CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-113 /SE____ - _____

Drug pamidronate disodium for Injection Applicant Bedford Labs

RPM R Hedin - Phone 827-6392

☐ 505(b)(1)
☒ 505(b)(2) Reference listed drug Aredia for Injection

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s) None

Application classifications:
Chem Class 5S
Other (e.g., orphan, OTC) ____

PDUFA Goal Dates:
Primary 3/6/02
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☒ User Fee Exemption

- Action Letter..... ☒ AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews..... 3/1/02
  Original proposed labeling (package insert, patient package insert) 2/25/02
  Other labeling in class (most recent 3) or class labeling..... NDA 20-036
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ☒ No
  Immediate container and carton labels 10/5/01
  Nomenclature review ..... NA

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — ☐ Materials requested in AP letter

- Post-marketing Commitments — None
  - Agency request for Phase 4 Commitments ..... —
  - Copy of Applicant's commitments ..... —

- Was Press Office notified of action (for approval action only)? ..... ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper ..... —

- Patent
  - Information [505(b)(1)] ..... NA
  - Patent Certification [505(b)(2)] 2/26/99
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] ..... 2/5/00 & 4/22/99

- Exclusivity Summary X

- Debarment Statement ..... No Clinical Studies

- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located ..... NA

- Correspondence/Memoranda/Faxes X

- Minutes of Meetings X
  - Date of EOP2 Meeting None
  - Date of pre NDA Meeting None
  - Date of pre-AP Safety Conference None

- Advisory Committee Meeting ..... None
  - Date of Meeting ..... NA
  - Questions considered by the committee ..... NA
  - Minutes or 48-hour alert or pertinent section of transcript ..... NA

- Federal Register Notices, DESI documents ..... None

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) ..... No Clinical Trials.

- Clinical review(s) and memoranda 6/23/00

Continued ⇨

- ♦ Safety Update review(s) ..... None

- ♦ Pediatric Information
  ☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... See Medical/Team Leader memo
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☒ Not Applicable

- ♦ Statistical review(s) and memoranda ..... None

- ♦ Biopharmaceutical review(s) and memoranda..... 5/7/99

- ♦ Abuse Liability review(s) ..... N/A
  Recommendation for scheduling ..... —

- ♦ Microbiology (efficacy) review(s) and memoranda 11/19/99

- ♦ DSI Audits ..... None
  ☐ Clinical studies ☐ bioequivalence studies ..... —

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ♦ CMC review(s) and memoranda 12/1/01

- ♦ Statistics review(s) and memoranda regarding dissolution and/or stability ..... None

- ♦ DMF review(s) ..... 11/12/99 + 8/2/01

- ♦ Environmental Assessment review/FONSI/Categorical exemption 8/8/01

- ♦ Micro (validation of sterilization) review(s) and memoranda 11/19/99

- ♦ Facilities Inspection (include EES report)
  Date completed Aug 7, 2001 ..... ☒ Acceptable ☐ Not Acceptable

- ♦ Methods Validation ..... ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ♦ Pharm/Tox review(s) and memoranda 5/4/01

- ♦ Memo from DSI regarding GLP inspection (if any) ..... NA

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... None
- CAC/ECAC report ..... None

APPEARS THIS WAY
ON ORIGINAL

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number and Name of Drug:

NDA 21-113 pamidronate sodium injection

Sponsor: Bedford Laboratories

Material Reviewed

Submission Dates: NDA 21-113, pamidronate sodium injection, Bedford Labs., September 5, 2001, and February 25, 2002

Compared to:

NDA 20-036, Aredia (pamidronate disodium for injection)
Novartis Pharmaceuticals
Submitted August 16, 2001, Approved August 20, 2001

Background and Summary:

Aredia is currently approved for the following:

1. Treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases.

2. Treatment of patients with moderate to severe Paget's disease of bone.

3. Treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma.

Bedford Laboratories submitted a 505(b)2 application (relying on studies in NDA 20-036 [Aredia] for approval) for pamidronate sodium injection on February 26, 1999. We sent an approvable letter on December 15, 1999, with multiple chemistry deficiencies including a statement on stability that states the toxicity for [redacted], leached from the glass needs to be identified, or shown to be safe and not toxic. The submission of February 28, 2000, constituted a complete response to our December 15, 1999 action letter. We subsequently sent another approvable letter on August 31, 2000, requesting a one-month rat toxicity study to assess the safety of the extractables leached from the glass, and some remaining chemistry deficiencies. The February 16, 2001 submission constituted a complete response to our August 31, 2000, action letter. We subsequently issued an approvable letter on August 20 2001, pending

resolution of chemistry deficiencies. The firm subsequently submitted a complete response on September 5, 2001.

Review

The Aredia label approved for supplement 024 on August 20, 2001 (Identifier # T2001-42 89008002 dated August 2001), was compared to the September 5, 2001, label submitted by Bedford Laboratories (Identifier #PMD-AQ-P01 dated August 2001).

- In the **DESCRIPTION** section the Aredia Label states "Aredia pamidronate disodium for injection," and Bedford Laboratories pamidronate label states "**PAMIDRONATE DISODIUM INJECTION.**"

- In the **DESCRIPTION** section the Aredia Label states "Each 30-mg, and 90-mg vial contains, respectively, 30 mg and 90 mg of sterile, lyophilized pamidronate disodium and 470 mg and 375 mg of mannitol, USP," and Bedford Laboratories pamidronate label states "Each mL contains respectively, 3 mg and 9 mg of pamidronate disodium; 47 mg and 37.5 mg of mannitol USP and water for injection q.s. phosphoric acid and/or sodium hydroxide have been added to adjust pH 6.2 to 7.0."

- In the **DESCRIPTION** section the Aredia Label states "Pamidronate disodium is designated chemically as phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt, pentahydrate, (APD), and its structural formula is . . .," and Bedford Laboratories pamidronate label states "Pamidronate disodium is designated chemically as disodium dihydrogen (3-amino-1-hydrosypropylidene) diphosphonate, and its structural formula is: . . ."

- In the **DESCRIPTION** section the Aredia Label states "Its molecular formula is $C_3H_9NO_7P_2Na_2 \bullet 5H_2O$ and its molecular weight is 369.1," and Bedford Laboratories pamidronate label states "Its molecular formula is $C_3H_9NO_7P_2Na_2$ and its molecular weight is 279.1."

