CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-113

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-113

Pamidronate Disodium Injection

Bedford Laboratories (A Division of Ben Venue Laboratories, Inc)

Sheldon Markofsky
DIVISION OF Metabolism and Endocrine DRUG PRODUCTS

File: N2113-4b

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-113

2. REVIEW #4

3. REVIEW DATE: 01-Dec.-2001

4. REVIEWER: Sheldon Markofsky

5. PREVIOUS DOCUMENTS

Previous Documents	Document Date
NDA (Original)	26-Feb.-1999
Amendment	21-May-1999
Amendment	30-Jul.-1999
Amendment	07-Sep.-1999
Amendment	28-Feb.-2000
Amendment	26-Jul.-2000
Amendment	05-Dec.-2000
Amendment	30-May-2001
IR letter (FAX)	12-Jul.-1999
Action letter	15-Dec.-1999
Action letter	31-Aug.-2000
Action letter	20-Aug.-01

6. SUBMISSION(S) BEING REVIEWED

Submission(s) Reviewed	Document Date
Amendment[1]	31-Jul.-2001
Amendment[2]	05-Sep.-2001
Correspondence[3]	12-Sep.-2001

1) The 7-31-01 amendment provided a revised method for residual solvents.
2) The 9-5-01 amendment provided revised labeling.
3) The correspondence dated 9-12-01, provided clarification of the revised method for residual solvents.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Bedford Laboratories (A Division of Ben Venue Laboratories, Inc)

Address: 300 Northfield Road
Bedford, Ohio 44146

Representative: Molly Rapp

Telephone: 440-201-3576

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Pamidronate Disodium Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type 3
- Submission Priority S

9. LEGAL BASIS FOR SUBMISSION

This is a 505 (b)(2) submission. The 3mg/ml and 9mg/ml dosage forms correspond to reconstituted solutions of the referenced drug, Aredia (NDA 20-036), marketed by Novartis.

10. PHARMACOL. CATEGORY:

Treatment of hypercalcemia associated with malignancy and/or for the treatment of Paget's Disease

11. DOSAGE FORM:

Injectable Solution

12. STRENGTH/POTENCY:

3mg/ml & 9mg/ml (both in 10ml vials)

13. ROUTE OF ADMINISTRATION:

IV Infusion

14. Rx/OTC DISPENSED:

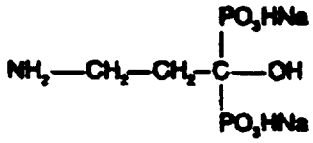
_X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical names:

1) Disodium dihydrogen (3-amino-1-hydroxypropylidene) diphosphonate

2) Phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt

Empirical formula (anhydrous salt): $C_3H_9NP_2O_7Na_2$

Molecular Weight (anhydrous): 279.1

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	8-2-01	----------
	III			3	Adequate	2-4-94	----------
	III	Company		3	Adequate	2-26-96	----------

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-036	Aredia, the referenced pamidronate drug, (a lyophilized powder marketed by Novartis)
ANDA	75-290	Generic version of Aredia

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	10-26-01	
Pharm/Tox	Acceptable	5-4-01	Davis-Bruno
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	Acceptable	8-7-01	Markofsky (Chem. Rev.#3)
Microbiology	Satisfactory	4-13-99	Stinavage

19. ORDER OF REVIEW OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-113

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry point of view, this NDA can be **approved**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

[None]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1) Drug Product

The drug product, Pamidronate Disodium Injection, is a sterile aqueous-based-solution, containing mannitol, in vials. The vials, which hold 10 ml of solution, are provided in either 3 mg/ml or 9 mg/ml strengths. Both strengths of the Drug are packaged in 10 cc, vials, equipped with protected by an The drug is indicated for the treatment of hypercalcemia associated with malignancy and/or for the treatment of Paget's Disease.

