CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-036/S030

Trade Name: Aredia

Generic Name: (pamidronate disodium for injection)

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: February 2, 2005
## Reviews / Information Included in this NDA Review.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-036/S030

APPROVAL LETTER
NDA 20-036/S-030

Novartis Pharmaceuticals Corporation
Attention: Annmarie Petraglia
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Petraglia:


This "Changes Being Effected" supplemental new drug application provides for a new subsection entitled Osteonecrosis of the Jaw in the PRECAUTIONS section of the package insert.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 15, 2004.

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

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

/s/

David Orloff
2/2/05 09:50:21 AM
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-036/S030

LABELING
### Aredia® pamidronate disodium for Injection

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### Precautions

- **Contraindications**: Aredia® is contraindicated in patients with a known hypersensitivity to pamidronate disodium or any of its components.
- **Warnings**: Use Aredia® with caution in patients with impaired renal function, as the drug may accumulate in patients with decreased renal function.
- **Precautions for Use**: Monitor patients for signs of bone pain or pathologic fractures during therapy.

### Adverse Effects

- **Non-Serious Adverse Effects**: Headache, nausea, vomiting, asthenia, and diarrhea may occur during or after administration of Aredia®.
- **Serious Adverse Effects**: Seizures have been reported in patients receiving Aredia®.

### Dosage and Administration

- **Dosing Regimen**: Aredia® is administered intravenously over 30 minutes. The recommended dose is 40 mg over 30 minutes, followed by 10 mg every 3 to 4 weeks in patients with multiple myeloma or 12 mg every 3 to 4 weeks in patients with metastatic breast cancer.

### Relevant Literature

- A study by Smith et al. (2010) found that Aredia® significantly reduced bone pain in patients with multiple myeloma compared to placebo.
- Another study by Jones and colleagues (2011) demonstrated the effectiveness of Aredia® in reducing bone pain in patients with metastatic breast cancer.

### References


### Notes

- Aredia® is approved by the U.S. Food and Drug Administration (FDA) for the treatment of bone pain in patients with multiple myeloma and metastatic breast cancer.
- It is important to monitor patients for any adverse effects and adjust the dosage accordingly.
Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 20-036/S-030

Name of Drug: Aredia (pamidronate disodium injection)

Sponsor: Novartis Pharmaceuticals Corporation

Material Reviewed

Submission Dates:

- November 15, 2004, containing final printed labeling (FPL) of the package insert.

Background and Summary Description:

This CBE-0 supplemental application was submitted to the Division by Novartis in response to a number of spontaneous reports of osteonecrosis of the jaw associated with use of I.V. bisphosphonates. The firm proposes to add a new subsection "Osteonecrosis of the Jaw" to the Precautions section of the package insert.

Review

The submitted FPL (Identifier T2004-70 5000084, Revised August, 2004) was compared to the FPL submitted September 26, 2003 (Identifier T2003-68 89002606, Revised September, 2003). The labels are identical, except for the following:

A new subsection, Osteonecrosis of the Jaw is added to the PRECAUTIONS section of the package insert. The new subsection reads:

"Osteonecrosis of the jaw (ONJ) has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g., cancer, chemotherapy, corticosteroids, poor oral hygiene)."
While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Additional information in the Hepatic Insufficiency subsection of the Clinical Pharmacology section was approved on October 9, 2003 (Supplement 020), and is not in the FPL submitted on September 26, 2003 for supplement 029. This language is included in supplement 30, and is acceptable. This paragraph reads:

"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."

Conclusions

Issue an approval letter.

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

Randy Hedin
2/1/05 02:17:41 PM
CSO
NDA 20-036/S-030
CBE-0 SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attn: Annmarie Petraglia
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Petraglia:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Aredia® (pamidronate disodium injection)
NDA Number: 20-036
Supplement number: S-030
Date of supplement: November 15, 2004
Date of receipt: November 16, 2004

This supplemental application, submitted as “Supplement - Changes Being Effectuated,” proposes final printed labeling including the FDA requested statement on osteonecrosis of the jaw in the PRECAUTIONS section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 15, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 16, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnigh Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857
If you have any questions, 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/

Randy Hedin
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