

Pharmacometrics Consult

PHARMACOMETRICS REVIEW

NDA:	22-080
Proprietary Drug Name:	RECLAST®
Generic Name:	Zoledronic Acid
Indication:	Treatment of postmenopausal osteoporosis
Dosage Form:	IV Solution
Dosing Regimen:	5 mg over 15 minutes administered once yearly
Applicant:	Novartis
Clinical Division:	DMEP (HFD-510)
Type of Submission:	Standard NDA
Submission Dates:	16 October 2007
Reviewers:	Christine Garnett, Pharm.D. Joo Yeon Lee, Ph.D.
Team Leader:	Joga Gobburu, Ph. D.

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Synopsis and recommendation

Synopsis

Renal deterioration, defined by elevated serum creatinine >0.5 mg/dL, occurs with zoledronic acid, and is correlated with factors such as baseline CL_{cr} and drug exposure as described in Drs. Brian Booth and Roshni Ramchandani's review of NDA 21-386. Furthermore, postmarketing data shows that 25% of the renal failure cases (N=72) occurred after the first dose of ZOMETA (Chang, 2003). Dose adjustments are recommended for patients with reduced renal function (CL_{cr} >30 to ≤60 ml/min) using ZOMETA® for multiple myeloma and metastatic bone lesions from solid tumors. The approved dosing regimen for cancer patients is 4 mg by IV infusion every 3 to 4 weeks.

The sponsor has submitted NDA 22-080 seeking approval of RECLAST® for the treatment of postmenopausal osteoporosis (PMO). The proposed dosing regimen is 5 mg IV infusion over no less than 15 minutes once yearly. No dose adjustment has been proposed for patients with a CL_{cr} >30 to ≤60 ml/min. Review objectives were 1) to review the renal safety data for the pivotal 3-year phase 3 study (ZOL446H2301) in 7746 women with PMO and 2) to determine if dose adjustment based on renal function is needed in patients with PMO.

The analysis showed that approximately twice (1.81% versus 0.81%) as many women receiving annual infusions of 5 mg zoledronic acid experienced renal deterioration, as defined as an increase in serum creatinine (SCr) by 0.5 mg/dL over baseline, compared to women receiving placebo. At this time, no dose adjustments are recommended for the following reasons.

1. RECLAST® is not recommended in women with severe renal impairment.
2. Overall, small numbers (42, 1.8%) of subjects experienced renal deterioration within 9 to 11 days of RECLAST® infusion compared to placebo (19, 0.8%). The following table presents the percentage of patients with renal deterioration by baseline renal function. The relative renal deterioration rates in placebo and Reclast arms are not consistent across the 3 baseline creatinine clearances. Placebo is apparently worse than RECLAST® in patients with normal baseline renal function.

Baseline Creatinine Clearance, ml/min	Percentage of Patients with an Increase in SCr of 0.5 mg/dL	
	RECLAST®	PLACEBO
30-50	2.69	1.39
50-80	1.83	0.43
>80	0.55	1.49
Overall	1.81	0.81

3. Renal deterioration was transient, in spite of some acute deterioration (as above). By the end of the first year, SCr concentrations were within 0.5 mg/dL of baseline values prior to subsequent dosing.
4. There was no trend for more patients to experience renal deterioration with repeat dosing of RECLAST®.

Potential reasons for the lower incidence of renal deterioration in PMO patient compared to cancer patients are 1) less frequent dosing of zoledronic acid, 2) less frequent monitoring for SCr changes in the clinical trial and 3) different disease state.

Since acute renal failure following Zometa treatment has occurred after the first dose (Markowitz 2003, Chang 2003), we recommend regular monitoring of renal function and discontinuation of treatment if renal function deteriorates.

Recommendation

OCP Pharmacometrics Group has reviewed the renal safety data obtained from study ZOL446H2301 submitted by the sponsor to support the proposed RECLAST label. OCP considers the sponsor's evaluation of the current renal safety data acceptable and does not recommend dose adjustments based on baseline renal function. We do, however, recommend regular monitoring renal function during treatment and _____

Reviewer

Christine Garnett, Pharm.D.
Office of Clinical Pharmacology
Pharmacometrics _____

Joga Gobburu, Ph.D.
Office of Clinical Pharmacology
Director, Pharmacometrics _____

cc:
NDA 22-080: Division File
OCP/DCPII: Lau, Choe, Sahajwalla
HFD510: Seymour

Background

ZOMETA® (zoledronic acid, NDA 21-386) has been approved for the treatment of hypercalcemia of malignancy and for the treatment of osteolytic bone metastases secondary to solid tumors (prostate, breast, lung, colon) or multiple myeloma. For these indications the dosing regimen is 4 mg IV infusion over no less than 15 minutes every 3 to 4 weeks.

