CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-223

MEDICAL REVIEW(S)

NDA 21-223
Zometa (zoledronic acid for injection)
Novartis Pharmaceuticals Corp.

The group leader is the primary reviewer; therefore, the medical officers review is the group leaders memo.

ADDENDUM TO MEDICAL REVIEW
For
ZOLEDRONATE

DATE: August 16, 2001

NDA: 21-223

DRUG: Zoledronate

COMPANY: Novartis

INDICATION: Treatment of Hypercalcemia of Malignancy

SUBJECT: Supplemental NDA (SE2) for pamidronate

This addendum to my review of the zoledronate NDA is in response to last week's revelation that the 2-hour dosing used for the pamidronate arms in the two zoledronate pivotal, active-control trials is an unapproved regimen. Shortly after this revelation, we learned that the Agency had agreed to the less-than-24-hour infusion time for the pamidronate arms during a July, 1997, End-of-Phase I meeting. During that meeting Novartis argued persuasively that they would be unable to recruit investigators if the pamidronate dose had to be infused over 24 hours, because it had become standard clinical practice to infuse the 90-mg dose of pamidronate over 2 hours (rather than 24 hours as the approved labeling recommends). In addition, as documented in the End-of-Phase I meeting minutes, the Agency agreed that the data from the zoledronate - pamidronate trials might support changes to the pamidronate label (i.e., new dosing instructions).

In light of the above information, all parties agreed that the most appropriate action would be for Novartis to submit a supplemental NDA for pamidronate requesting modification to the Dosage and Administration section of the labeling. The company did this on August 13, 2001.

Review of the supplemental application indicates that the 90-mg dose of pamidronate infused over 2 hours is an efficacious and safe means to treat hypercalcemia of malignancy. This supplement will be approved, thereby allowing the zoledronate label to include pamidronate 2-hour infusion data.

Eric Colman, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
8/20/01 07:35:42 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW OF A COMPLETE RESPONSE TO AN APPROVABLE LETTER

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-223

Application Type: NDA (priority)

Sponsor: Novartis

Proprietary Name: Zometa

Pharmaceutical Category: Bisphosphonate

Route of Administration: Intravenous

Indication: Tumor-Induced Hypercalcemia

Dosage: 4 — mg

Reviewer: Eric Colman, MD

Date Review Completed: April 25, 2001

Chemistry Reviewer: Sheldon Markofsky, Ph.D.

Pharmacology Reviewer: Gemma Kuipers, Ph.D.

Biopharmaceutics Reviewer: Robert Shore, PharmD

Statistical Reviewer: Japobrata Choudhury, Ph.D.

RECOMMENDED REGULATORY ACTION: N drive location: _____

New clinical studies _____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement: _____	**Approvable**	_____	**Not Approvable**
XXX	**Approve**		

SIGNATURES: **Medical Reviewer:** _____. **Date:** _____.

Medical Team Leader: _____. **Date:** _____.

APPEARS THIS WAY
ON ORIGINAL

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Executive Summary

I. Recommendations

A. Recommendations on Approvability

The data submitted in response to the September 1999 Approvable Letter indicate that increasing the infusion time from 5 to 15 minutes eliminates the excess risk for renal toxicity of the 4-mg dose of zoledronate. Therefore, this reviewer recommends **approval** of the 4-mg dose of zoledronate for the treatment of tumor-induced hypercalcemia (TIH).

B. Recommendations on Phase 4 Studies and Risk Management Steps

[redacted]

As regards risk management, adherence to the 15-minute infusion time, measurement of pre-dose serum creatinine, and maintenance of adequate patient hydration will greatly reduce the risk for renal toxicity following treatment with zoledronate.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The primary data to support approval of zoledronate for the treatment of TIH come from two randomized, double-blind, active-controlled, multicenter trials of approximately 300 cancer patients. The studies were of identical design allowing for analyses of combined datasets. Patients with TIH (serum calcium >12.0 mg/dl) were randomized to one of three groups: IV zoledronate 4 mg (n=86), IV zoledronate 8 mg (n=90), or IV pamidronate 90 mg (n=99). The primary efficacy endpoint was the proportion of patients who had a complete response (serum calcium < 10.8 mg/dl) by day 10 after study drug administration. Nearly all subjects in the zoledronate groups received the drug over a 5-minute period, whereas the pamidronate subjects received the drug over 2 hours, as recommended in the approved product labeling. Regardless of initial treatment, patients with recurrent or recalcitrant TIH received a single dose of 8 mg of zoledronate.

Near completion of the TIH trials, it became evident from ongoing bone metastases studies, in which study drug is administered every 3-4 weeks, that zoledronate was associated with an increased risk for renal injury when compared pamidronate or placebo treatment[1]. Therefore, in June 1999, all ongoing zoledronate trials switched from a 5-minute to a 15-minute infusion time. While increasing the length of drug infusion appeared to decrease the risk for renal toxicity in the zoledronate 4-mg groups, subjects treated with the 8-mg dose of zoledronate continued to have a greater incidence of elevations in serum creatinine. Consequently, in June 2000, Novartis eliminated the 8-mg dose from clinical development. Patients in ongoing

[1] Renal injury is defined as: 1) An increase in serum creatinine of more than 0.5 mg/dl in patients with baseline levels < 1.4 mg/dl, or 2) An increase in serum creatinine of more than 1.0 mg/dl in patients with baseline levels ≥ 1.4 mg/dl, or 3) A doubling or more of the baseline serum creatinine.

studies who were originally randomized to the 8-mg groups were switched to 4 mg of zoledronate.

B. Efficacy

The primary efficacy endpoint — the proportion of patients in each group who had a complete response (corrected serum calcium < 10.8 mg/dl) by Day 10 after drug infusion — was achieved by 88% of zoledronate 4-mg subjects (p=0.002 vs. pamidronate), 87% of zoledronate 8-mg subjects (p=0.015 vs. pamidronate), and 70% of the pamidronate subjects[2]. In a secondary analysis, subjects in the pamidronate group had a median time to relapse of TIH of 17 days, whereas the zoledronate 4-mg subjects had a median time to relapse of 30 days (p<0.05 vs. pamidronate), and the 8-mg subjects, 40 days (p<0.05 vs. pamidronate).

Of the patients who required retreatment for recurrent or recalcitrant TIH, roughly 50% had a complete response following an 8-mg dose of zoledronate (all retreated patients received 8 mg of zoledronate; there was no comparator arm).

