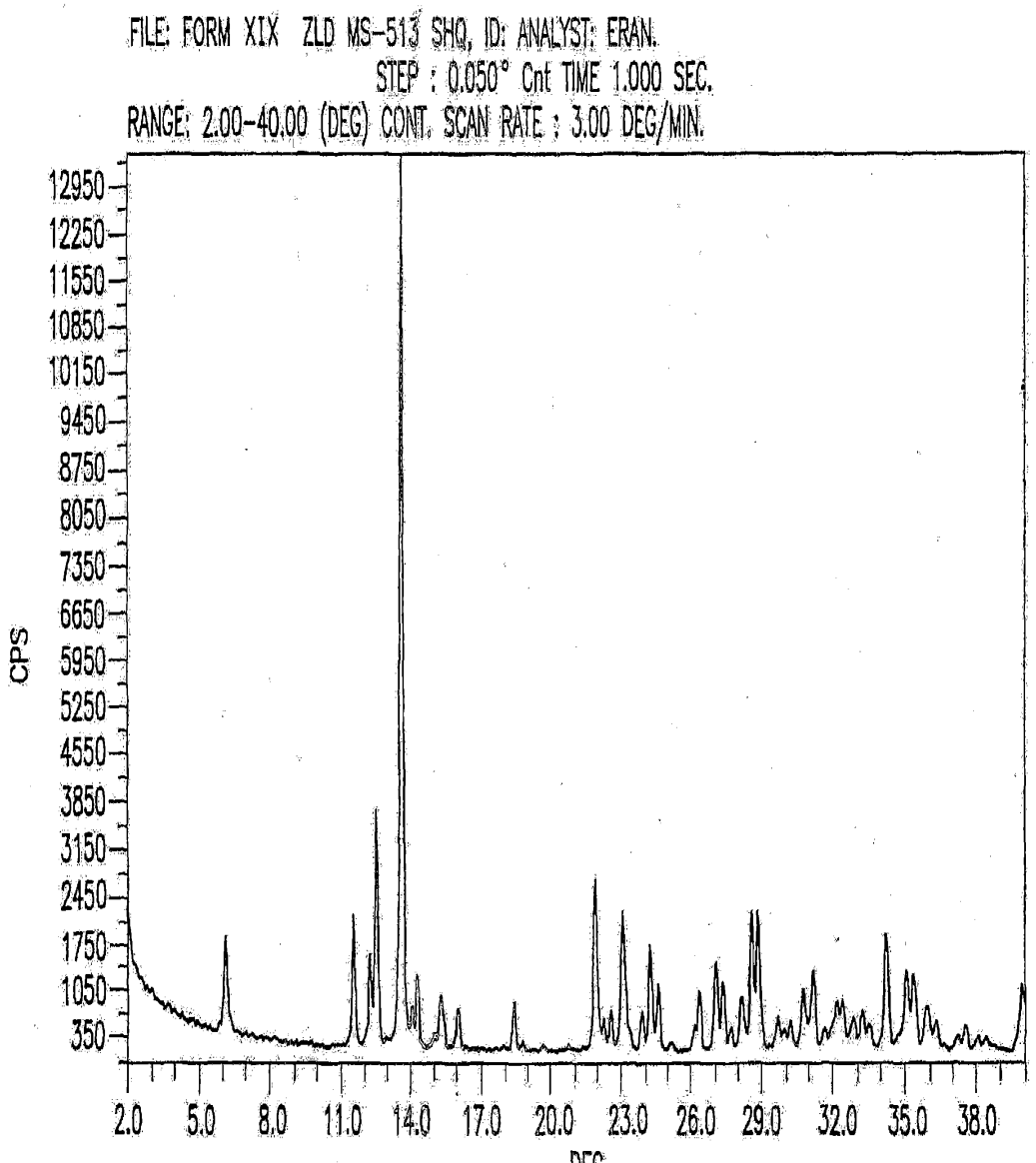


FIG.18 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XIX

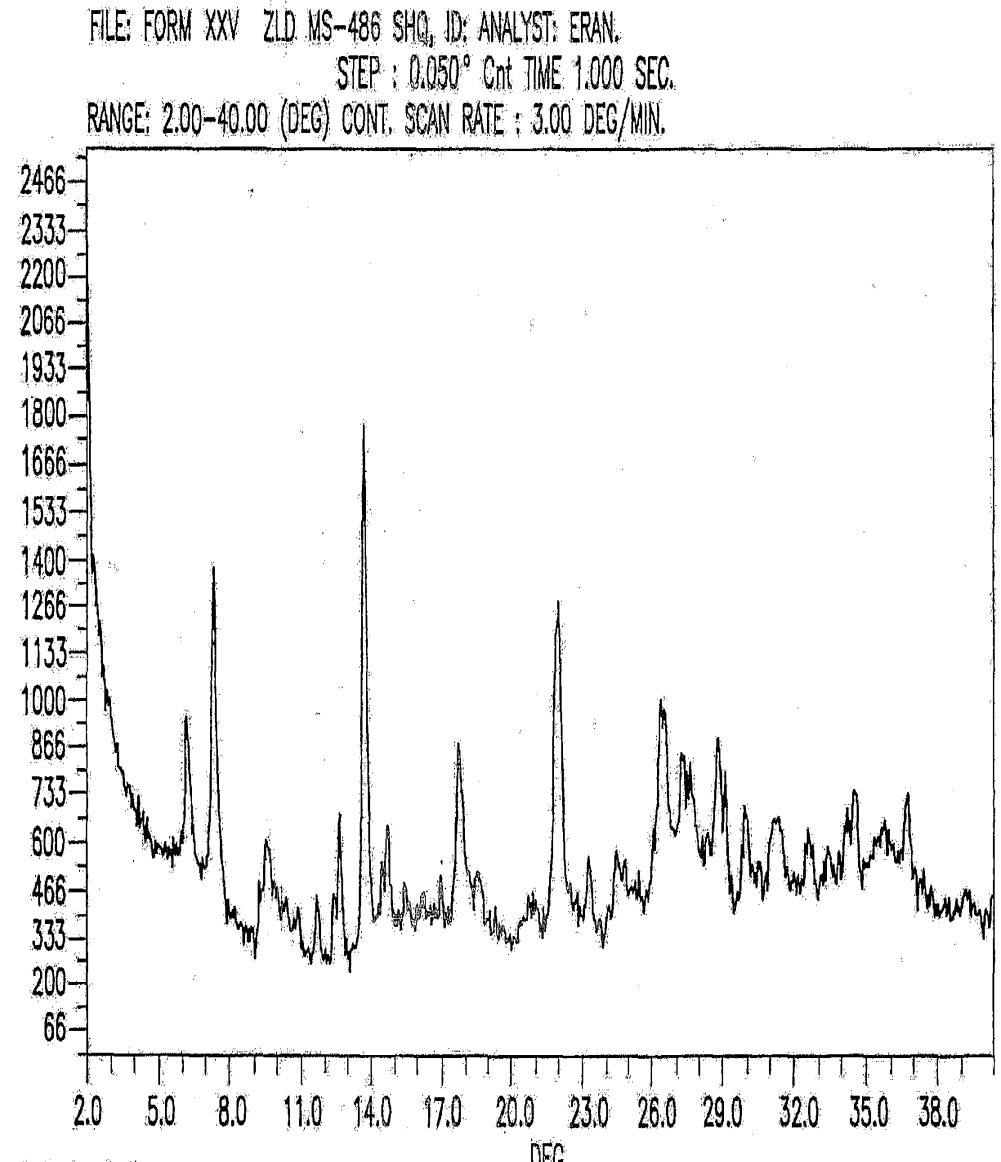


FIG.19 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XXV

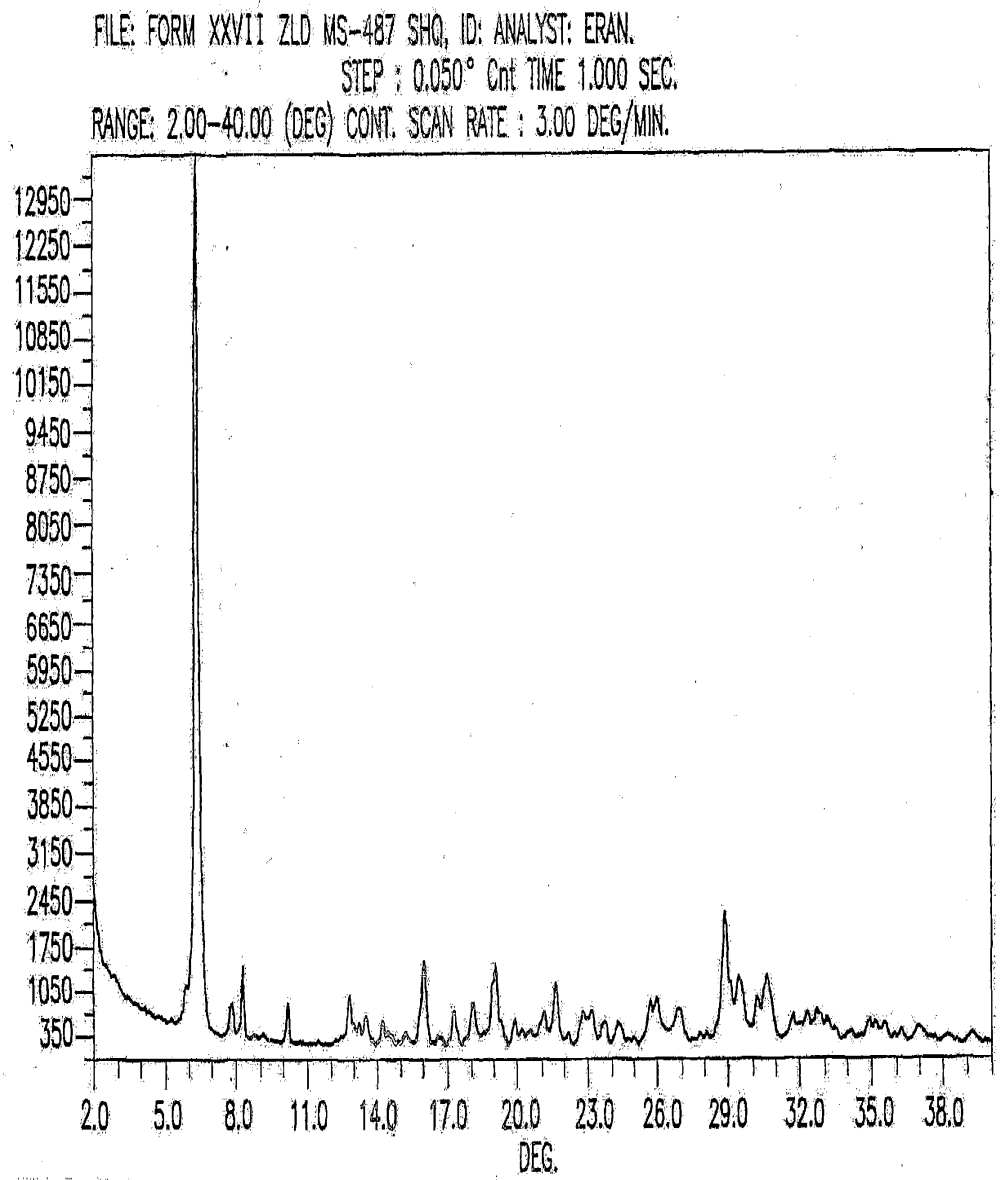


FIG.20 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XXVII

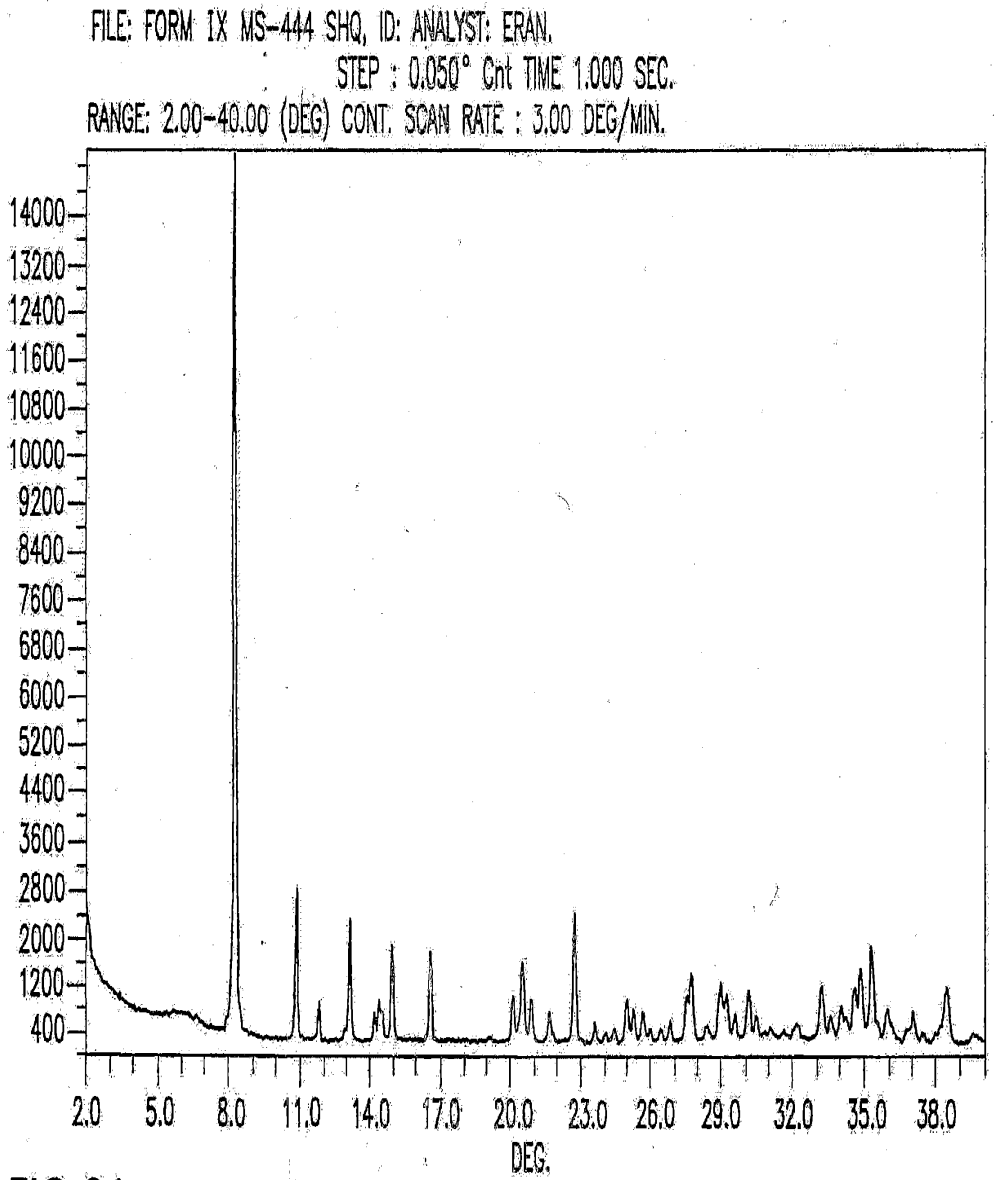


FIG.21 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM IX

