DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-113/S-006

Bedford Laboratories
Attn: Molly Rapp
Director, Regulatory Affairs
300 Northfield Road
Bedford, Ohio 44146

Dear Ms. Rapp:

Please refer to your supplemental new drug application dated April 15, 2008, received April 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pamidronate Disodium Injection.

This "Changes Being Effected" supplemental new drug application provides for the following revisions:

To the **WARNINGS** section:

- Added the following subheading **Deterioration in Renal Function** (becomes the first subheading)

1. Moved the statement: "Bisphosphonates, including pamidronate disodium, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure," under this subheading.

2. The bolded warning: "**DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF PAMIDRONATE DISODIUM SHOULD NOT EXCEED 90 MG (see DOSAGE AND ADMINISTRATION for appropriate infusion durations)"** was placed under this subsection

3. Added the statement (in bold type): "**Renal deterioration, progression to renal failure, and dialysis have been reported in patients after the initial or a single dose of pamidronate disodium"** at the end of the bolded warning in this subsection. This was immediately followed by:

4. The new statements, "Focal segmental glomerulosclerosis (including the collapsing variant) with or without nephritic syndrome, which may lead to renal failure, has been reported in pamidronate disodium-treated patients, particularly in the setting of multiple myeloma and

breast cancer. Some of these patients had gradual improvement in renal status after pamidronate disodium was discontinued."

- Moved the following two paragraphs from **WARNINGS** into a new subsection called ***Animal Toxicology*** that follows the ***Carcinogenesis, Mutagenesis, Impairment of Fertility*** subsection in the **PRECAUTIONS** section:

1. "In both rats and dogs, nephropathy has been associated with intravenous (bolus and infusion) administration of pamidronate disodium.

   Two 7-day intravenous infusion studies were conducted in the dog wherein pamidronate disodium 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 ≥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 ≥1 mg/kg after each infusion time. Pamidronate disodium 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 ≥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 ≥6 mg/kg and renal tubular degeneration at ≥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)."

To the **PRECAUTIONS** section:

- **General** subsection

1. Added the statement, "Patients with a history of thyroid surgery may have relative hypoparathyroidism that may predispose to hypocalcemia with pamidronate disodium." as a second paragraph.

- **Renal Insufficiency** subsection

1. Deleted the statement in third paragraph, "Pamidronate disodium 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 ≥3.0 mg/dl."

2. Added the statement in the third 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, <30ml/min."

- **Drug Interactions** subsection

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

- **Animal Toxicology** subsection (new)

    1. See above (changes to **WARNINGS)** for the three paragraphs moved to this new subsection that follows the **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection.

- **Geriatric Use** subsection (new) – follows **Pediatric Use** subsection

    1. The following paragraph was added, "Of the total number of subjects in clinical studies of pamidronate disodium, approximately 20% were 65 and over, while approximately 15% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

To the **ADVERSE REACTIONS** section

- **Post-Marketing Experience** subsection

    1. The following statements were added 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; **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."

To the **DOSAGE AND ADMINISTRATION** section

- **Calcium and Vitamin D Supplementation** subsection (new) – follows the **Osteolytic Bone Metastases of Breast Cancer** subsection

    1. The following information was added to this new subsection: "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 have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

We note that your April 15, 2008, submission included content of labeling in the structured product labeling (SPL) format.

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:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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 Pat Madara, Regulatory Project Manager, at (301) 796-1249.

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 and Research

Enclosure: Package Insert

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

10/17/2008 03:03:46 PM

Eric Colman for Mary Parks