- In the **DESCRIPTION** section the Aredia Label states "*Inactive Ingredients.* Mannitol, USP, and phosphoric acid (for adjustment to pH 6.5 prior to lyophilization)," and in the Bedford Laboratories pamidronate label this sentence is deleted; however, these ingredients are in the first sentence of the label.

  The above changes to the **DESRIPTION** section are acceptable

- In the ***Excretion*** subsection of the **CLINICAL PHARMACOLOGY** section, the last word of the first sentence of Bedford Laboratories' pamidronate label is "and," and should be, "an." The sentence should read, ". . . and 90 mg of pamidronate disodium over 24 hours, an overall mean . . ."

- In the ***Clinical Trials*** subsection of the **Hypercalcemia of Malignancy** section, the 60 mg dose is left out in numerous places. In order to have the clinical trial numbers match what was actually done in the trials this information should be put back in the section.

- In the ***Clinical Trials*** subsection of the **Hypercalcemia of Malignancy** section, the paragraph before **Paget's Disease**, is missing from Bedford Laboratories' pamidronate label. This paragraph deals with the 2-hour infusion study, which was approved with Aredia's supplement 024. Aredia was granted exclusivity for the labeling changes in supplement 024; therefore, it is appropriate for Bedford Laboratories to not include this paragraph with the label.

- In the ***Clinical Trials*** subsection of the **Osteolytic Bone Metastases of Breast Cancer and Osteolytic Lesions of Multiple Myeloma** section, the table labeled "Breast Cancer Patients Receiving Chemotherapy and Breast Cancer Patients Receiving Hormonal Therapy," does not contain the N (pertaining to the number of patients) in the upper left corner of the table. Also, in the same table the word, "of" is missing from the first sentence after the table. The sentence should read, "Fractured and radiation to bone were two <u>of</u> several secondary endpoints."

- In the ***Hypercalcemia of Malignancy*** subsection of the **Clinical Studies** subsection of the **ADVERSE REACTIONS** section, the paragraph that begins, "There are no controlled clinical trials comparing the efficacy and safety of 90 mg Aredia over 24 hours to 2 hours . . ." is missing for Bedford Laboratories pamidronate label. This paragraph deals with the 2-hour infusion study, which was approved with Aredia's supplement 024. Aredia was granted exclusivity for the labeling changes in supplement 024; therefore, it is appropriate for Bedford Laboratories to not include this paragraph with the label.

- In the ***Moderate Hypercalcemia*** and ***Severe Hypercalcemia*** subsections of the **DOSAGE AND ADMINISTRATION** section, the Bedford Laboratories pamidronate label uses the language of the Aredia label before approval of supplement 024. The Bedford laboratories label correctly states for ***Moderate Hypercalcemia***, "The recommended dose of pamidronate disodium injection in moderate hypercalcemia (corrected serum calcium* of approximately 12 to 13.5 mg/dL) is 60 to 90 mg. The 60 mg dose is given as an initial, SINGLE DOSE, intravenous infusion over at least 4 hours. The 90 mg dose must be given by an initial, SINGLE DOSE, intravenous infusion over 24 hours." And for ***Severe Hypercalcemia,*** "The recommended dose of pamidronate disodium in severe hypercalcemia (corrected serum calcium* >13.5 mg/dL) is 90 mg. The 90 mg dose must be given by an initial, SINGLE DOSE, intravenous infusion over 24 hours." This is acceptable

- The ***Reconstitution*** subsection of the **Preparation of Solution** section is appropriately left out of the Bedford Laboratories label, as it is a solution.

- In the ***Hypercalcemia of Malignancy*** subsection of the **Preparation of Solution subsection of the DOSAGE AND ADMINISTRATION** section , Bedford Laboratories pamidronate label uses the language of the Aredia label before approval of supplement 024. The Bedford laboratory label correctly states, "The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60 mg dose, and over 24 hours for the 90 mg dose. The recommended dose should be diluted in 1000 mL of sterile 0.45% or 0.9% sodium chloride injection, or 5% dextrose injection. This infusion solution is stable for up to 24 hours at room temperature."

- The **HOW SUPPLIED** section is appropriately changed (See chemistry reviews).

Conclusions

The firm was requested to submit revised labeling, which was received on March 1, 2002. The labeling was reviewed, and found acceptable.

Randy Hedin 2/19/02 Revised 2/28/02
Finalized:
Filename: C:\My Documents\Documents in DFS\N21113Label Review 001.doc

PM LABELING REVIEW

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

/s/

Randy Hedin
3/4/02 01:05:44 PM
CSO

January 30, 2002

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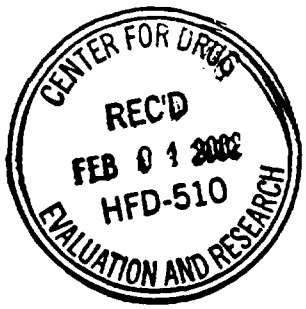
DUPLICATE



N 000 L
NEW CORRESP

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-113
Product: Pamidronate Disodium Injection; 3 mg and 9 mg per mL; 10 mL per vials

Dear Sir:

This letter is being sent with regard to a telephone conversation between Randy Hedin of the Agency and Molly Rapp of Ben Venue Laboratories, concerning the patent certifications and the legal status of the two dosages which are the subject of this NDA, 3 mg/mL, 10 mL and 9 mg/mL, 10 mL.

A Paragraph IV certification regarding U.S. Patent 4,711,880 for NDA 21-113 was submitted to the Agency for the 3 mg/mL dosage on 2-26-99. A notice was sent to the patent holder, Novartis Corp., on 4-7-99 and was received by them on 4-20-99. The NDA was subsequently amended to include the 9 mg/mL dosage. A Paragraph IV notification was again sent to the patent holder for the 9 mg/mL dosage on 1-5-00 and was received on 1-7-00. Novartis Corp. filed legal action against Ben Venue Laboratories, Inc. in May 1999. A summary judgement was granted by the U.S. District Court for the District of New Jersey in favor of non-infringement on September 29, 2000. This summary judgement included both dosages (refer to page 3 of the opinion of the summary judgement). The order (2 pages) and the first three pages of the opinion are provided for your review. The entire order can be provided if necessary.