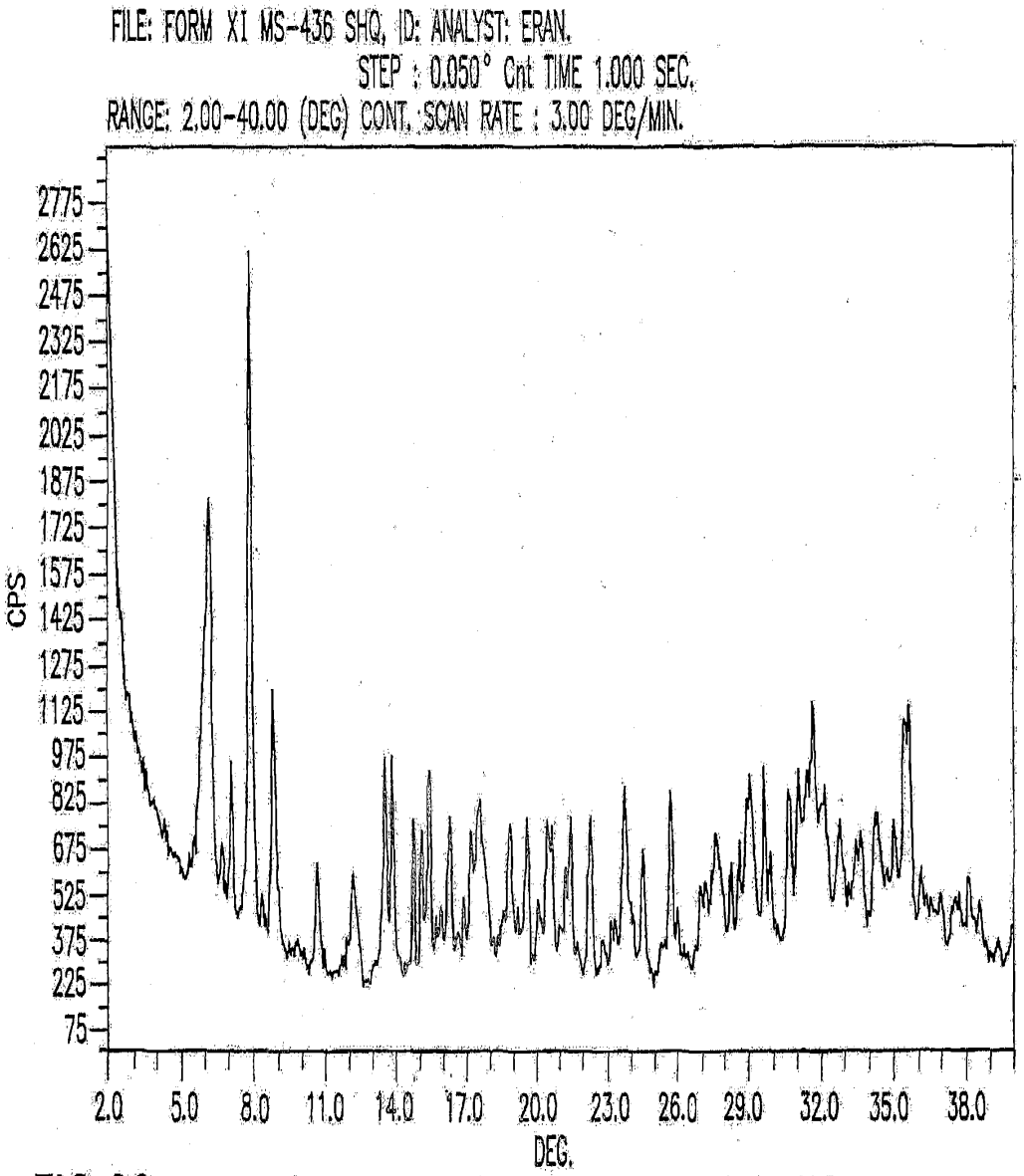


FIG.22 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE DISODIUM FORM XI

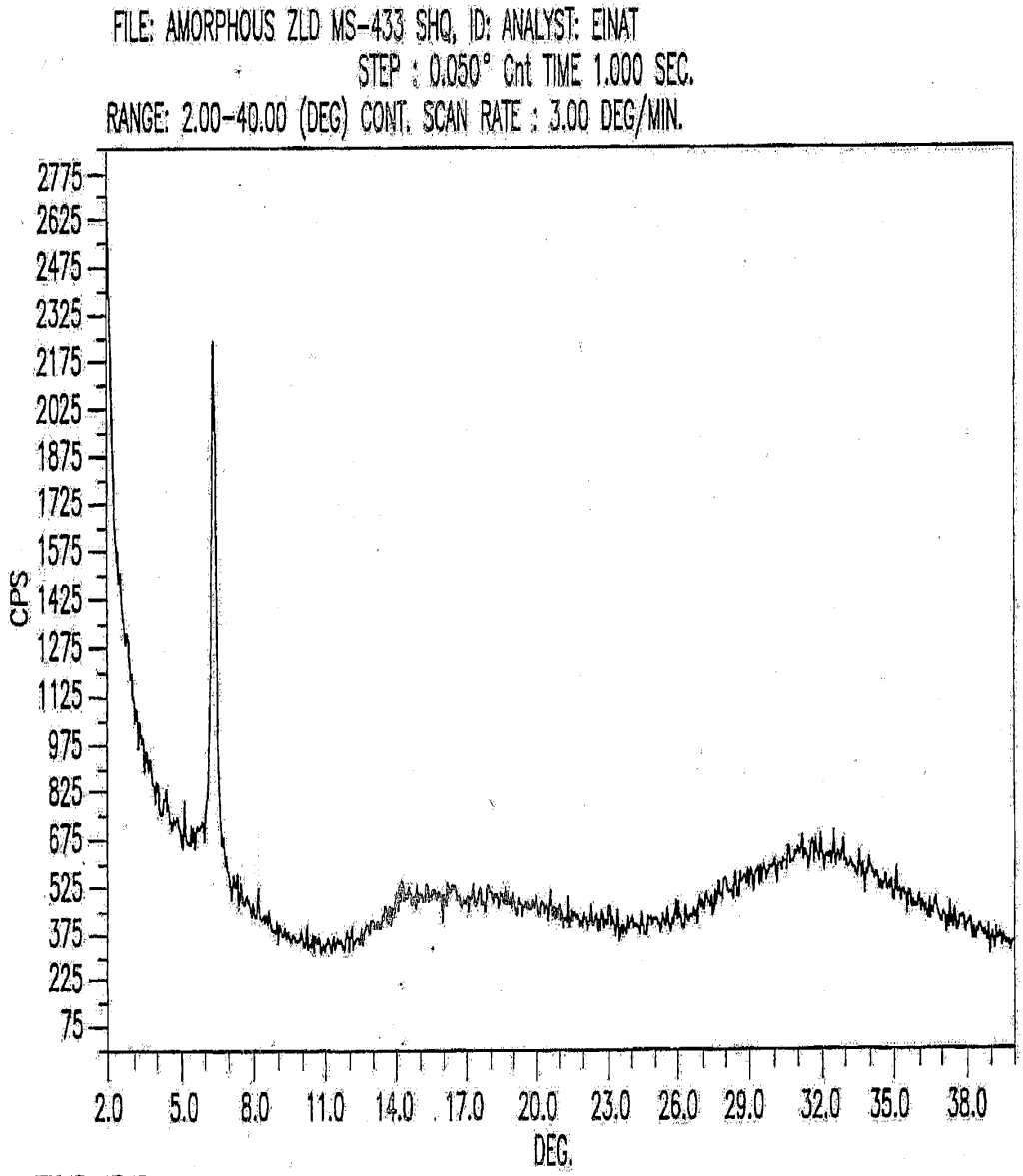
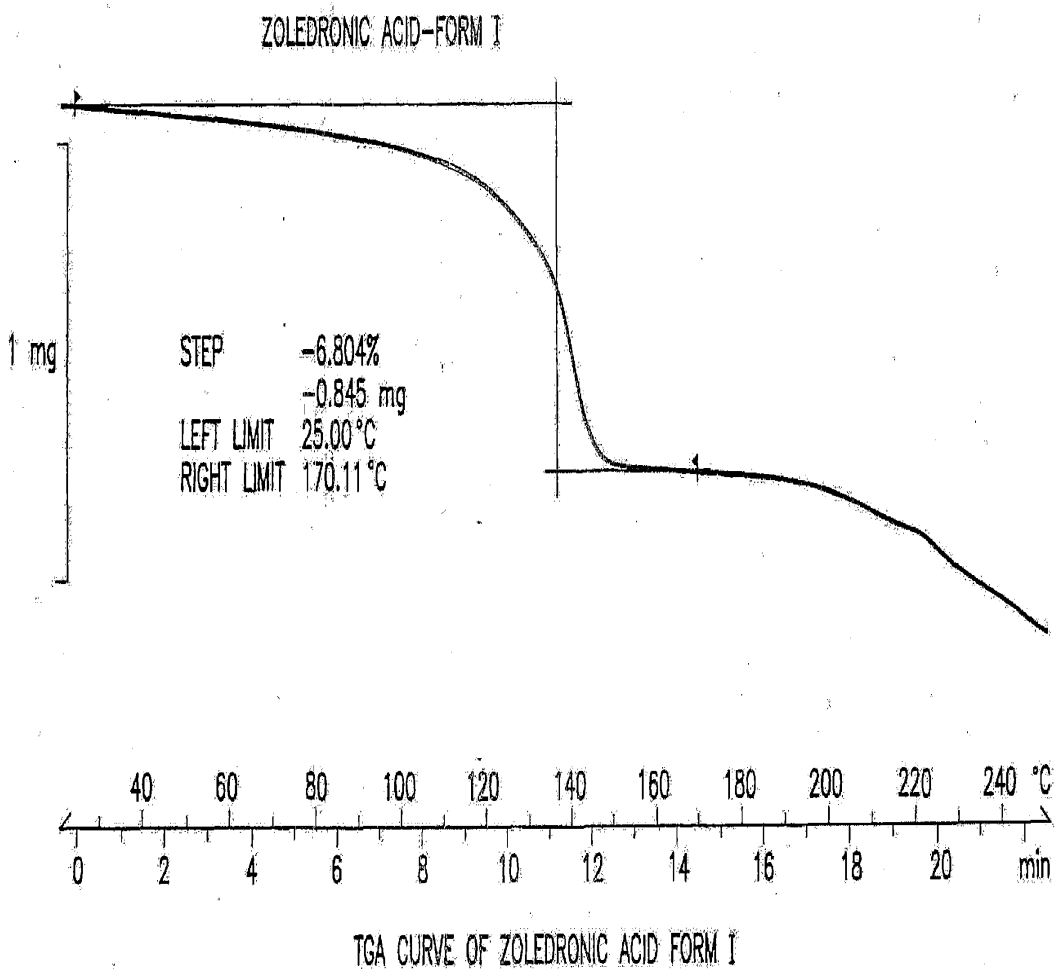


FIG.23 X-RAY POWDER DIFFRACTION OF ZOLEDRONATE SODIUM AMORPHOUS



TGA CURVE OF ZOLEDRONIC ACID FORM I

FIG.24

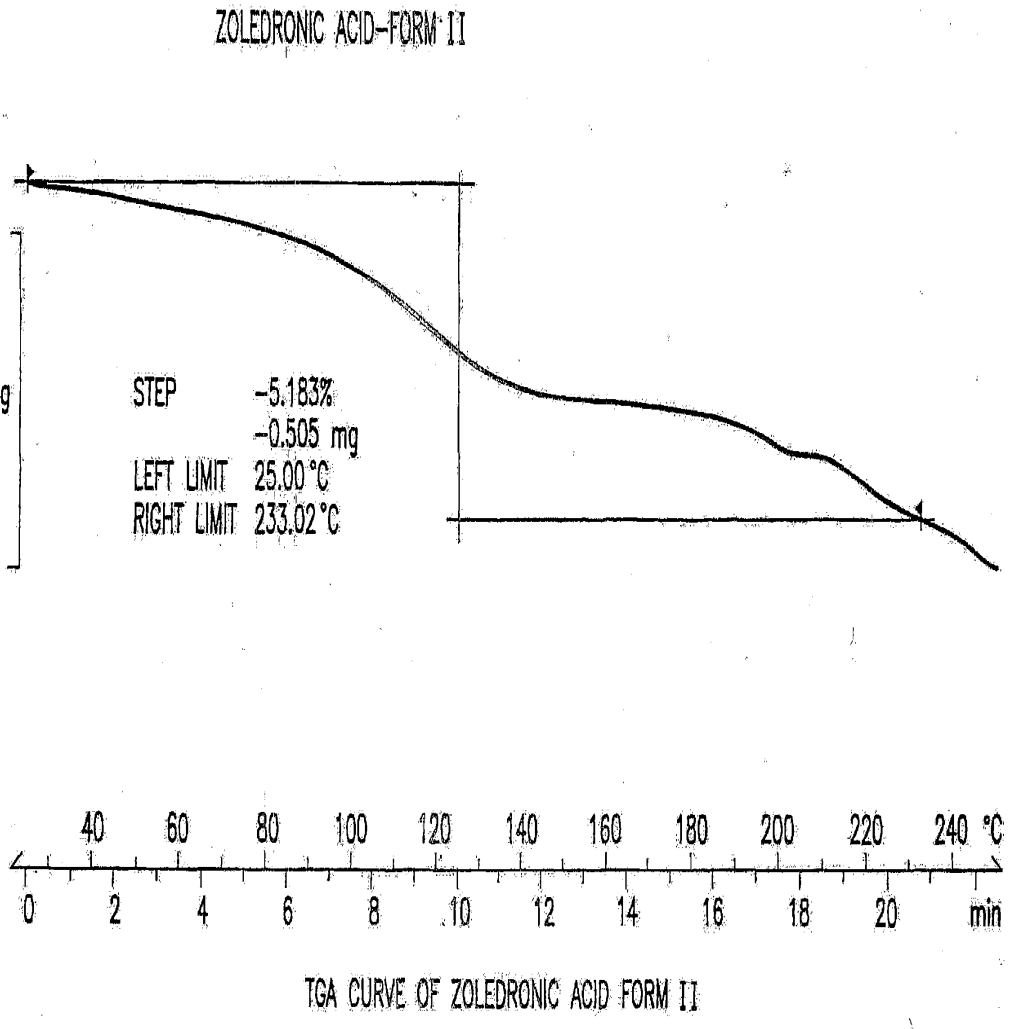


FIG.25

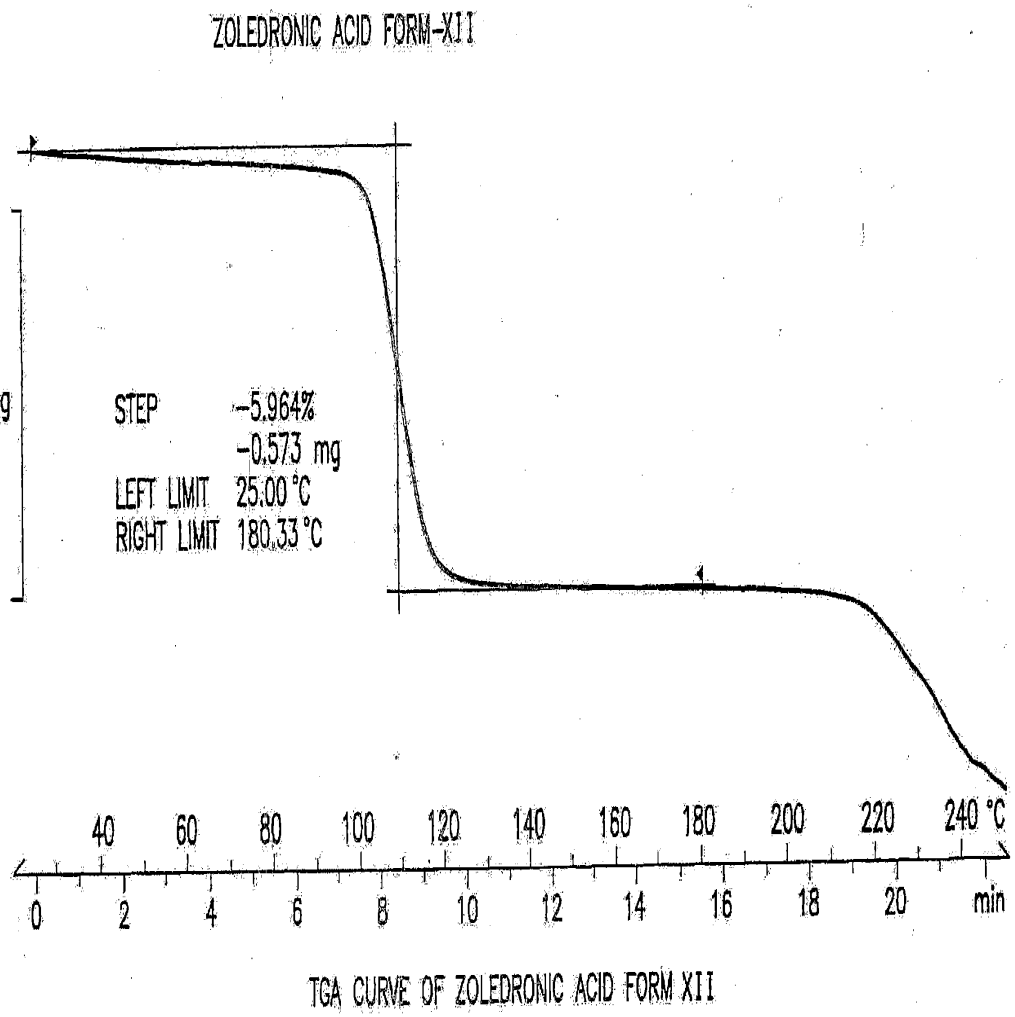
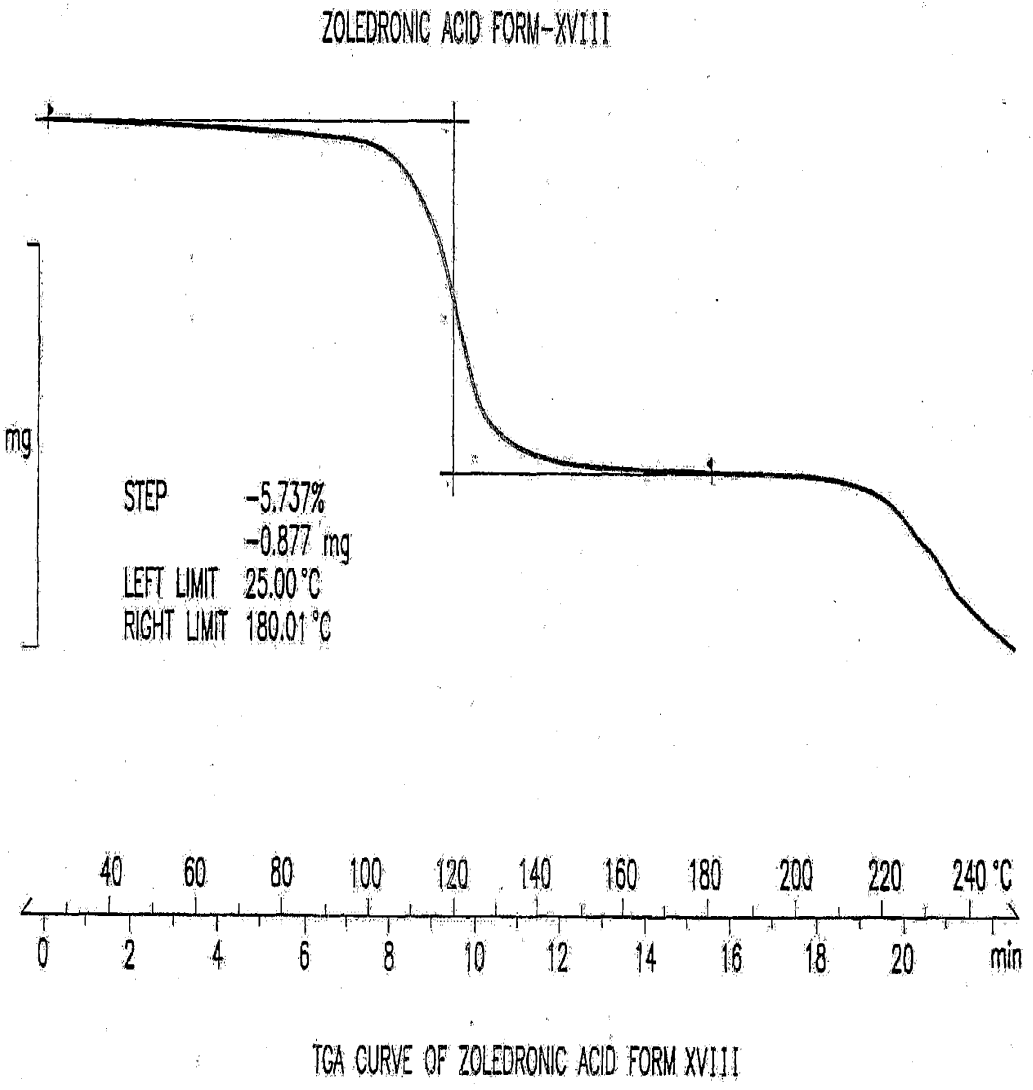


