OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-223/S016	Submission Date(s): 9/21/07, 11/20/07
Brand Name	Zometa®
Generic Name	Zoledronic acid
Reviewer	Jaya bharathi Vaidyanathan, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	DCP-2
OND division	Metabolic and Endocrine Products
Sponsor	Novartis
Submission Type; Code	SE5 (Pediatric Exclusivity); Priority
Formulation; Strength(s)	IV infusion; 5 mg/100 ml vial
Indication	Treatment of Osteogenesis Imperfecta

Table of Contents

I. Executive Summary

Osteogenesis imperfecta (OI) comprises a group of disorders affecting type I collagen which result in increased bone fragility ("brittle bone disease"). The severity of the clinical characteristics increases in the following order, as follows: type I< type IV, V VI, VII< type III < type II. Type I patients have mild non-deforming disease typically associated with a premature stop codon in COL1A1 demonstrated as a reduction in the rate of collagen production. Children with severe OI suffer recurrent fractures resulting in severe deformity and stunted growth and usually accompanied by chronic bone pain with loss of independent ambulation by the teenage years in over 50% of cases. Currently there is no approved drug treatment for OI, excluding neridronate in Italy.

Bisphosphonates are potent inhibitors of bone resorption. These compounds are widely used for the treatment of adults suffering from bone loss and increased bone fragility. Literature data suggest that pamidronate, a second generation bisphosphonate to be of benefit to children with severe forms of OI.

Zometa (zoledronic acid) is a more potent bisphosphonate than pamidronate and administered at a lower dose and over a much shorter time interval. Zoledronic acid has not been tested in children prior to this pediatric study which was designed according to FDA Written Request. The study evaluated the pharmacokinetics (PK) of zoledronic acid and compared the efficacy, safety and tolerability of zoledronic acid to pamidronate during treatment of children with severe OI for 1 year.

A Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology-2 (OCP/DCP-2) has reviewed NDA 21-223(S16) submitted on 9/21/07 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

B Phase IV Commitments

Not applicable.

C Summary of CPB Findings

Plasma zoledronic acid concentration data were obtained from 10 patients: 4 in the age group of 3-8 years and 6 in the age group of 9-17 years. The pediatric dose was 0.05 mg/kg infused over 30 min. Mean Cmax and AUCinf were 167 ng/ml and 220 ng.h/ml

respectively. The concentration of zoledronic acid in the pediatric patients was generally lower than those of the adults. The profiles appeared to be similar to that of the adults and represent a multi-exponential decline of plasma concentration with time. The inter-subject variability in AUC values for the pediatric and adult patients was comparable. The coefficient of variation (CV) was 39% in the pediatric patients and 37% in the 16 adult patients. The sponsor has tried to determine the urine PK parameters for zoledronic acid, however the results were unacceptable because the urine volumes in the samples were not collected.

There was no correlation between zoledronic acid systemic exposure and intrinsic factors such as age, gender, body weight, and creatinine clearance in pediatric patients.

II QBR

A General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and Biopharmaceutics of the drug?

FDA issued the Pediatric Written Request on August 19, 2002 and subsequent amendments #1 and #2 were issued on November 19, 2002 and August 30, 2006 respectively. In alignment with the Written Request, the sponsor conducted the following studies:

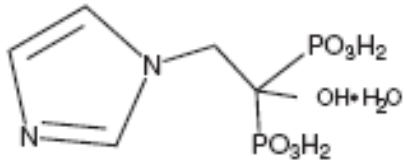
[Study 1:] *An international, multicenter, randomized, open-label, parallel efficacy and safety trial of intravenous zoledronic acid compared to intravenous pamidronate in children with severe osteogenesis imperfecta: Single dose pharmacokinetics in a subset of patients*

[Study 2:] *Study 2202-A Multicenter, randomized, parallel-group study to compare the efficacy and safety and efficacy of zoledronic acid 0.05 mg/kg) to intravenous pamidronate (3.0 mg/kg) in the treatment of pediatric patients with severe osteogenesis imperfecta.*

Based on the Written Request amendment #2 statement, "the population PK study (Study 1) may be part of the clinical safety and efficacy study (Study 2)", the sponsor included the report of the PK study in the final study report for Study 2. In addition, the sponsor stated that they did not conduct a population PK analysis due to the limited number of patients studied and the Agency agreed with the sponsor's conclusion.