Novartis appealed this decision in the United States Court of Appeals for the Federal Circuit. A decision was again granted in favor of non-infringement on November 7, 2001. This decision included both the 3 mg/mL and 9 mg/mL dosages, which are the subject of NDA 21-113 (please refer to page 4 of 18 of the Appellate Court decision). A copy of the decision by the U.S. Court of Appeals for the Federal Circuit is attached for your review.

It is our position that the timing of the Paragraph certification and patent holder notice for the 9 mg/mL dosage has no impact on the approval, nor should it delay the approval of the 9 mg/mL dosage. The litigation for both dosages was consolidated into one case and hence the court decisions apply to both dosages. The final court decision is the mechanism for approval of both dosages, and precludes the 30 month stay of approval period. In accordance with 21CFR314.107(b)(3)(B)(ii), the application can be approved prior to the expiration of the 30 month time period as follows:

"If before the expiration of the 30-month period, or 7 1/2 years where applicable, the court issues a final order that the patent is invalid, unenforceable, or not infringed, approval may be made effective on the date the court enters judgement."

A DIVISION OF BEN VENUE LABORATORIES, INC.

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD
LABORATORIES™

Based on the regulations and the November 7, 2001 Appeals Court decision, both the 3 mg/mL and 9 mg/mL dosages are eligible for approval immediately and should not be be subject to differing approval times.

I would welcome the opportunity to speak with you regarding this issue. I can be reached by phone at (440)-201-3576 (direct) and by fax at (440)-232-2772.

Sincerely,
for Bedford Laboratories™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

BEDFORD LABORATORIES™

October 5, 2000

"PATENT AMENDMENT"

John K. Jenkins, M.D.
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 21-113/PATENT AMENDMENT**
Product: **Pamidronate Disodium Injection; 3 mg and 9 mg per mL; 10 mL per vials**

Dear Sir:

We wish to amend our approvable New Drug Application, NDA 21-113, for Pamidronate Disodium Injection, 3 mg and 9 mg per mL; 10 mL per vials by providing a copy of final court order.

FDA 356h form is provided in this amendment.

Attached, please find the copy of Bedford Laboratories' motion for summary judgement of non-infringment of U.S. Patent 4,711,880, which is granted by United States District Court of New Jersey on September 29, 2000.

If the Agency has any questions regarding this matter, the phone numbers for contact are (440)-232-3320, ext.3333 (direct) and (440)-232-2772 (fax).

Sincerely,
for Bedford Laboratories™

Shahid Ahmed
Vice President, Regulatory Affairs
Ben Venue Laboratories, Inc.

FOXKISER
750 17TH STREET, N.W.
SUITE 1100
WASHINGTON, D.C. 20006
(202) 778-2300

March 14, 2000

Via Facsimile & Federal Express

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products/ HFD-510
Attn: Document Control Room 14 B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: Novartis Corporation v. Ben Venue Laboratories, Inc. and Bedford Laboratories, D.N.J., Civil Action No. 2:00cv00769 (WGB)
Bedford Laboratories' NDA No. 21-113 For 9 mg/ml, 10 ml per vial

Dear Dr. Sobel:

On behalf of Novartis Corporation, the purpose of this letter is to inform the Division that Novartis Corporation, on February 18, 2000, filed a patent infringement lawsuit against Bedford Laboratories ("Bedford"), as well as Ben Venue Laboratories, in the U.S. District Court for the District of New Jersey, Novartis Corporation v. Ben Venue Laboratories and Bedford Laboratories, D.N.J., Civil Action No. 2:00cv00769 (WGB), in response to Bedford's Notice of Paragraph IV Patent Certification, dated January 5, 2000, covering Bedford's 505(b)(2) application, NDA No. 21-113, which the notice states is for "a generic version of Aredia® to include a 9 mg/mL; 10 mL per vial dosage."

Enclosed for the Division's reference is a copy of the Complaint that was filed in the above-referenced action.

FOXKISER

Please feel free to contact me, on (202) 778-2354, if you have any questions or require additional information in connection with this matter.

Respectfully Submitted,

John M. Engel

John M. Engel

Enclosure

cc: Mr. Durand M. Hedin, Project Manager, HFD-510

Mr. Gary Buehler, Acting Director, Office of Generic Drugs, HFD-600

APPEARS THIS WAY
ON ORIGINAL

BEDFORD LABORATORIES™

January 5, 2000

Certified/Return Receipt Requested

General Counsel
Novartis Consumer Health, Inc.
560 Morris Avenue
Summit, NJ 07901-1312

Re: Patent Certification Notice - AREDIA®
Ben Venue Laboratories, Inc.

Dear Sir/Madam:

The purpose of this communication is to provide the notice and information indicated by the Food and Drug Administration to be required as a result of Ben Venue Laboratories, Inc.'s ("Ben Venue") amendment to its paper New Drug Application ("pNDA") No. 21-113 and pursuant to Section 505(b)(3)(A) of the Federal Food, Drug, and Cosmetic Act ("the Act") relevant to the filing of pNDAs.

While it is believed no additional notice is required, Ben Venue hereby gives notice that it has amended, under Section 505(j) of the Act (21 U.S.C. § 355), its pNDA No. 2 1-113 for a generic version of AREDIA® to include a 9 mg/ml; 10 ml per vial dosage strength. In submitting this amendment to its pNDA, Ben Venue seeks to obtain approval to engage in the commercial manufacture, use, sale and offer for sale of the amended dosage strength prior to the expiration of U.S. Patent No. 4,711,880 ("the '880 patent"), which is allegedly directed to crystalline forms of disodium 3-amino-1-hydroxypropane-1, 1 diphosphonate.

A detailed statement of the factual and legal basis of Ben Venue's opinion as to why its manufacture, use, sale, or offer for sale of the amended dosage strength (9 mg/ml) will not infringe the above-identified patent is contained in the Statement of Factual and Legal Basis for Non-Infringement, a copy of which is attached hereto as Appendix 1.

If you have any reason to disagree with our conclusion, please contact me.

Thomas R. Russillo
President and Chief Operating Officer

NOVARTIS

December 9, 1999

Solomon Sobel, MD
Director
Division of Metabolic and Endocrine Drug Products/HFD-150
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-036
Aredia (pamidronate disodium)
Vials

General Correspondence

Dear Dr. Sobel:

Please find attached a document confirming that Novartis has filed a lawsuit against Bedford Laboratories as well as Ben Venue Laboratories for patent infringement pertaining to their 505 (b)(2) application for "Pamidronate Disodium Injection" (NDA No. 21-113).

