

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***  
**NDA 20-036 S020**

***Trade Name:*** Aredia

***Generic Name:*** pamidronate disodium injection

***Sponsor:*** Novartis Pharmaceuticals Corporation

***Approval Date:*** October 9, 2003

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***APPLICATION NUMBER:***  
**NDA 20-036 S020**

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***APPLICATION NUMBER:***  
**NDA 20-036 S020**

**APPROVAL LETTER**



NDA 20-036/S-020

Novartis Pharmaceuticals Corporation  
Attention: Robyn Konecne, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Konecne:

Please refer to your supplemental new drug application dated September 15, 2000, received September 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium injection).

We acknowledge receipt of your submission dated April 8, 2003 which constituted a complete response to our December 20, 2002 action letter.

This supplemental new drug application provides additional information for the *Hepatic Insufficiency* subsection of the **Clinical Pharmacology** section. This application was submitted in response to a postmarketing commitment in the October 31, 2001 approval letter for NDA 20-036.

We have completed the review of this supplemental application, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 8, 2003) with the following change. In the *Hepatic Insufficiency* subsection of the **Special Populations** section, add the sentence "Aredia has not been studied in patients with severe hepatic impairment." to the end of the paragraph. (b)(4)-----

(b)(4)-----

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-036/S-020." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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David Orloff  
10/9/03 03:14:39 PM

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*APPLICATION NUMBER:*  
**NDA 20-036 S020**

**APPROVABLE LETTER**



NDA 20-036/S-020

Novartis Pharmaceuticals Corporation  
Attention: Paula Rinaldi  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Rinaldi:

Please refer to your supplemental new drug application dated September 15, 2000, received September 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium injection).

This supplemental new drug application provides additional information for the *Hepatic Insufficiency* subsection of the **Clinical Pharmacology** section. This application was submitted in response to a postmarketing commitment in the October 31, 2001 approval letter for NDA 20-036.

We have completed the review of this supplemental application, and it is approvable. Before this application may be approved, however, you must address the following deficiencies:

1. The PK data were re-analyzed by the Agency, and it was found that patients with abnormal liver function had 68% and 72% higher values in AUC(0-last) and AUC(0-Inf), respectively, than those of patients with normal hepatic function. Since the extrapolated areas from the last measurable time point to infinity was less than 20% of total AUC, the AUC(0-inf) is recommended to be presented in the labeling.
2. Provide justification as to why the dose adjustment for patients with mild to moderate abnormal hepatic function is not recommended. In addition, explain why no changes in dosing regimen are recommended for patients with renal impairment.

Further, you must submit draft labeling revised as follows:

***Hepatic Insufficiency***

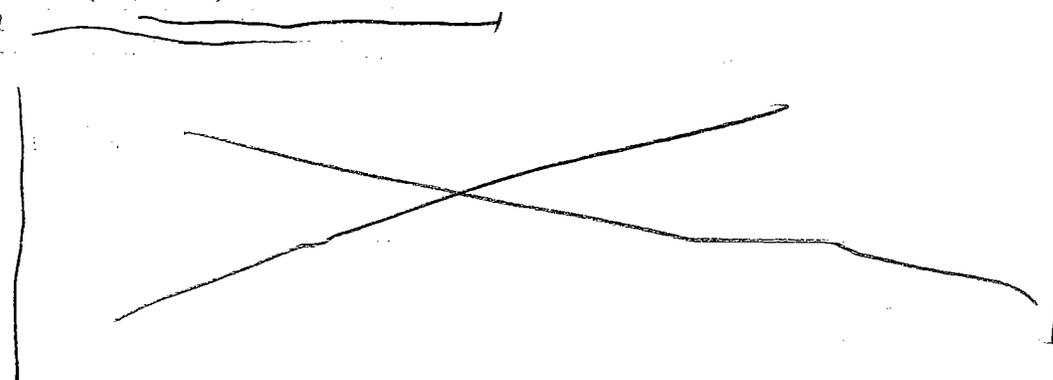
~~There are no human pharmacokinetic data for Aredia in patients who have hepatic insufficiency.~~

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7).

Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment had higher mean AUC ( ) and Cmax ( )

Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function.

Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients



In addition, all previous revisions of the labeling, as reflected in the most recently approved labeling (Supplement 026, approved on July 12, 2002), must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of this drug becomes available, additional revisions of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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David Orloff  
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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 20-036 S020**

**LABELING**





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*APPLICATION NUMBER:*  
**NDA 20-036 S020**

**MEDICAL REVIEW**

# MEMO to the FILE

October 8, 2003

**NDA:** 20-036/SLR020AZ

**DRUG:** Aredia (pamidronate)

**COMPANY:** Novartis

**SUBJECT:** Labeling supplement: Phase 4 study to examine the PK parameters of pamidronate in patients with mild-to-moderate hepatic impairment.

**PRIMARY REVIEWER:** Wei Qiu, Ph. D.

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After review of Novartis's PK data and proposed language for the product labeling, Dr. Wei Qiu has concluded that the proposal (with a minor modification noted below in bolded font) is acceptable.

Under **CLINICAL PHARMACOLOGY** Section *Special Population* subsection:

### *Hepatic Insufficiency*

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53%) and Cmax (29%), and decreased plasma clearance (33%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function. **Aredia has not been studied in patients with severe hepatic impairment.**

**Comment:** I agree with Dr. Wei Qiu and recommend that the supplement be approved with the language provided in the box above. (the last sentence should not be bolded in the final printed label).

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Eric Colman, MD  
Clinical Team Leader

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/s/

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Eric Colman  
10/8/03 10:07:58 AM  
MEDICAL OFFICER

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*APPLICATION NUMBER:*  
**NDA 20-036 S020**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

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NDA: 20-036/SLR020AZ	Submission Date(s): April 8, 2003
Brand Name	Aredia®
Generic Name	Pamidronate disodium injection
Reviewer	Wei Qiu, Ph. D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products/HFD-510
Sponsor	Novartis
Submission Type; Code	Phase IV commitment
Formulation; Strength(s)	Vials for injection
Indication	Hypercalcemia of malignancy; Paget's disease; Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma

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**Synopsis:**

Novartis Pharmaceuticals Corporation submitted a response to the Agency's review comments dated December 20, 2002 for the approved Aredia® (pamidronate disodium for injection) regarding the Clinical Pharmacology section Hepatic Insufficiency subsection of the package insert.

The Agency's comments sent to the sponsor:

- 1. The PK data were re-analyzed by the Agency, and it was found that patients with abnormal liver function had 68% and 72% higher values in AUC(0-last) and AUC(0-inf), respectively, than those of patients with normal hepatic function. Since the extrapolated areas from the last measurable time point to infinity was less than 20% of total AUC, the AUC(0-inf) is recommended to be presented in the labeling.**

The sponsor agreed that the mean percent difference in AUC values between patients with mild to moderate abnormal liver function and patients with normal liver function are consistent with the Agency's calculated values, of 68% in AUC(0-last) and 72% in AUC(0-inf). Since it has been demonstrated that renal function impacts pamidronate pharmacokinetic and Patient No. 15 showed considerable renal impairment, the sponsor claimed that this patient should be excluded from final calculation of pharmacokinetic parameters. When this patient is excluded, the difference in the mean AUC(0-inf) values between the two groups is 53%. The difference in mean C<sub>max</sub> values between the two groups is 29%. The difference in pamidronate mean clearance between the two groups is 33%. It is agreed that the data excluding Patient No. 15 will be presented in the labeling.

**2. Provide justification as to why the dose adjustment for patients with mild to moderate abnormal hepatic function is not recommended. In addition, explain why no changes in dosing regimen are recommended for patients with renal impairment.**

The sponsor acknowledged that there was a statistically significant difference in AUC (53% higher) and CL (33% lower) between patients with mild to moderate abnormal and normal hepatic function. The sponsor stated that there is no evidence that the magnitude of, and differences between, plasma concentrations of a bisphosphonate drug have any clinical relevance.

Regarding the safety profile of pamidronate, this reviewer consulted with Dr. Eric Colman. Dr. Colman suggested no objection to sponsor's proposed labeling language.

Regarding to the dosing regimen for patients with renal impairment, the sponsor indicated that renal impairment was outside of the scope of this supplement (S-020) and the issue of dose adjustment for patients with renal impairment had been resolved in the FDA approval of supplement 009 on September 1, 1995. This matter was not mentioned in the referred FDA approval letter, implying this issue was solved during previous NDA review.