Pediatric exclusivity was granted to the sponsor for Zometa.

What is the chemical structure of Zometa?



What is the mechanism of action and therapeutic indication?

The principle pharmacologic action of zoledronic acid is inhibition of bone resorption. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

No indication is being sought in this application.

Are the active moieties in the plasma appropriately identified and measured?

Yes.

B Clinical Study Description

What was the design of the clinical study?

The PK assessments were part of the clinical study which was an open-label, active-controlled, parallel-group efficacy and safety study in pediatric patients with severe OI. Patients were randomized to either zoledronic acid or pamidronate in a 1:1 ratio. The duration of the study was approximately 13 months; the actual study was 12 month long which was preceded by a 4 to 9 week screening period.

The doses of zoledronic acid administered as an i.v. infusion based on age and body weight are shown above in Table 1. The majority of patients received the study drug every 3 months, except pamidronate treated patients who were younger than 2 years of age whose study drug infusions were every 2 months.

Zoledronic acid was provided as either 5 mg/5 ml or 5 mg/100 ml vials. The 5 mg/100 ml vials was used in patients < 3 years old while the 5 mg/5 ml vials was used in patients ≥3 years of age. The dosing was as follows:

Table 1: Zoledronic acid pediatric dosing schedule

Age	Dose of zoledronic acid	Frequency
1 to <3 years	0.025 mg/kg diluted in 50 mL of normal saline †	30 to 45 minute infusion every 3 months
3 to 17 years	0.05 mg/kg diluted in 100 mL of normal saline ‡	30 minute infusion every 3 months

Note: No infants aged <1 year were included in this study.
† Zoledronic acid dose must not exceed 2.0 mg, except when a 2 year old patient had a birthday during the study, then he/she was switched to the higher dosing schedule at the next infusion.
‡ Zoledronic acid dose must not exceed 4.0 mg

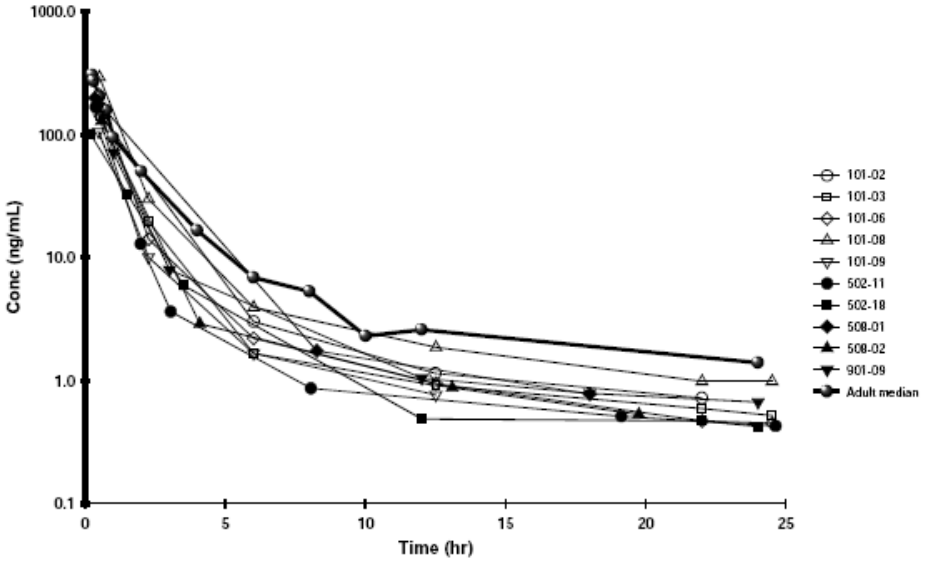
The primary objective of the clinical study was to assess percentage changes in lumbar spine bone mineral density measured by DEXA at month 12 relative to baseline in zoledronic acid treated pediatric patients with severe OI compared to those in pamidronate treated patients who were ≥1 year to ≤17 years of age. The efficacy of zoledronic acid was considered to be demonstrated in this study, if it were shown to be non-inferior to pamidronate.