Zoledronic acid is excreted unchanged by the kidneys via glomerular filtration. Therefore, zoledronic acid exposure is directly related to renal clearance. Zoledronic acid systemic clearance in individual patients can be calculated from the population clearance of zoledronic acid and the individual creatinine clearance using the Cockcroft-Gault equation (CL_{Cr}), $CL (L/h) = 6.5(CL_{Cr}/90)^{0.725}$. These formulae can be used to predict the AUC in patients, where $CL = \text{Dose}/\text{AUC}$.

Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment ($CL_{Cr} < 30 \text{ mL/min}$). For ZOMETA, dose adjustments are recommended for patients with reduced renal function as shown in Table 1.

Table 1. The Recommended ZOMETA Doses for Cancer Patients with Reduced Renal Function

Baseline Creatinine Clearance (mL/min)	Zometa® Recommended Dose*
> 60	4.0 mg
50 - 60	3.5 mg
40 - 49	3.3 mg
30 - 39	3.0 mg

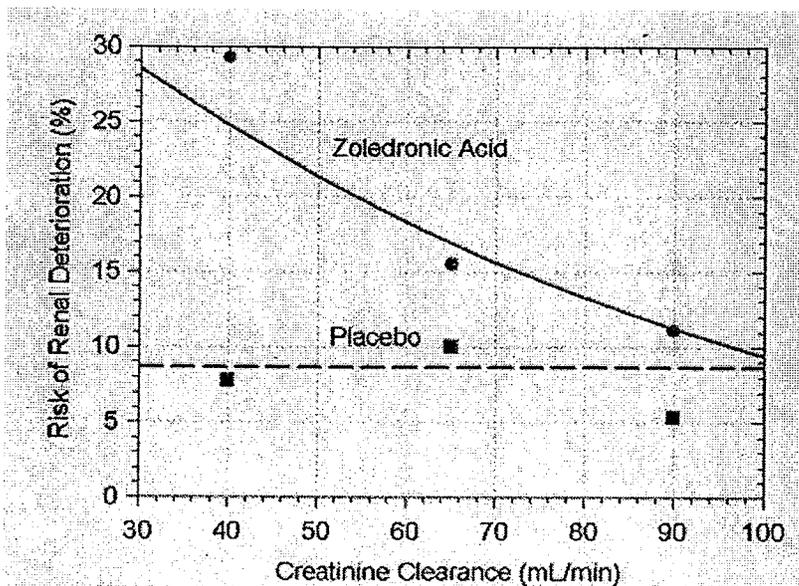
*Doses calculated assuming target AUC of 0.66(mg·hr/L) ($CrCl=75 \text{ mL/min}$)

Source: ZOMETA Label

Renal deterioration occurs with ZOMETA use, and is correlated with factors such as baseline CL_{Cr} (Figure 1) and drug exposure (Figure 2). In these figures renal deterioration was defined as 1) an increase in SCr of 0.5 mg/dL for subjects with normal baseline SCr and 2) an increase in SCr of 1 mg/dL for subjects with abnormal baseline SCr. A detailed description of the renal deterioration with ZOMETA can be found in Drs. Brian Booth's and Roshni Ramchandani's clinical pharmacology reviews for NDA 21-386.

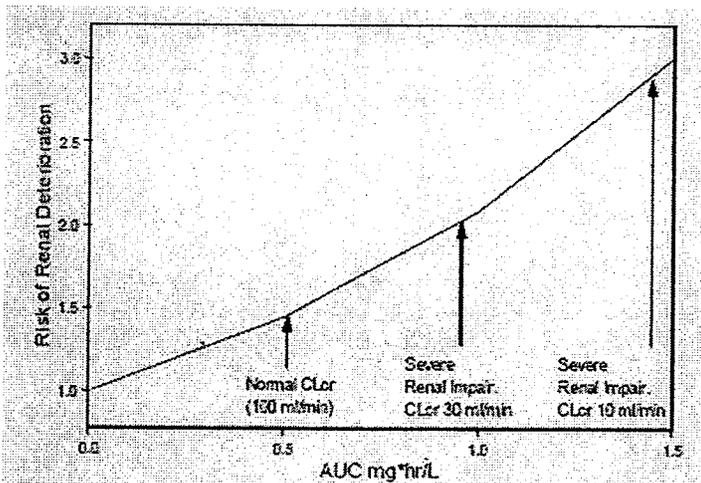
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Figure 1. Percentage of Patients with Renal Deterioration as a Function of Baseline CL_{Cr}