If you have any questions or need any further information, please contact me at (973) 781-8180.

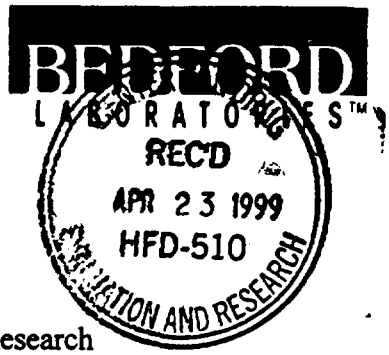
Sincerely,

Mal Cutler for

Ellen Cutler
Assistant Director
Drug Regulatory Affairs

Attachment (8 pages)
Submitted in duplicate

Desk Copies: Mr. Randy Hedin HFD-510 (via fax)
Mr. Douglas Sporn HFD-600 (via fax)



NEW CORRESP

DUPLICATE

April 22, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-113
Product: Pamidronate Disodium Injection; 3 mg/mL; 10 mL per vial

Dear Sir/Madame:

We wish to amend our unapproved New Drug Application, NDA 21-113, for Pamidronate Disodium Injection, 3 mg/mL; 10 mL per vial, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and 21 CFR 314.95.

Bedford Laboratories™ is amending its application to certify that notice has been provided to the patent holder, Novartis Corporation, that Bedford Laboratories NDA 21-113 for Pamidronate Disodium Injection; 3 mg/mL; 10 mg per vial was submitted and accepted for filing and review by the Agency. A copy of Bedford Laboratories™ Paragraph IV Certification was provided to the patent holder explaining the basis for our opinion that Patent Number 4,711,880 (expiring July 29, 2005) will not be infringed.

Additionally, please refer to the attached copy of the return receipt to document that the patent holder has received the Paragraph IV Certification notice.

If the Agency has any comment or further requests, or if we could be of any assistance in the review, we welcome direct and immediate telephone contact at (440) 232-3320, ext. 333.

Sincerely,
for Bedford Laboratories™

P. Patel for

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

BEDFORD LABORATORIES™
Pamidronate Disodium Injection; 3 mg per mL; 10 mL per vials

Section III Patent Certification

Paragraph IV Certification [21 CFR 314.94 (a)(12)(i)]

Bedford Laboratories hereby certifies that, in its opinion and to the best of its knowledge, U.S. patent No. 4,711,880 issued on December 8, 1987, which expires on July 29, 2005, has been referred to as claiming the listed drug product Aredia® manufactured by Novartis Pharmaceuticals Corporation ("Novartis"). This patent is listed in the 18th Edition of Approved Drug Products With Therapeutic Equivalence ("Orange Book"). Upon information and belief, Bedford Laboratories believes Novartis is the owner of be above-referenced patent and that Novartis is the holder of the NDA of the listed drug product mentioned above. Bedford Laboratories, by and thru this paper-NDA, is requesting approval of its application for a generic version of Aredia® ("the Bedford Laboratories Product").

Pursuant to Section 505 (j) (2) (A) (vii) (IV) of the Federal Food Drug and Cosmetic Act, Bedford Laboratories hereby certifies that the above-referenced patent will not be infringed by the manufacture, use, sale, or offer for sale of the Bedford Laboratories' Product. The claims of the "880 patent require the presence or use of pamidronate disodium in a crystalline form. Bedford Laboratories' Product does not contain any crystalline form of pamidronate disodium. The active ingredient (pamidronic acid) in Bedford Laboratories' product is dissolved in solution and will be sold as such. Moreover, to obtain the active ingredient in its product, Bedford Laboratories dissolves pamidronic acid in solution and neutralizes the acid with a sodium containing base, yielding dissolved pamidronate disodium *in situ.*

Bedford Laboratories states that a Notice to the Patent Owner and to the NDA owner required by Sections 505(j)(2) B(I) of the Federal Food, Drug and Cosmetic Act will be provided concurrently with the filling of this certification along with a Detailed Statement of Factual and Legal Basis For Non-Infringement. Such Notice states that an application has been filed by Bedford Laboratories under Section 505(b)2 for the Bedford Laboratories Product seeking approval to make, use, sell, and offer for sale the Bedford Laboratories Product prior to the expiration of U.S. patent No. 4,711,880.

BEDFORD LABORATORIES™
Pamidronate Disodium Injection; 3 mg per mL; 10 mL per vials

Section III Patent Certification

Patent Certification [21 CFR 314.94 (a)(12)(i)]

Patent and Exclusivity Search Results from query on 020036 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
020036	001	4711880	JUL 29,2006	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020036	001	I-135	SEP 01,1998
020036	001	I-158	JUL 16,1999

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-113 SUPPL # _____

Trade Name None Generic Name pamidronate disodium injection

Applicant Name Bedford Laboratories HFD-510
Approval Date March 4, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

   If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

   YES /___/ NO / X /

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /__/ NO /_X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-036 Aredia for Injection

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

BEDFORD LABORATORIES™
Pamidronate Disodium Injection; 3 mg per mL; 10 mL per vials

Section III Patent Certification

Statement of Exclusivity [21 CFR 314.94 (a)(3)]

In the opinion of Bedford Laboratories, and to the best of its knowledge, and in accordance with the listed published in the Approved Drug products with Therapeutic Equivalence, Cumm. Supp. 12, 18th Ed. ("Orange Book", copy attached), the status of marketing exclusivity is as follows:

The marketing exclusivity based upon the New Indication ("I") designation shall expire on July 16, 1999, for the reference drug. Bedford Laboratories hereby certifies the proposed drug product will not be marketed until July 17, 1999.

For BEDFORD LABORATORIES™

Shahid Ahmed
Director, Regulatory Affairs
Ben Venue Laboratories, Inc.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # NDA 21-113 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-510__ Trade and generic names/dosage form: pamidronate disodium injection Action: AP

Applicant Bedford Laboratories Therapeutic Class 5S

Indication(s) previously approved None

Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Proposed indication in this application: This new drug application provides for the use of pamidronate disodium injection for the treatment of moderate or severe hypercalcemia associated with malignancy, with or without bone metastases, for the treatment of patients with moderate to severe Paget's disease of bone, and for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesion of multiple myeloma in conjunction with standard antineoplastic therapy.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

__ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

__ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

__ c. The applicant has committed to doing such studies as will be required.
__ (1) Studies are ongoing,
__ (2) Protocols were submitted and approved.
__ (3) Protocols were submitted and are under review.
__ (4) If no protocol has been submitted, attach memo describing status of discussions.

__ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes __X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Review/Memo (e.g., medical review, medical officer, team leader)

Randy Hedin, Senior Regulatory Management Officer — February 28, 2002
Signature of Preparer and Title — Date

cc: Orig NDA/BLA # NDA 21-113
HFD-510__/Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

APPEARS THIS WAY
ON ORIGINAL

MEMO TO THE FILE

February 27, 2002

NDA: 21-113

DRUG: Pamidronate

INDICATIONS: Hypercalcemia of malignancy, Paget's Disease of bone, osteolytic bone lesions of breast cancer and multiple myeloma.

COMPANY: Bedford Labs

RE: Waiver for pediatric studies

In a letter of 25 February 2002, Bedford Labs requested a full waiver of the requirements for submission of data that are adequate to assess the safety and effectiveness of pamidronate for the claimed indications of hypercalcemia of malignancy, Paget's disease of bone, and osteolytic bone lesions of breast cancer and multiple myeloma.

Paget's disease, breast cancer, and multiple myeloma are diseases of adults and very few, if any, pediatric patients are diagnosed with these conditions. The inability to conduct studied in pediatric patients is therefore self-evident. Hypercalcemia of malignancy does occur in pediatric patients, but the number with this condition is very small: it is estimated that approximately 10-15 pediatric patients with hypercalcemia of malignancy are available nationally each year for study1. With such low numbers clinical studies would be highly impractical.

I recommend that Bedford Labs's request for a full waiver for pediatric studies be granted.

Eric Colman, MD

APPEARS THIS WAY
ON ORIGINAL

1 Zometa NDA 21-223 approval package

BEDFORD LABORATORIES™

February 25, 2002

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21-113
Product: Pamidronate Disodium Injection; 3 mg and 9 mg per mL; 10 mL per vials

Dear Sir:

This letter is being sent with regard to a telephone conversation between Randy Hedin of the Agency and Molly Rapp of Ben Venue Laboratories, concerning NDA21-113, 3 mg/mL, 10 mL and 9 mg/mL, 10 mL. Form 356h is attached.

There were several minor labeling changes that were needed to the package insert. The revisions are enumerated below:

1. CLINCAL PHARMACOLOGY section, Excretion subsection, first sentence:
"...and 90 mg of pamidronate disodium over 24 hours, **an** overall mean..."
The previous version of the insert read "and", which has ben corrected to "an".

2. CLINCAL PHARMACOLOGY section, Hypercalcemia of Malignancy/Clinical Trials subsection:
"60 mg" has been added between the 30mg and 90 mg in the first paragraph, second paragraph, and twice in the third paragraph (third and fourth sentences).

3. CLINCAL PHARMACOLOGY section, Osteolytic Bone Metastases of Breast Cance and Osteolytic Lesions of Multiple Myeloma/Clinical Trials subsection:
"N" added to the upper left corner of the first table in order to match the innovator labeling.

These changes have been highlighted for your convenience on the following pages. Also, 12 copies of final printed labeling are included.

In addition, Bedford Laboratories™ requests a Pediatric waiver for the proposed drug product in accordance with 21CFR314.55(c)(2). The proposed drug product is indicated for Hypercalcemia of Malignancy, Paget's Disease, and Osteolytic Bone Metastases of Breast Cancer and Osteolytic lesions of Multiple Myeloma. Please note that the necessary clinical studies are highly impractible because the number of patients is so small and also, this drug product does not represent a meaningful therapeutical benefit over existing treatments for pediatic patients and is not likely to be used in a substantial number of pediatric patients.

A DIVISION OF BEN VENUE LABORATORIES, INC

300 Northfield Road • Bedford, Ohio 44146 • (440) 232-3320 • Fax (440) 232-6264

BEDFORD LABORATORIES™

I trust this meets with your approval. If you have further questions or comments I can be reached by phone at (440)-201-3576 (direct) and by fax at (440)-232-2772.

Sincerely,
for Bedford Laboratories™

Molly Rapp
Supervisor, Regulatory Affairs
Ben Venue Laboratories, Inc.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

A debarment statement is not needed because the firm did not do clinical studies..

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

Clinical trial audits are not needed because the firm did not do clinical studies.

NDA 21113
Pamidronate Disodium Injection
Bedford Laboratories

This section is not needed at this time.

APPEARS THIS WAY
ON ORIGINAL

MEMO TO THE FILE

February 27, 2002

NDA: 21-113

DRUG: Pamidronate

INDICATIONS: Hypercalcemia of malignancy, Paget's Disease of bone, osteolytic bone lesions of breast cancer and multiple myeloma.

COMPANY: Bedford Labs

RE: Waiver for pediatric studies

In a letter of 25 February 2002, Bedford Labs requested a full waiver of the requirements for submission of data that are adequate to assess the safety and effectiveness of pamidronate for the claimed indications of hypercalcemia of malignancy, Paget's disease of bone, and osteolytic bone lesions of breast cancer and multiple myeloma.

Paget's disease, breast cancer, and multiple myeloma are diseases of adults and very few, if any, pediatric patients are diagnosed with these conditions. The inability to conduct studied in pediatric patients is therefore self-evident. Hypercalcemia of malignancy does occur in pediatric patients, but the number with this condition is very small: it is estimated that approximately 10-15 pediatric patients with hypercalcemia of malignancy are available nationally each year for study[1]. With such low numbers clinical studies would be highly impractical.

I recommend that Bedford Labs's request for a full waiver for pediatric studies be granted.

Eric Colman, MD

[1] Zometa NDA 21-223 approval package

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
2/27/02 08:25:42 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

August 23, 2000

NDA# : 21-113

DRUG: Pamidronate Disodium Injection

INDICATION: Treatment of hypercalcemia of malignancy and Paget's Disease of the bone.

COMPANY: Bedford Labs.