Blood samples for PK were collected from patients 1 to 17 years of age while the urine samples for PK were collected only from children ≥3 years of age. PK sampling was done at Visit 2 (randomization/Dose 1). The samples were collected at pre-dose and any time during the specified time intervals after the start of the infusion. For younger patients (≤ 8 years old), these intervals were 5-30 min, 3-6h, 8-16 h and 18-22h. The same intervals applied to the older patients with the addition of 1-2h and 24-30h. Due to the limited enrollment of PK patients, the population PK analysis was not done and only the non-compartmental analysis was performed to calculate the PK parameters. At the end of the study, the PK population included 11 patients and met the requirements of the Written Request (i.e., at least 4 patients in the age group of 1-8 years and 9-17 years old from Written Request # 2). The PK results are discussed in the section below.

What are the pharmacokinetics characteristics of zoledronic acid in pediatric patients and how does it compare to adults?

Plasma PK: Plasma zoledronic acid concentration data were obtained from 10 patients out of 11 enrolled: The plasma concentration versus time data for each patient is shown below along the median concentration versus time curve of subsets of adult cancer patients with normal renal function from two previous studies. The adults (with normal renal function) received a dose of 4 mg i.v. over 15 minutes (average body weight = 80 kg). The pediatric dose was 0.05 mg/kg. The infusion time for pediatric patients was 30 minutes, which theoretically would result in a lower Cmax compared to the same dose infused over a 15-min period. In agreement with this, the concentration of zoledronic acid in the pediatric patients was lower than those of the adults.

Figure 1: Plasma zoledronic acid concentration versus time in pediatric patients compared to adult patients



Adult median data were derived from 7 patients in study ZOL446D0503 and 9 patients in study ZOL446E0506 who received a dose of 4 mg zoledronic acid infused over 15 minutes and had normal renal function.

The profiles in pediatric patients represent a multi-exponential decline of plasma concentration with time as seen with adult patients. The inter-subject variability in AUC values for the pediatric and adult patients was comparable. The coefficient of variation (CV) was 39% in the pediatric patients and 37% in the 16 adult patients.

PK parameters were calculated using non-compartmental analysis and are shown in Table 2 below. The terminal elimination half-life could not be estimated in 3 patients, while in other 7 patients it was in the range of 8-18.5 hours. The systemic total clearance was 5-15.8 L/h and volume of distribution based on terminal elimination was 45-340 L in these patients.

Table 2: Summary of PK parameters for zoledronic acid

Statistic	Cmax (ng/mL)	Tmax (h)	AUC(0-18h) (ng.h/mL)	AUC (0-last) (ng.h/mL)	Lambda-z (1/h)	t-half (h)	AUC inf (ng.h/mL)	Vz (L)	CL (L/h)
n	10	10	10	10	7	7	7	7	7
Mean	167		217	220	0.095	12.0	233	156	8.45
SD	57		85	86	0.038	4.6	70	108	3.86
CV (%)	34.0		39.3	39.2	39.7	38.4	29.9	69.2	45.7
Min	102	0.17	125	123	0.054	6.32	165	45.7	5.01
Median	158	0.5	189	194	0.094	10.6	217	128	6.72
Max	293	0.58	373	373	0.158	18.6	370	340	15.8
Geometric mean	159		204	207	0.089	11.2	225	126	7.81

Urine PK: Urine concentration data were also obtained from the above 10 patients plus another patient in the 9-17 group. The sponsor has stated that the quality of the data on renal excretion of zoledronic acid was compromised by the failure to measure the volume

of each of the urine collections and therefore the amount of drug excreted in the urine could not be calculated accurately. Therefore the sponsor has tried to estimate the urine volumes from the serum and urine creatinine concentrations and creatinine clearance values using the following equation:

Vu = 600 x CLcr x sCr x t x BSA/(113 x 1.73 x uCr),

where CLcr is creatinine clearance (ml/min/1.73 m^2), sCr is serum creatinine concentration (mg/dl), t is the duration of collection (h), BSA is body surface area (m^2), uCr is urinary creatinine concentration (mmol/L), 600 is the factor converting hours to minutes and liters to deciliters, 113 is the molecular weight of creatinine and 1.73 m^2 is the factor normalizing CLcr by BSA.