This application was originally submitted as an ANDA, but was subsequently reclassified as an NDA under Section 505 (b)(2) of the Federal, Food Drug, and Cosmetic Act. [The 3mg/ml and 9mg/ml dosage forms correspond to reconstituted solutions of the referenced drug, Aredia (NDA 20-036), marketed by Novartis.] A generic version of this drug, submitted to the office of Generic Drugs by the applicant (ANDA 75-290), for a lyophilized powder was recently approved on 4-30-01.

Unlike the lyophilized powder version of this drug, the stability data from these aqueous based solutions of Pamidronate Disodium showed that the drug product was slowly extracting from the glass vials. Accordingly, the applicant proposed a stability limit for in both strengths of their drug product. This level of , presumably present as some unknown molecule(s), raised a possible safety concern. Consequently, the Agency's "Action Letter', dated 8-31-2000, requested that the applicant conduct and submit the results of a one-month intravenous toxicity study in rats to assess the safety of the extractables in the liquid pamidronate formulation. The Pharmacology/Toxicology Review and Evaluation of the study, dated 5-4-01, noted that the toxicology profiles of the aged (18 month) aqueous solutions (9-mg/ml strength, Lot # 2018-49-103679) and equal amounts, on an active ingredient basis, of the lyophilized formulations (Aredia from Novartis) are essentially identical. Since there were no

further objections from the Division of Pharmacology/Toxicology to the use of — solutions of the drug product, the proposed — stability limit for — was deemed acceptable; and an 18-month expiry is granted.

All of the other chemistry-related issues in the "Action Letters", dated 12-15-99, 8-31-00, and 8-20-01, were minor and satisfactorily addressed by the applicant.

2) Drug Substance

Pamidronate disodium is known to be a bone-resorption inhibitor. Its manufacture is described in — The chemistry, manufacturing, and controls information in — is now considered satisfactory, after the DMF was revised based on reviewer's recommendations. All test method and acceptance criteria are considered to be **adequate** to assure consistent quality of the drug substance from batch to batch.

B. Description of How the Drug Product is Intended to be Used

The daily dose for Hypercalcemia of Malignancy should be administered by IV 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. For Paget's disease, the recommended daily dose of 30 mg should be diluted in 500 ml of sterile 0.45% or 0.9% sodium chloride injection or 5% dextrose injection and administered over a 4 hour period for 3 consecutive days. These infusion solutions are stable for up to 24 hours at room temperature. However, Pamidronate disodium must not be mixed with calcium-containing infusion solutions, such as Ringer's solution; and the pamidronate infusion should be given in a line separate for from all other drugs.

C. Basis for Approvability or Not-Approval Recommendation

Satisfactory CMC information has bee provided, and the cGMP compliance status is acceptable. Therefore the application is approvable from a Chemistry point of view.

III. Administrative

A. Reviewer's Signature

Sheldon Markofsky (Acting Team Leader)

B. Endorsement Block (OGD only)

C. CC Block (OGD only)

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

/s/

Sheldon Markofsky
12/1/01 10:48:00 AM
CHEMIST
S. Markofsky was both chemistry reviewer and acting Chemistry team leader, when this review was completed.

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

7 pages

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-113 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 8-7-01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	12-5-00	12-6-00	12-11-00
Amendment	5-30-01	5-31-01	6-1-01

NAME & ADDRESS OF APPLICANT:
Bedford Laboratories (A Division of Ben Venue Laboratories, Inc)
300 Northfield Road
Bedford, Ohio 44146

DRUG PRODUCT NAME:
Proprietary: None
Nonproprietary: Pamidronate Disodium Injection
Chem. type/Ther. Class: 3 S

PHARMACOL.CATEGORY/INDICATION:
Treatment of hypercalcemia associated with malignancy and/or for the treatment of Paget's Disease

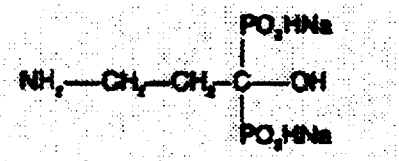
DOSAGE FORM: Injectable Solution

STRENGTHS: 3mg/ml & 9mg/ml (both in 10ml vials)