Reviewer comments:

Subject No. 15 can be excluded from the final calculation of pharmacokinetic parameters due to renal insufficiency status.

**Comments to Be Sent to the Sponsor:**

Subject No. 15 can be excluded from the final calculation of pharmacokinetic parameters due to renal insufficiency status.

**Labeling Comments:**

Under **CLINICAL PHARMACOLOGY** Section *Special Population* subsection:

*Hepatic Insufficiency*

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53%) and C<sub>max</sub> (29%), and decreased plasma clearance (33%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function. Aredia has not been studied in patients with severe hepatic impairment.

**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 20-036/SLR020AZ submitted on April 8, 2003 and finds it acceptable. The recommendation and labeling comments should be conveyed to the sponsor as appropriate.

Wei Qiu, Ph.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader\_\_\_\_\_

FT initialed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_

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Wei Qiu  
10/7/03 01:00:10 PM  
BIOPHARMACEUTICS

Hae-Young Ahn  
10/7/03 04:54:37 PM  
BIOPHARMACEUTICS

NDA 20-036/S-020  
Aredia® (pamidronate disodium injection)  
Novartis Pharmaceuticals Corp.  
Submission Date: September 15, 2000

Addendum: FDA Recommended Changes to Aredia® Label

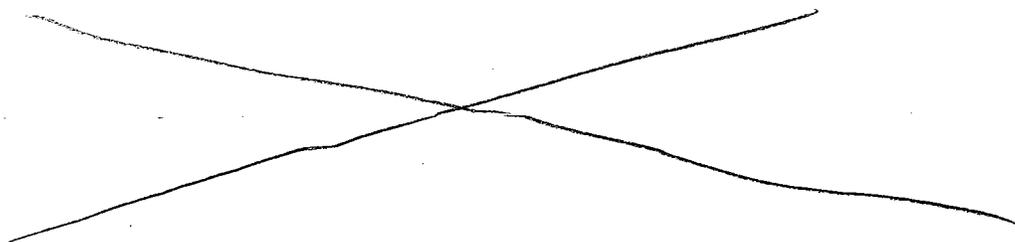
Under **CLINICAL PHARMACOLOGY** Section *Special Population* subsection:

Reviewer recommends:

**Hepatic Insufficiency**

~~There are no human pharmacokinetic data for Aredia in patients who have hepatic insufficiency. The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC and Cmax. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function.~~

~~Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients~~



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/s/

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Wei Qiu  
12/13/02 09:51:11 AM  
PHARMACOLOGIST

Hae-Young Ahn  
12/19/02 12:42:08 PM  
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
REVIEW**

---

NDA: 20-036/SLR020	Submission Date(s): September 15, 2000
Brand Name	Aredia®
Generic Name	Pamidronate disodium injection
Reviewer	Wei Qiu, Ph. D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products/HFD-510
Sponsor	Novartis
Submission Type; Code	Phase IV commitment
Formulation; Strength(s)	Vials for injection
Indication	Hypercalcemia of malignancy; Paget's disease; Osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma

---

**Synopsis:**

Novartis Pharmaceuticals Corporation submitted an update to the approved Aredia® (pamidronate disodium for injection) package insert on September 15, 2000. This submission is a part of the Phase IV commitments for Aredia® as outlined in our October 31, 1991 approval letter. The change was based on a pharmacokinetic study performed in cancer patients with hepatic impairment.

In this single dose parallel pharmacokinetics study (Study No. 28), patients received one 4-hour infusion of pamidronate 90 mg, diluted in 5% dextrose in water (D5W). The sponsor included the cancer patients with abnormal hepatic functions. However, the enrolled patients were not categorized according to Child-Pugh classifications as originally planned, but all grouped under "abnormal liver function" for the purpose of data analyses. The sponsor indicated that the patients with Child-Pugh classification B were very difficult to find and did not survive long enough for actual trial participation, due to their metastatic disease and degree of hepatic dysfunction. It was also indicated that other patients with less severe hepatic dysfunction did not fit clearly into Child-Pugh class A, and were therefore classified as "abnormal hepatic function" group.