Thus, data from approximately 300 patients demonstrate that single infusions of 4 and 8 mg of zoledronate are more efficacious than a single infusion of 90 mg of pamidronate in the treatment of TIH

C. Safety

The major safety concern that emerged during initial review of this NDA — and led to issuance of an Approvable rather than an Approval letter — was renal toxicity. While there was not a strong signal for renal injury from the two TIH trials, an interim analysis of safety data from long-term, multi-dose bone metastases trials indicated that, compared with placebo and pamidronate, zoledronate increased the risk for renal injury. In response to this finding, the company, in June 1999, increased the infusion time from 5 to 15 minutes. And a year later, when it was apparent that increasing the infusion time did not eliminate the toxicity of the 8-mg dose, Novartis discontinued the higher dose from clinical development. As an additional safeguard, from June 2000 onward, all patients were required to have their serum creatinine level measured before receiving any dose of study drug.

By delaying approval of zoledronate, the Division is now able to compare the incidence of renal toxicity before and after the dosing regimen was changed from a 5- to a 15-minute infusion.

Additional safety issues include zoledronate's effect on serum levels of phosphate, magnesium, and of course, calcium. Owing to its greater potency on bone metabolism, there

[2] Given that the AUC following a 15-minute infusion of 4 mg of zoledronate is about 70% higher than when the same dose is infused over 5 minutes, it is extremely unlikely that zoledronate's efficacy is diminished by a 10-minute increase in the infusion time.

were more zoledronate-treated patients (5-13%) compared with pamidronate-treated subjects (2-5%) who developed hypophosphatemia, hypomagnesemia, or hypocalcemia. In a small number of cases, patients required IVmineral supplementation.

In addition to potential adverse effects on the kidney and serum mineral levels, bisphosphonates as a class have been associated with uveitis, scleritis, episcleritis, fever, and gastrointestinal problems – mainly esophagitis, nausea, vomiting, and upper GI bleeding (generally more common with oral than IV administration). There was no evidence from the two TIH trials, however, that treatment with zoledronate compared with pamidronate is associated with a significantly higher risk for the above mentioned adverse events. Because of the relatively small sample size and the limited number of doses administered per patient in the TIH trials, these results should be viewed with a degree of circumspect.

D. Dosing

The recommended dosing for TIH is 4 mg IV over 15 minutes.

As aforementioned, data accrued within the last year from the ongoing bone metastases trials suggest that multiple, monthly doses of zoledronate 4 mg (infused over 15 minutes) are not associated with a significantly increased risk for renal injury. During treatment with zoledronate, it is important to maintain adequate patient hydration and to check serum creatinine prior to dosing.

E. Special Populations

NA

III. Administrative Background

On September 21, 2000, the Office of Drug Evaluation II issued an Approvable Letter to Novartis for NDA 21-223 – IV zoledronate for the treatment of tumor-induced hypercalcemia (TIH).

The Approvable Letter stated that the review division had serious concerns about the potential renal toxicity of IV zoledronate. [redacted]. In these studies, a higher percentage of patients receiving both the 4-mg and 8-mg doses of zoledronate had increases in serum creatinine compared to patients treated with 90 mg of pamidronate or placebo. The risk appeared to be related to drug dose, duration of use, patient age, baseline renal function, and length of drug infusion.

In response to these findings, the company, in June 1999, increased the infusion time from 5 minutes to 15 minutes. After an additional year of experience, this change appeared to reduce the risk for renal injury (i.e., increases in serum creatinine) for the 4-mg dose of zoledronate, but not the 8-mg dose. Therefore, in June 2000, all patients receiving 8 mg of zoledronate were switched to the 4-mg dose.

In order to gain a more complete appreciation of the renal safety profile of zoledronate, the review division requested that the sponsor submit study reports from the 3 bone metastases trials (010, 011, and 039) after the trials were completed (in early 2001).

On December 14, 2000, the sponsor met with representatives of DMEDP and ODE II to re-review the risk- benefit profile of zoledronate when used as a treatment for TIH and to discuss Novartis's proposed response to the September 21 Approvable Letter. All parties agreed that the most appropriate step was for the company to provide the division with a proposal for what they considered to be a complete response.

In a letter of December 21, 2000, Novartis provided details of what they considered a complete response to the Approvable Letter. The following information was felt to address the division's concerns regarding the safety of zoledronate when used to treat TIH. The following was specifically proposed as a complete response:

1. Provide a final updated report of defined renal events. Also provide renal abnormalities associated with each patients with a renal adverse event term and plots describing the time course of creatinine values for patients receiving zoledronate 4 mg infused over 15 minutes and the corresponding control group.
2. Provide updated labeling that includes language emphasizing measures to enhance the safe use of the drug in the TIH population.
3. From the bone metastases trials: provide overall safety update with data in-house on December 30, 2000; provide updated report of renal events; provide worldwide safety experience. From all other studies: provide all SAEs from the 120-day safety update cutoff to present.
4. Provide English translations of approved labeling from other countries.
5. Provide clarification of financial disclosure information.

During a phone call on January 8, 2001, Mr. Randy Hedin of this division informed Eileen Ryan of Novartis that the sponsor's proposal for a complete response to the Approvable Letter was accepted by the division.

IV. Regulatory Background

Related INDs:

[redacted]

[ ]

Worldwide Regulatory Status: Since initial review of this NDA, zoledronate has received marketing approval for the treatment of TIH in the following countries: Canada, Latvia, Brazil, Thailand, Switzerland, Dominican Republic, Peru, Venezuela, Mexico, Columbia, Chile, and the EU.

V. Evaluation of Financial Disclosure

In addition to the information discussed in the initial review of this NDA, the company reports that there were no disclosures for Outcome Payments, Proprietary Interest, or Equity Interests.

VI. Review of Clinical Data

Because the signal for renal toxicity was an elevation in serum creatinine, the focus of this review is the data on the incidence of elevations in serum creatinine (also referred to as renal deterioration, renal injury, and renal toxicity) in the zoledronate groups compared with the pamidronate and placebo groups from the ongoing bone metastases trials – 010, 011, and 039. Other aspects of the drugs safety will also be addressed.

The critical question that needs to be answered before this drug is approved for TIH is: Did increasing the infusion time from 5 to 15 minutes eliminate, or substantially reduce, the risk associated with repeat administration of 4 mg of IV zoledronate in comparison to 90 mg of pamidronate?