Sponsor used the method of Shull (1978) in estimating creatinine clearance, which is based on the following formula:
CLcr = Creatinine excretion ratio (ER) x 100/Serum creatinine, where the ER = (0.035x age) + 0.236
Ref: Clinical chemistry, vol: 24(7), 1978, Shull et al., A useful method for predicting creatinine clearance in children.

Comments: (Based on discussions with Agency expert in pediatric nephrology)

- In the United States, the National Kidney Foundation's Kidney Disease Quality Outcomes Initiative (KDOQI) specifically recommends estimation of GFR using a formula that "takes into account the serum creatinine concentration and the patient's height and gender". The Shull formula only uses the age and serum creatinine as shown above. The two formulas used in pediatrics are the Schwartz and the Counahan-Barratt formulas (*Ref: Pediatrics 2003;111:1416-1421, Hogg RJ, et al. National Kidney Foundation's kidney disease outcome quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: Evaluation, classification and stratification*).

Table 3: Estimation of GFR in children using serum creatinine and height

Author, Year (No. of Subjects)	Equation
Schwartz et al[12] (N = 186)	$C_{Cr}\,(\text{mL/min/1.73 m}^2) = \frac{0.55 \times Height\,(cm)}{S_{Cr}\,(mg/dL)}$
Counahan et al[15] (N = 108)	$GFR\,(\text{mL/min/1.73 m}^2) = \frac{0.43 \times Height\,(cm)}{S_{Cr}\,(mg/dL)}$

C_{Cr} indicates creatinine clearance; S_{Cr}, serum creatinine.
In the Schwartz equation, the constant to be used in young children (<1 year of age) is 0.45,[13] in adolescent boys the value of the constant changes to 0.7.[14] To convert serum creatinine in μmol/L to mg/dL, the value in umol/L is multiplied by 0.0113.

- The estimation of urine volume based upon the serum creatinine and estimated GFR, assumes that the excretion of creatinine is independent of age and gender, which it is not as shown by Hellerstein S, et al. Pediatric Nephrology 2001;16:637-643, Creatinine excretion rates for renal clearance studies.

- Given the measurement errors introduced with an estimated GFR not accounting for gender, age, or height (such as the Shull formula), and the incorrect assumption about creatinine excretion, the PK calculations done by the sponsor are unreliable and needs to be validated.

- Therefore, the plasma PK data is more reliable than urine PK data in this case and will be reflected in the label.

How was the analytical assay performed and validated?

Plasma concentrations of zoledronic acid (ZOL446/zoledronate) were determined using a validated radioimmunoassay method with a lower limit of quantification of 0.4 ng/ml in human plasma and 10.0 ng/ml in human urine.

Bias and precision of concentrations in plasma samples (Standard)

N	6	6	6	6	6	6	6
Mean	0.098	0.197	0.419	1.10	2.02	4.04	9.73
SD	0.018	0.017	0.064	0.24	0.10	0.19	0.49
Bias %	-2.0	-1.5	4.7	10.0	1.0	1.0	-2.7
CV %	18.4	8.6	15.3	21.8	5.0	4.7	5.0

Bias and precision of concentrations in urine samples (Standard)

N	13	13	13	13	13	13	13
Mean	2.25	3.66	10.0	21.1	39.1	101	379
SD	0.39	0.43	0.7	1.0	1.9	7	39
Bias %	12.5	-8.5	0.0	5.5	-2.3	1.0	-5.3
CV %	17.3	11.7	7.0	4.7	4.9	6.9	10.3

Bias and precision of concentrations in plasma samples (Quality control)

