CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-113

Bedford Laboratories
Attention: Ms. Molly Rapp
Supervisor, Regulatory Affairs
270 Northfield Road
Bedford, OH 44146

Dear Ms. Rapp:

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

We acknowledge receipt of your submissions dated September 5 and 12, October 2 and 9, 2001, and January 30, and February 25, 2002. Your submission of September 5, 2001, constituted a complete response to our August 20, 2001, action letter.

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 lesions of multiple myeloma in conjunction with standard antineoplastic therapy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted on February 25, 2002, immediate container labels, and carton labels submitted on September 5, 2001). Accordingly, the application is approved effective on the date of this letter.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We are waiving the pediatric study requirement for the indications of this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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

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

Sincerely,

{See appended electronic signature page}

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

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

David Orloff
3/4/02 05:12:55 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICE

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-113

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 pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for pamidronate disodium injection, 3 and 9 mg/mL.

We acknowledge receipt of your submissions dated October 5, and December 5, 2000, and February 16, April 24, May 16 and 30, and July 31, 2001. Your submission of February 16, 2001 constituted a complete response to our August 31, 2000 action letter.

We also refer to your submission dated July 31, 2001, to revise the test methods and method validation reports for residual solvents in the drug substance. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to this letter.

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 amend the application. The amendment should reference the July 31, 2001, submission, and request that it be reviewed.

In addition, sufficient stability data has been submitted to support an [redacted] expiry date. However, the long-term drug product stability study was carried out at 25° C. Therefore, the storage statement in all of the labeling should be changed to, "Store at 25° C (77° F)." Also, the pH range in the DESCRIPTION section of the package insert should be changed to reflect the revised pH specification.

Revised draft labeling should be submitted to reflect these changes. If additional information relating to the safety or effectiveness of this drug becomes available, additional 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.

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, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

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

**APPEARS THIS WAY
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/s/

Eric Colman
8/20/01 02:21:09 PM
Eric Colman for David Orloff

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NDA 21-113

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

AUG 31 2000

Dear Mr. Ahmed:

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

We acknowledge receipt of your submissions dated February 28, July 20, and July 26, 2000. Your submission of February 28, 2000, constituted a complete response to our December 15, 1999, action letter.

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. We have concluded that your proposed specification ——— during stability testing has not yet been justified from a safety and toxicity point of view. In order to address the concerns, conduct and submit the results of a one-month intravenous toxicity study in rats to assess the safety of the extractables in your liquid pamidronate formulation. The study should evaluate drug product that has aged to the end of the shelf-life. We recommend that the study be designed with half the terminations for each dose group at the end of dosing and half after a two month drug-free interval. Please submit the protocol for review and comment before conducting the study.

2. ——— or pamidronic acid is not adequate to support your NDA. A separate deficiency letter has been forwarded to the DMF holder, and ——— has been asked to notify you when their amended DMF has been submitted to the Agency.

3. You have not provided adequate validation for your HPLC method for ——— ——— in pamidronate disodium injection. Provide a complete validation package, which addresses such issues as specificity, accuracy, precision, detection limit, quantitation limit, linearity, range, and robustness. For data that should be submitted in your validation package, you may want to consult the FDA (CDER) Reviewer Guidance on "Validation of Chromatographic Methods."

4. An ——— expiry for your drug products cannot be granted. An ——— expiry

should be supported by at least 12 months of stability data, and you have provided complete stability data from only the —— time point. Accordingly, submit additional and complete long-term stability data for your pamidronate disodium injection.

5. The marketing of your product would lead to increased use of the active moiety; therefore, 21 CFR.25.31(a) is not an appropriate reason for a categorical exclusion for an environmental assessment. If your calculations show that the marketing of your products will give rise to an estimated concentration of your active moiety below one part per billion (at the point of entry into the aquatic environment) you should claim a categorical exclusion under 21 CFR.25.31(b).

6. Please change the pH range in the DESCRIPTION section of the package insert to reflect your revised pH specification.

7. We must receive a satisfactory establishment inspection report for _ —— _ or for an equivalent substitute facility.

Also, revisions of the draft labeling submitted on February 26, 1999, may be required after we have reviewed the additional material or if additional information relating to the safety or effectiveness of this drug becomes available.

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, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

/S/

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

RH 8/31/00

cc:
Archival NDA 21-113
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
HFD-002/ORM
HFD-102/ADRA
HFD-42/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: RH/August 24, 2000
Initialed by: Draft #1/SMarkosfsky/DWu/8.24/JElHage/8.25/EGalliers/8.26/EColman/8.28/
LRarick/8.30.00/Draft #2/KDavis-Bruno/DWu/8.31.00
final: RHedin/8.31.00
filename: N21113AE.LT2

APPROVABLE (AE)

In DFS

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] s 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] n the drug product will be conducted either by Ben Venue Laboratories o[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 silicon species 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 ——— 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 ——— and the ——— laboratories.

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

cc:
Archival NDA 21-113
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
HFD-002/ORM
HFD-102/ADRA
HFD-40/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: RH/December 9, 1999
Initialed by: BSchneider/GTroendle/RSteigerwalt/SMarkofsky/DWu/MFossler for HAhn/12.10/EGalliers/12.11 and 12.15.99
final:RHedin 12.15.99
filename: N21113AE_LT1.doc

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