For the purposes of this review, renal deterioration is defined as:

1. Increase in serum creatinine of more than 0.5 mg/dl in patients with baseline levels < 1.4 mg/d
2. Increase in serum creatinine of more than 1.0 mg/dl in patients with baseline levels ≥ 1.4 mg/dl
3. A doubling or more of the baseline serum creatinine

A. Renal Deterioration with a 5-minute vs. 15-minute Infusion Time

Extent of Exposure: As shown in the following table, in general, the extent of exposure (number of patients and number of infusions) in trial 010 is now comparable for the 5-minute and 15-minute infusions. This is also the case with studies 011 and 039 (data not shown).

EXTENT OF EXPSOSURE TO 5 AND 15 MINUTES INFUSIONS – STUDY 010				
	5-MINUTE INFUSION		15-MINUTE INFUSION	
Approx. # Infusions	# Subjects		# Subjects	
	Zol 4 mg	Pam 90 mg	Zol 4 mg	Pam 90 mg
1	268	265	261	260
3	257	256	251	247
6	227	237	232	228
9	203	210	207	192
12	161	178	178	158
15	75	72	66	54
18	17	20	2	4

There is less exposure in the categories > 15 and > 18 infusions for the 15-minute infusion compared with the 5-minute infusion. Given the short life expectancy of patients with TIH compared with many patients with bony metastases, this is of less relevance to the TIH indication than to the bone metastases indication.

Incidence of Renal Deterioration: The following table provides the rates of renal deterioration (see page 7 for definition) for the 3 bone metastases trials pre and post the infusion amendment.

INCIDENCE OF RENAL DETERIORATION WITH 5 AND 15 MINTUE INFUSIONS						
	5-MINUTE INFUSION			15-MINUTE INFUSION		
	# Patients	# Events	%	# Patients	# Events	%
Study 010						
Zol 4 mg	271	35	13*	270	22	8
Zol 8 mg	240	47	20*	262	48	18*
Pam 90 mg	270	17	6	263	20	8
Study 011						
Zol 4 mg	61	10	16	164	17	10
Zol 8mg	55	7	13	178	21	12
Placebo	54	3	6	163	10	6
Study 039						
Zol 4 mg	107	19	18*	92	13	14
Zol 8 mg	119	41	35*	87	19	22
Placebo	119	10	8	78	9	12

*$p<0.05$ vs. control

It is evident that lengthening the infusion time to 15 minutes has lowered the absolute and relative risks of renal deterioration following treatment with zoledronate 4 mg. The difference in incidence rates of renal deterioration between the zoledronate 4-mg groups and the control groups, in particular the pamidronate group, are the same or very similar following 15-minute infusions.

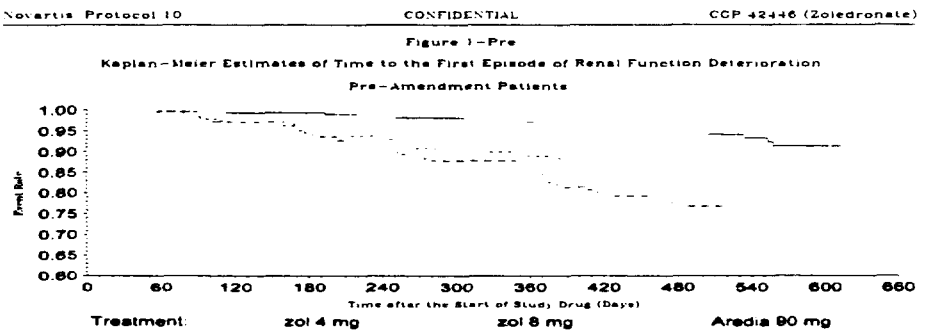
The above data also indicate that while increasing the infusion time to 15 minutes decreased the absolute risk of renal deterioration in the 8-mg groups, there is still an appreciable increase in the relative risk when compared with placebo or pamidronate treatment.

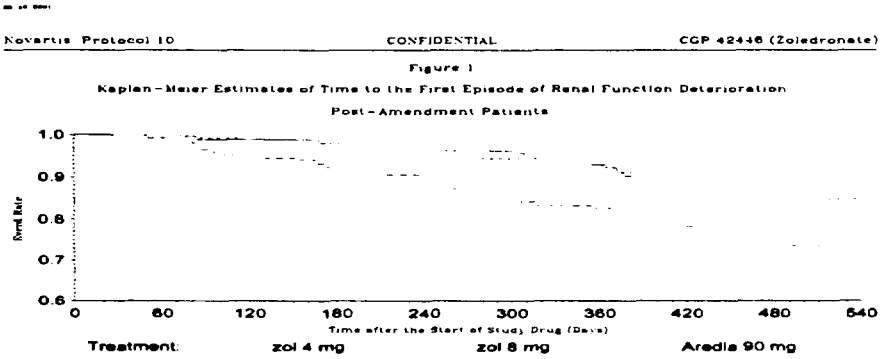
Although Novartis has eliminated the 8-mg dose of zoledronate from all ongoing clinical trials,

[redacted]

Given that pamidronate is the most widely used treatment for TIH in this country, the data from study 010, in which pamidronate was the active control, are the most relevant to the review of this NDA. In study 010, the incidence rates of renal deterioration in the zoledronate 4-mg and the pamidronate groups were identical at 8%.

Time to Event: The following figures depict the time to first episode of renal function deterioration in study 010 with 5- (pre-amendment) and 15-minute (post-amendment) infusions.





With the 5-minute infusion (top figure), the lines depicting the zoledronate 4 and 8 mg groups begin to diverge from the pamidronate group after approximately 90 to 120 days (or 3-4 infusions). With the 15-minute infusion (bottom figure), the 4-mg zoledronate and pamidronate lines follow similar paths up to approximately 500 days (or 17 infusions). In contrast, the line depicting the zoledronate 8-mg group diverges from both the zoledronate 4 mg and the pamidronate groups after 90 to 120 days.

The data are similar for studies 011 and 039, where the control groups received placebo (data not shown).

B. Supplemental Renal Safety Data from Studies 010, 011, and 039

Incidence of Grade 3 and 4 Creatinine Elevations: The following table provides the incidence rates of Grade 3 (3.1-6.0 X ULN) and 4 (> 6.0 X ULN) serum creatinine changes (see Appendix for case narrative).