N	12	12	12
MEAN	3.88	1.05	0.431
SD	0.20	0.11	0.051
CV %	5.2	10.5	11.8
Bias (%)	-3.0	5.0	7.7

Bias and precision of concentrations in urine samples (Quality control)

N	26	26	26
MEAN	104	52.5	10.6
SD	10	5.6	1.5
CV %	9.6	10.7	14.2
Bias (%)	4.0	5.0	6.0

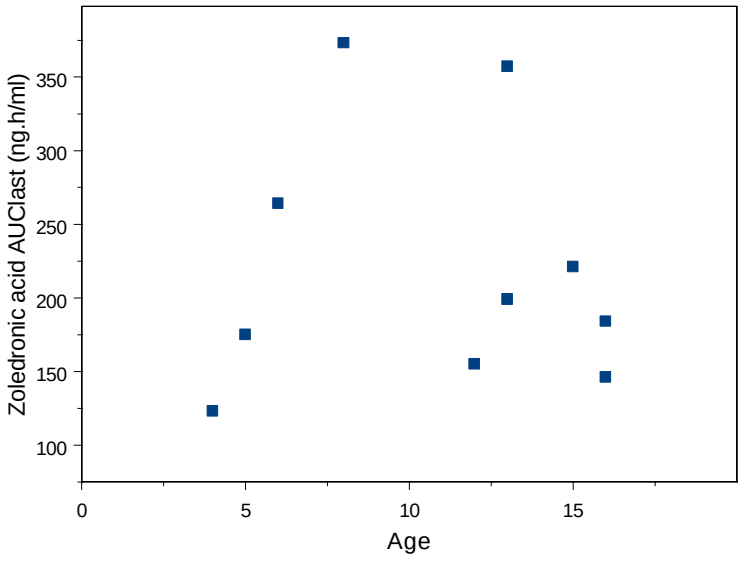
C Intrinsic Factors

What is the influence of age, gender, body weight and other covariates on PK in pediatric patients?

Plasma zoledronic acid AUClast was plotted for each pediatric patient to determine any effect of age, body weight, gender, or creatinine clearance.

Effect of Age: There were four patients in the age group of 4-8 years and six patients in that age group of 9-17 years. The plot does not show any trend in the zoledronic acid AUClast with age.

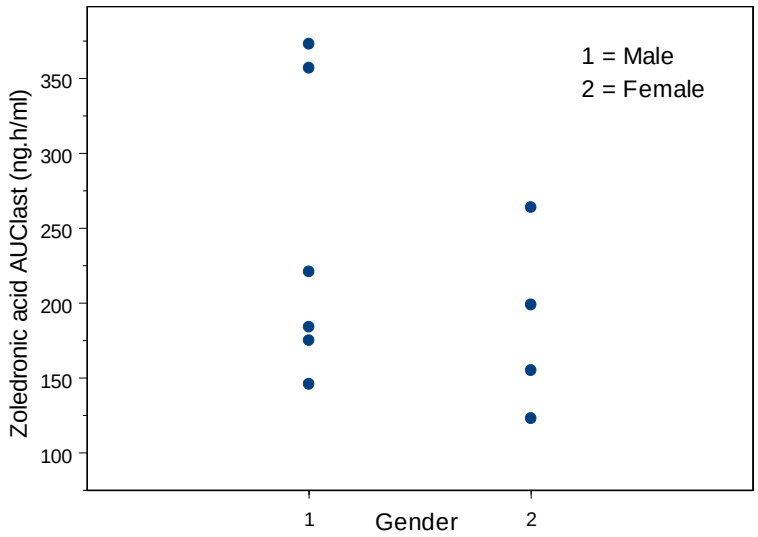
Figure 2: Effect of age on zoledronic acid AUC



Effect of Gender: There were four female patients and six male patients. The plot shows a trend towards high plasma zoledronic acid exposure in male patients, which is mainly driven by two male patients who had very high drug exposure compared to other patients (AUC>300 ng/ml). In one of the two patients, blood sampling was performed at 33 minutes post-dose and then not until 8.5 h post start of infusion which might have