FIG.26

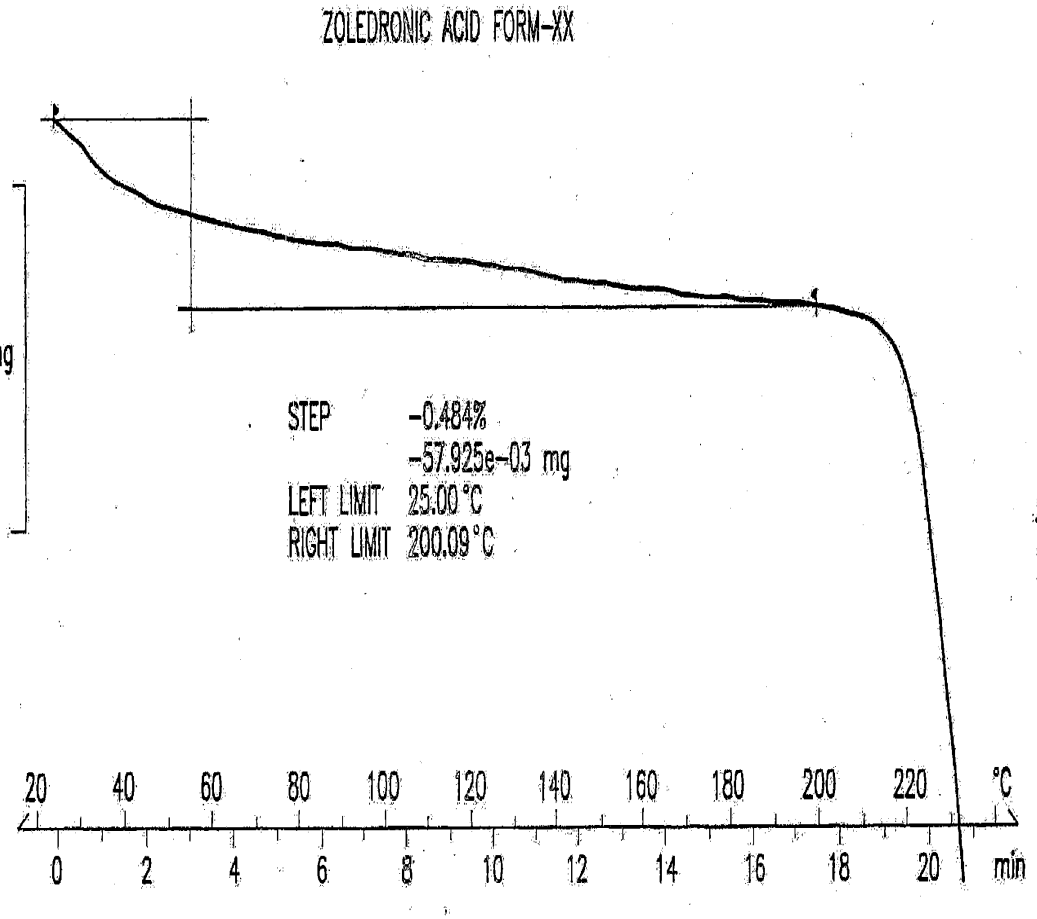
TGA CURVE OF ZOLEDRONIC ACID FORM XV

FIG.27



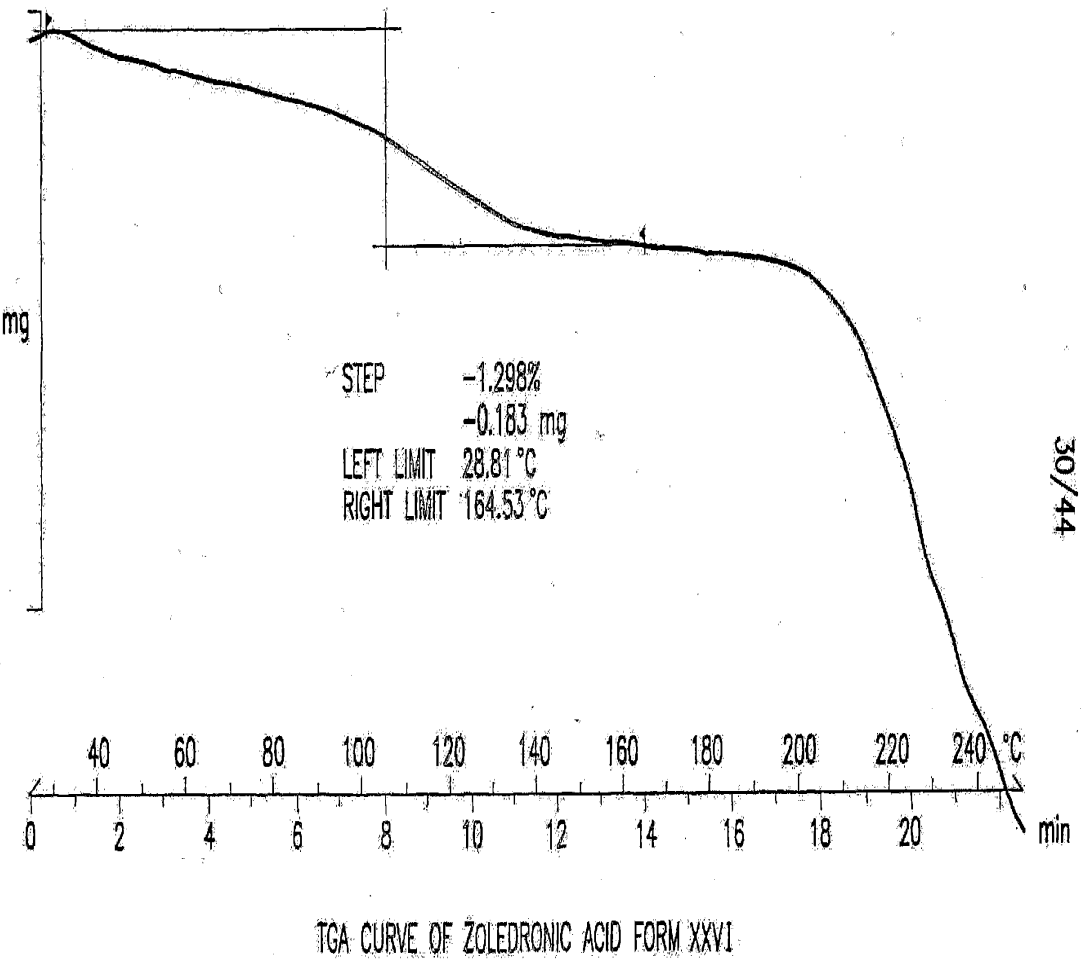
TGA CURVE OF ZOLEDRONIC ACID FORM XVIII

FIG.28



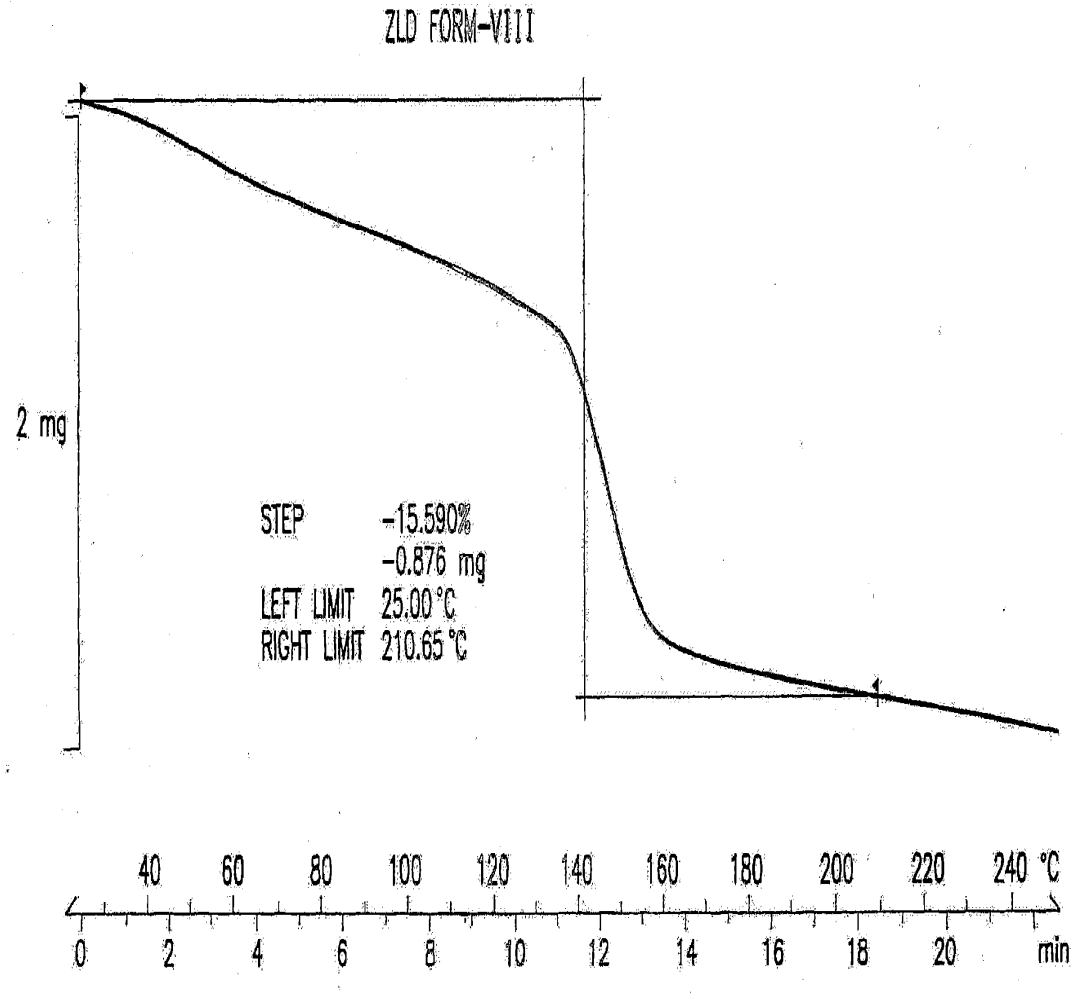
TGA CURVE OF ZOLEDRONIC ACID FORM XX

FIG.29



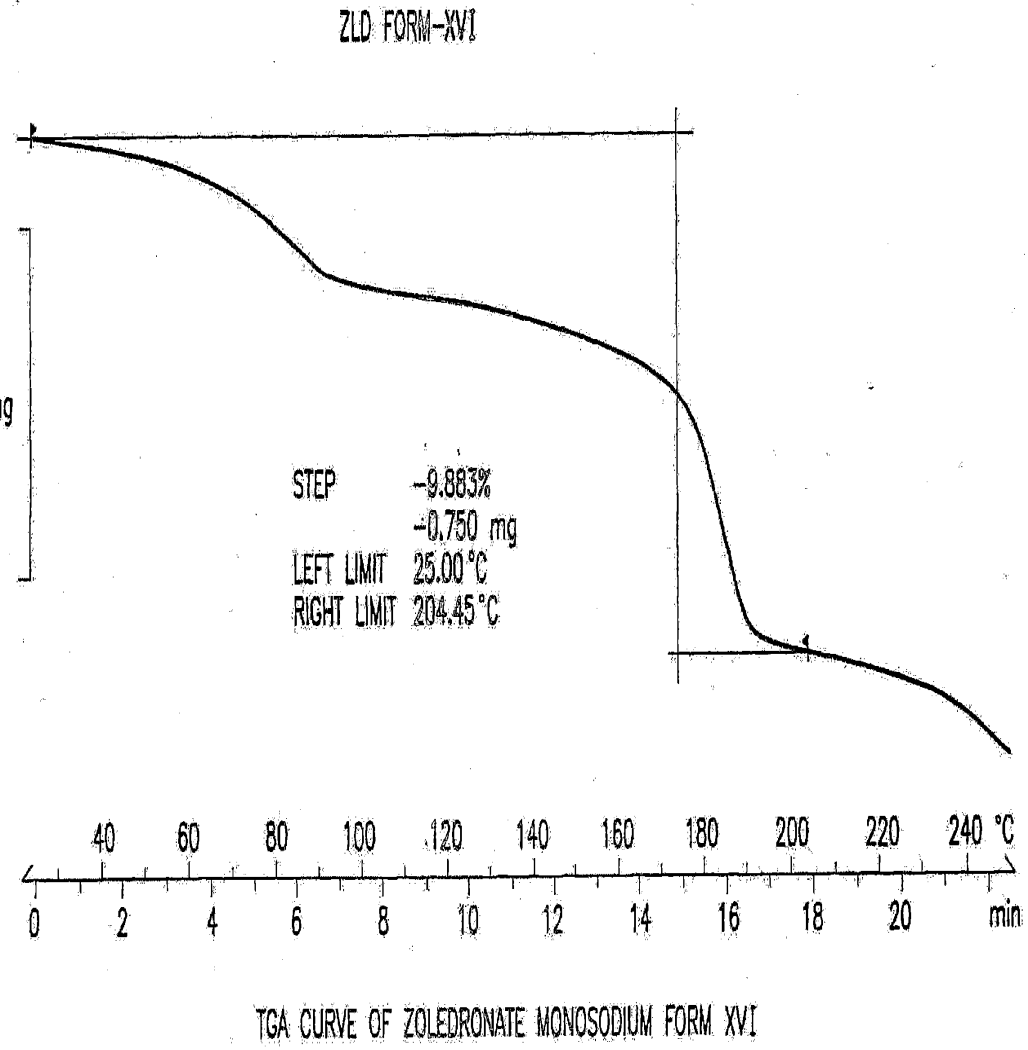
TGA CURVE OF ZOLEDRONIC ACID FORM XXVI

FIG.30



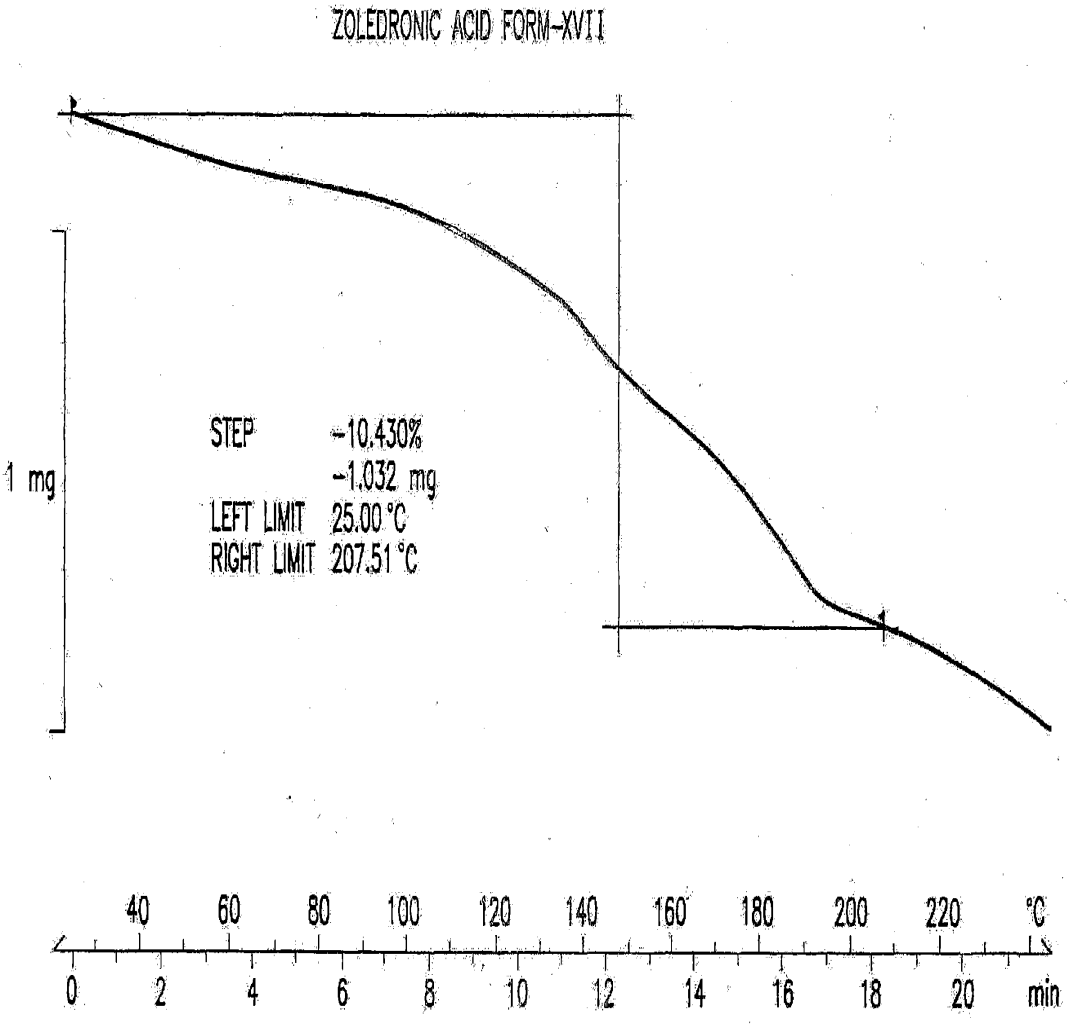
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM VIII

FIG.31



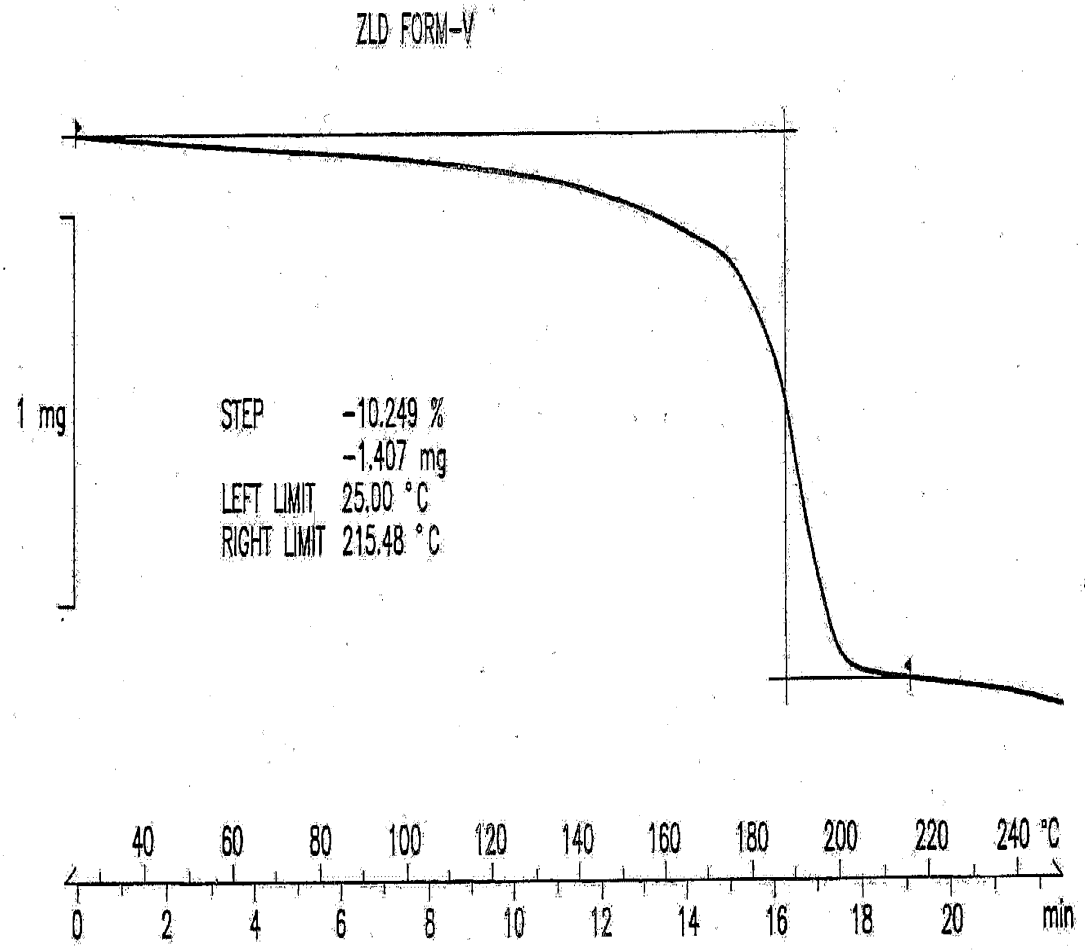
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM XVI