Source: NDA-21-386, Dr. Roshni Ramchandani's NDA-supplemental Review (SE8001AZ 27-Aug-2003); IND 55831, Response to N293 Dose Adj (N293 IB, 28-Sep-2004), Table 5, Page 5

Figure 2. The Hazard Ratio Relative to Baseline for Renal Deterioration vs. ZOMETETA Exposure



Source: NDA-21-386, Dr. Brian Booth's NDA-supplemental Review (SE8001, 16-Oct-2002), Figure 2, Page 6.

RECLAST® has been approved for the treatment of Paget's disease of the bone (zoledronic acid, NDA 21-817). The recommended dose in patients with CL_{Cr} >35 ml/min is a single 5 mg IV infusion over no less than 15 minutes. In two 6-month clinical trials in Paget's disease there was no evidence of renal deterioration. No dose adjustment is required for patients with a CL_{Cr} >30 ml/min. RECLAST is not recommended for patients with severe renal impairment.

Pharmacometrics Consult Objective

The sponsor has submitted NDA 22-080 seeking approval of RECLAST for the treatment of postmenopausal osteoporosis (PMO). The proposed dosing regimen is 5 mg IV infusion over no less than

15 minutes once yearly. No dose adjustment has been proposed for patients with a CL_{Cr} >30 to ≤ 60 ml/min. The purpose of the pharmacometrics consult is 1) to review the renal safety data for the pivotal 3-year phase 3 study in 7746 women with PMO and 2) to determine if dose adjustment based on renal function is needed in patients with PMO.

Clinical data

As part of the NDA, the sponsor has conducted study ZOL446H2301 which is a multicenter, randomized, double-blind, placebo-controlled trial that enrolled women with PMO. The trial was designed to assess the safety and effectiveness of once yearly IV infusion over 15 minutes of 5 mg zoledronic acid. A total of 7746 women were randomized to zoledronic acid (3875) or placebo (3871).

A calculated CL_{Cr} >30 ml/min using the Cockcroft-Gault equation was required for study entry. This criterion was applied for annual dosing with zoledronic acid. If the predose CL_{Cr} was <30 ml/min, the patient did not receive her next dose and received appropriate medical care. The patient was not discontinued from the trial. Appropriate follow up included but was not limited to a repeat assessment of SCr within 2 weeks after the most recent abnormal SCr measurement, unless other medical care interventions had supervened.

Short-term changes in serum creatinine were monitored in a subset of patient (5035, 65%) via laboratory testing 9 to 11 days post-infusion. Long-term changes in renal function were performed in all patients at their annual visits. In this analysis, renal deterioration is defined as an increase in SCr of 0.5 mg/dL from baseline. Renal safety data from this trial was reviewed and analyzed. The data set used for the analysis is located: \\CDSESUB1\NONECTD\N22080\N_000\2007-07-03\crt\datasets\2301\renal.xpt

For this analysis, renal function was classified as moderate renal impairment (CL_{Cr} >30 to ≤ 50 ml/min), mild renal impairment (CL_{Cr} >50 to ≤ 80 ml/min), and normal renal function (CL_{Cr} >80 ml/min) to be consistent with Zometa analyses. The sponsor, however, considered CL_{Cr} >60 ml/min to be normal for PMO women greater than 65 years.

Evaluation of renal safety database for study 2301

Patient Population

The majority of patients (54.58%) enrolled in the study had age-appropriate renal function (creatinine clearance ≥ 60 mL/min) at baseline for postmenopausal women greater than 65 years of age (Table 2).