A total of six patients with normal liver function and nine patients with abnormal liver function were enrolled. One patient with abnormal liver function did not have PK data due to analytical interferences in plasma samples. Pamidronate was determined in plasma using high performance liquid chromatography with ~~fluorescence detection~~. The following table summarizes the PK results presented by the sponsor.

PK Parameters	Patients with Normal Hepatic Function (n=6)	Patients with Impaired Hepatic Function (n=8)
	Mean (%CV)	Mean (%CV)
C <sub>max</sub> (µg/mL)	1.61 (24.1)	2.55 (61.2)
AUC(0-36) (µg.h/mL)	7.59 (16.9)	12.0 (38.2)
CL (L/h)	12.2 (18.0)	8.32 (31.5)

The mean AUC(0-36) and C<sub>max</sub> values were higher in patients with hepatic impairment. On average, the plasma clearance of pamidronate was lower in patients with hepatic impairment. The inter-subject variability expressed by the CV% was higher in patients with impaired hepatic function as compared to patients with normal hepatic function. The extent of exposure to pamidronate in hepatic impaired cancer patients was statistically significant higher by 58% than that in cancer patients with normal hepatic function.

**Reviewer comments:**

1. With the available data of serum bilirubin and serum albumin provided by the sponsor, five patients in abnormal hepatic group had Child-Pugh score of not less than 7. Therefore, these patients can be categorized to Child-Pugh classification B. The remaining three patients in the same group who would have Child-Pugh score of not less than 5 can be classified to Child-Pugh classification A.
2. Although this drug is exclusively eliminated by renal excretion as claimed by the sponsor, the present study showed that patients with hepatic impairment had statistically significant lower clearance. It was noted that two patients in abnormal hepatic group had abnormal creatinine clearance. One of these two patients had relatively low clearance compared to the remaining members of the same group. Excluding these two patients would not change the conclusion.
3. In the approved labeling, after infusion of 90 mg for 4 hours in cancer patients, the total clearance of pamidronate was 6.18 L/h. The total clearance of patients with normal hepatic function from the present study is approximately two-fold of that value.
4. This reviewer discussed with medical team leader Dr. Eric Colman regarding whether the dose adjustment for hepatic impairment is needed. Dr Colman suggested to ask the sponsor to justify why the dose adjustment for patients with mild to moderate abnormal hepatic function was not recommended. In addition, the sponsor is encouraged to explain why no changes in dosing regimen were recommended for patients with renal impairment.

**Comments to Be Sent to the Sponsor:**

1. The PK data were re-analyzed and it was found that the patients with abnormal liver function had 68% and 72% higher values in AUC(0-last) and AUC(0-inf) than those of patients with normal hepatic function, respectively. Since the extrapolated areas from the last measurable time point to infinity was less than 20%, the AUC(0-inf) is recommended to be used to calculate total clearance and to be presented in the labeling.
2. The sponsor is recommended to justify why the dose adjustment for patients with mild to moderate abnormal hepatic function was not recommended. In addition, the sponsor is encouraged to explain why no changes in dosing regimen were recommended for patients with renal impairment.

**Labeling Comments:**

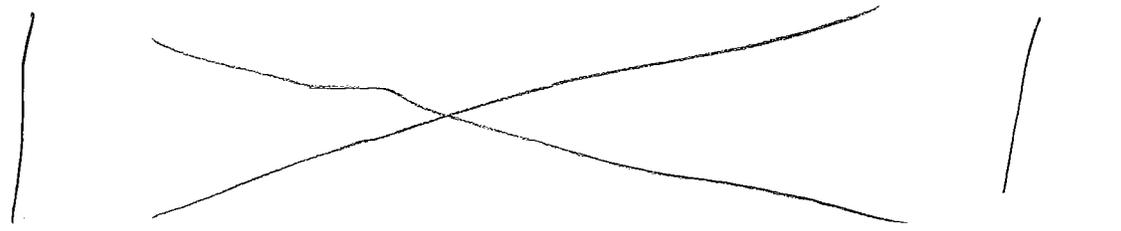
Under **CLINICAL PHARMACOLOGY** Section **Special Population** subsection:

***Hepatic Insufficiency***

There are no human pharmacokinetic data for Aredia in patients who have hepatic insufficiency. The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7)

Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC and Cmax. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12-36 hours after drug infusion. Because Aredia is administered on a monthly basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function.