SUBJECT: [redacted]

The division is currently reviewing a 505(b)(2) application from Bedford Labs for pamidronate disodium in solution. Novartis is the sponsor for an approved pamidronate product that is sold as a lyophilized powder. The company [redacted] because of, among other things, [redacted]

Bedford Labs received an approvable letter in December of 1999 for the above referenced NDA. Reference was made in the approvable letter that the Agency was concerned about the [redacted] which increases with storage time, [redacted]
While the list of [redacted] includes [redacted] . is of greatest concern because its level is the greatest relative to the other elements and to the product release specifications (see Dr. Jeri El-Hage's memo dated 8/7/2000).

Dr. El-Hage is not concerned about the relatively small levels of [redacted] found in the drug product solution, as these are unlikely to pose real safety issues. However, the level [redacted] is worrisome. In the absence of any toxicological data on [redacted] I support Dr. El-Hage's [redacted] (the details of which to be worked out with the sponsor at a later date). Furthermore, the Division should review the data from this study before a decision regarding approval is made.

/S/

Eric Colman, MD
Medical Team Leader

NDA Arch

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

This section is not needed at this time.

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

The firm did not do clinical studies; therefore a statistical review is not needed.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21113/000**
Priority: **5S** Org Code: **510**
Stamp: **02-MAR-1999** Regulatory Due: **31-AUG-2000**
Action Goal: District Goal: **03-NOV-1999**
Applicant: **BEDFORD LABS**
300 NORTHFIELD RD
BEDFORD, OH 44146
Brand Name: **PAMIDRONATE DISODIUM INJ 3MG/ML/10MLVIAL**
Established Name:
Generic Name: **PAMIDRONATE DISODIUM INJ 3MG/ML/10MLVIAL**
Dosage Form: **INJ (INJECTION)**
Strength: **3MG/ML & 9MG/ML**

FDA Contacts:

D. HEDIN	**(HFD-510)**	**301-827-6392**	**, Project Manager**
S. MARKOFSKY	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
D. WU	**(HFD-510)**	**301-827-6375**	**, Team Leader**

Overall Recommendation:

WITHHOLD on 04-JAN-2000 by B. HARTMAN (HFD-324) 301-827-0067

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568
DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities [redacted]

Establishment: [redacted]
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Milestone Date: **06-OCT-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **04-JAN-2000**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities:
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

07-AUG-2001 FDA CDER EES Page 2 of 3
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted]

Profile: CTL OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-AUG-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: CTL OAI Status: NONE Responsibilities: [redacted]
Last Milestone: SUBMITTED TO DO
Milestone Date: 03-AUG-2001

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: CTL OAI Status: NONE Responsibilities:
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-AUG-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: [redacted] DMF No:
AADA No:

[redacted]

Profile: CTL OAI Status: NONE Responsibilities: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-MAY-2001
Decision: WITHHOLD
Reason: FACILITY (FIRM) WITHDRAWN

Establishment: [redacted] DMF No: [redacted]

07-AUG-2001 FDA CDER ERS Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

AADA No:

[redacted]

Profile: CBN OAI Status: NONE Responsibility: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 07-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

Establishment: [redacted]

DMF No:
AADA No:

[redacted]

Profile: CTL OAI Status: NONE Responsibility: [redacted]
Last Milestone: OC RECOMMENDATION
Milestone Date: 08-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21113/000**
Priority: **5S** Org Code: **510**
Stamp: **02-MAR-1999** Regulatory Due: **02-JAN-2000**
Action Goal: District Goal: **03-NOV-1999**
Applicant: **BEDFORD LABS**
300 NORTHFIELD RD
BEDFORD, OH 44146
Brand Name: **PAMIDRONATE DISODIUM INJ 3MG/ML/10MLVIAL**
Established Name:
Generic Name: **PAMIDRONATE DISODIUM INJ 3MG/ML/10MLVIAL**
Dosage Form: **INJ (INJECTION)**
Strength: **3MG/ML & 9MG/ML**

FDA Contacts:

D. HEDIN	**(HFD-510)**	**301-827-6392**	**, Project Manager**
S. MARKOFSKY	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
D. WU	**(HFD-510)**	**301-827-6375**	**, Team Leader**

Overall Recommendation:

Establishment: **1519257**
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568
DMF No:
AADA No:

Profile: **SVT** OAI Status: **POTENTIAL OAI** Responsibilities: **FINISHED DOSAGE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: ———
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: ———
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **16-SEP-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: ———
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: ———
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **06-OCT-1999**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **12-MAY-1999**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **07-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTION TO IB**
Milestone Date: **12-MAY-1999**

Responsibilities: [redacted]

07-AUG-2001 FDA CDER EES Page 1 of 3

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21113/000 Priority: SS Org Code: 510
Stamp: 02-MAR-1999 Regulatory Due: 30-AUG-2001 Action Goal: District Goal: 21-JUN-2001
Applicant: BEDFORD LABS
300 NORTHFIELD RD
BEDFORD, OH 44146
Proprietary Name: PAMIDRONATE DISODIUM INJ 300G/ML/10ML VIAL
Established Name:
Generic Name: PAMIDRONATE DISODIUM INJ 300G/ML/10ML VIAL
Dosage Form: INJ (INJECTION)
Strength: 300G/ML & 90G/ML

FDA Contacts:
B. HEDIN (HFD-510) 301-827-6262 , Project Manager
S. MARKOPSKY (HFD-510) 301-827-6420 , Review Chemist
B. WU (HFD-510) 301-827-6375 , Team Leader

Overall Recommendation:
WITHHOLD on 25-JUN-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 07-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 03-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 01-MAY-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 04-JAN-2000 by B. HARTMAN (HFD-324) 301-827-0067

Establishment: 1519257
BEN VENUE LABORATORIES INC
270 & 300 NORTHFIELD RD
BEDFORD, OH 441460568
DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: SUBMITTED TO DO
Milestone Date: 03-AUG-2001
Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: [redacted]
DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-MAY-2001
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Responsibilities [redacted]

Establishment: [redacted]
DMF No: [redacted]
AADA No:

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

This section is not needed at this time.

NDA 21-113
Pamidronate Disodium Injection
Bedford Laboratories

This section is not needed at this time.

NDA 21113
Pamidronate Disodium Injection
Bedford Laboratories

This section is not needed at this time.