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Table 2. Sponsor's Table: Calcium and Renal Related Baseline Characteristics

Other Baseline Variables	Zoledronic acid N=3875	Placebo N=3861	Total N=7736
Creatinine Clearance (mL/min)			
N	3875	3861	7736
Mean	63.413	63.873	63.643
SD	17.3334	17.6522	17.4898
Median	61.500	62.000	61.800
Min	30.500	25.300	25.300
Max	184.800	160.000	184.800
Creatinine Clearance Groups (mL/min)- n(%)			
< 30 mL/min ⁽¹⁾	0 (0.00%)	3 (0.08%)	3 (0.04%)
≥ 30 - < 35 mL/min	73 (1.88%)	93 (2.41%)	166 (2.15%)
≥ 35 - < 40 mL/min	187 (4.81%)	148 (3.83%)	315 (4.07%)
≥ 40 - < 50 mL/min	624 (16.10%)	625 (16.19%)	1249 (16.15%)
≥ 50 - < 60 mL/min	821 (23.77%)	860 (22.27%)	1781 (23.02%)
≥ 60 mL/min	2090 (53.94%)	2132 (55.22%)	4222 (54.58%)
Urinary Protein by Dipstick - n(%)			
< 1+	3821 (98.61%)	3788 (98.06%)	7607 (98.33%)
1+	39 (0.98%)	59 (1.50%)	98 (1.24%)
2+ ⁽¹⁾	13 (0.34%)	13 (0.34%)	26 (0.34%)
≥ 3+ ⁽¹⁾	2 (0.05%)	3 (0.08%)	5 (0.06%)
Missing	1 (0.03%)	1 (0.03%)	2 (0.03%)
Serum calcium level (mmol/L)			
N	3875	3861	7736
Mean	2.394	2.393	2.393
SD	0.1072	0.1058	0.1064
Median	2.390	2.390	2.390
Min	1.800	1.950	1.800
Max	2.750	2.750	2.750

Source: PI-Table 7.4-5

⁽¹⁾ Denotes a protocol violation.

Source: Report for Study ZOL446H2301, table 7-8, page 208.

Short-Term Changes in Renal Function

Figure 3 and

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Table 3 show a trend for a higher percentage of patients with $CL_{Cr} < 80$ ml/min treated with zoledronic acid to have an increase in serum creatinine compared to those treated with placebo. The percentage of patients, however, is small and is not increasing with repeat dosing (*Reviewer's Analysis, data source: a_renal.xpt*

Figure 4). There were only 3 women in the zoledronic acid group who had an increase in Scr > 0.5 mg/dL after two consecutive infusions.

Because subjects were followed for 36 months, changes in renal function from baseline that occurred following the 2nd and 3rd infusion may also reflect deterioration of renal function due to other underlying diseases. Therefore the sponsor also assessed renal deterioration between the pre-infusion and post-infusion time (*Reviewer's Analysis, data source: a_renal.xpt*

Table 4). According to the sponsor, of the 31 subjects receiving zoledronic acid, the serum creatinine values declined progressively over time, such that by 12 months after the original event, no patient had an increase in serum creatinine > 0.5 mg/dL relative to their preinfusion value.

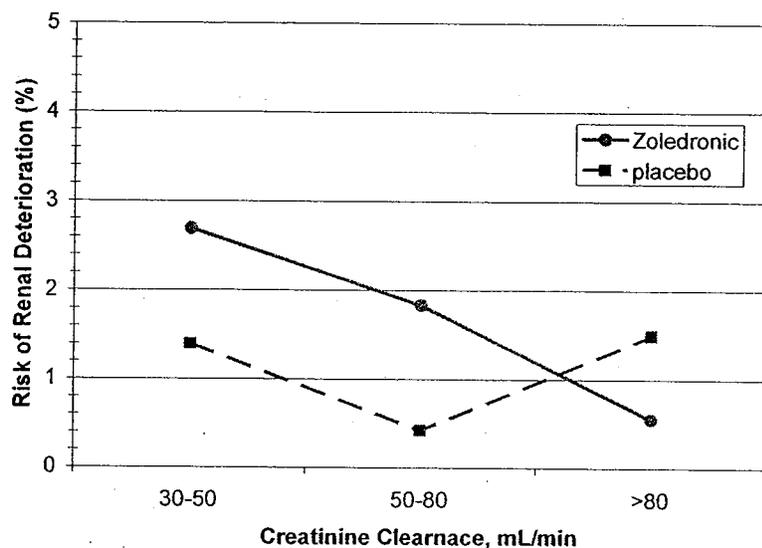
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Table 3. Increase from Baseline in SCr Within 9 to 11 days Post-Infusion