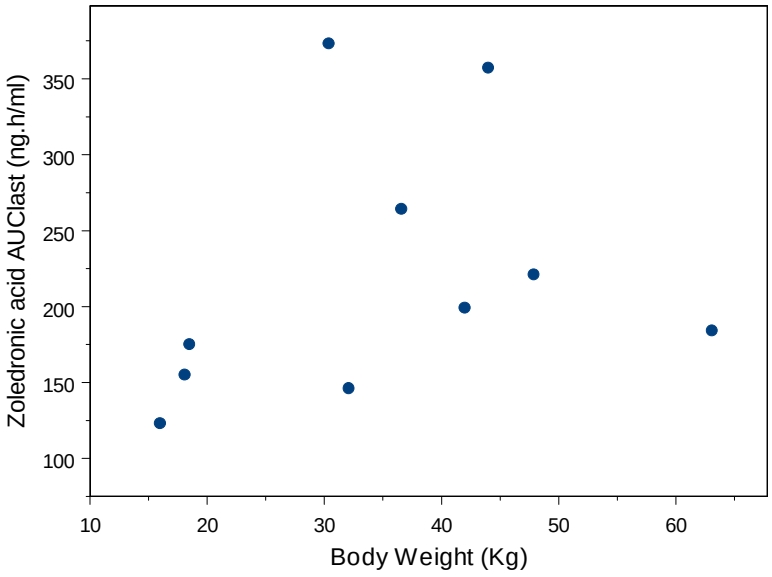
resulted in the overestimation of AUC. Due to the limited number of patients in each group, a definite conclusion cannot be drawn regarding the effect of gender.

Figure 3: Effect of gender on zoledronic acid AUC



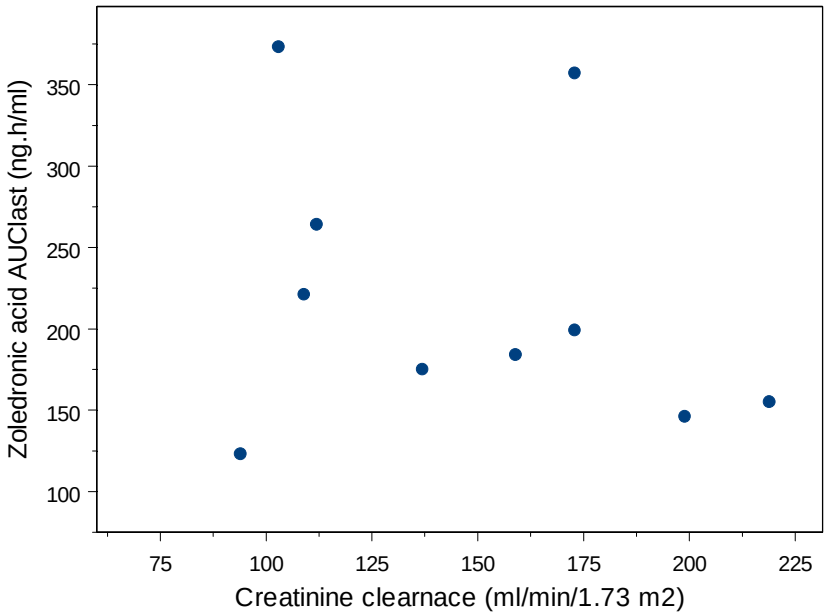
Effect of Body weight: The 10 patients in the PK study had body weights in the range of 16-63 kg. The plot does not show any obvious correlation of the zoledronic acid AUClast with body weight. The dosing regimen is weight adjusted and therefore this lack of any effect of body weight on exposure is not surprising.

Figure 4: Effect of body weight on zoledronic acid AUC



Effect of Creatinine clearance: There was no apparent effect of renal function on zoledronic acid exposure over the range of creatinine clearance (94-219 ml/min/1.73 m^2) observed in the 10 patients who did not have any renal impairment. *Note*: Sponsor used the method of Shull (1978) in estimating creatinine clearance (see comments under urine PK).