FIG.32



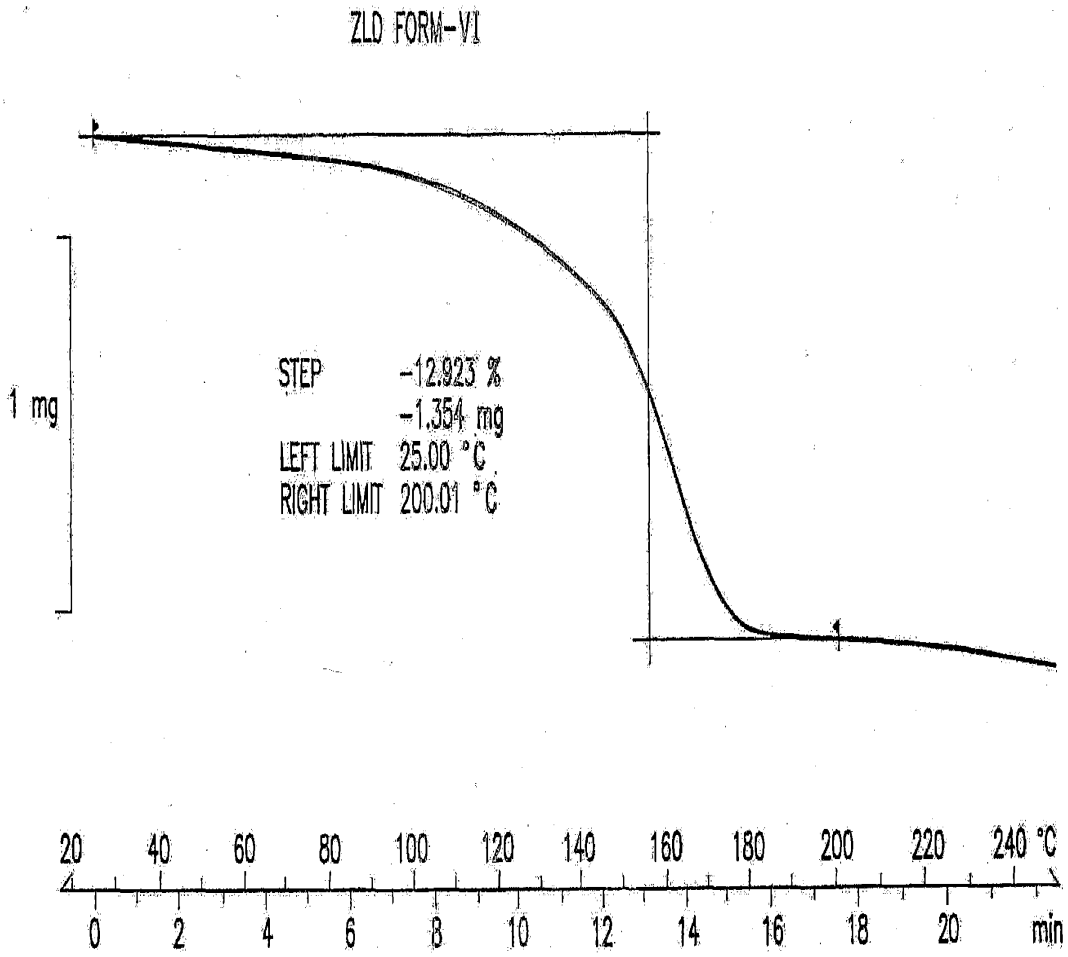
TGA CURVE OF ZOLEDRONATE MONOSODIUM FORM XVII

FIG.33



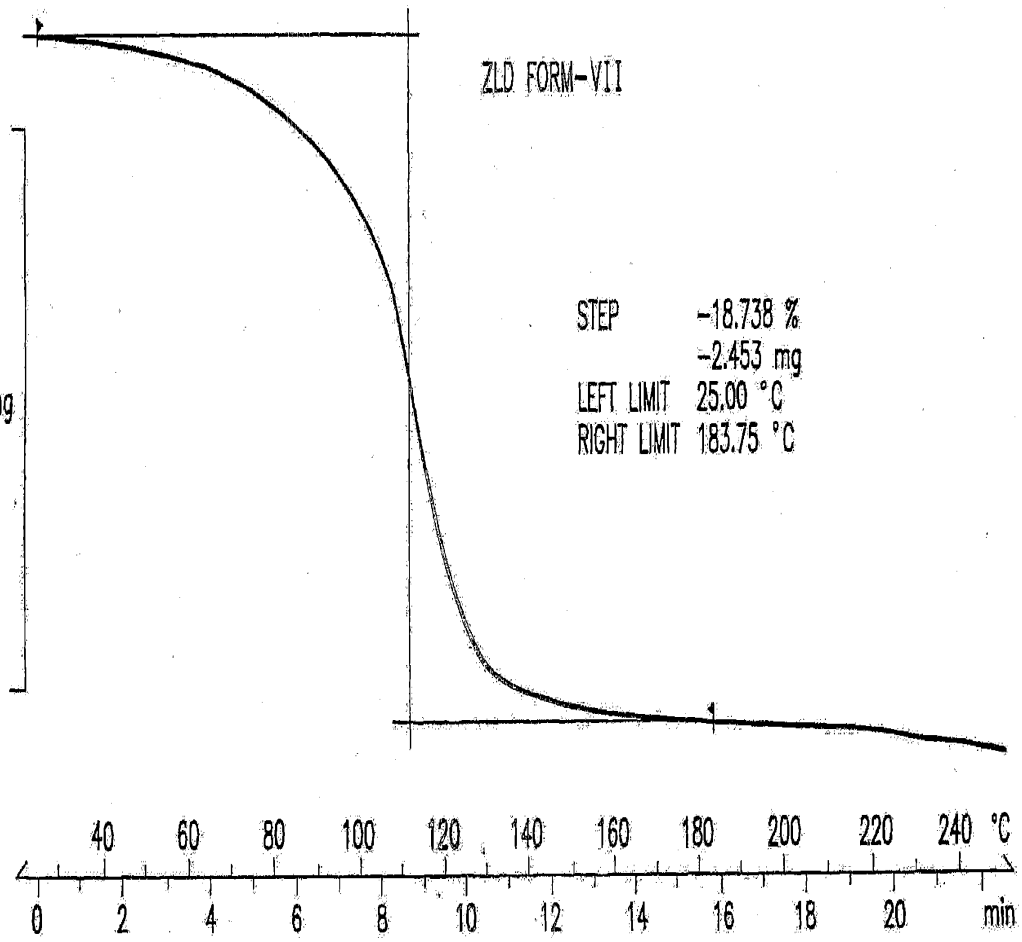
TGA CURVE OF ZOLEDRONATE DISODIUM FORM V

FIG.34



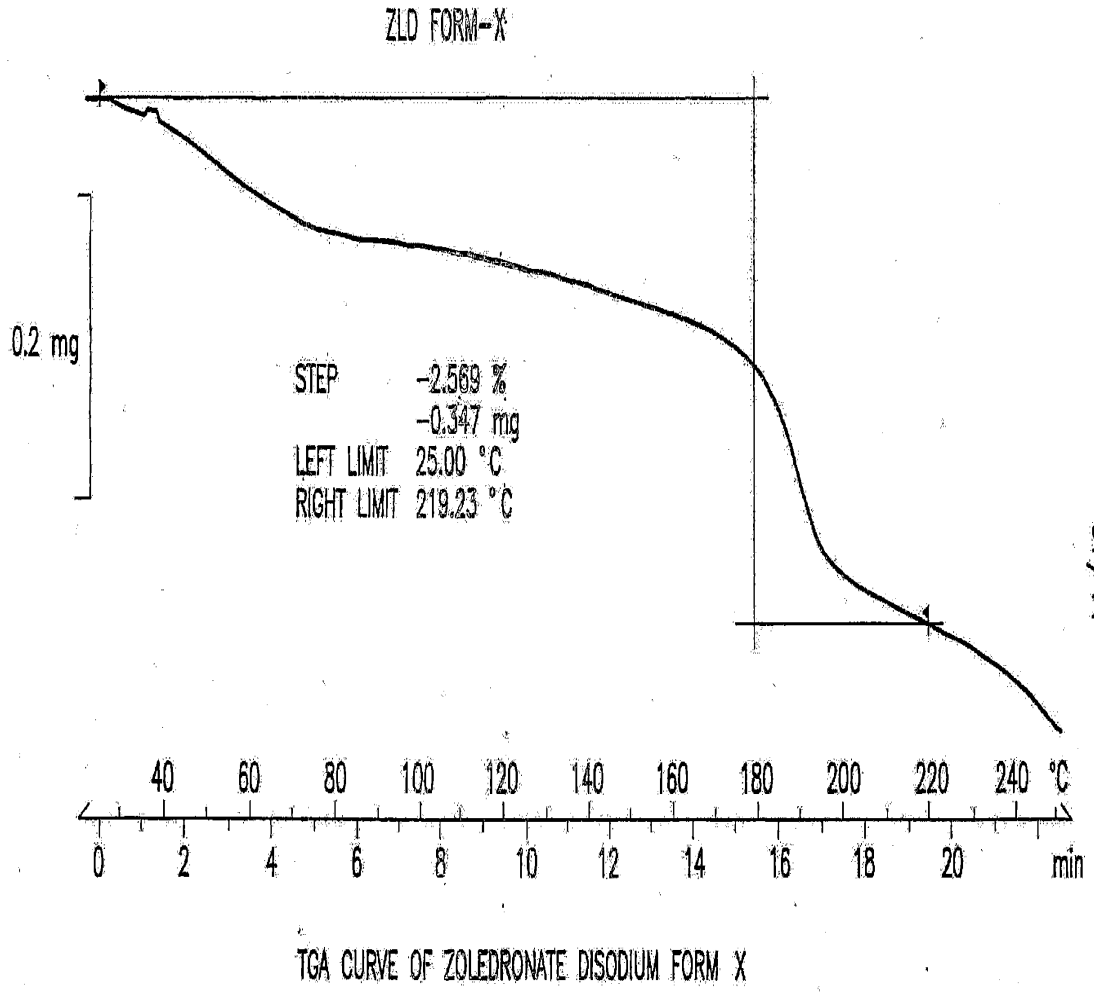
TGA CURVE OF ZOLEDRONATE DISODIUM FORM VI

FIG.35



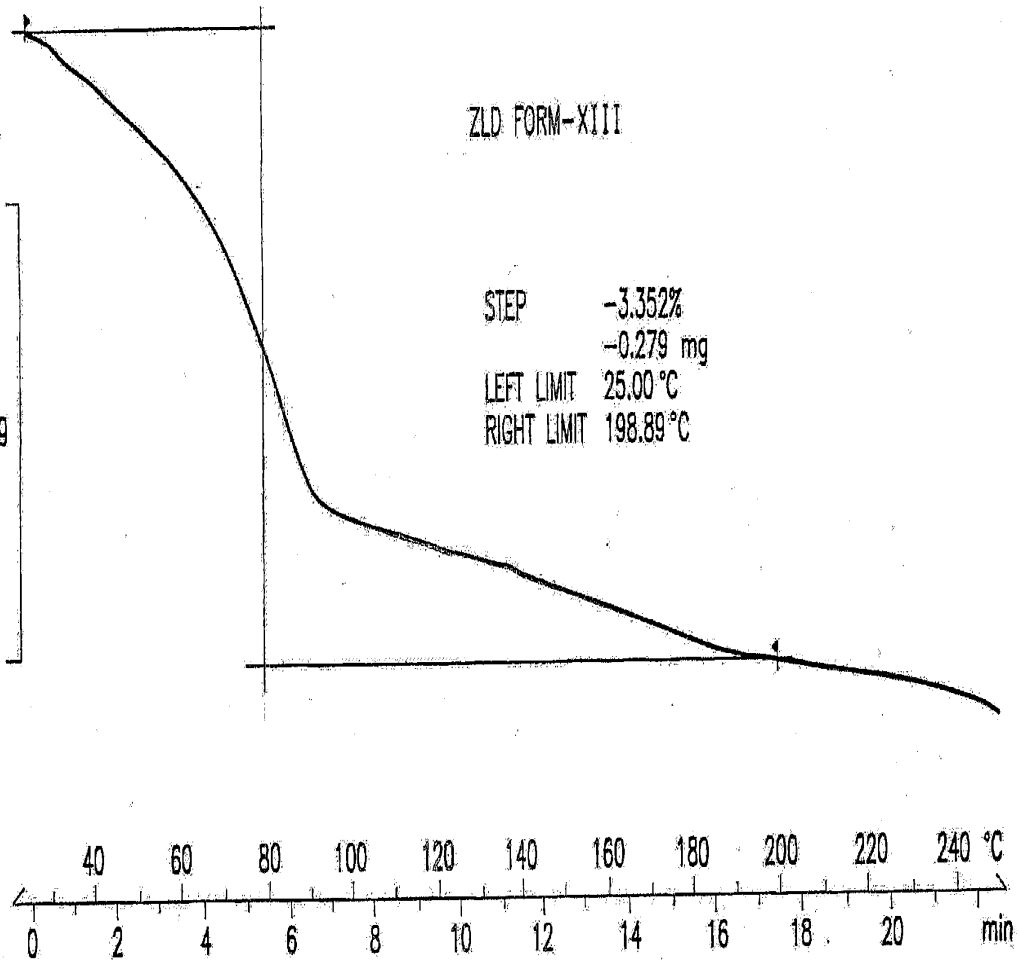
TGA CURVE OF ZOLEDRONATE DISODIUM FORM VII

FIG:36



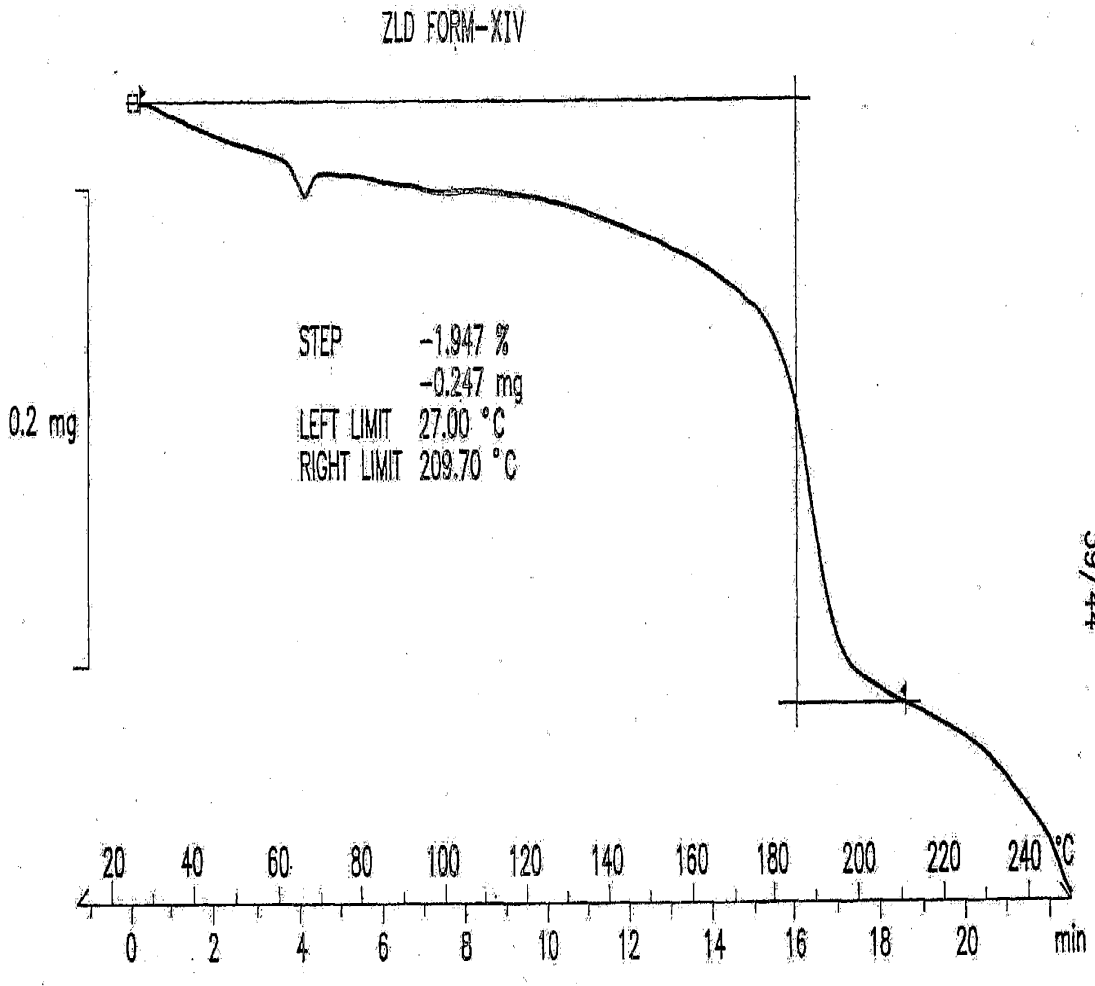
TGA CURVE OF ZOLEDRONATE DISODIUM FORM X

FIG.37



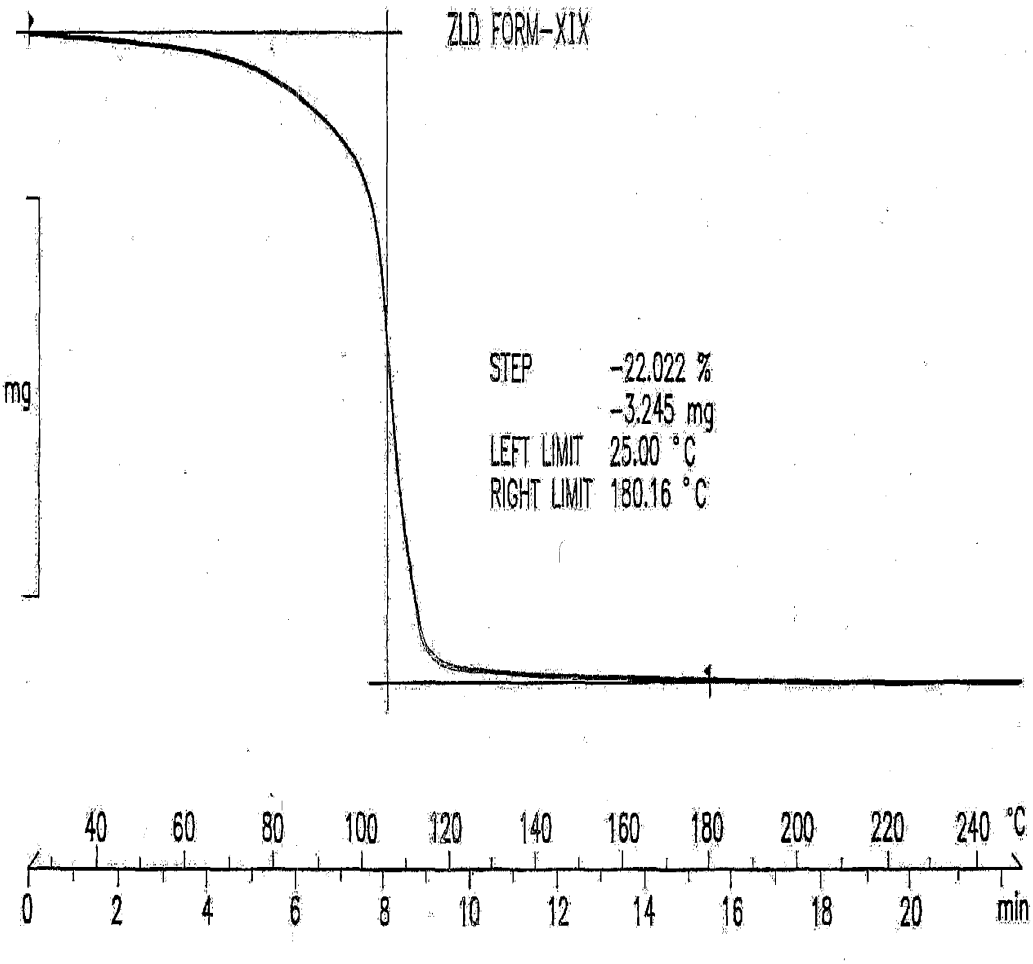
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIII

FIG.38



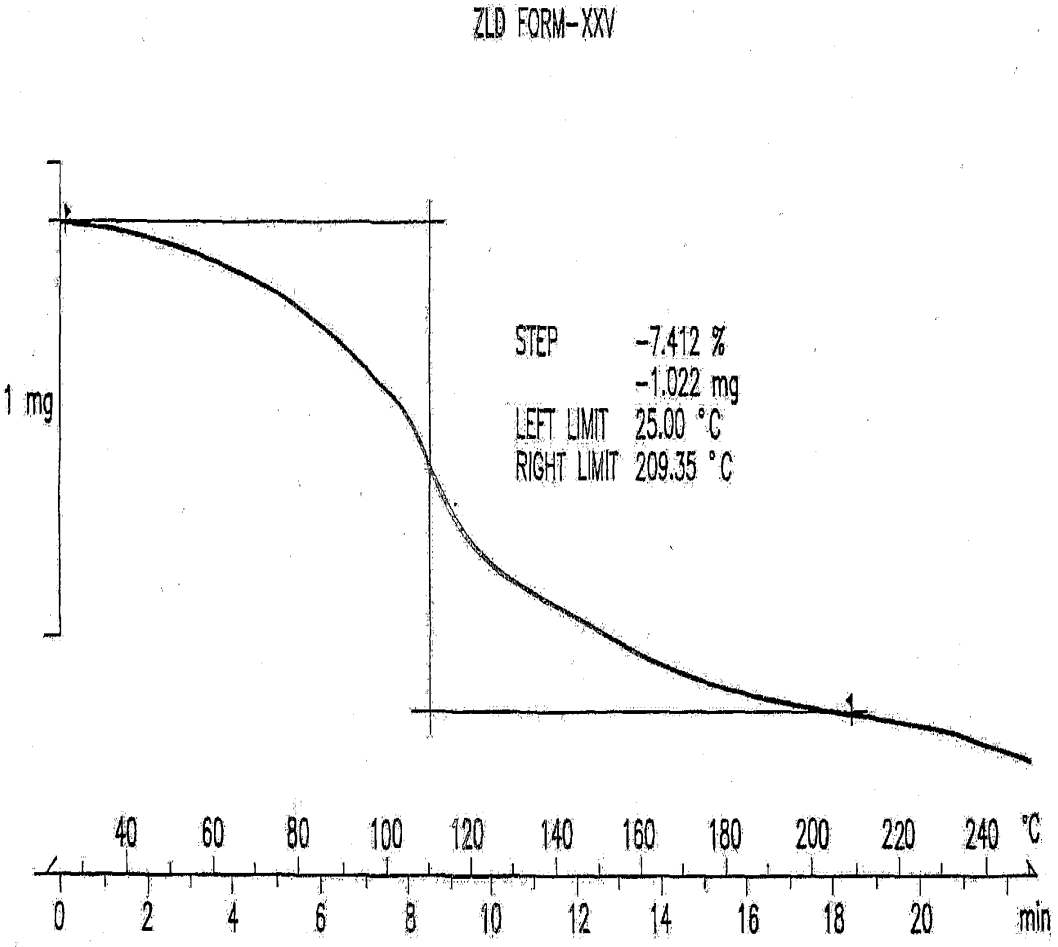
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIV

FIG.39



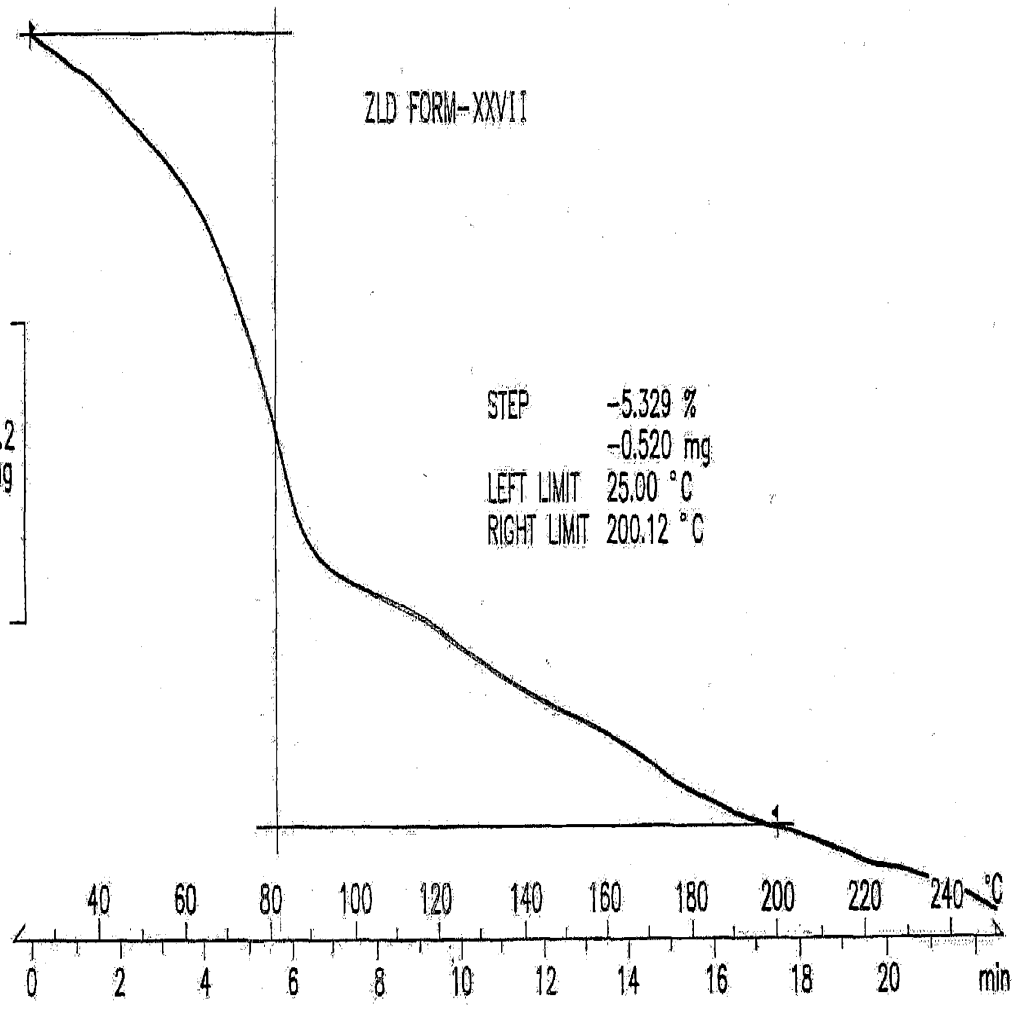
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XIX

FIG.40



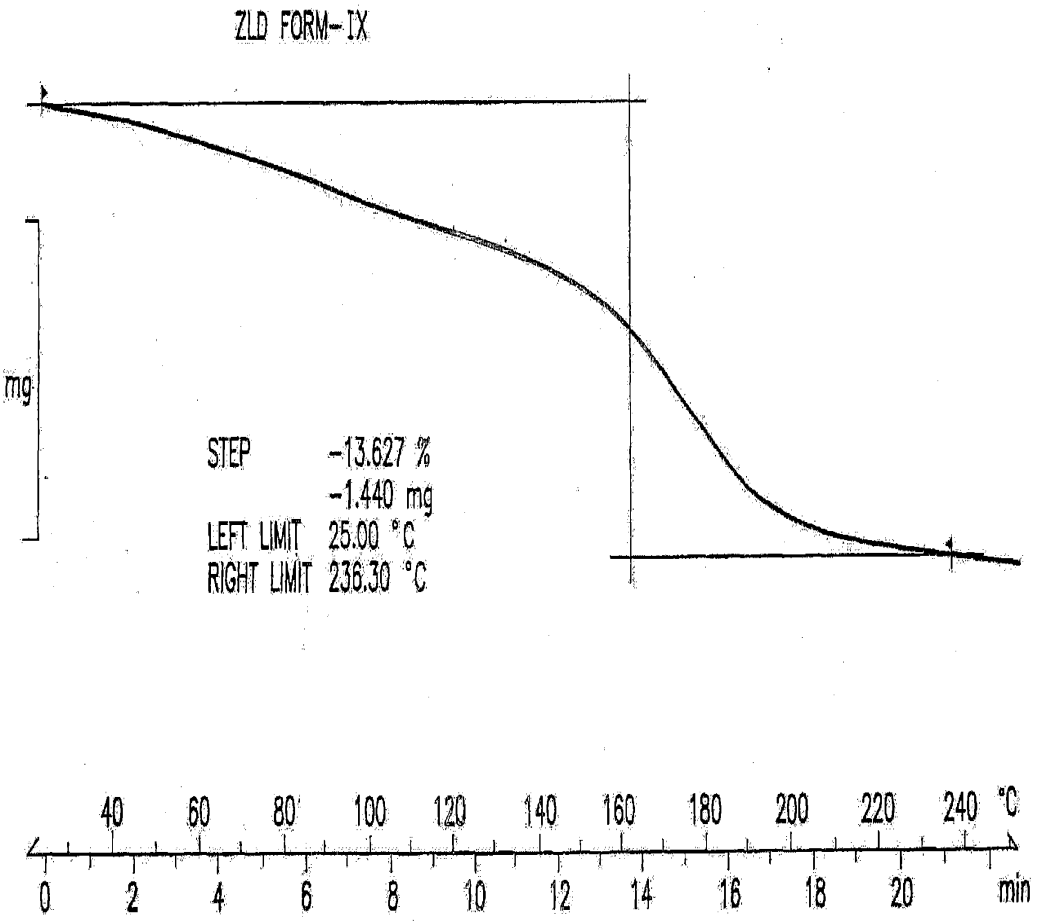
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XXV

FIG.41



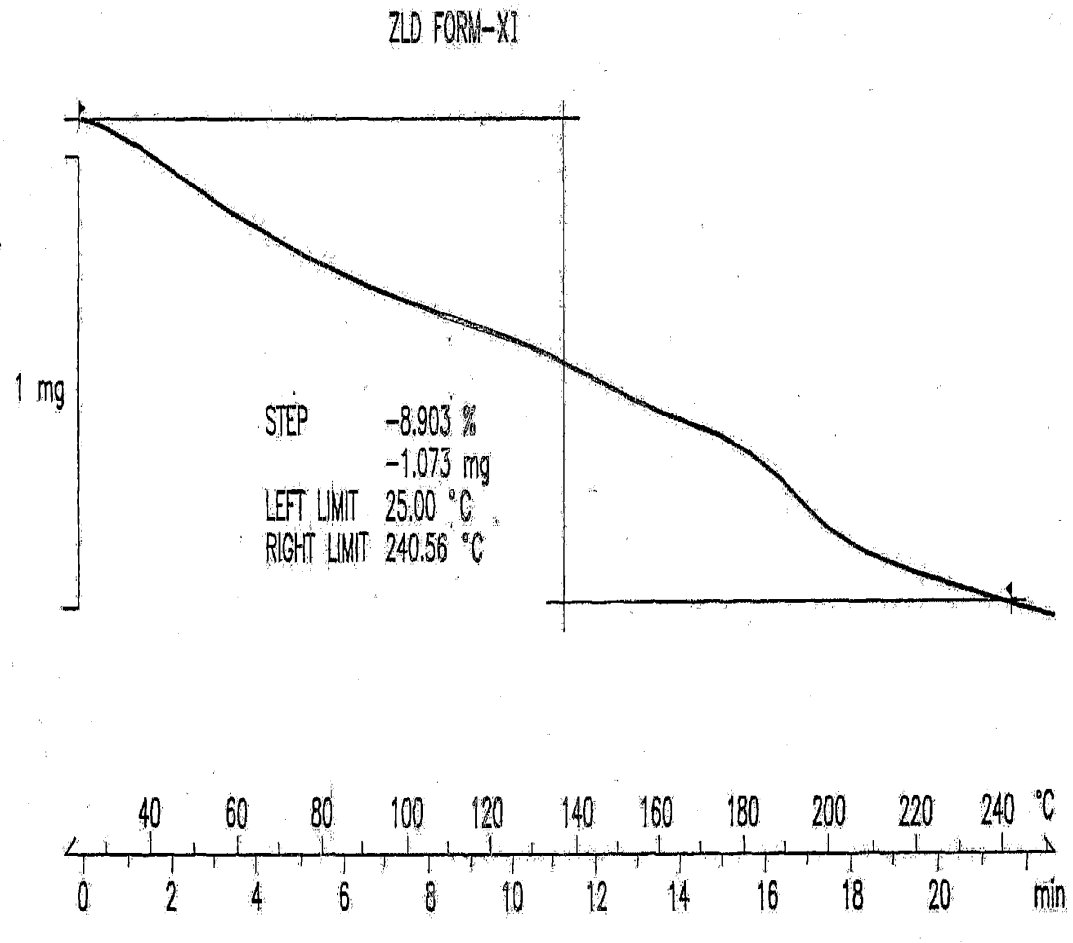
TGA CURVE OF ZOLEDRONATE DISODIUM FORM XXVII

FIG.42



TGA CURVE OF ZOLEDRONATE DISODIUM FORM IX

FIG.43



TGA CURVE OF ZOLEDRONATE DISODIUM FORM XI

FIG.44

5. L.A. Sorbera et al., *Zolendronate Disodium,* 25(3) DRUGS OF THE FUTURE 259 (2000) ("Sorbera").

Drugs of the Future 2000, 25(3): 259-268

CCC: 0377-8282/2000

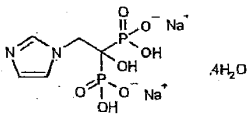
Zoledronate Disodium

USAN

Treatment of Tumor-Induced Hypercalcemia
Angiogenesis Inhibitor