	Baseline CL _{cr} , ml/min	Zoledronic Acid n/N (%)	Placebo n/N (%)
Overall Increase in SCr >0.5 mg/dL from baseline	30- <40	7/131 (5.3%)	4/160 (2.5%)
	≥40 - ≤50	7/372 (1.9%)	4/358 (1.1%)
	50 - <60	7/550 (1.3%)	2/513 (0.4%)
	> 60	21/1267 (1.7%)	19/2338 (0.8%)
	All Patients	42/2320 (1.8%)	19/2338 (0.8%)

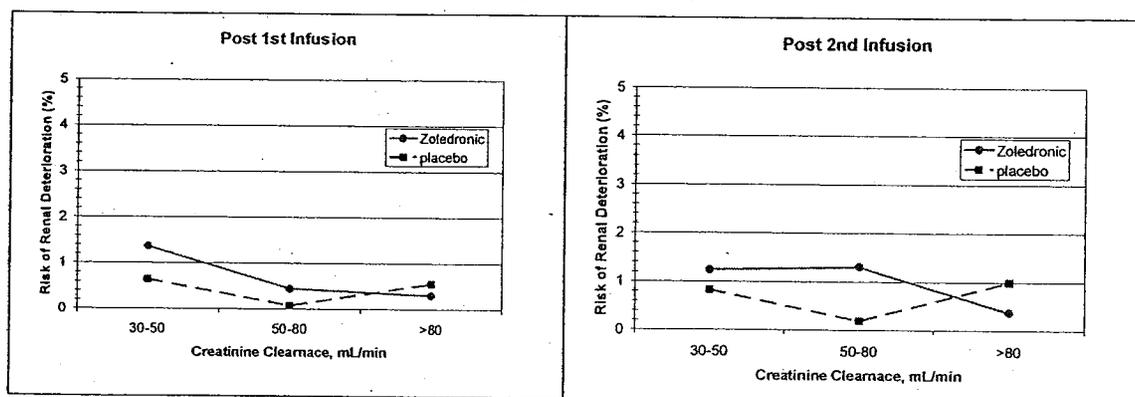
Source: Report ZOL446HPMO, table 3-1, page 19.

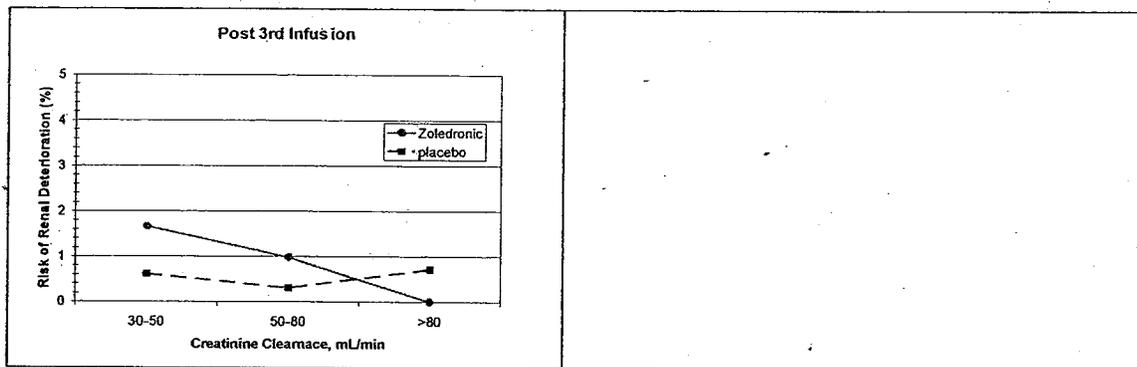
Figure 3. Percentage of Patients with Renal Deterioration within 9 to 11 Days of Dosing as a Function of Baseline CL_{cr} (Post 1st-3rd Infusion)



Reviewer's Analysis, data source: a_renal.xpt

Figure 4. Percentage of Patients with Renal Deterioration within 9 to 11 Days of Dosing as a Function of Baseline CL_{cr}: Stratified by Infusion





Reviewer's Analysis, data source: a_renal.xpt

Table 4. Sponsor's Table: Increase from pre-infusion in serum creatinine >0.5 mg/dL by 9-11 days post-infusion visit and baseline creatinine clearance