Figure 5: Effect of creatinine clearance on zoledronic acid AUC



III Labeling Comments

The Division of Clinical Pharmacology -2 (OCP/DCP-2) has reviewed the package insert labeling for Zometa and finds it acceptable pending the following revision:

(~~Strikethrough text~~ is recommended to be deleted and **underlined text** is recommended to be added.)

8 Use in Specific Population

8.4 Pediatric Use

Zometa is not indicated for use in children.

Plasma zoledronic acid concentration data after 0.05 mg/kg dose infused over 30 min were obtained from 10 patients with severe osteogenesis imperfecta: 4 in the age group of 3-8 years and 6 in the age group of 9-17 years. Mean Cmax and $AUC_{(0\text{-}last)}$ was 167 ng/ml and 220 ng.h/ml respectively. The plasma concentration time profile of zoledronic acid in pediatric patients

represent a multi-exponential decline, as patients at an approximately equivalent mg/k

12 Clinical Pharmacology

Special Population

Pediatrics

Zometa is not indicated for use in

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C OCP Filing Memo

1.1.1 Office of Clinical Pharmacology

2 *New Drug Application Filing and Review Form*

2.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	**21-223/SE5-016**	**Brand Name**	**Zometa**
OCP Division	**2**	**Generic Name**	**Zoledronic acid**
Medical Division	**DMEP**	**Drug Class**	**Bisphosphonate**
OCP Reviewer	**Jayabharathi Vaidyanathan, Ph.D.**	**Indication(s)**	**Severe osteogenesis imperfecta**
OCP Team Leader	**Sally Choe, Ph.D.**	**Dosage Form**	**Sterile solution for injection**
		Dosing Regimen	**Patents 3 -17 years: 0.05 mg/kg up to a maximum of 4 mg every 3 months intravenously for one year. Patents aged 1 to < 3 years: 0.025 mg/kg up to a maximum of 2 mg every 3 months for one year.**
Date of Submission	**9/21/07**	**Route of Administration**	**Intravenous**
Estimated Due Date of OCPB Review	**1/24/08**	**Sponsor**	**Novartis**
PDUFA Due Date	**3/24/08**	**Priority Classification**	**Priority**
2.1.1.2 Division Due Date	**2/24/08**		

2.1.1.2.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
2.2 Healthy Volunteers-				
single dose:				
multiple dose:				
2.2.1 Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x	1		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		
2.2.1.1.1.1				

2.2.1.1.1.2 Filability and QBR comments		
2.2.1.2	**"X" if yes**	2.2.1.2.1.1.1.1 Comments
2.2.1.3 Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable)
2.2.1.4 Comments sent to firm ?		**Please submit the PK data set for study 2202 electronically as SAS transport files. In addition please submit the lumbar spine BMD in these patients.**
2.2.1.5		
QBR questions (key issues to be considered)	1) Is the PK of zoledronic acid different in pediatric patients as compared to adults?	
Other comments or information not included above		
Primary reviewer Signature and Date	**Jaya bharathi Vaidyanathan, Ph.D.**	

Secondary reviewer Signature and Date	Sally Choe, Ph.D.

Background:

Zoledronic acid is approved for the prevention of skeletal-related events (pathological fractures, spinal compression, radiation or surgery to bone or tumor–induced hypercalcemia) in adult patients with advanced malignancies involving bone and for treatment of hypercalcemia of malignancy as Zometa®, for Pagets's disease of bone and post-menopausal osteoporosis as Aclasta® outside the US and for Paget's disease of bone as Reclast® within the US. Zoledronic acid has not been tested in children prior to the study submitted in this supplement.

Novartis has conducted this pediatric study CZOL446H2202 which was designed based on the Written Request dated 8/19/2002 & amendments dated 11/19/2002 and 8/30/2006. The study evaluated the PK of zoledronic acid and compared the efficacy, safety and tolerability of zoledronic acid to pamidronate during treatment of children with severe osteogenesis imperfecta (OI) for 1 year.