Meeting Date: November 9, 2000 Time: 11:00 - 11:30 AM Location: 14B-45

NDA 21-113 Bedford Labs. pamidronate

Type of Meeting: Guidance

External participant: Bedford Laboratories

Meeting Chair: Dr. Karen Davis-Bruno

External participant lead: Mr. Shahid Ahmed

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Jeri El-Hage, Pharmacology Team Leader, DMEDP
Dr. Karen Davis-Bruno, Pharmacology Team Leader, DMEDP
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Mr. Shahid Ahmed, Vice President, Regulatory Affairs

Meeting Objectives:

The meeting was requested by Bedford Laboratories to discuss the rat toxicity study protocol.

Discussion Points and Decisions (agreements) reached:

- The Division stated it has reviewed the draft protocol with the following comments:

  1. Based on the dosing regimens used for another product, we recommend a once-weekly IV dose instead of daily dosing as proposed.

  2. We recommend evaluation of both sexes with 15 animals/sex/group; 10 animals/sex/group should be sacrificed after one month with the remainder completing the 2-month recovery period.

  3. We suggest urinalysis evaluation at day 30, and histopathologic evaluation of lung, liver, and kidney at day 90, regardless of findings at 30 days.

- The firm agreed with these recommendations and stated it will submit a revised

protocol for review and comment.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer:_____

Concurrence Chair:_____

APPEARS THIS WAY
ON ORIGINAL

/s/

Randy Hedin
11/22/00 11:04:20 AM

Karen Davis-Bruno
11/27/00 09:01:21 AM

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: October 25, 2000 Time: 11:00 - 12:00 AM Location: Conf. Rm. "K"

NDA 21-113 Bedford Labs. pamidronate

Type of Meeting: Guidance

External participant: Bedford Laboratories

Meeting Chair: Dr. Eric Colman

External participant lead: Mr. Shahid Ahmed

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. David Orloff, Director, DMEDP
Dr. Eric Colman, Clinical Team Leader, DMEDP
Dr. Bruce Schneider, Clinical Reviewer, DMEDP
Dr. Shelly Markofsky, Chemistry Reviewer, DNDCII
Dr. Duu-Gong Wu, Chemistry Team Leader, DNDCII
Dr. Jeri El-Hage, Pharmacology Team Leader, DMEDP
Dr. Karen Davis-Bruno, Pharmacology Team Leader, DMEDP
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

Mr. Shahid Ahmed, vice President, Regulatory Affairs
Mr. James Cradock, Vice President, Process and Product Development
Mr. David Weeda, Partner, Olsson, Frank, and Weeda

Meeting Objectives:

The meeting was requested by Bedford Laboratories to discuss our approvable letter, and their rationale why a toxicity study in rats is not needed.

Discussion Points and Decisions (agreements) reached:

- The firm presented background information on why it feels the level of —— in its pamidronate is not a health issue (see attached slides). The Division stated that this misses the point. This is an unknown ——— , most likely ——— . with pamidronate; and the toxicity and metabolic clearance rate of this species is unknown. The Division would not feel comfortable approving the NDA without some reassurance that the uncharacterized ——— s not toxic. The firm stated that

the —— disassociates from the pamidronate in solution, and the Division stated that if this is true the firm should prove it. Similarly, the firm suggested that the major —— extractable was a polymer derived from ——. Again, the Division maintained that such a claim should be substantiated with appropriate scientific evidence. The Division stated the firm should characterize the unknowr —— if they wish to show that they do not have a —— pamidronate. The firm asked whether if they do characterize the molecule and can show that it is a safe form of —— , will this satisfy the Division, and the Division responded affirmatively.

- The Division stated that the toxicity study requested in our approvable letter (1-month toxicity study in rats with a 2-month follow-up) is very reasonable. The 2-month follow-up data may be submitted during the review cycle of the resubmission. The study may be a simple study with a no-effect dose, and a known toxic dose of pamidronate lyophilized powder compared to comparable doses of aged pamidronate solution. The firm stated it will do the toxicity study, and submit a protocol to the Division for review and comment.

Unresolved or issues requiring further discussion:

- None

Action Items:

- None

Signature, minutes preparer:_____

Concurrence Chair:_____

/s/

David Orloff
11/22/00 04:09:17 PM

Randy Hedin
11/22/00 03:53:53 PM

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pages

NDA 21-113

DEC 15 1999

Bedford Laboratories
Attention: Mr. Shahid Ahmed
Director, Regulatory Affairs
300 Northfield Road
Bedford, OH 44146

Dear Mr. Ahmed:

Please refer to your new drug application (NDA) dated February 26, 1999, received March 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pamidronate disodium injection, 3 and 9 mg/mL.

We acknowledge receipt of your submissions dated April 22, May 21, July 30, and September 7, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. [redacted] for pamidronic acid is not adequate to support your NDA. A separate deficiency letter has been forwarded to the DMF holder and [redacted] has been asked to notify you when their amended DMF has been submitted to the Agency. In your response include, the date [redacted] submitted the information to its DMF.

2. In Vol. 1.2, pp. 810, you list the method for Loss on Drying as USP <733>. Shouldn't this be USP <731>?

3. You indicated (Vol. 1.2, pp. 766) that the testing for [redacted] in the drug product will be conducted either by Ben Venue Laboratories or by [redacted] Please also indicate which laboratories will do the testing for [redacted]

4. Your in-process pH limits (6.5-6.9) for the filtered solutions of pamidronate disodium and your stability data (provided in Vol. 2.2 pp. 454-483 of your May 21, 1999, amendment) do not justify your broad pH specification (6.0-7.4) for the drug product. Accordingly, please narrow the pH range in your regulatory specifications for the drug product.

5. Since this NDA is not for a reconstituted solution, please revise your specifications for the color of the drug product (Vol. 1.2, pp. 766 & Vol. 2.2, pp. 434 of the May 21, 1999, amendment) as appropriate.

6. Please provide a copy of a representative HPLC chromatogram resulting from the assay of an actual pilot or commercial size batch typical of your drug product.

7. Are the specifications for the impurities in your drug product, which are determined by HPLC, listed as weight percent or area percent?

8. Please validate your HPLC method for ——— in pamidronate disodium injection.

9. In your specifications for the Finished Dosage Forms (Vol. 1.2, pp. 766 & pp. 434 of the May 21, 1999, amendment), the USP methods cited for Particulate Matter and Bacterial Endotoxins (<85> and <788> were apparently inadvertently switched. Please revise your specifications accordingly.