~~Mean (SD, CV%) Pamidronate Pharmacokinetic Parameters in Cancer Patients~~



**RECOMMENDATION:**

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 20-036/SLR020 submitted on September 15, 2000 and finds it acceptable. The recommendation and labeling comments should be conveyed to the sponsor as appropriate.

Wei Qiu, Ph.D.  
Division of Pharmaceutical Evaluation II  
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_

FT initialed by Hae-Young Ahn, Ph.D., Team Leader \_\_\_\_\_

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Wei Qiu  
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PHARMACOLOGIST

Xiao-xiong Wei  
12/5/02 02:14:07 PM  
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 20-036 S020.**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**



NDA 20-036

Novartis Pharmaceuticals Corporation  
Attention: Robyn Konecne, Pharm.D.  
Associate Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Konecne:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium injection).

We also refer to the postmarketing commitment included in the October 31, 1991 approval letter to conduct pharmacokinetic (PK) studies in patients with renal and hepatic impairment.

The commitment to conduct a PK study in patients with renal impairment was fulfilled with the approval of supplement-009 on September 1, 1995.

The commitment to conduct a PK study in patients with hepatic impairment was fulfilled with the approval of supplement-020 on October 9, 2003.

This completes all of your postmarketing study commitments acknowledged in our October 31, 1991 letter.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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Kati Johnson  
12/9/03 01:26:13 PM  
signing fr David G. Orloff, MD

**Division of Metabolic and Endocrine Drug Products**

**PROJECT MANAGER LABELING REVIEW**

**Application Number:** 20-036/S-020

**Name of Drug:** Aredia (pamidronate disodium injection)

**Sponsor:** Novartis Pharmaceuticals Corporation

**Material Reviewed**

**Submission Dates:**

- April 8, 2003, containing a revised draft package insert (PI).

**Background and Summary Description:**

This supplemental application was submitted on September 15, 2000. The Division sent an approvable letter to the firm on December 20, 2002. On April 8 2003 Novartis submitted a complete response to our approvable letter. This supplemental new drug application provides additional information for the *Hepatic Insufficiency* subsection of the **Clinical Pharmacology** section.

**Review**

The submitted draft labeling (No Identifier Number, Revised April 2003) was compared to the final printed labeling (FPL) submitted September 10, 2002 (Identifier T2002-67 89002604, Revised July 2002, Acknowledged and Retained January 31, 2003 [Supplement -026]).

The following changes have been made:

1. **Hepatic Insufficiency**

The pharmacokinetics of pamidronate were studied in male cancer patients at risk for bone metastases with normal hepatic function (n=6) and mild to moderate hepatic dysfunction (n=7). Each patient received a single 90 mg dose of Aredia infused over 4 hours. Although there was a statistically significant difference in the pharmacokinetics between patients with normal and impaired hepatic function, the difference was not considered clinically relevant. Patients with hepatic impairment exhibited higher mean AUC (53%) and C<sub>max</sub> (29%), and decreased plasma clearance (33%) values. Nevertheless, pamidronate was still rapidly cleared from the plasma. Drug levels were not detectable in patients by 12 to 36 hours after drug infusion. Because Aredia is administered on a monthly

basis, drug accumulation is not expected. No changes in Aredia dosing regimen are recommended for patients with mild to moderate abnormal hepatic function.

2. The Biopharm reviewer recommends adding the following sentence to the end of the above paragraph, "Aredia has not been studied in patients with severe hepatic impairment."
3. There are no other changes in the draft package insert.

### **Conclusions**

Issue an approval letter.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

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/s/

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Randy Hedin  
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CSO



NDA 20-036/S-020

Novartis Pharmaceuticals Corporation  
Attention: Paula Rinaldi  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Rinaldi:

We acknowledge receipt on April 9, 2003, of your April 8, 2003 resubmission to your supplemental new drug application for Aredia<sup>®</sup> (pamidronate disodium injection).

We consider this a complete, class 2 response to our December 20, 2002 action letter. Therefore, the user fee goal date is October 9, 2003.

If you have any question, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin, R.Ph.  
Senior Regulatory Management Officer  
Division of Metabolic & Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/

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Randy Hedin  
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