INCIDENCE OF GRADE 3 AND 4 CREATININE INCREASES WITH 5 AND 15 MINTUE INFUSIONS						
	5-MINUTE INFUSION			15-MINUTE INFUSION		
	# Patients	# Events	%	# Patients	# Events	%
Study 010						
Zol 4 mg	271	7	3	270	1	0.4
Zol 8 mg	240	2	0.8	262	7	2.7
Pam 90 mg	270	1	0.4	263	5	1.9
Study 011						

INCIDENCE OF GRADE 3 AND 4 CREATININE INCREASES WITH 5 AND 15 MINTUE INFUSIONS						
	5-MINUTE INFUSION			15-MINUTE INFUSION		
	# Patients	# Events	%	# Patients	# Events	%
Zol 4 mg	61	0	0	164	3	1.8
Zol 8mg	55	2	4	178	2	1.1
Placebo	54	0	0	163	2	1.2
Study 039						
Zol 4 mg	107	2	2	92	5	5.4
Zol 8 mg	119	3	3	87	2	2.3
Placebo	119	1	1	78	0	0

The 5.4% incidence rate observed in the zoledronate 4-mg group from study 039 is unexpected, and I do not have an explanation for it. As these studies are ongoing, it will be of interest to compare the incidence rates at the completion of the trials.

Incidence of Patients Requiring Dialysis: In contrast to the 4 patients who underwent dialysis after receiving pamidronate or placebo, 6 zoledronate 4-mg patients and 5 zoledronate 8-mg subjects required dialysis after receiving the drug with a 5-minute infusion. For those patients who received zoledronate over 15 minutes, 1 of the 4-mg subjects and 5 of the 8-mg subjects underwent dialysis; none of the placebo or pamidronate patients required dialysis after the zoledronate dosing amendment was implemented.

C. Renal Adverse Events – TIH Trials

In the two TIH trials (036 and 037) the incidence rates of renal deterioration were not significantly different between the zoledronate and pamidronate groups.

See the Appendix for review of the case narratives for the 15 patients who experienced renal adverse events in the two TIH trials.

D. Additional Safety Information

Additional safety information from four sources (A-D below) was requested by the division and provided by Novartis.

A. TIH Trials (completed)
B. Adverse Events from Ongoing Bone Metastases Trials (ongoing – cutoff date for this submission Jan. 12, 2001)
C. Spontaneous Adverse Events from Countries where the Drug is Marketed
D. Serious Adverse Events from All other Studies (from time of the 120-day safety update to the present)

A. TIH Trials: Because the two TIH trials were completed before Feb. 29, 2000 (the time covered by the 120-day safety update), there are no new adverse events from these trials.

As for serious adverse events, the table below provides the incidence rates for the more common serious adverse events (15-minute infusions only).

SERIOUS ADVERSE EVENTS – BONE METASTASES TRIALS – INCIDENCE AT LEAST 4% IN ONE OF THE ZOLEDRONATE GROUPS AND GREATER THAN IN CONTROL GROUP			
	Pam 90 mg	Zol 4 mg	Zol 8 mg
Study 010	%	%	%
Fever	5	5	6
Progression of Cancer	3	6	6
Nausea	2	5	3
Anemia	2	4	1
Granulocytopenia	2	4	6
Dehydration	1	4	4
Dyspnea	4	5	3
Pneumonia	4	4	5
	Zol 4 mg	Zol 8 mg	Placebo
Study 011	%	%	%
Progression of Cancer	7	7	6
Vomiting	2	6	4
Anemia	4	3	3
	Zol 4 mg	Zol 8 mg	Placebo
Study 039	%	%	%
Fever	2	6	1
Progression of Cancer	3	5	1
Vomiting	5	2	1
Nausea	5	3	1
Anemia	3	5	1
Skeletal Pain	6	10	4
Urinary Retention	0	5	4
Hematuria	4	2	2

In general, across the three studies, a slightly higher percentage of patients treated with zoledronate compared with pamidronate or placebo had the following serious adverse events: progression of cancer, anemia, nausea, vomiting. It is interesting and inexplicable that a greater percentage of patients treated with zoledronate vs. pamidronate or placebo were reported to have progression of cancer. In addition, aside from urinary retention and hematuria in study 039, there were very few serious renal adverse events and no meaningful difference in incidence rates between the zoledronate and control groups.

Turning to laboratory abnormalities, as noted in the initial review of the zoledronate NDA, there were more zoledronate-treated patients who developed hyperkalemia, hypophosphatemia, and hypomagnesemia in comparison to pamidronate- or placebo-treated subjects.

C. Spontaneous Adverse Events from Countries where the Drug is Marketed: Only one spontaneous adverse event has been reported to the company. This was a female patient who experienced a urticarial skin reaction after a dose of zoledronate 4 mg. She reportedly made a complete recovery.

[redacted]

VII. Consultation from the Cardio-Renal Division

In his consultation, Dr. Doug Throckmorton, provides interpretation of the most recently submitted renal safety data. His thoughts can be summarized as follows:

1. Based on the most recently received information, there is no clear signal for excess renal toxicity of zoledronate 4 mg given over 15 minutes, when compared with pamidronate. Dr. Throckmorton cautions, however, that additional exposure will be needed to further define the relative risk of the two products (zoledronate and pamidronate).
2. The data suggest that some recovery of renal function follows discontinuation of zoledronate in the majority of patients who have increased creatinine levels following treatment with this drug.
3. From the data from the ongoing bone metastases trials, renal injury is slow to develop in most patients, rather than becoming severe with a single dose.

IX. Dosing Regimen and Administration Issues

Approval of this NDA has been delayed because of concerns about renal toxicity. It appears from recently acquired data that increasing the infusion time from 5 to 15 minutes reduces the risk for renal injury to a level similar to that associated with use of pamidronate. Because patients with TIH have a poor short-term survival rate, most will not receive multiple doses of drug, thereby further decreasing the risk for drug-related toxicity.

To enhance safe use of zoledronate, patients should be adequately hydrated prior to and during treatment. Furthermore, serum creatinine levels should be checked before each dose is administered. In the event of a significant increase in serum creatinine, the drug should be withheld until a thorough evaluation of renal function is completed and the expected benefit of continued treatment outweighs expected risk.

Some patients with recurrent or recalcitrant TIH will require retreatment. Because all patients in the two TIH trials who required retreatment received 8 mg of zoledronate, it is impossible to judge the relative efficacy or safety of this dosing regimen. Until the sponsor demonstrates that 8 mg of zoledronate is superior to 4 mg of zoledronate in the retreatment of TIH, I support a recommendation that patients with recurrent or recalcitrant TIH be treated with a second course of zoledronate 4 mg. This would parallel the dosing instructions for pamidronate.

X. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

An analysis of the percentage of patients' with complete responses by Day 10 according to gender indicates that both doses of zoledronate are equally effective relative to pamidronate in males and females. The rates in males and females were similar to the overall rates of response observed in the pooled analysis.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Roughly half of the patient population was over 65 years of age. Efficacy, defined as a complete response at Day 10, was similar in all treatment groups for patients over and under 65 years.

Over 75% of the patient population in the two TIH trials were Caucasian. Therefore, analyses of results by race would not be reliable. Having said that, the complete response rates in all groups were comparable for Blacks and Caucasians.

In terms of safety, there were no differences between treatment groups in the frequency or nature of serious adverse events, including renal serious adverse events, for males or females. Patients < 65 years in the zoledronate groups had a higher frequency of anorexia than those in the pamidronate group (23.4% vs 12.0%, respectively). No difference in anorexia was observed across groups for those > 65 years. Acute renal failure and uremia were reported more frequently overall for those > 65 years compared to those < 65 years, but there were no differences in frequency between the zoledronate groups and the pamidronate group in either age sub-group. Acute renal failure was reported in 3/109 (2.8%) of patients > 65 years in the zoledronate groups compared to 1/23 (4.3%) in the pamidronate group. Uremia was reported in 5/109 (4.6%) of patients > 65 years in the zoledronate groups compared to 3/23 (13.0%) in the pamidronate group. Too few Black subjects preclude comment about safety compared with Caucasians.

C. Evaluation of Pediatric Program

Citing insufficient pediatric patients with TIH, the company requested, and received, a waiver to study zoledronate in pediatric patients with TIH.

[redacted]

D. Comments on Data Available or Needed in Other Populations

[redacted]

XI. Conclusions and Recommendations

A. Conclusions

In terms of efficacy, there is convincing evidence that 4 mg of IV zoledronate is a superior treatment for TIH relative to treatment with 90 mg of IV pamidronate. From a safety perspective, following a signal for renal toxicity in three bone metastases trials, the infusion time was increased from 5 to 15 minutes and the 8-mg dose of zoledronate was eliminated from further study. From an examination of equal sized bodies of data with 5-and 15-minute infusion times, there is no evidence that the risk for renal injury (including serious renal adverse events) is appreciably increased in patients receiving multiple doses of the 4-mg dose of zoledronate when administered over 15 minutes relative to treatment with 90 mg of pamidronate.

B. Recommendations

This reviewer recommends approval of zoledronate 4 mg for the treatment of TIH.

XII. Labeling Review

In the following labeling review, I have struckout material that I do not believe is appropriate, provide commentary in shaded text, and offer suggestions over double underline.

WITHHOLD 8 PAGES

Draft

Labeling

XIII. Appendix

Below I review the serum creatinine values and patient narratives for the 30 patients who had grade 3 or 4 increases in serum creatinine or required dialysis in the bone metastases studies 010, 011, and 039, and for the 15 patients who experienced deterioration in renal function during treatment in the TIH studies. After a brief description of the case, I assess the likelihood that the study drug was the principal inciting agent for the renal event.

Case Narratives of Patients Who Experienced Grade 3 or 4 Increases in Serum Creatinine or Required Dialysis in Studies 010, 011, and 039 – Post the 15-Minute Infusion Amendment.

1. Patient 10398

This 89-year-old patient with multiple myeloma received her first dose of **pamidronate** on July 12, 1999. Her first increase in creatinine occurred on April 12, 2000, after she had received 14 infusion. The patient died on June 6, 2000 from respiratory failure. The study drug was not withheld due to the bump in creatinine. Her last known creatinine was 3.3 mg/dl (baseline was 1.1 mg/dl).

Relationship to Study Medication: **Possible.**

2. Patient 10889

This 60-year-old patient with multiple myeloma received his first dose of **pamidronate** on July 11, 1999. His creatinine increased to 4.1 mg/dl on January 5, 2000, after he had received 5 infusions. The study drug was withheld and he dropped out of the study in January 2000, but remained on dialysis as of December 15, 2000.

Relationship to Study Medication: **Possible**.

3. Patient 11217

This 62-yearl-old patient with multiple myeloma received her first dose of **pamidronate** on August 26, 1999. Approximately one year later, after having received 7 infusions, her creatinine increased to 2.3 mg/dl. The study drug was withheld and she died on October 1, 2000. Her last known creatinine was 2.7 mg/dl on September 14, 2000.

Relationship to Study Medication: **Possible.**

4. Patient 13275

This 51-year-old patient with multiple myeloma received her first dose of **pamidronate** on August 3, 1999. On September 14, 2000 her creatinine was 3.2 mg/dl (baseline 1.7 mg/dl); she had received 14 infusions prior to the renal event. The study drug was withheld and she discontinued from the trial in September 2000. Her last known creatinine was 2.2 mg/dl in December 2000.

Relationship to Study Medication: **Possible.**

5. Patient 10807

This 44-year-old male patient with multiple myeloma received his first dose of **8 mg of zoledronate** on July 2, 1999. He received a total of 2 infusions (one over 5 minutes and one over 15 minutes) prior to being admitted to the hospital on August 17, 1999 for suspected GVHD. He developed pneumonia and then renal failure requiring dialysis. He subsequently died, in the investigator's opinion, due to progression of disease.

Relationship to Study Medication: **Unlikely.**

6. Patient 10856

This 58-year-old patient with multiple myeloma received her first dose of **8 mg of zoledronate** on September 9, 1999. She received a total of 11 infusions. On May 16, 2000 she was evaluated for increasing creatinine and was found to have Bence Jones paraproteinuria. She was subsequently withdrawn from the study; her last known creatinine in June 2000 was 3.1 mg/dl.

Relationship to Study Medication: **Unlikely**.

7. Patient 11269

This 74-year-old male with multiple myeloma received his first dose of **8 mg of zoledronate** on August 19, 1999. He received a total of 11 infusions before he was admitted to the hospital on July 19, 2000 for CHF and anemia. On July 24, 2000 he underwent dialysis for worsening renal deterioration. He died on October 10, 2000. His last creatinine on July 25, 2000 was 8.4 mg/dl.

Relationship to Study Medication: **Unlikely.**

8. Patient 12729

This 70-year-old female with multiple myeloma received her first dose of **8 mg of zoledronate** on September 23, 1999. She developed an increased creatinine value (4.3 mg/dl) on December 28, 1999 – after she had received a total of 4 infusions. Her condition worsened and she died on January 6, 2000.