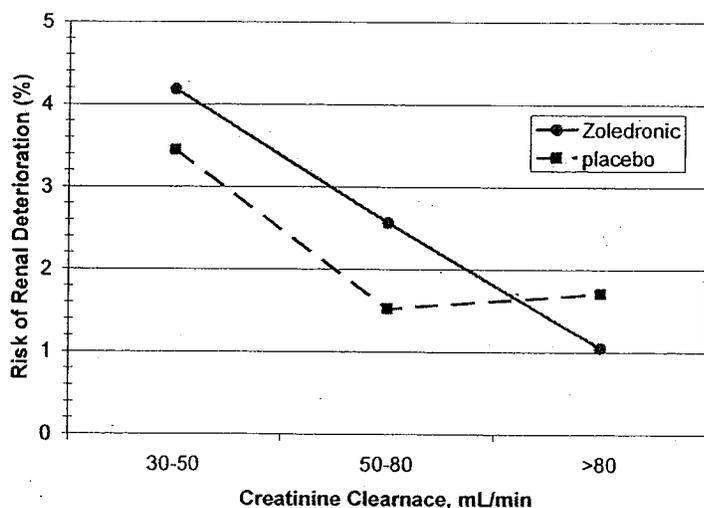
Visit / Lab Test	Zoledronic acid			Placebo		
	N	n	(%)	N	n	(%)
9-11 days post 1st infusion						
Increase in serum creatinine > 0.5mg/dL	2115	13	(0.61)	2133	8	(0.00)
9-11 days post 2nd infusion						
Increase in serum creatinine > 0.5mg/dL	1652	12	(0.72)	1721	1	(0.06)
9-11 days post 3rd infusion						
Increase in serum creatinine > 0.5mg/dL	1550	8	(0.51)	1500	3	(0.00)
Overall						
Increase in serum creatinine > 0.5mg/dL	2520	31	(1.34)	2333	10	(0.28)

Source: Report for Study ZOL446H2301, table 10-13, page 248.

Long-Term Changes in Renal Function

Figure 5 also shows a trend for a higher percentage of patients with $CL_{Cr} < 80$ ml/min treated with zoledronic acid to have an increase in serum creatinine compared to those treated with placebo. It should be noted that long-term changes in SCr concentrations were evaluated annually.

Figure 5. Percentage of Patients with Renal Deterioration of Dosing as a Function of Baseline CL_{Cr} (Pooled Pre-Infusion Data)



Reviewer's Analysis, data source: a_renal.xpt

Reviewer's Comments

The analysis of the renal data collected in study ZOL446H2301 showed renal deterioration within 9 to 11 days of infusion in small numbers (42, 1.8%) of PMO women who received annual infusions of 5 mg zoledronic acid. This analysis is consistent

with the sponsor's assessment of the renal safety of this dosing regimen (Special Expert Evaluation Report of the Renal Effects of 5 mg Zoledronic Acid Given Once Yearly, CZOL446H, Dated 05 January 2007).

There are several key differences between renal deterioration observed with RECLAST and ZOMETA that should be noted.

- 1) The dosing regimen for ZOMETA is 4 mg by IV infusion every 3 to 4 weeks whereas the dosing regimen for RECLAST is 5 mg by IV infusion every year. Therefore, the kidneys of women with PMO have more time to recover from exposure to zoledronic acid compared to cancer patients. Women who experienced a >0.5 mg/dL increase in SCr within 9 to 11 days post-infusion with RECLAST did not have elevated SCr at their next dosing.
- 2) Changes in SCr were monitored annually in the RECLAST trial compared to monthly evaluations in the ZOMETA studies. Less frequent monitoring may contribute to less observed long-term events for RECLAST.

References

Chang JT *et al.* Renal Failure with the Use of Zoledronic Acid. *NEJM* 2003;349(17): 1676-78.