Zoledronic Acid Disodium Salt Hydrate (Rec INNM)
CGP-42446A
ZOL-446
Zometa™

1-Hydroxy-2-(1-imidazolyl)ethylene-1,1-diphosphonic acid disodium salt tetrahydrate

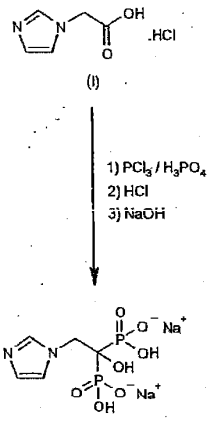


$C_5H_8N_2Na_2O_7P_2.4H_2O$ Mol wt: 388.1124

CAS: 165800-07-7
CAS: 157432-59-2 (as Mg salt)
CAS: 157432-58-1 (as Zn salt)
CAS: 131654-46-1 (anhydrous)
CAS: 118072-93-8 (as anhydrous free acid)
CAS: 165800-06-6 (as free acid monohydrate)

EN: 144428

Scheme 1: Synthesis of Zoledronate Sodium



Synthesis

Zoledronate sodium can be prepared by reaction of 2-(1-imidazolyl)acetic acid hydrochloride (I) with PCl_3, with optional presence of phosphoric acid, in refluxing chlorobenzene, followed by hydrolysis with refluxing 9N hydrochloric acid and final formation of the sodium salt by treatment with aqueous NaOH (1). Scheme 1.

Description

Free acid, m.p. 239 °C (decomp.); disodium salt dihydrate, m.p. 291-3 °C (decomp.).

Introduction

Metastatic bone disease is a common complication of several cancer types, particularly breast, prostate and lung carcinomas, and bone destruction is an integral part of other malignancies, notably myeloma. Frequently, the first sign of disseminated disease in cancer patients is bone metastasis, which results in bone pain, spinal cord compression, fractures and hypercalcemia, which in turn may be the cause of renal insufficiency. All of these events dramatically reduce the quality of life for patients.