Relationship to Study Medication: **Unlikely.**

9. Patient 20082

This 51-year-old female with breast cancer received her first dose of **8 mg of zoledronate** on July 15, 1999. Her baseline creatinine was 5.9 mg/dl and she had bilateral hydronephrosis due to obstruction with tumor. She received a total of 10 infusions of study drug before she died on June 10, 2000. Her course was complicated by multiple episodes of worsening hydronephrosis from disease progression.

Relationship to Study Medication: Unlikely.

10. Patient 21025

This 47-year-old with breast cancer received her first dose of **8 mg of zoledronate** on September 7, 1999. Following 8 infusions of study drug she developed an increase in serum creatinine, 2.2 mg/dl, which subsequently rose to 5.9 mg/dl on March 21, 2000. Even though the drug was stopped, it was reported that the patient's serum creatinine continued to increase.

Relationship to Study Medication: **Possible to Probable**

11. Patient 37781

This 58-year-old with breast cancer received her first infusion of **8 mg of zoledronate** on August 11, 1999. She received a total of 3 infusions, the last on October 6, 1999. On October 31, 1999 her creatinine increased from 1.0 mg/dl to 3.3 mg/dl. She was hospitalized and diagnosis with obstructive uropathy. She recovered and was discharged.

Relationship to Study Medication: **Possible.**

12. Patient 21749

This 65-year-old male with adenocarcinoma of unknown origin received his first dos of **8 mg of zoledronate** on November 5, 1999. He developed renal failure at the end of November 1999 with a creatinine of 4.0 mg/dl (baseline 1.3 mg/dl). He received another dose of study drug on December 22, 1999 with a creatinine of 6.0 mg/dl. On January 12, 2000 the patient was hospitalized with a creatinine of 9.0 mg/dl. His condition worsened and he died on January 13, 2000.

Relationship to Study Medication: **Possible to Probable.**

13. Patient 27008

This 52-year-old with prostate cancer received his first dose of study drug on July 2, 1999. He received a total of 7 doses **of zoledronate 8 mg**. On October 8, 1999 he was admitted for fever, nausea, and vomiting – subsequently diagnosed with renal failure. He was treated for an UTI and released. His last known creatinine was 1.5 mg/dl on January 3, 2000.

Relationship to Study Medication: **Possible to Probable.**

14. Patient 27030

This 70-year-old with prostate cancer received his first dose of **zoledronate 8 mg** on October 6, 1999. At the time of his increase in creatinine, he had received a total of 4 infusions. His maximal creatinine was 2.5 mg/dl. He received two additional doses of study drug without further deterioration in renal function.

Relationship to Study Medication: **Possible.**

15. Patient 18005

This patient with multiple myeloma received his initial infusion of **zoledronate 8 mg** on November 9, 1999. He received 4 infusions. He had mildly elevated serum creatinine values throughout his treatment, but on March 10, 2000 he was admitted with a creatinine of 9.0 mg/dl and subsequently placed on dialysis. His last infusion of study drug was March 1, 2000 – he died on March 24, 2000.

Relationship to Study Medication: **Possible.**

16. Patient 20604

This 61-year-old male with bladder cancer received his first dose of **zoledronate 8 mg** on September 21, 1999. After an unknown number of study drug infusions, the patient was hospitalized in February 2000 for renal failure and was started on dialysis. A diagnosis of obstructive uropathy was made. He was eventually discharged to a nursing home – last known creatinine 9.0 mg/dl (July 2000).

Relationship to Study Medication: **Unlikely.**

17. Patient 51110

This 86-year-old with prostate cancer received a total of 4 infusions of **zoledronate 8 mg** before he developed a serum creatinine of 3.6 mg/dl (baseline 2.2 mg/dl). On January 4, 2000 he started dialysis because of a creatinine of 11.5 mg/dl. The diagnosis was acute renal failure with "mutlifocal etiology". On January 5, 2000 the patient died.

Relationship to Study Medication: **Possible.**

18. Patient 51740

This 68-year-old with prostate cancer received his first dose of **zoledronate 8 mg** on September 29, 1999. He received a total of 8 infusions, with the last infusion given on February 22, 2000. He was hospitalized

on February 24, 2000 for hypokalemia, V tach, obstructive uropathy, and renal failure. He was intubated and started on dialysis; but did on March 10, 2000.

Relationship to Study Medication: **Possible.**

19. Patient 10889

This 78-year-old female with lung cancer received her first dose of study drug **(placebo)** on November 5, 1999. She received a total of 6 infusions. On November 30, 1999 her creatinine was noted to be 3.7 mg/dl. By December 2 her creatinine was at baseline.

20. Patient 20745

This 54-year-old female with esophageal cancer received her first dose of **placebo** on August 23, 1999. She developed a creatinine of 3.4 mg/dl on September 15, 1999. No follow-up information was provided.

21. Patient 11388

This 74-year-old female with multiple myeloma received her first dose of **zoledronate 4-mg** on November 26, 1999. Her creatinine increased from 2.1 mg/dl to 3.2 mg/dl on February 10, 2000. The study drug was held due to the event. She had a history of mild renal failure and continued in the study with a creatinine of 2.7 mg/dl on December 18, 2000.

Relationship to Study Medication: **Unlikely**

22. Patient 30510

This 50-year-old with breast cancer received her first dose of **pamidronate** on August 25, 1999. At the time of the initial increase in creatinine (5.5 mg/dl), she had received a total of 10 infusions. On June 26, 2000 she was hospitalized for acute renal failure; her ace-inhibitor was stopped and her creatinine rapidly returned to within normal limits.

Relationship to Study Medication: **Unlikely**

23. Patient 11058

This 89-year-old female with lung cancer received her first dose of **zoledronate 4 mg** on January 17, 2000. On March 21, 2000 she received her third, and final, infusion. On April 6, 2000 she was admitted for dementia and renal failure with a creatinine of 3.9 mg/dl. She was hydrated and her creatinine returned to normal.

Relationship to Study Medication: **Unlikely**

24. Patient 20639

This 70-year-old male with lung cancer received his first dose of **zoledronate 4-mg** on September 8, 1999 and his last on October 20, 1999. He was hospitalized on November 3, 1999 for respiratory failure secondary to pneumonia; he was also noted to be in renal failure (creatinine 8.4 mg/dl). He died on November 11, 1999.