Markowitz GS *et al.* Toxic Acute Tubular Necrosis Following Treatment with Zoledronate (Zometa) *Kidney International*. 2003;64: 281-289

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**Office of Clinical Pharmacology
New Drug Application Filing and Review Form**

General Information About the Submission			
	Information	Brand Name	Information
NDA	22-080	RECLAST®	
OCP Division	2	Generic Name	Zoledronic acid
Medical Division	DMEP, HFD-510	Drug Class	Bisphosphonate
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat postmenopausal osteoporosis
OCP Team Leader	Hae-Young Ahn	Dosage Form	5 mg solution
Date of Submission	16-OCT-2006	Dosing Regimen	5 mg/year
Estimated Due Date of OCP Review	8-JUN-2007	Route of Administration	Intravenous infusion
PDUFA Due Date	17-AUG-2007	Sponsor	Novartis Pharmaceutical Corporation
Division Due Date	29-JUN-2007	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information				
	"X" if Included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
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:				
Metabolism in different species:				
Isozyme characterization:				
Metabolite Identity				
Metabolism Inhibition:				
Plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Cancer Patients (bone metastases)-				
single dose:	x	3		Studies J001, 503, 1101
multiple dose:	x	2		Studies 503, 1101
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:				
geriatrics:				
renal impairment:	X	1		Study 506
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		Study 0041 (dose finding)
Phase 3 clinical trial:	x	1		Study 2301 (pivotal)
Population Analyses -				
Meta-analysis:				
NONMEM:	x	3		Studies J001, 503, 506

II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence				
Relative bioavailability				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design, 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				
Phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies		6		Studies J001, 503, 1101, 506, 0041, 2301
Fillability and QBR comments				
	"X" if yes	Comments		
Application fillable?	X			
Comments to be sent to firm?		For the dose-finding study 0041's bone mineral density and bone turnover markers datasets, please advise the location in the NDA or submit them.		
QBR questions (key issues to be considered)		The requested Study 0041's data would be useful for the attempt to learn the dose-response relationship when combined with the pivotal clinical efficacy and safety study 2301's data.		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

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CLINICAL PHARMACOLOGY

NDA: 22-080
Compound: Zoledronic acid (RECLAST[®]; 5 mg)
Sponsor: Novartis Pharmaceutical Corporation
Submission Date: October 16, 2006
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor markets 4 mg zoledronic acid/5 mL (dilute to 100 mL and infuse over 15 minutes) to treat hypercalcemia of malignancy, multiple myeloma, and bone metastases of solid tumors in the US. The sponsor submitted NDA 22-080 to seek approval for the 5 mg zoledronic acid intravenous infusion over 15 minutes once yearly to treat postmenopausal osteoporosis in women. Zoledronic acid is a bisphosphonate.

Findings

To support NDA 22-080, the sponsor conducted the following studies or submitted the following information:

- Summary of 4 clinical pharmacology studies (see Attachment). Studies J001 and 503 were reviewed under NDA 21-223 by Dr. Robert Shore. Study 506 was reviewed under NDA 21-386 by Dr. Brian Booth. Study 1101 was reviewed under NDA 21-817 by Sandra Suarez-Sharp.
- Summary of population pharmacokinetic analysis for Studies J001, 503, and 506's data.
- The sponsor did not study IV zoledronic acid pharmacokinetics (PK) in postmenopausal osteoporosis patients but in cancer patients with bone metastases. This is acceptable because:
 1. Although Cremers et al stated "Pharmacokinetic data derived in patient populations with bone diseases other than osteoporosis, such as Paget's disease of bone or bone metastases, should not be used for osteoporosis, as biodistribution in the skeleton in these bone diseases is different from that in osteoporosis." in [Page 555, *Clin Pharmacokinet* 44:551-570 (2005)], IV ibandronate (another bisphosphonate) PK does not appear to be different between healthy postmenopausal women and patients with metastatic bone disease [Table III, Barrett et al. *J Clin Pharmacol* 44:951-965 (2004)].
 2. Per the minutes for August 30, 2001's meeting with the sponsor for the prevention and treatment of postmenopausal osteoporosis, it is acceptable not to have additional pharmacokinetic evaluations in the Phase 3 program (DFSed October 11, 2001).
- The sponsor did not study IV 5 mg zoledronic acid PK. However, IV 5 mg zoledronic acid PK can be extrapolated from the IV 4 mg zoledronic acid PK since IV zoledronic acid PK is dose proportional between IV 4 mg and 16 mg zoledronic acid per Dr. Brian Booth's NDA 21-386 Clinical Pharmacology review (DFSed February 24, 2004).
- Reports of a dose-finding study (0041) and the pivotal clinical efficacy and safety study (2301) (see Attachment)
- Study 2301 used 2 formulations (5 mg zoledronic acid/5 mL saline vial and the new 5 mg zoledronic acid/100 mL mannitol vial; see Attachment). The to-be-marketed formulation is the mannitol containing formulation. Dr. Suarez's clinical pharmacology NDA 21-817 review addressed this formulation difference issue that mannitol in the amount of 5 g in the to-be-marketed formulation most likely will not affect the pharmacokinetics of zoledronic acid.
- Proposed labeling for review
- SAS transport files for Study 2301's data

Attachment starts here.