L.A. Sorbera, X. Rabasseda, J. Castañer. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Bone lysis and sclerosis rely on a disruption of the balance between the actions of bone-resorbing cells (osteoclasts) and bone-forming cells (osteoblasts). Cancer-associated lytic bone destruction depends on soluble factors synthesized and released by tumor cells that stimulate osteoclasts to resorb bone. Osteoclasts are specialized cells that erode mineralized bone via acids and lysosomal enzymes. Factors that activate osteoclasts include parathyroid hormone-related peptide, growth factors, interleukins-1 and -6, tumor necrosis factor-β, lymphotoxins, colony-stimulating factors and prostaglandins. Osteoclast activation results in disruption of bone remodeling, unbalancing the equilibrium to increased resorption. Bisphosphonates stop bone destruction directly by inhibiting the recruitment and function of osteoclasts and indirectly by stimulating osteoblasts to produce an inhibitor of osteoclast formation. Their exact mechanism is not fully understood, but may include direct toxic effects on mature osteoclasts, inhibition of osteoclast differentiation and/or impaired osteoclast chemotaxis (2, 3).

Bisphosphonates are analogs of simple phosphates used to treat osteoporosis, Paget's disease, hypercalcemia and osteolytic bone metastases. However, recent findings have shown that these drugs also reduce the incidence and the number of bone and soft tissue metastases in patients with breast and other cancers and, thus, may represent an important advance in the management of cancer. Bisphosphonates are useful as adjuvant therapy in patients with bone metastases to reduce hypercalcemia, bone pain and the risk of fractures, and may even be useful in delaying the occurrence of bone metastases (4). Bisphosphonates vary markedly in potency and are concentrated in bone, where they remain until the bone is resorbed. However, all the available compounds are poorly absorbed from the gastrointestinal tract.

Bisphosphonates are indicated for the treatment of a variety of metabolic bone diseases characterized by increased bone resorption, which is a prominent feature of bone disease in cancer patients. Therefore, they are used to inhibit osteoclast activity in cancer-related hypercalcemia in patients with multiple myeloma, breast, kidney, lung or prostate cancer or any other malignancy associated with hypercalcemia and/or osteolytic bone metastases. The use of these compounds has been shown to decrease bone pain and the risk of fractures and to delay the occurrence of skeletal complications. Similarly, bisphosphonates have been shown to slow the progression or inhibit the development of bone metastases in cancer patients, probably by inhibiting the resorption of bone, which would reduce the release of growth factors stored in the bone matrix, or by inhibiting the adhesion of cancer cells to bone matrix.

Zoledronate is a third-generation bisphosphonate characterized by a side chain that includes an imidazole ring.

Pharmacological Actions

Zoledronate was found to be extremely potent in inhibiting 1,25-$(OH)_2D_3$-induced calcium release from mouse calvarial cultures *in vitro*; IC_{50} values of 0.002 and 0.2 μM were obtained for zoledronate and pamidronate, respectively. Zoledronate also markedly and dose-dependently inhibited parathyroid, parathyroid-related protein and recombinant human interleukin-1β-induced calcium release with IC_{50} values ranging from 2-7 nM, which was 40-100 times more potent than pamidronate (5). Another *in vitro* study showed that the IC_{50} values for zoledronate to inhibit squalene synthesis in rat liver microsomes and sterol synthesis in a mouse osteoblast-like cell line (MC3T3) were 11.1 and 17 μM, respectively (6).

An ED_{50} value for zoledronate to reduce hypercalcemia in 1,25-$(OH)_2D_3$-treated thyroparathyroidectomized rats *in vivo* of 0.072 ± 0.018 μg/kg s.c. was reported, which was 850 times more potent than values obtained for pamidronate (61 ± 7.5 μg/kg s.c.). Zoledronate treatment resulted in dose-dependent inhibition of 1,25-$(OH)_2D_3$-induced hypercalcemia with maximum effects (100%) observed with a dose of 1.4 μg/kg. Zoledronate showed a low oral bioavailability when administered orally for 4 days in the same model but remained 120-fold more potent than pamidronate (ED_{50} = 0.19 ± 0.06 *vs.* 23 ± 2.9 mg/kg p.o.). Following i.v. administration, zoledronate was 690 times more active than pamidronate (ED_{50} = 0.16 *vs.* 110 μg/kg i.v.) (5).

Short-term zoledronate treatment (0.028, 0.28 and 28 μg/kg s.c. for 10 days) of growing rats (7 weeks old) was shown to dose-dependently suppress cancellous bone turnover and resorption, resulting in an increase in cancellous bone. An increase in radiographic density of the tibial proximal metaphysis (ED_{50} = 1.7 μg/kg) was observed as well as increases in femoral trabecular calcium (ED_{50} = 0.17 μg/kg) and hydroxyproline (ED_{50} = 1.1 μg/kg) content and decreases in the mineral apposition rate (37-39%); no changes were observed in cortical bone. Short-term zoledronate treatment was concluded to be 100 times more potent than treatment with pamidronate (3.7-370 μg/kg) in this model (5, 7).

A study using female Balb/c mice implanted with mouse mammary tumor cells (4T1) demonstrated the efficacy of zoledronate (0.1-1 mg/kg i.v. bolus at week 1 with primary tumor formation and before detection of metastases) when combined with anticancer agents (tegafur and uracil; 5-20 mg/kg/day p.o. for 3 weeks) against bone and non-bone metastases. Osteolytic bone metastases were significantly reduced and a decrease in tumor burden was observed through histomorphometrical analysis in mice treated with zoledronate alone; soft organ (lung and liver) metastases were unaffected by zoledronate treatment. Although zoledronate treatment alone had no effects on survival, when combined with the anitcancer agents, survival was markedly extended (8).

The effect of zoledronate on ovariectomized animals has also been assessed. Long-term zoledronate treatment (0.3, 1.5 or 1.7 μg/kg s.c. once/week for 1 year) in ovariectomized mature rats (4 months) was effective and resulted in significant, dose-dependent prevention of

bone loss. The agent was shown to inhibit augmented bone remodeling due to estrogen deficiency (9).

Results from studies using adult ovariectomized rhesus monkeys showed that long-term zoledronate treatment (0.5, 2.5 or 12.5 μg/kg s.c. once weekly for 69 weeks) was well tolerated and prevented development of absolute osteopenia. After 13 weeks of treatment, total body and lumbar spinal bone mass and skeletal turnover were decreased in a dose-dependent manner. Histological analysis of biopsies from the 7th rib at 6 months after treatment showed that the mineralizing Haversian systems and formation rates of animals treated with 2.5 and 12.5 mg/kg zoledronate were significantly less than untreated animals and those treated with 0.5 mg/kg; only the 12.5 mg/kg dose was found to significantly decrease the mineral apposition rate (10, 11).

Arthritic bone destruction could be another usage for zoledronate. A study using an experimental inflammatory arthritis model in which the right tibiofemoral joint of rabbits was repeatedly (over 49 days) injected with carrageenan, showed that zoledronate (3 μg/kg/day s.c. from day 1, 14 or 28 after arthritis induction for 49 days) significantly decreased metaphyseal intracortical defects. Rabbits treated with zoledronate 14 days after arthritis induction showed the greatest reduction in defect area which was not significantly different from normal rabbits. Moreover, analysis of cellular pathology showed a significant difference in fibroblast and adipocyte populations in zoledronate-treated as compared to untreated arthritic animals. These alterations suggest that zoledronate may affect other cell types in addition to osteoblast/osteoblast lineages (12, 13).

Another study using carrageenan intraarticular injection in the right knee (for 4 weeks) to induce arthritis in rabbits, showed partial chondroprotective effects of zoledronate (10 μg/kg s.c. 3 times/week for 4 weeks). Although zoledronate treatment had no effect on carrageenan-induced synovitis, indicating that the agent had no antiinflammatory effects, treatment resulted in only 1 animal exhibiting extensive cartilage erosion and 3 and 1 animals showing focal cartilage erosion and cartilage fibrillation, respectively. In contrast, 6/7 untreated animals displayed extensive cartilage erosion. Zoledronate maintained subchondral bone thickness and hardness and cancellous bone volume, in addition to preventing focal breaks in the osteochondral barrier. The effects of the drug were concluded to be due to prevention of bone resorption (14). A similar study showed that zoledronate treatment (3 μg/kg/day s.c. for 49 days during arthritis induction) resulted in a reduction in type II collagen loss and a decrease in the percentage of denatured collagen present in tibia samples (15).

The intestinal tolerability of zoledronate was examined both in an acute *in vivo* model in rats involving luminal perfusion of ileal loops and *In vitro* using monolayers of intestinal epithelial cells (Caco-2). Although zoledronate (1-100 mM) inhibited bone resorption 2- to 3-fold more potently than pamidronate, it was 2- to 4-fold less effective in disrupting the permeability barrier of monolayers. Moreover, zoledronate only at concentrations of 30 mM disrupted the intestinal permeability barrier within 1 h *in vivo*, while 1 and 10 mM had no effect. Thus, zoledronate's ability to inhibit bone resorption while having low potential to increase damage to intestinal mucosal may result in a higher therapeutic ratio in humans as compared to pamidronate (16).

Pharmacokinetics and Metabolism

Zoledronate showed a low oral bioavailability when administered orally in 1,25-dihydroxyvitamin D_3-treated, thyroparathyroidectomized rats (5).

Clinical Studies

The tolerability and efficacy of a single infusion of zoledronate (24, 72, 216 and 400 μg i.v. over 1 h) was demonstrated in an open-label, ascending dose, 2-week trial in 16 patients with active Paget's disease of the bone. No significant changes in bone resorption markers were observed with doses of 24 and 72 μg. However, with doses of 216 and 400 μg, urinary hydroxyproline/creatinine excretion decreased by 16-19% on postinfusion days 3, 7, 10 and 14 and by 33-48% on days 1, 7 and 10, respectively; urinary calcium/creatinine was reduced by 15-40% on days 1, 3, 7, 10 and 14 and by 55-71% on days 3, 7, 10 and 14, respectively. No acute phase reactions, leukopenia or renal or hepatic toxicities were observed (17) (Box 1).

A randomized, double-blind, placebo-controlled, dose ranging study in 176 patients with active Paget's disease of the bone showed the tolerability and efficacy of single i.v. infusion of zoledronate (50, 100, 200 or 400 μg for 2 h). A rapid decrease in median fasting urinary hydroxyproline/creatinine excretion was observed (nadir at day 10) with significant differences from placebo noted with the 200 and 400 μg doses. In addition, all dose groups displayed a significant reduction in serum alkaline phosphatase activity by day 5 (nadir on day 60) as compared to placebo; activity continued to decrease by day 90 posttreatment for the group receiving 400 μg. Dose-dependent responses were observed in the number of therapeutic responders for serum alkaline phosphatase activity. In the group receiving 400 μg, 46% had a 50% decrease in alkaline phosphatase from baseline and 20% showed normalized values. Dose-dependent increases in serum calcium and phosphate were observed within the first 3 weeks following zoledronate infusion. The incidence of drug-related adverse events was similar in both treated and placebo groups with fever, back pain and skeletal pain the most common. Asymptomatic hypocalcemia (< 8 μg/dl) developed 5-10 days posttreatment in 3 patients given 400 μg and was resolved without treatment. No drug-related alterations in hematological parameters were seen (18) (Box 2).

Box 1: Antiresorptive effect of zoledronate in Paget's disease of bone (17) [Prous Science CSline database].

Design	Open, dose-finding, multicenter clinical study
Population	Patients with active Paget's disease of bone (n = 16)
Treatments*	Zoledronate, 24 µg i.v. (n = 4) Zoledronate, 72 µg i.v. (n = 4) Zoledronate, 216 µg i.v. (n = 4) Zoledronate, 400 µg i.v. (n = 4)
Results	Mean hydroxyproline/creatinine ratio, change (%) @ 1 d: Z400 (–34) > Z216 (–12) > Z24 (–9) > Z72 (–14) @ 7 d: Z400 (–47) > Z216 (–20) > Z24 (–5) > Z72 (–6) @ 14 d: Z216 (–20) ≥ Z400 (–18) > Z24 (–17) > Z72 (–0) Mean calcium/creatinine ratio, change (%) @ 1 d: Z216 (–20) > Z400 (–4) > Z24 (–2) > Z72 (–14) @ 7 d: Z400 (–58) > Z216 (–30) > Z24 (–20) > Z72 (–15) @ 14 d: Z400 (–65) > Z216 (–35) > Z24 (–30) > Z72 (–15)
Conclusions	Single infusions of microgram amounts of zoledronate inhibited bone resorption in active Paget's disease of bone during a 2-week study interval, without any significant clinical or biochemical toxicity observed

*Zoledronate was administered as a single 1-h infusion

Box 2: Zoledronate in the treatment of Paget's disease of bone (18) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding, multicenter clinical study
Population	Patients with Paget's disease of bone (n = 176)
Treatments*	Zoledronate, 50 µg i.v. (n = 35) Zoledronate, 100 µg i.v. (n = 38) Zoledronate, 200 µg i.v. (n = 33) Zoledronate, 400 µg i.v. (n = 35) Placebo (n = 35)
Adverse Events	Z50: fatigue 4/35 (11.6%), arthralgia 4/35 (11.6%), back pain 2/35 (5.7%) Z100: arthralgia 5/38 (13.2%), fatigue 3/38 (7.9%), back pain 3/38 (7.9%), skeletal pain 2/38 (5.3%) Z200: back pain 4/33 (12.1%), skeletal pain 3/33 (9.1%), fatigue 2/33 (6.1%), fever 2/33 (6.1%) Z400: arthralgia 5/35 (14.3%), back pain 5/35 (14.3%), skeletal pain 5/35 (14.3%), fever 4/35 (11.8%), fatigue 3/35 (8.6%) P: arthralgia 3/35 (8.6%), skeletal pain 2/35 (5.7%)
Results	Maximum median serum alkaline phosphatase reduction (%): Z400 (46.9) ≥ Z200 (32.7) > Z100 (16.8) ≥ Z50 (10.8) ≥ P (6.2); bone-specific: Z400 (60.8) > Z200 (41.1) > Z100 (29.2) > Z50 (25.2) > P (17.8) Maximum median urinary hydroxyproline reduction (%): Z400 (59) > Z200 (37) > Z100 (28) > Z50 (27.9) > P (16.7) Maximum median pyridinoline/creatinine ratio reduction (%): Z400 (40) > Z200 (32.3) > Z50 (22.8) ≥ P (16.5) ≥ Z100 (15.9) Maximum median deoxypyridinoline/creatinine ratio reduction (%): Z400 (51.6) > Z200 (33.8) > Z50 (30.9) > Z100 (22.7) > P (19.5)
Conclusions	Zoledronate was an effective agent for the treatment of Paget's disease of bone

*Zoledronate was administered as a single 5-min infusion in 60 ml dextrose in water

Two further, dose-finding, placebo-controlled trials in 176 and 180 patients with Paget's disease confirmed zoledronate to be safe and effective in Paget's disease, with doses of 200 or 400 µg as single i.v. infusion being optimal (19, 20) (Boxes 3 and 4).

A subpopulation (28 patients) from this same study was used to monitor the urinary excretion of nonisomerized and β-isomerized forms of type I collagen breakdown products to determine the efficacy of single i.v. injections of zoledronate (200 or 400 µg). Serum type I collagen

Box 3: A double-blind placebo-controlled trial of zoledronate in Paget's disease (19) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Patients with Paget's disease (n = 176)
Treatments	Zoledronate, 50 µg i.v. Zoledronate, 100 µg i.v. Zoledronate, 200 µg i.v. Zoledronate, 400 mg i.v. Placebo
Results	Serum alkaline phosphatase levels, mean maximum % change @ 90 d: Z400* (−46.6) ≥ Z200* (−33.7) ≥ Z100* (−20.9) ≥ Z50* (−15.2) ≥ P (−6.6) [*p <0.001 *vs.* P; **p = 0.003 *vs.* P] 2-Hour urine hydroxyproline/creatinine ratio, mean maximum % change @ 90 d: Z400* (−51.7) ≥ Z200* (−38.0) ≥ Z100** (−24.2) ≥ Z50 (−16.5) ≥ P (−14.4) [*p <0.001 *vs.* P; **p = 0.009 *vs.* P] Urine calcium/creatinine ratio, mean maximum % change @ 90 d: Z400* (−64.8) ≥ Z200 (−59.6) ≥ P (−48.7) ≥ Z100 (−30.1) ≥ Z50 (−21.6) [*p = 0.003 *vs.* P] Urine pyridoline/creatinine ratio, mean maximum % change @ 90 d: Z400* (−41.6) ≥ Z200* (−30.7) ≥ Z50 (−23.5) ≥ P (−16.8) ≥ Z100 (−9.9) [*p <0.001 *vs.* P] Urine deoxypyridinoline/creatinine ratio, mean maximum % change @ 90 d: Z400* (−50.1) ≥ Z200* (−35.9) ≥ Z50** (−28.3) ≥ P (−18.3) ≥ Z100 (−15.7) [*p <0.001 *vs.* P; **p = 0.008 *vs.* P] Bone alkaline phosphatase levels, mean maximum % change @ 90 d: Z400* (−56.5) ≥ Z200* (−43.3) ≥ Z100 (−25.4) ≥ Z50 (−27.9) ≥ P (−16.1) [*p <0.001 *vs.* P]
Conclusions	Zoledronate at 200 and 400 µg i.v. was safe and effective in Paget's disease

*Zoledronate was administered as a 60-min infusion

Box 4: Zoledronate in the treatment of Paget's disease (20) [Prous Science CSline database].