Relationship to Study Medication: **Possible**

25. Patient 21549

This 26-year-old female with a malignancy of unknown primary was treated with **4 mg of zoledronate** on October 7, 1999. She received a total of 10 infusions with the last received on May 2, 2000. She was

diagnosed with renal insufficiency secondary to obstruction and was treated with nephrostomy tubes with resolution of her renal insufficiency.

Relationship to Study Medication: **Unlikely**

26. Patient 15079

This 68-year-old male with prostate cancer received **4 mg of zoledronate** on July 8, 1999. He received 22 infusions before his creatinine increased to 4.1 mg/dl on November 9, 2000. He only had one functional kidney and after a stent was placed in the functional kidney his creatinine returned to baseline.

Relationship to Study Medication: **Unlikely**

27. Patient 15083

This 76-year-old with prostate cancer received **4 mg of zoledronate** on September 16, 1999. At the time of the increase in creatinine, the patient had received a total of 6 infusions. On April 4, 2000 his creatinine increased to 5.5 mg/dl. Cystoscopy in May indicated that the renal failure was due to obstruction by tumor and adenopathy.

Relationship to Study Medication: **Unlikely**

28. Patient 17025

This 67-year-old with prostate cancer received his first dose of **zoledronate 4 mg** on September 3, 1999. At the time of the renal event he had received a total of 3 infusions. On November 9, 1999 his creatinine was 5.6 mg/dl. A permanent urinary catheter was placed and his renal function improved, but did not return to baseline by the time he died in January 2000.

Relationship to Study Medication: **Possible.**

29. Patient 26027

This 78-year-old with prostate cancer received **4 mg of zoledronate** on September 15, 1999. He received a total of 6 infusions with the last on December 30, 1999. In January 2000 routine labs revealed a creatinine of 3.4 mg/dl. An ultrasound showed b/l urethral obstruction. He was treated for the obstruction with partial resolution of the renal deterioration.

Relationship to Study Medication: **Unlikely**

30. Patient 55135

This 90-year-old with prostate cancer received his first dose of **4 mg of zoledronate** on September 10, 1999. By the time his creatinine increased he had received a total of 10 infusions. In April 2000 his creatinine began to increase (2.2 mg/dl). A work up indicated a poorly functioning left kidney and partial obstruction of the left kidney. He refused intervention and died in May 2000.

Relationship to Study Medication: Unlikely

Case Narratives for Patients Who Experienced Renal Deterioration in the TIH Trials.

1. Patient 101

This 60-year-old patient with breast cancer was treated with a single dose of **4 mg of zoledronate** on Dec. 23, 1997. On February 17, 1998 she developed acute renal failure (serum creatinine 4.4 mg/dl).

Relationship to Study Medication: **Unlikely** given the time lapse between study drug administration and date of renal event.

2. Patient 117

This 70-year-old patient with lung cancer was treated with a single dose of **4 mg of zoledronate** on Nov. 12, 1998 and retreated with a single dose of **zoledronate 8 mg** on Dec 11, 1998. On Jan 2, 1999 she developed abnormal renal function (serum creatinine 1.9 mg/dl).

Relationship to Study Medication: **Unlikely** given the time lapse between study drug administration and date of renal event.

3. Patient 148

This 41-year-old patient with rectal carcinoma and a history of bilateral hydronephrosis and baseline renal insufficiency (Cr 3.6 mg/dl) received **90 mg of pamidronate** for hypercalcemia on Aug 30, 1999. Unresponsive, she received a single dose of **zoledronate 8 mg** on Sept 3, 1999. The patients condition deteriorated quickly – her creatinine increased to 8.4 mg/dl on Sept 9 – and she died on Sept 11, 1999.

Relationship to Study Medication: **Possible.**

4. Patient 155

This 69-year-old patient with lung cancer received a single dose of **zoledronate 8 mg** on Aug 16, 1999. An adverse event termed uremia was made on Aug 19, 1999 (serum creatinine increased from 1.1 mg/dl to 1.9 mg/dl). His creatinine decreased to baseline and he was lost to follow up.

Relationship to Study Medication: **Possible**.

5. Patient 185

This 59-year-old patient with lung cancer received a single infusion of **zoledronate 8mg** on Apr. 24, 1998. Serum creatinine increased from 1.0 mg/dl at baseline to 1.5 mg/dl on Apr. 28, 1998. The patient died on Apr. 30, 1998.

Relationship to Study Medication: **Possible.**

6. Patient 213

This 57-year-old patient with lymphoma with a history of renal insufficiency (baseline creatinine 2.8 mg/dl) received a single dose of **zoledronate 8 mg** on Jan. 13, 1999. On Feb. 8, 1999 he was admitted to the hospital for pneumonia and worsening renal insufficiency – creatinine 7.2 mg/dl). He subsequently became septic, developed heart failure and was dialyzed on Feb 10. He did recover, however, and was discharged from the hospital on March 22, 1999 with his serum creatinine back to baseline.

Relationship to Study Medication: **Unlikely.**

7. Patient 230

This 62-year-old patient with breast cancer received a single dose of **zoledronate 4 mg** on Oct. 15, 1998. The next day she experienced paralytic ileus and pyelonephritis along with abnormal renal function (serum creatinine increased from 2.0 mg/dl at the time of study drug administration to 4.6 mg/dl on Oct 18, 1998. On Oct. 26 her creatinine had returned to baseline. She died two days later.

Relationship to Study Medication: **Possible**.

8. Patient 245

This 50-year-old patient with head and neck cancer received a single dose of **zoledronate 8 mg** on Feb. 25, 1998. His serum creatinine increased from 1.4 mg/dl at baseline to 1.8 mg/dl the day following study drug administration. The patient died on the 26th of Feb. from multiple organ failure.

Relationship to Study Medication: **Possible.**

9. Patient 251

This 42-year-old patient with lung cancer and brain mets was treated with a single dose of **zoledronate 4 mg** on Apr. 17, 1998. He was also treated for septicemia the same day. His serum creatinine increased from 1.3 mg/dl at the time of study drug administration to 1.7 mg/dl on Apr. 20, 1998. He died on Apr. 20th from progression of disease.

Relationship to Study Medication: **Possible**.

10. Patient 317

This 63-year-old patient with lung cancer received a single infusion of **pamidronate 90 mg** on Apr. 8, 1999 and was treated with **zoledronate 8 mg** on May 6, 1999. On May 12, 1999 the patient was admitted to the hospital for worsening health, anemia, pneumonia, and acute renal failure (creatinine 6.0 mg/dl). On May 20, 1999 he was dialyzed. By June 17, 1999 the patient had recovered and was discharged from the hospital with a creatinine of 3.5 mg/dl. Review of serial creatinine values indicates that this patient had periodic increases of up to 8.3 mg/dl from Apr. 14 on.