Table 3-1 Summary of key pharmacokinetic studies

Study No.	Study Objective, Population	No. of Patients	Treatment	Medication IV dose / infusion time	Parameters
cancer patients					
J001	Single dose PK and safety of zoledronic acid, effect on bone markers	9	1 dose	2 mg zol / 5 min 4 mg zol / 5 min 8 mg zol / 5 min	C_{max} , AUC, $Ae_{(0-24h)}$ bone markers
503 (503E)	Single and multiple dose PK and safety, effects of single dose on bone resorption markers	36 (27)	1 dose (+2 doses, 4 wks apart)	4 mg zol / 5 min 4 mg zol / 15 min 8 mg zol / 15 min 16 mg zol / 15 min	C_{max} , AUC, $Ae_{(0-24h)}$ bone markers
506 (506E)	Effects of renal function on single and multiple dose PK and bone resorption markers, ADME study	19 (19)	3 x 1dose, (4 wks apart)	4 mg zol / 15 min	C_{max} , AUC, $Ae_{(0-24h)}$ bone markers
1101	Single dose PK, multiple dose safety, effects on bone resorption	10	1 dose (+2 doses, 4 wks apart)	4 mg zol / 15 min	C_{max} , AUC, $Ae_{(0-24h)}$ bone markers

C_{max} = maximum plasma concentration, AUC = area under the (plasma level) curve, Ae = elimination amount

Table 4-1 Summary of dose-finding studies

Study No.	Study objective/ Population	No. of patients ¹	Study duration	Medication, dosing scheme	Primary efficacy endpoint(s)
0041	Phase II, double-blind, randomized, placebo-controlled, dose-ranging study in postmenopausal women with osteopenia or osteoporosis	351	12 months	4 x 0.25 mg/3 months Zol 4 x 0.5 mg/3 months Zol 4 x 1 mg/3 months Zol 2 x 2 mg/6 months Zol 1 x 4 mg/12 months Zol (5-minute IV infusion) Placebo	Percent change from baseline in lumbar spine BMD at Month 12

¹ Randomized

Key: BMD = bone mineral density, IV = intravenous, Zol = zoledronic acid (ZOL446)

Table 4-3 Summary of placebo-controlled Phase III studies

Study No.	Study objective/ Population	No. of patients ¹	Study - duration	Medication, dosing scheme	Primary efficacy endpoint(s)
2301	Phase III, double-blind, randomized, placebo-controlled efficacy/safety study in postmenopausal women with osteoporosis	7765	36 months	3 x 5 mg Zol/12 months (15-minute IV infusions) Placebo	(a) Proportion of patients with at least 1 new vertebral fracture over 36 months in Stratum I patients ² (b) Time to first hip fracture in Strata I and II patients

¹ Randomized

² Stratum I: patients taking calcium and vitamin D only and no additional concomitant osteoporosis medications. Stratum II: patients taking calcium and vitamin D and additional concomitant osteoporosis medications (but not bisphosphonates).

Key: IV = intravenous, Zol = zoledronic acid (ZOL446)

Table 1-1 Phase III trials using the saline formulation, mannitol formulation or both

Saline (5mg/5ml vials)	Mannitol (5mg/100ml vials)	Both
CZOL446H2304	CZOL446H2301E1	CZOL446H2301 (Saline changed to mannitol for most patients' 3rd dose) 3144 patients received 3720 doses of the mannitol formulation: 2569 (1 dose), 574 (2 doses), 1 (3 doses)
CZOL446H2305	CZOL446M2308 CZOL446N2312 CZOL446O2306	
	CZOL446H2202E1	CZOL446H2310 (Saline changed to mannitol in November 2004) 824 patients received a total of 1108 doses: 544 (1 dose), 276 (2 doses) and 4 (3 doses)
	CZOL446H2313 CZOL446H2315	CZOL446H2202 (Saline changed to mannitol for the younger patients (<3 yrs), starting August 2004) 9 patients received a total of 18 doses.

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S.W. Johnny Lau
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Hae-Young Ahn
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S.W. Johnny Lau
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Joo-Yeon Lee
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