Design	Randomized, multicenter, double-blind, placebo-controlled, crossover, dose-finding clinical study
Population	Patients with Paget's disease (n = 190)
Treatments	Zoledronate, 50 µg i.v. (n = 35) Zoledronate, 100 µg i.v. (n = 35) Zoledronate, 200 µg i.v. (n = 35) Zoledronate, 400 µg i.v. (n = 35) Placebo (n = 35)
Adverse Events	Z50: fever (2.9%), arthralgia (11.8%) Z100: fever (not done), arthralgia (13.2%) Z200: fever (11.4%), arthralgia (3%) Z400: fever (%), arthralgia (14.3%) P: fever (0%), arthralgia (8.6%)
Results	Suppression (%) of hydroxyproline/creatinine excretion @ 10 d: Z400 (−50) > Z126 (−15) ≥ Z72 (−10) ≥ Z24 (5) Urinary hydroxyproline/creatinine excretion, maximum mean % change @ 10 d: Z400* (−58) ≥ Z200* ≥ Z100* ≥ Z50* > P [*p <0.0125 *vs.* P]; mean % change @ 90 d: Z400* ≥ Z200* ≥ Z100* ≥ Z50* > P [*p <0.0125 *vs.* P] Urinary deoxypyridinoline/creatinine excretion, mean % change @ 90 d: Z400* ≥ Z200* ≥ Z100* > Z50* > P [*p <0.0125 *vs.* P] Response rate (50% reduction or normalization of alkaline phosphatase) @ 90 d in patients with lower alkaline phosphatase: Z400 (33%); in patients with higher alkaline phosphatase: Z400 (55%) Rate of normalization of alkaline phosphatase @ 90 d in patients with lower alkaline phosphatase: Z400 (27%); in patients with higher alkaline phosphatase: Z400 (15%)
Conclusions	Zoledronate was safe and effective in Paget's disease, with 200 and 400 µg i.v. being the optimal doses

*Zoledronate was administered as a single 60-min infusion

Box 5: Monitoring the effects of zoledronate treatment in Paget's disease of bone (21) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled clinical study
Population	Patients with Paget's disease of bone (n = 28)
Treatments	Zoledronate, 200 or 400 µg i.v. (n = 20) Placebo (n = 8)
Results	Mean α-CTX [type I collagen C-telopeptide] (µg/mmol Cr) change: @ 10 d: Z* (–27) > P (–3) [*p <0.001 *vs.* baseline] @ 30 d: Z* (–27) > P (–10) [*p <0.001 *vs.* baseline] @ 60 d: Z* (–25) > P (–15) [*p<0.001 *vs.* baseline] Mean β-CTX [type I collagen C-telopeptide] (µg/mmol Cr) change: @ 10 d: Z* (–10) > P (–2) [*p <0.001 *vs.* baseline] @ 30 d: Z* (–6) > P (–2) [*p <0.01 *vs.* baseline] @ 60 d: Z (–4) = P (–2) Mean α/β-CTX [type I collagen C-telopeptide] (µg/mmol Cr) change: @ 10 d: Z* (–0.49) > P (–0.01) [*p <0.01 *vs.* baseline] @ 30 d: Z* (–0.86) > P (–0.14) [*p<0.001 *vs.* baseline] @ 60 d: Z* (–0.95) > P (–0.7) [*p < 0.001 *vs.* baseline]
Conclusions	The determination of the urinary ratio of nonisomerized (alpha) to β-isomerized type I collagen C-telopeptide (CTX) may be useful for monitoring the effect of bisphosphonate treatment in restoring bone quality

Box 6: Phase I trial of zoledronate in patients with osteolytic bone metastases (22) [Prous Science CSline database].

Design	Open, dose-finding clinical study
Population	Patients with osteolytic bone metastases [36 multiple myeloma, 17 breast cancer, 6 other cancer] (n = 59)
Treatments*	Zoledronate, 0.1 mg i.v. (n = 7) Zoledronate, 0.2 mg i.v. (n = 7) Zoledronate, 0.4 mg i.v. (n = 6) Zoledronate, 0.8 mg i.v. (n = 7) Zoledronate, 1.5 mg i.v. (n = 10) Zoledronate, 2.0 mg i.v. (n = 8) Zoledronate, 4.0 mg i.v. (n = 7) Zoledronate, 8.0 mg i.v. (n = 7)
Adverse Events	Conjunctivitis 1/59 (1.7%), flu symptoms 2/59 (3.4%), fatigue 2/59 (3.4%), transient bone pain 4/59 (6.8%), eye irritation 5/59 (8.5%), sore throat 1/59 (1.7%) ZO [: severe bone pain 1/7 (14.3%)
Results	Urine calcium/creatinine ratio, % change @ 4 wk: Z > P (–62.3) Urine hydroxyproline/creatinine ratio, % change @ 90 d: Z < baseline Urine deoxypyridinoline/creatinine ratio, % change @ 90 d: Z < baseline
Conclusions	Zoledronate was safe and effective in patients with osteolytic bone metastases

*Zoledronate was administered as a 5-30 min infusion once monthly for 3 months

C-terminal extension propeptide (PICP) and urinary excreted N-telopeptide breakdown products (NTX) and C-telopeptide products (αCTX and βCTX), which were increased in patients at baseline, were decreased within 5 days of zoledronate treatment (200 or 400 µg); serum bone alkaline phosphatase (BAP) and urinary excreted free deoxypyridinoline (free D-Pyr) were reduced on day 10. Although NTX and αCTX reductions in urinary excretion were sustained for 60 days, βCTX excretion increased between days 10-30 and reached pretreatment values by 2 months. The significant reduction in the urinary ratio of αCTX / βCTX seen between days 10 and 60 and later reaching normal values within 2 months, may indicate the restoration of bone quality in these patients. Therefore, monitoring of this ratio may be helpful in assessing the efficacy of zoledronate treatment (21) (Box 5).

A phase I trial in 59 patients with osteolytic bone metastases (*e.g.*, multiple myeloma, breast cancer) showed that zoledronate may be safely administered as short monthly i.v. infusions (0.1, 0.2, 0.4, 0.8, 1.5, 2, 4 and 8 mg for 3 months). Thirty-minute infusions of the low

Box 7: Zoledronate versus pamidronate in patients with osteolytic bone metastases (24) [Prous Science CSline database].

Design	Randomized, double-blind, comparative, multicenter, dose-finding clinical study
Population	Patients with breast cancer or multiple myeloma and osteolytic bone metastases (n = 285)
Treatments*	Zoledronate, 0.4 mg i.v. Zoledronate, 2 mg i.v. Pamidronate, 90 mg i.v.
Adverse Events	Therapy was well tolerated and no significant hematological and biochemical changes were observed
Conclusions	Zoledronate at a dose range of 0.4-4 mg was well tolerated as a monthly infusion during 9 months in addition to standard therapy for breast cancer or multiple myeloma with osteolytic bone metastases

*Zoledronate was administered as a 5-min infusion and pamidronate as a 2-h infusion, both once monthly for 9 months

Box 8: Phase II study of zoledronate in patients with osteolytic lesions (25) [Prous Science CSline database].

Design	Comparative, randomized, double-blind, dose-finding clinical study
Population	Patients with osteolytic lesions resulting from breast cancer [171] or multiple myeloma [109] (n = 208)
Treatments*	Zoledronate, 0.4 mg i.v. Zoledronate, 2 mg i.v. Zoledronate, 4 mg i.v. Pamidronate, 90 mg i.v.
Results	Bone radiotherapy rate (%) @ 9 mo: Z2 (< 30), Z4 (< 30), P (< 30) Incidence (%) of skeletal events of fracture, radiotherapy, surgery, spinal cord compression or hypercalcemia) @ 9 mo: Z0.4 (46) > Z2 (35) > Z4 (33) > P (30)
Conclusions	The efficacy of low doses of zoledronate was similar to that of 90 mg of pamidronate in osteolytic disease

*Zoledronate was administered as a 5-min infusion and pamidronate as a 2-h infusion, both once daily for 9 months

doses (0.1-0.2 mg) were well tolerated although higher doses were well tolerated when given as 5-min infusions. Adverse events were mild except 1 case of severe bone pain reported after 3 weeks with the 0.1 mg dose and 1 case of moderate conjunctivitis. The most common adverse effects, most of which were not concluded to be drug-related, were bone pain, eye irritation, flu-like symptoms and fever. Significant decreases in bone resorption markers were observed in zoledronate-treated patients with marked decreases in the urine calcium/creatinine ratio (with doses of 0.2-2 mg) and decreases in hydroxyproline/creatinine and deoxypyridinoline/creatinine ratios. Moreover, pain scores of treated patients were reported to decrease and an analgesic effect was seen at 12 weeks in 7 patients given 8 mg indicated by a median percent change of 50% (22, 23) (Box 6).

Results from a randomized, double-blind, parallel phase II trial in 285 patients with osteolytic bone metastases showed that zoledronate infusion (0.4-4.0 mg i.v. over 5 min every 4 weeks for 9 months) was well tolerated in combination with standard chemotherapy for breast cancer and multiple myeloma. No significant hematologic or biochemical changes were seen. The efficacy of zoledronate was also compared to pamidronate (90 mg i.v. infusion over 2 h every 4 weeks). Preliminary analysis of results indicate equivalent efficacies and safety profiles for both agents. The most common adverse effects were skeletal pain, low-grade fever and mild flu-like symptoms from 24-48 h postinfusion. The 5-min zoledronate infusion was concluded to be more advantageous than the longer pamidronate infusion since it requires less nursing time, use of office space and time spent by the patient at the clinic (24) (Box 7).

Results from another randomized trial in 280 patients (171 with breast cancer and 109 with multiple myeloma) with osteolytic lesions confirmed the safety and efficacy of zoledronate, which at doses of 4 mg i.v. monthly was comparable to pamidronate 90 mg i.v. monthly (25) (Box 8).

The clinical efficacy of zoledronate in hypercalcemic cancer patients has been fully confirmed in a number of additional clinical trials (26-29) (Boxes 9-12).

Novartis has filed for marketing approval for zoledronate (Zometa®) for tumor-induced hypercalcemia in the U.S., Canada, the EU, Switzerland and Australia (30). The FDA has granted priority review status and is

Box 9: Dose-finding study of zoledronate in patients with tumor-induced hypercalcemia (26) [Prous Science CSline database].

Design	Dose-finding, multicenter, open clinical study
Population	Patients with cancer hypercalcemia (n = 30)
Treatments*	Zoledronate, 0.002 mg/kg i.v. (n = 3) Zoledronate, 0.005 mg/kg i.v. (n = 3) Zoledronate, 0.01 mg/kg i.v. (n = 4) Zoledronate, 0.02 mg/kg i.v. (n = 5) Zoledronate, 0.04 mg/kg i.v. (n = 15)
Adverse Events	↑ increase in body temperature 10/30 (30.3%), transient subclinical hypophosphatemia 7/30 (23.3%), transient subclinical hypocalcemia
Results	Normocalcemia rate: >0.02 (5/5 [100%]) ≥ Z0.04 (14/15 [93.3%]) > Z0.002 (1/3 [33.3%]) ≥ Z0.005 (1/3 [33.3%]) > Z0.01 (1/4 [25%])
Conclusions	Very low doses of zoledronate (0.02 and 0.04 mg/kg) administered as a short-time infusion effectively treated patients with tumor-induced hypercalcemia and were well tolerated; the effects were usually maintained over several weeks

*Zoledronate was administered as a single 30-min infusion

Box 10: Phase I study of zoledronate in patients with osteolytic bone metastases (27) [Prous Science CSline database].

Design	Open, dose-finding, multicenter clinical study
Population	Patients with osteolytic bone metastases (n = 51)
Treatments*	Zoledronate, 100 µg i.v. (n = 7) Zoledronate, 200 µg i.v. (n = 7) Zoledronate, 400 µg i.v. (n = 6) Zoledronate, 800 µg i.v. (n = 7) Zoledronate, 1500 µg i.v. (n = 10) Zoledronate, 2000 µg i.v. (n = 8) Zoledronate, 4000 µg i.v. (n = 6)
Adverse Events	Grade I–II: eye irritation 5/51 (9.8%), bone pain 4/51 (7.8%), sore throat/mouth 4/51 (7.8%), fever/fatigue 2/51 (3.9%), asymptomatic hypocalcemia 1/51 (2%)
Results	
Conclusions	Zoledronate was well tolerated

*Zoledronate was administered as a 5-min infusion once monthly

Box 11: Zoledronate in the treatment of osteolytic bone metastases (28) [Prous Science CSline database].

Design	Open, dose-finding, multicenter clinical study
Population	Patients with osteolytic bone metastases (n = 44)
Treatments*	Zoledronate, 100 µg i.v. (n = 7) Zoledronate, 200 µg i.v. (n = 7) Zoledronate, 400 µg i.v. (n = 6) Zoledronate, 800 µg i.v. (n = 7) Zoledronate, 1500 µg i.v. (n = 10) Zoledronate, 2000 µg i.v. (n = 7)
Adverse Events	Grade I–II: eye irritation 5/51 (9.8%), bone pain 4/51 (7.8%), sore throat/mouth 4/51 (7.8%), fever/fatigue 2/51 (3.9%), asymptomatic hypocalcemia 1/51 (2%)
Results	Median reduction (%) in osteocalcin levels: Z2000 (70) > Z1500 (62.3) > Z800 (56.7) > Z200 (38.8) > Z100 (29.8) ≥ Z400 (27.3)
Conclusions	Zoledronate effectively lowered surrogate markers of bone resorption in cancer patients; once monthly doses of up to 2000 mg were well tolerated

*Zoledronate was administered as a 5-min infusion once monthly

Box 12: Phase I trial of zoledronate in patients with osteolytic bone lesions (29) [Prous Science CSline database].

Design	Open, dose-finding clinical study
Population	Patients with osteolytic bone lesions [32 multiple myeloma, 12 breast cancer, 1 both] (n = 45)
Treatments*	Zoledronate, 100 µg i.v. (n = 7) Zoledronate, 200 µg i.v. (n = 7) Zoledronate, 400 µg i.v. (n = 6) Zoledronate, 800 µg i.v. (n = 6) Zoledronate, 1500 µg i.v. (n = 10) Zoledronate, 2000 µg i.v. (n = 7)
Adverse Events	Conjunctivitis 1/45 (2.2%), bone pain 4/45 (8.9%), eye irritation 5/45 (11.1%), sore throat 1/45 (2.2%), fever 2/45 (4.4%), flu symptoms 2/45 (4.4%), and fatigue 2/45 (4.4%), asymptomatic hypocalcemia 1/45 (2.2%) Z100: severe bone pain 1/7 (14.3%)
Results	Urine calcium/creatinine ratio, % change @ 4 wk: Z2.0 (−67.4) Urine hydroxyproline/creatinine ratio, % change @ 90 d: Z < baseline Urine deoxypyridinoline/creatinine ratio, % change @ 90 d: Z < baseline
Conclusions	Zoledronate was safe and effective in patients with cancer and osteolytic bone lesions

*Zoledronate was administered as a 5-30 min infusion once monthly for 3 months

expected to rule on the approvability of zoledronate by June 21, 2000 (31).

Manufacturer

Novartis AG (CH).

References

1. Jaeggi, K.A., Widler, L. (Ciba-Geigy Corp.). *Substituted alkanediphosphonic acids and pharmaceutical use.* AU 8781453, EP 0275821, JP 1988150291, US 4939130.

2. Raisz, L.G. *Physiology and pathophysiology of bone remodeling.* Clin Chem 1999, 45: 1353-8.

3. Morton, A.R. *The role of bisphosphonates in patients with bony metastases.* Cancer J 1995, 8: 231-3.

4. Delmas, P.D. *Bisphosphonates in the treatment of bone diseases.* New Engl J Med 1996, 335: 1836-7.

5. Green, J.R., Muller, K., Jaeggi, K.A. *Preclinical pharmacology of CGP 42,446, a new, potent, heterocyclic bisphosphonate compound.* J Bone Miner Res 1994, 9: 745-51.

6. Seltenmeyer, Y., Green, J.R. *A comparison of the antiresorptive potency of various bisphosphonates in vivo with their inhibitory effect in vitro on squalene synthase and cellular sterol synthesis.* Bone 1997, 20(4, Suppl.): Abst P376.

7. Pataki, A., Müller, K., Green, J.R., Ma, Y.F., Li, Q.N., Lee, W.S.S. *Effects of short-term treatment with the bisphosphonates zoledronate and pamidronate on rat bone: A comparative histomorphometric study on the cancellous bone formed before, during, and after treatment.* Anat Rec 1997, 249: 458-68.

8. Hiraga, T., Hata, K., Nishimura, R., Takeda, S., Dallas, M., Mundy, G.R., Yoneda, T. *Combined treatment with bisphosphonates and oral UFT inhibits bone and soft organ metastases and prolongs survival.* J Bone Miner Res 1999, 14(Suppl. 1): Abst T039.

9. Glatt, M., Pataki, A. *Longterm zoledronate treatment prevents bone loss in estrogen-deficient rats.* J Bone Miner Res 1999, 14(Suppl. 1): Abst SA373.

10. Binkley, N., Kimmel, D., Bruner, J., Haffa, A., Davidowitz, B., Meng, C., Schaffer, V., Green, J. *Zoledronate prevents the development of absolute osteopenia following ovariectomy in adult rhesus monkeys.* J Bone Miner Res 1998, 13: 1775-82.

11. O'Rourke, C., Bare, S., Kimmel, D., Binkley, N., Schaffer, V., Green, J. *Zoledronate (CGP 42,446) suppresses turnover in cortical bone of the ovariectomized non-human primate.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S481.

12. Pysklywec, M.W., Moran, E.L., Bogoch, E.R. *Zoledronate (CGP 42,446), a bisphosphonate, protects against metaphyseal intracortical defects in experimental inflammatory arthritis.* J Orthop Res 1997, 15: 858-61.

13. Fornasier, V.L., Moran, E.L., Bogoch, E.R. *The bisphosphonate zoledronate modifies the intraosseous response of cell populations in experimental inflammatory arthritis (EIA).* J Bone Miner Res 1997, 12(Suppl. 1): Abst S639.

14. Podworny, N.V., Kandel, R.A., Renlund, R.C., Grynpas, M.D. *Partial chondroprotective effect of zoledronate in a rabbit model of inflammatory arthritis.* J Rheumatol 1999, 26: 1972-82.

15. Bogoch, E.R., Moran, E.L., Reiner, A., Poole, A.R. *Degradation of cartilage type II collagen in experimental inflammatory arthritis (EIA) may be prevented by CGP 42,446.* Bone 1995, 17(6): 598.

16. Green, J.R., Clay, V., Richardson, J., Hassan, I.F. *The effect of zoledronate and pamidronate on the intestinal permeability barrier in vitro and in vivo.* Int J Pharm 1997, 153: 59-66.

17. Arden-Cordone, M., Siris, E.S., Lyles, K.W., Knieriem, A., Newton, R.A., Schaffer, V., Zelenakas, K. *Antiresorptive effects*

of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. Calcif Tissue Int 1997, 60: 415-8.

18. Buckler, H., Fraser, W., Hosking, D. et al. *Single infusion of zoledronate in Paget's disease of bone: A placebo-controlled, dose-ranging study.* Bone 1999, 24: 81S-5S.