Relationship to Study Medication: **Unlikely**.

11. Patient 382

This 66-year-old patient with multiple myeloma received a single dose of **zoledronate 4 mg** on June 30, 1999. On July 21, 1999 he developed a serum creatinine of 1.9 mg/dl along with symptoms of pneumonia and dehydration. Following hydration and treatment of the pneumonia, serum creatinine returned to baseline.

Relationship to Study Medication: **Unlikely**

12. Patient 1092

This 57-year-old patient with renal cancer received a single dose of **zoledronate 4 mg** on Feb. 10, 1999. On March 6, 1999 the patient was admitted to the hospital for fluid overload and uremia. His baseline creatinine was 1.8 mg/dl and serial evaluations indicate that the creatinine slowly increased from about 2.0 mg/dl at the end of Feb. to a high of 4.8 mg/dl on March 9, 1999. The patient died on March 15, 1999 – due to progression of underlying malignancy.

Relationship to Study Medication: **Unlikely.**

13. Patient 1152

This 42-year-old patient with rectal cancer and mets to the ureters received a single dose of **zoledronate 4 mg** on May 22, 1998. She presented to the hospital on May 24, 1998 complaining of abdominal pain. She was found to have significant progression of her malignancy. On June 8 and 12, 1998 her creatinine had increased to 3.8 mg/dl and 5.7 mg/dl, respectively. She died on June 12.

Relationship to Study Medication: **Possible.**

14. Patient 1158

This 42-year-old patient with liver cancer was treated with a single dose of **pamidronate 90 mg** on Apr. 30, 1998. At this time his creatinine was 5.9 mg/dl (this patient is a protocol violation due to renal insufficiency at the time of drug administration). The company reports that no baseline creatinine values are available prior to study drug administration. On May 4, 1998 the patient was hospitalized for confusion, hypercalcemia and decreased renal status (creatinine 12.4 mg/dl). By May 10 his creatinine had decreased to 7.5 mg/dl. The patient died on May 10, 1998.

Relationship to Study Medication: **Possible**

15. Patient 1220

This 77-year-old patient with multiple myeloma and a history of renal insufficiency (baseline creatinine 2.3 mg/dl), received a single dose of **zoledronate 8 mg** on Aug. 25, 1999. Serum creatinine values were stable until Sept 7, 1999 when a value of 3.2 mg/dl was reported. On Sept 21 his creatinine was 4.5 mg/dl. On Oct. 19, 1999 the patient's creatinine was 3.0 mg/dl.

Relationship to Study Medication: **Unlikely**

Comment: If anything can be concluded from an unblinded review of the above case narratives it is that assigning a causal link between zoledronate and deterioration in renal function is extremely difficult. Given the poor state of health of most cancer patients with TIH and the frequent use of concomitant medications that may cause renal injury, it is the rare case in which one can confidently assign sole blame for renal toxicity to zoledronate.

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/s/

Eric Colman
7/5/01 10:28:51 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

SEP 18 2000

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application # 21-223	**Application Type:** NDA (priority)
Sponsor Novartis	**Proprietary Name:** Zometa
Pharmaceutica Category Bisphosphonate	**Route of Administration:** Intravenous
Indication Tumor-Induced Hypercalcemia	**Dosage:** 4 ——— mg
Reviewer Eric Colman, MD	**Date Review Completed:** September 18, 2000

Chemistry Reviewer: Sheldon Markofsky, Ph.D.

Pharmacology Reviewer: Gemma Kuipers, Ph.D.

Biopharmaceutics Reviewer: Robert Shore, PharmD

Statistical Reviewer: Japobrata Choudhury, Ph.D.

REVIEW SUMMARY: Two randomized, double-blind, active-controlled, multicenter studies (of identical design) were conducted in nearly 300 cancer patients to assess the relative efficacy and safety of 4mg and 8mg of IV zoledronate in the treatment of tumor-induced hypercalcemia (TIH). Approximately 87% of the patients treated with both doses of zoledronate had complete responses (normalization of serum calcium by Day 10 following treatment) vs. approximately 70% of pamidronate-treated subjects ($p < 0.02$). The secondary efficacy endpoints, corrected serum calcium and time-to-relapse, were also favorably affected by zoledronate treatment. Unfortunately, the studies were not designed to compare the relative efficacy or safety of multiple doses of drug treatment, as used in patients with recalcitrant or recurrent TIH.

The renal safety profile of zoledronate has become a serious concern. Preliminary analyses indicate that the risk for renal injury is related to dose, duration of treatment, length of infusion, age, and baseline renal function. A more comprehensive assessment of zoledronate's effect on the kidney will be available after ongoing bone metastases trials are completed in early 2001.

OUTSTANDING ISSUES: Renal toxicity

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____	**Clinical Hold**	_____	**Study May Proceed**
NDA, Efficacy/Label supplement: XXX	**Approvable**	_____	**Not Approvable**
_____	**Approve**		

SIGNATURES:

Medical Reviewer: /S/ **Date:** 9/18/00

Medical Team Leader: /S/ **Date:** 9/18/00

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Volumes Reviewed

1.1, 2.0, 58.0, 61.0, 64.0, 70.0, 75.0, 77.0, 140.0, 141.0, 142.0, 157.0

Division of Scientific Investigation (DSI) Report

One of the three clinical sites inspected by DSI was found to have significant deficiencies. These deficiencies included the enrollment of 5 subjects (out of a total of 12 at this site) despite the presence of protocol-defined exclusion criteria and the use of prohibited concomitant medications by an additional two patients.

It is difficult to say if or how these various protocol violations affected the overall study results. Therefore, Dr. Japo Choudhury re-ran the primary analysis without the data from these seven patients. The results were not appreciably altered.

Financial Disclosure

Financial disclosure information was reviewed for clinical studies 036 and 037. None of the investigators were employees of Novartis

Study 036

The financial compensations received by the above investigators are unlikely to have significantly biased the results of the study given the that they represent a small percentage of the total number of clinical investigators.

Administrative Background

In response to questions regarding the renal safety profile of zoledronate, the company submitted a major amendment to the NDA in late May, 2000. The review clock was accordingly extended three months to September 21, 2000.

Bisphosphonates Currently Approved for Tumor-Induced Hypercalcemia (TIH)

Etidronate and pamidronate are currently approved by the FDA for the treatment of TIH.