



NDA 20-036/S-034

Novartis Pharmaceuticals Corporation  
Lynne McGrath, Ph.D.  
Director, Regulatory Affairs  
One Health Plaza  
East Hanover, New Jersey 07936

Dear Dr. McGrath:

Please refer to your supplemental new drug application dated March 6, 2007, received March 7, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aredia (pamidronate disodium) for injection.

We acknowledge receipt of your submissions dated September 28, October 30 and November 20, 2007.

This "Changes Being Effected" supplemental new drug application provides for changes in the language regarding safety information to the US prescribing information (PI) in the following areas:

**Warnings**

- Added the following subheading to **Warnings: *Deterioration in Renal Function***.
- Moved statement: *Bisphosphonates, including Aredia, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure*, under subheading ***Deterioration in Renal Function***.
- Added statement: *Renal deterioration, progression to renal failure, and dialysis have been reported in patients after the initial or single dose of Aredia* which is part of the end of the bolded warning.
- Added statement as the paragraph following the bolded warning: *Focal segmental glomerulosclerosis (including the collapsing variant) with or without nephrotic syndrome, which may lead to renal failure, has been reported in Aredia-treated patients, particularly in the setting of multiple myeloma and breast cancer. Some of these patients had gradual improvement in renal status after Aredia was discontinued.*
- Moved the following three paragraphs from **Warnings** into a new section called ***Animal Toxicology*** that follows the ***Carcinogenesis, Mutagenesis, Impairment of Fertility*** section.

*In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) administration of Aredia.*

*Two 7-day intravenous infusion studies were conducted in the dog wherein Aredia was given for 1, 4, or 24 hours at doses of 1-20 mg/kg for up to 7 days. In the first study, the compound was well tolerated at 3 mg/kg (1.7 x highest recommended human dose [HRHD] for a single intravenous infusion) when administered for 4 or 24 hours, but renal findings such as elevated BUN and creatinine levels and renal tubular necrosis occurred when 3 mg/kg was infused for 1 hour and at doses of  $\geq 10$  mg/kg. In the second study, slight renal tubular necrosis was observed in 1 male at 1 mg/kg when infused for 4 hours. Additional findings included elevated BUN levels in several treated animals and renal tubular dilation and/or inflammation at  $\geq 1$  mg/kg after each infusion time.*

*Aredia was given to rats at doses of 2, 6, and 20 mg/kg and to dogs at doses of 2, 4, 6, and 20 mg/kg as a 1-hour infusion, once a week, for 3 months followed by a 1-month recovery period. In rats, nephrotoxicity was observed at  $\geq 6$  mg/kg and included increased BUN and creatinine levels and tubular degeneration and necrosis. These findings were still present at 20 mg/kg at the end of the recovery period. In dogs, moribundity/death and renal toxicity occurred at 20 mg/kg as did kidney findings of elevated BUN and creatinine levels at  $\geq 6$  mg/kg and renal tubular degeneration at  $\geq 4$  mg/kg. The kidney changes were partially reversible at 6 mg/kg. In both studies, the dose level that produced no adverse renal effects was considered to be 2 mg/kg (1.1 x HRHD for a single intravenous infusion).*

### **Precautions**

- Added statement as the second paragraph of the **General** subsection, *Patients with a history of thyroid surgery may have relative hypoparathyroidism that may predispose to hypocalcemia with Aredia.*

### **Renal Insufficiency**

- Deleted statement in second paragraph, *Aredia has not been tested in patients who have class Dc renal impairment (creatinine  $> 5.0$  mg/dL), and has been tested in few multiple myeloma patients with serum creatinine  $\geq 3.0$  mg/dl.*
- Added statement in second paragraph, *In clinical trials, patients with renal impairment (serum creatinine  $> 3.0$  mg/dL) have not been studied. Limited pharmacokinetic data exist in patients with creatinine clearance,  $< 30$  ml/min .*

### **Drug Interactions**

- Added statement as third paragraph, *In multiple myeloma patients, the risk of renal dysfunction may be increased when Aredia is used in combination with thalidomide.*

### ***Post-Marketing Experience***

- Added statement at the beginning of the first paragraph, *The following adverse reactions have been reported in post-marketing use: **General:** reactivation of Herpes simplex and Herpes zoster, influenza-like symptoms; **Gastrointestinal;** **CNS:** confusion and visual hallucinations, often in the presence of hypocalcemia; **Skin:** rash, pruritus; **Special senses:** conjunctivitis; **Renal:** focal segmental glomerulosclerosis including the collapsing variant, nephrotic syndrome; **Laboratory abnormalities:** hyperkalemia, hypernatremia, hematuria.*

### ***Dosage and Administration***

- Added new section immediately before ***Preparation of Solution: Calcium and Vitamin D Supplementation*** with statement, *In the absence of hypercalcemia, patients with predominantly lytic bone metastases or multiple myeloma, who are at risk of calcium or vitamin D deficiency, and patients with Paget's disease of the bone, should be given oral calcium and vitamin D supplementation in order to minimize the risk of hypocalcemia.*

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed labeling (text for the package insert submitted November 20, 2007.) Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 20-036/034.**"

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

### **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see [www.fda.gov/cder/ddmac](http://www.fda.gov/cder/ddmac).

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

**LETTERS TO HEALTH CARE PROFESSIONALS**

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch  
Food and Drug Administration  
HFD-001, Suite 5100  
5515 Security Lane  
Rockville, MD 20852

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Haley Seymour, Regulatory Project Manager, at (301) 796-2443.

Sincerely,

*{See appended electronic signature page}*

Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Mary Parks  
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