19. Zelenakas, K., Buckler, H., Schaffer, V., Richardson, P. *A double-blind placebo-controlled trial using intravenous CGP-42446 in patients with Paget's disease of bone.* Bone 1995, 17(6): 618.

20. Siris, E. *Zoledronate in the treatment of Paget's disease.* Br J Clin Pract 1996, Suppl. 87: 19-20.

21. Garnero, P., Gineyts, E., Schaffer, A.V., Seaman, J., Delmas, P.D. *Measurement of urinary excretion of monisomerized and β-isomerized forms of type I collagen breakdown products to monitor the effects of the bisphosphonate zoledronate in Paget's disease.* Arthritis Rheum 1998, 41: 354-60.

22. Berenson, J.R., Lipton, A., Rosen, L.S., Savage, A., Kowalski, M., Heffeman, M., Knight, R. *Phase I clinical study of a new bisphosphonate, zoledronate (CGP-42446), in patients with osteolytic bone metastases.* Blood 1996, 88(10, Suppl. 1): Abst 2334.

23. Fulfaro, F., Casuccio, A., Ticozzi, C., Ripamonti, C. *The role of bisphosphonates in the treatment of painful metastatic bone disease: A review of phase III trials.* Pain 1998, 78: 157-69.

24. Lipton, A., Berenson, J., Porter, L., Rosen, L., Levy, E., Knight, R. *Zoledronate: Phase II study in patients with osteolytic bone metastases.* Cancer Invest 1999, 17(Suppl. 1): 12.

25. Lipton, A., Berenson, J., Knight, R., Grace, H., Levy, E.R. *Phase II trial of zoledronate vs. pamidronate in multiple myeloma and breast cancer.* 17th Chemother Found Symp Innovative Cancer Chemother Tomorrow (Nov 3-6, New York) 1999, Abst 53.

26. Body, J.J., Lortholary, A., Romieu, G., Vigneron, A.M., Ford, J. *A dose-finding study of zoledronate in hypercalcemic cancer patients.* J Bone Miner Res 1999, 14: 1557-61.

27. Lipton, A., Berenson, J., Rosen, L., Harvey, H., Kowalski, M., Hefferman, M., Knight, R., Seaman, J. *Phase I study of zoledronate (CGP 42446) in patients with osteolytic bone metastases.* Ann Oncol 1996, 7(Suppl. 5): Abst 639P.

28. Lipton, A. *Zoledronate in the treatment of osteolytic bone metastases.* Br J Clin Pract 1996, Suppl. 87: 21.

29. Rosen, L.S., Lipton, A., Savage, A., Kowalski, M., Miller, J.A., Knight, R., Seaman, J., Berenson, J.R. *Phase I trial of zoledronate (CGP 42446), a new bisphosphonate, in patients with osteolytic bone lesions.* Proc Amer Soc Clin Oncol 1996, 15: Abst 1570.

30. *Novartis files regulatory dossiers for Zometa around the world.* DailyDrugNews.com (Daily Essentials) December 27, 1999.

31. *Novartis bisphosphonate (Zometa) granted priority review status.* DailyDrugNews.com (Daily Essentials) February 11, 2000.

Additional References

Binkley, N., Bruner, J., Haffa, A., Davidowitz, B., Kimmel, D., Schaffer, V., Green, J. *Zoledronate (CGP 42,446) prevents persistent absolute osteopenia after ovariectomy in primates.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S480.

Podworny, N., Kandel, R., Renlund, R., Grynpas, M. *The effect of zoledronate on cartilage and bone quality of the joint in a rabbit model of inflammatory arthritis.* J Bone Miner Res 1997, 12(Suppl. 1): Abst F280.

Bare, S., Kimmel, D., Binkley, N., Schaffer, V., Green, J. *Zoledronate (CGP 42,446) suppresses turnover without affecting mineralization in cancellous bone of the ovariectomized non-human primate.* J Bone Miner Res 1997, 12(Suppl. 1): Abst S482.

Green, J.R., Hassan, I., Jaeggi, K.A. *The intestinal tolerability of the bisphosphonate CGP 42,446: Effects in vitro on Caco-2 cell monolayers and in vivo on perfused rat ileal loops.* Bone Miner 1994, 25(Suppl. 1): Abst 46.

Pataki, A., Green, J.R., Müller, K., Schneider, R., Studer, A., Jaeggi, K.A. *A histomorphometric comparison of the effects on rat bone of short-term treatment with the two bisphosphonates CGP 42,446 and pamidronate: Static parameters.* Bone Miner 1994, 25(Suppl. 1): Abst 12.

Green, J. *Zoledronate: The preclinical pharmacology.* Br J Clin Pract 1996, Suppl. 87: 16-8.

Podworny, N., Kandel, R., Renlund, R., Grynpas, M. *The effect of the bisphosphonate CGP 42,446 on the joint in a rabbit model of inflammatory arthritis.* Bone 1995, 17(6): 601.

Lipton, A., Berenson, J., Savage, A., Kowalski, M., Seaman, J., Knight, R. *The effects of the bisphosphonate, zoledronate, when administered as a short intravenous infusion in patients with bone metastases: A phase I study.* Proc Amer Soc Clin Oncol 1997, 16: Abst 848.

Hupkes, M., Givant, F. *Zoledronate, a new 3rd generation bisphosphonate: Implications for nursing practice.* Eur J Cancer 1999, 35(Suppl. 4): Abst 152.

6. Fosamax® (alendronate sodium) tablets, for oral use, approved 1995, revised Feb. 2012, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021575s017lbl.pdf ("Fosamax label")

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FOSAMAX safely and effectively. See full prescribing information for FOSAMAX.

FOSAMAX® (alendronate sodium) tablets, for oral use
FOSAMAX (alendronate sodium) oral solution
Initial U.S. Approval: 1995

----------INDICATIONS AND USAGE----------
FOSAMAX is a bisphosphonate indicated for:
- Treatment and prevention of osteoporosis in postmenopausal women (1.1, 1.2)
- Treatment to increase bone mass in men with osteoporosis (1.3)
- Treatment of glucocorticoid-induced osteoporosis (1.4)
- Treatment of Paget's disease of bone (1.5)

Important limitations of use: The optimal duration of use has not been determined. The need for continued therapy should be re-evaluated on a periodic basis. (1.6)

----------DOSAGE AND ADMINISTRATION----------
- Must be taken with 6-8 oz plain water at least 30 minutes before the first food, drink, or medication of the day; do not lie down for at least 30 minutes after taking FOSAMAX and until after food. (2.6)
- Oral solution: Should be followed by at least 2 oz of water. (2.6)
- Treatment of osteoporosis in postmenopausal women and in men: 10 mg daily or 70 mg (tablet or oral solution) once weekly. (2.1, 2.3)
- Prevention of osteoporosis in postmenopausal women: 5 mg daily or 35 mg once weekly. (2.2)
- Glucocorticoid-induced osteoporosis: 5 mg daily; or 10 mg daily in postmenopausal women not receiving estrogen. (2.4)
- Paget's disease: 40 mg daily for six months. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 5 mg, 10 mg, 35 mg, 40 mg and 70 mg (3)
Oral Solution: 70 mg (3)

----------CONTRAINDICATIONS----------
- Abnormalities of the esophagus which delay emptying such as stricture or achalasia (4, 5.1)
- Inability to stand/sit upright for at least 30 minutes (2, 4, 5.1)
- Do not administer FOSAMAX oral solution to patients at increased risk of aspiration. (4)
- Hypocalcemia (4, 5.2)
- Hypersensitivity to any component of this product (4, 6.2)

----------WARNINGS AND PRECAUTIONS----------
- Severe irritation of upper gastrointestinal (GI) mucosa can occur. Follow dosing instructions. Use caution in patients with active upper GI disease. Discontinue if new or worsening symptoms occur. (5.1)
- Hypocalcemia can worsen and must be corrected prior to use. (5.2)
- Severe bone, joint, muscle pain may occur. Discontinue use if severe symptoms develop. (5.3)
- Osteonecrosis of the jaw has been reported. (5.4)
- Atypical femur fractures have been reported. Evaluate new thigh or groin pain to rule out an incomplete femoral fracture. (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥3%) are abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Calcium supplements, antacids, or oral medications containing multivalent cations interfere with absorption of alendronate. (2.6, 7.1)
- Aspirin and nonsteroidal anti-inflammatory drug use may worsen GI irritation; use caution. (7.2, 7.3)

----------USE IN SPECIFIC POPULATIONS----------
- FOSAMAX is not indicated for use in pediatric patients. (8.4)
- FOSAMAX is not recommended in patients with renal impairment (creatinine clearance <35 mL/min). (2.8, 5.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2012

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1 INDICATIONS AND USAGE

1.1 Treatment of Osteoporosis in Postmenopausal Women

FOSAMAX is indicated for the treatment of osteoporosis in postmenopausal women. In postmenopausal women, FOSAMAX increases bone mass and reduces the incidence of fractures, including those of the hip and spine (vertebral compression fractures). *[See Clinical Studies (14.1).]*

1.2 Prevention of Osteoporosis in Postmenopausal Women

FOSAMAX is indicated for the prevention of postmenopausal osteoporosis *[see Clinical Studies (14.2)]*.

1.3 Treatment to Increase Bone Mass in Men with Osteoporosis

FOSAMAX is indicated for treatment to increase bone mass in men with osteoporosis *[see Clinical Studies (14.3)]*.

1.4 Treatment of Glucocorticoid-Induced Osteoporosis

FOSAMAX is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women receiving glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who have low bone mineral density *[see Clinical Studies (14.4)]*.

1.5 Treatment of Paget's Disease of Bone

FOSAMAX is indicated for the treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone who have alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease. *[See Clinical Studies (14.5).]*

1.6 Important Limitations of Use

The safety and effectiveness of FOSAMAX for the treatment of osteoporosis are based on clinical data of four 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.

2 DOSAGE AND ADMINISTRATION

2.1 Treatment of Osteoporosis in Postmenopausal Women

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one bottle of 70 mg oral solution once weekly
  or
- one 10 mg tablet once daily

2.2 Prevention of Osteoporosis in Postmenopausal Women

The recommended dosage is:

- one 35 mg tablet once weekly
  or
- one 5 mg tablet once daily

2.3 Treatment to Increase Bone Mass in Men with Osteoporosis

The recommended dosage is:

- one 70 mg tablet once weekly
  or
- one bottle of 70 mg oral solution once weekly
  or
- one 10 mg tablet once daily

2.4 Treatment of Glucocorticoid-Induced Osteoporosis

The recommended dosage is one 5 mg tablet once daily, except for postmenopausal women not receiving estrogen, for whom the recommended dosage is one 10 mg tablet once daily.

2.5 Treatment of Paget's Disease of Bone

The recommended treatment regimen is 40 mg once a day for six months.

Re-treatment of Paget's Disease

Re-treatment with FOSAMAX may be considered, following a six-month post-treatment evaluation period in patients who have relapsed, based on increases in serum alkaline phosphatase, which should be measured periodically. Re-treatment may also be considered in those who failed to normalize their serum alkaline phosphatase.

2.6 Dosing Instructions

FOSAMAX must be taken *at least* one-half hour before the first food, beverage, or medication of the day with plain water only *[see Patient Counseling Information (17.2)]*. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of FOSAMAX *[see Drug Interactions (7.1)]*. Waiting less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water) or other medications will lessen the effect of FOSAMAX by decreasing its absorption into the body.

FOSAMAX should only be taken upon arising for the day. To facilitate delivery to the stomach and thus reduce the potential for esophageal irritation, a FOSAMAX tablet should be swallowed with a full glass of water (6-8 oz). To facilitate gastric emptying FOSAMAX oral solution should be followed by at least 2 oz (a quarter of a cup) of water. Patients should not lie down for at least 30 minutes and until after their first food of the day. FOSAMAX should not be taken at bedtime or before arising for the day. Failure to follow these instructions may increase the risk of esophageal adverse experiences *[see Warnings and Precautions (5.1) and Patient Counseling Information (17.2)]*.

2.7 Recommendations for Calcium and Vitamin D Supplementation

Patients should receive supplemental calcium if dietary intake is inadequate *[see Warnings and Precautions (5.2)]*. Patients at increased risk for vitamin D insufficiency (e.g., over the age of 70 years, nursing home-bound, or chronically ill) may need vitamin D supplementation. Patients with gastrointestinal malabsorption syndromes may require higher doses of vitamin D supplementation and measurement of 25-hydroxyvitamin D should be considered.

Patients treated with glucocorticoids should receive adequate amounts of calcium and vitamin D.

2.8 Dosing in Severe Renal Impairment

FOSAMAX is not recommended for patients with creatinine clearance <35 mL/min due to lack of experience in this population *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg tablets are white, round, uncoated tablets with an outline of a bone image on one side and code MRK 925 on the other.
- 10 mg tablets are white, oval, wax-polished tablets with code MRK on one side and 936 on the other.
- 35 mg tablets are white, oval, uncoated tablets with code 77 on one side and a bone image on the other.
- 40 mg tablets are white, triangular-shaped, uncoated tablets with code MSD 212 on one side and FOSAMAX on the other.
- 70 mg tablets are white, oval, uncoated tablets with code 31 on one side and an outline of a bone image on the other.
- 70 mg oral solution is a clear, colorless solution with a raspberry flavor.

4 CONTRAINDICATIONS

- Abnormalities of the esophagus which delay esophageal emptying such as stricture or achalasia *[see Warnings and Precautions (5.1)]*
- Inability to stand or sit upright for at least 30 minutes *[see Dosage and Administration (2.6); Warnings and Precautions (5.1)]*
- Do not administer FOSAMAX oral solution to patients at increased risk of aspiration.
- Hypocalcemia *[see Warnings and Precautions (5.2)]*
- Hypersensitivity to any component of this product. Hypersensitivity reactions including urticaria and angioedema have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Upper Gastrointestinal Adverse Reactions

FOSAMAX, like other bisphosphonates administered orally, may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when FOSAMAX is given to patients with active upper gastrointestinal problems (such as known Barrett's esophagus, dysphagia, other esophageal diseases, gastritis, duodenitis, or ulcers).

Esophageal adverse experiences, such as esophagitis, esophageal ulcers and esophageal erosions, occasionally with bleeding and rarely followed by esophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates including FOSAMAX. In some cases these have been severe and required hospitalization. Physicians should therefore be alert to any signs or symptoms signaling a possible esophageal reaction and patients should be instructed to discontinue FOSAMAX and seek medical attention if they develop dysphagia, odynophagia, retrosternal pain or new or worsening heartburn.

The risk of severe esophageal adverse experiences appears to be greater in patients who lie down after taking oral bisphosphonates including FOSAMAX and/or who fail to swallow oral bisphosphonates including FOSAMAX with the recommended full glass (6-8 oz) of water, and/or who continue to take oral bisphosphonates including FOSAMAX after developing symptoms suggestive of esophageal irritation. Therefore, it is very important that the full dosing instructions are provided to, and understood by, the patient *[see Dosage and Administration (2.6)]*. In patients who cannot comply with dosing instructions due to mental disability, therapy with FOSAMAX should be used under appropriate supervision.

There have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications, although no increased risk was observed in controlled clinical trials *[see Adverse Reactions (6.2)]*.

5.2 Mineral Metabolism

Hypocalcemia must be corrected before initiating therapy with FOSAMAX *[see Contraindications (4)]*. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcemia should be monitored during therapy with FOSAMAX.

Presumably due to the effects of FOSAMAX on increasing bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated, and in patients receiving glucocorticoids, in whom calcium absorption may be decreased.

Ensuring adequate calcium and vitamin D intake is especially important in patients with Paget's disease of bone and in patients receiving glucocorticoids.

5.3 Musculoskeletal Pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates that are approved for the prevention and treatment of osteoporosis *[see Adverse Reactions (6.2)]*. This category of drugs includes FOSAMAX (alendronate). Most of the patients were postmenopausal women. 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.

In placebo-controlled clinical studies of FOSAMAX, the percentages of patients with these symptoms were similar in the FOSAMAX and placebo groups.

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ), which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients taking bisphosphonates, including FOSAMAX. Known risk factors for osteonecrosis of the jaw include invasive dental procedures (e.g., tooth extraction, dental implants, boney surgery), diagnosis of cancer, concomitant therapies (e.g., chemotherapy, corticosteroids), poor oral hygiene, and co-morbid disorders (e.g., periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk for ONJ. Clinical judgment of the treating physician and/or oral surgeon should guide the management plan of each patient based on individual benefit/risk assessment.

Patients who develop osteonecrosis of the jaw while on bisphosphonate therapy should receive care by an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of bisphosphonate therapy should be considered based on individual benefit/risk assessment.

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 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 Renal Impairment

FOSAMAX is not recommended for patients with creatinine clearance <35 mL/min *[see Dosage and Administration (2.8)]*.

5.7 Glucocorticoid-Induced Osteoporosis

The risk versus benefit of FOSAMAX for treatment at daily dosages of glucocorticoids less than 7.5 mg of prednisone or equivalent has not been established *[see Indications and Usage (1.4)]*. Before initiating treatment, the gonadal hormonal status of both men and women should be ascertained and appropriate replacement considered.

A bone mineral density measurement should be made at the initiation of therapy and repeated after 6 to 12 months of combined FOSAMAX and glucocorticoid treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials 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

Daily Dosing

The safety of FOSAMAX in the treatment of postmenopausal osteoporosis was assessed in four clinical trials that enrolled 7453 women aged 44-84 years. Study 1 and Study 2 were identically designed, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational n=994); Study 3 was the three year vertebral fracture cohort of the Fracture Intervention Trial [FIT] (n=2027) and Study 4 was the four-year clinical fracture cohort of FIT (n=4432). Overall, 3620 patients were exposed to placebo and 3432 patients exposed to FOSAMAX. Patients with pre-existing gastrointestinal disease and concomitant use of non-steroidal anti-inflammatory drugs were included in these clinical trials. In Study 1 and Study 2 all women received 500 mg elemental calcium as carbonate. In Study 3 and Study 4 all women with dietary calcium intake less than 1000 mg per day received 500 mg calcium and 250 IU Vitamin D per day.

Among patients treated with alendronate 10 mg or placebo in Study 1 and Study 2, and all patients in Study 3 and Study 4, the incidence of all-cause mortality was 1.8% in the placebo group and 1.8% in the FOSAMAX group. The incidence of serious adverse event was 30.7% in the placebo group and 30.9% in the FOSAMAX group. The percentage of patients who discontinued the study due to any clinical adverse event was 9.5% in the placebo group and 8.9% in the FOSAMAX group. Adverse reactions from these