10. Provide an identification test for mannitol in your specifications for the drug products.

11. Please lower your specifications for ———, since the stability data that you provided, in your July 30, 1999, amendment (pp. 099) and September 7, 1999, amendment (pp. 024), show much lower levels of these elements.

12. Your stability data shows that your drug product is slowly extracting material from your glass vials. Therefore, an expiry can not be established until you provide the Agency with justifiable acceptance limits for safety and toxicity for the ——— and other materials, such as the ——— molecules that are extracted from ——— . USP glass.

13. Since a ——— expiration date can not be granted due to the presence of high levels of materials extracted from the glass vials, your stability protocol should also be modified so that the final sterility, endotoxin, and particulate matter determinations are carried out at the end of the expiry that is granted, rather than at———

14. Since the extraction of materials from glass is currently a concern, monitoring the levels of [redacted] should be carried out more frequently than is called for in the existing proposed Post and Pre-Approval Stability Protocols. Both your Pre-and Post-Approval Stability Protocols should also be modified so that these tests are also done with drug products from upright containers, to maximize the contact of the pamidronate disodium with the glass of the vials. For this reason long term stability tests with upright vials should not be discontinued after the first three commercial stability batches, as proposed on pp. 156 of your July 30, 1999, amendment.

15. Please provide a copy of a representative HPLC chromatogram resulting from the assay of an actual sample vial in your stability program.

16. In Vol., 1.2, pp. 852 you claimed that no Environmental Assessment is required under Section 25.24(c)(1) of the regulations. This section of the regulations is out of date and was applicable to an ANDA (not an NDA). Please provide an appropriate request for a Categorical Exclusion from the requirement for an Environmental Assessment.

17. The name " Pamidronate" is above and twice the font size as the words "Disodium Injection". The words "Pamidronate Disodium Injection" should be the same size below the proprietary name, in a font size that is at least one half the size of the trade name.

18. The statement on the carton referring to the concentration of the active ingredients, should be revised to read:

    "Each 10ml vial contains pamidronate disodium 90 mg; mannitol USP 375 mg; and phosphoric acid and/or sodium hydroxide to adjust pH . . . ."

    Similar wording should be employed with the 2mg/ml strength, as appropriate.

19. Please change the pH range in all of your labeling to reflect a revised pH specification.

20. Further, a satisfactory current Good Manufacturing Practices inspection needs to be completed for the [redacted] .s.

21. Also, you must submit to the Division proof of the date of receipt by the patent holder of notification that you have submitted the amendment to this NDA dated May 21, 1999, which provides for a 9 mg/mL strength.

Also, revisions of the draft labeling submitted on February 26, 1999, may be required after we have reviewed the additional material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.
Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, 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 application. 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

12/15/99

APPEARS THIS WAY
ON ORIGINAL

NDA 21-113

MESSAGE CONFIRMATION

07/12/99 12:52
ID=DMEDP-CDER-FDA

J.	MODE	BOX	GROUP
845	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
07/12 12:52	00'51"	4402322772	003/003	OK		0000

TELEFAX

To: Mr. Shahid Ahmed
Bedford Laboratories

FAX: 440-232-2772
PHONE: 440-232-3320

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: July 12, 1999

Pages: __3__ [inclusive]

TELEFAX

To: Mr. Shahid Ahmed
Bedford Laboratories

FAX: 440-232-2772
PHONE: 440-232-3320

From: Randy Hedin, R.Ph.

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: (301) 443-9282
PHONE: (301) 827-6392

Date: July 12, 1999

Pages: __3__ [inclusive]

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

NDA 21-113
Pamidronate Disodium Injection

Dear Mr. Ahmed:

Please refer to your pending December 18, 1998 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pamidronate disodium injection.

We are reviewing the chemistry section of your submission and have the following comments and information requests:

1. The Agency typically requests that applicants provide 12 months of long term (25 0C/60% RH) and 6 months of accelerated (40 0C/75% RH) stability data on three batches, for each intended formulation, at the time of an NDA submission. Two of the three batches should be at least 1/10th of the proposed commercial size batch. You have provided data from only one batch of sufficient size for each strength (3 mg/ml and 9 mg/ml) of pamidronate disodium injection. Therefore, please provide, at a minimum, 6 months of accelerated and long term stability data from at least one more appropriately sized batch from both of your 3 mg/ml and 9 mg/ml strengths of drug product.

2. It is known that aqueous solutions of [redacted] s, such as your product, will slowly leach components from [redacted] USP glass. Accordingly, as soon as possible, please evaluate all of the samples in your stability program (long term and accelerated) for the levels of [redacted] and other materials which may have been extracted from the glass. The method used for this analysis should be validated for each material that is extracted into the aqueous pamidronate disodium injection.

3. Please modify your stability protocol so that all of the substances mentioned above are frequently monitored in both your long term and accelerated testing, as appropriate.

4. Based on your stability data, please establish specifications for those substances that are found to leach from the glass into the drug product.

5. Please establish acceptance limits, for safety and toxicity, for the [redacted] s extracted into the drug product (for injection). Similarly, please establish acceptance limits, for safety and toxicity, for other materials that are extracted from [redacted]. USP glass into your product, which will be given to humans by I.V. injection.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

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

Sincerely,

/S/

Dr. Duu-Gong Wu, Ph.D.
Chemistry Team Leader II, DNDC II for the
Division of Metabolic and Endocrine Drug Products,
Office of New Drug Chemistry
Center for Drug Evaluation and Research

N21113_Fax1.doc

APPEARS THIS WAY
ON ORIGINAL

Bedford Laboratories
Attention: Shahid Ahmed, agent for Bedford Laboratories
Director, Regulatory Affairs
Ben Venue Laboratories
270 Northfield Road
Bedford, OH 44146

MAR 19 1999

Dear Mr. Ahmed:

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

Name of Drug Product:	NO TRADEMARK (pamidronate disodium injection) 3 mg/mL
Therapeutic Classification:	Standard (S)
Date of Application:	February 26, 1999
Date of Receipt:	March 2, 1999
Our Reference Number:	NDA 21-113

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 1, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 2, 2000, and the secondary user fee goal date will be March 2, 2000.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Randy Hedin, R.Ph., Regulatory Project Manager, at (301)827-6392.

Sincerely yours,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-113
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: emg/March 19, 1999
filename: n:\egallier\N21113AC.WPD

ACKNOWLEDGEMENT (AC)