Summary:

Study CZOL446H2202 was an open-label, randomized, parallel efficacy and safety trial of intravenous zoledronic acid compared to intravenous pamidronate in children with severe OI. The primary objective was to assess the percentage change in lumbar spine (LS) bone mineral density (BMD) at month 12 relative to baseline in zoledronic acid treated pediatric patients compared to pamidronate treated patients who were 1 to 17 years of age. The secondary objective was to demonstrate the safety of zoledronic acid. The PK objective was to assess the PK of zoledronic acid in 24 consenting patients. Urine samples were obtained in patients ≥ 3 years of age. The sponsor has stated that sample size was changed to 11 consenting patients after discussion with FDA.

Bioanalytics: Due to the limited enrollment of PK patients, the population PK analysis could not be done. Instead, a non-compartmental analysis was performed using WinNonlin Professional, v. 5.0.1 to calculate the following PK parameters: Cmax, Tmax, AUC(0-18h), AUC(0-t), $t_{½}$, AUC(0-∞), Vz and CL. AUC(0-18h) for each patient was plotted along with various patient characteristics (age, gender, body weight and creatinine clearance). Urinary excretion and renal clearance were estimated

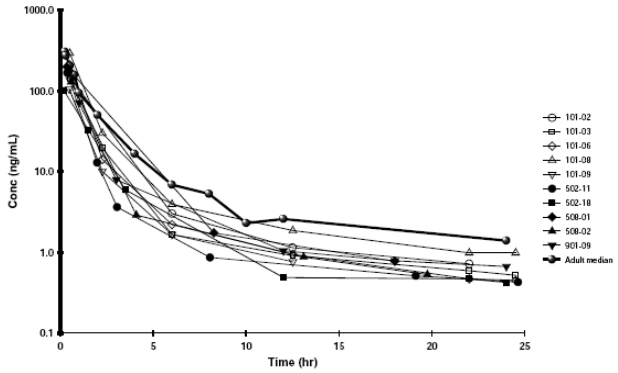
A direct immunoassay with a limit of quantitation of 0.4 ng/ml in human serum and plasma and 5 ng/ml in urine was used to detect zoledronic acid.

PK conclusions

The pharmacokinetics of plasma zoledronic acid in 10 pediatric patients with osteogenesis imperfecta appear to be similar to that in adult cancer patients at approximately the same mg/kg dose. Plasma concentrations in the pediatric patients were generally at or below the median concentrations in adults. The lower levels may be an advantage in consideration of drug safety and tolerability. There appeared to be no effect of age, gender, body weight and creatinine clearance on zoledronic acid exposure.

The pharmacokinetics of urinary zoledronic acid in 11 pediatric patients with osteogenesis imperfecta appear to be similar to that in adult cancer patients at approximately the same mg/kg dose. The percentage of dose excreted in urine, the time course of urinary excretion, and the estimated renal clearance in pediatric OI patients appeared to be similar to those in adult cancer patients. However, the lack of direct measurements of the volumes of the pooled urine collections led to a rough estimation of the urine volumes based on uCr, sCr, CLcr and BSA. The dependence on so many other parameters introduces a degree of uncertainty into the volume estimates, and makes the conclusions about the urinary excretion of zoledronic acid speculative.

The plasma concentration time profiles in pediatric patients who received 4 mg zoledronic acid are shown in comparison with adult median data in the following figure.



Adult median data were derived from 7 patients in study ZOL446D0503 and 9 patients in study ZOL446E0506 who received a dose of 4 mg zoledronic acid infused over 15 minutes and had normal renal function.

Efficacy conclusions

In children with severe osteogenesis imperfecta, every 3-monthly infusions of zoledronic acid were statistically significantly superior to pamidronate in terms of:

- increased lumbar spine BMD after 12 months of treatment (evaluated in patients aged 2 - 17 years)
- sustained reductions in serum biomarkers of bone resorption, β-CTx, and bone formation, P1NP and bone specific ALP (evaluated in patients aged 3 - 17 years)

Conclusions: The Clinical Pharmacology section of this application is filable**.**

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/s/

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3/5/2008 12:40:08 PM
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