ROUTE OF ADMINISTRATION: IV Infusion

DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1) Disodium dihydrogen (3-amino-1-hydroxypropylidene) diphosphonate
2) Phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt
Empirical formula (anhydrous salt): $C_3H_9NP_2O_7Na_2$
Molecular Weight (anhydrous): 279.1



CAS # (anhydrous) 57248-88-1

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
			Acceptable	5-18-01	NA
			Acceptable	2-4-94	NA
			Acceptable	2-26-96	NA

RELATED DOCUMENTS : NDA 20-036; ANDA 75-290

CONSULTS: None

REMARKS/COMMENTS:

This application was originally submitted as an ANDA, but was subsequently reclassified as an NDA under Section 505 (b)(2) of the Federal, Food Drug, and Cosmetic Act. [The 3mg/ml and 9mg/ml dosage forms correspond to reconstituted solutions of the referenced drug, Aredia (NDA 20-036), marketed by Novartis.] A generic version of this drug, submitted to the office of Generic Drugs by the applicant (ANDA 75-290), for a lyophilized powder was recently approved on 4-30-01.

The responses to the Chemistry deficiencies described in Chemistry Review #2, and communicated to the applicant in the 8-31-00 Approvable Letter and in the meeting between Bedford and the Agency on 10-25-00, are the subject of Bedford's 12-5-00 amendment. The amendment, dated 5-30-01, provides a revision to the drug substance acceptance specifications. This Review (#3) discusses these responses and revisions. This Review (#3) also makes reference to Chemistry Review #5 of ——— for the drug substance. As stated in Review #5, ——— is now considered adequate to support the use of ——— pamidronic acid for this NDA (21-113).

An amendment, dated 7-31-01, to revise the test methods and method validation reports for residual solvents in the drug substance was submitted too close to the Action Date (8-20-01) to be reviewed. Accordingly, we can not deem this analytical methodology (and, therefore, the NDA) acceptable at this time.

From a chemistry point of view, the NDA is satisfactory pending a determination that the information in the 7-31-01 amendment is acceptable. A satisfactory response [to our Final Update Request (FUR)] that indicates that all of the relevant facilities have an acceptable cGMP status will also be required before this NDA could be deemed satisfactory. The CSO should also ask the applicant to change the storage statement in all of the labeling to:

Store at 25°C (77°F)
[see USP Controlled Room Temperature]

An expiry of 18 months for the drug product has been granted based on stability data.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable from a Chemistry point of view, pending an acceptable cGMP status for all of the relevant manufacturing and control facilities and a determination, in the next Review Cycle, that the information in the recently submitted amendment, dated 7-31-01, is acceptable. See Draft List of Deficiencies and Comments, to be forwarded to the applicant.

cc:
Orig. NDA 21-113
HFD-510/Division File
HFD-510/Sheldon Markofsky/(Review Chemist)
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)

Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n21113-3c

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

14 pages

AUG 2 3 2000

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-113 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 8-23-00

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	2-28-00	2-29-00	3-2-00
Amendment	7-26-00	7-27-00	7-28-00

NAME & ADDRESS OF APPLICANT:
Bedford Laboratories (A Division of Ben Venue Laboratories, Inc)
300 Northfield Road
Bedford, Ohio 44146

DRUG PRODUCT NAME:
Proprietary: None
Nonproprietary: Pamidronate Disodium Injection
Chem. type/Ther. Class: 3 S

PHARMACOL.CATEGORY/INDICATION:
Treatment of hypercalcemia associated with malignancy and/or for the treatment of Paget's Disease

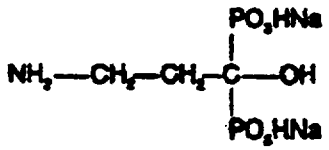
DOSAGE FORM: Injectable Solution

STRENGTHS: 3mg/ml & 9mg/ml (both in 10ml vials)

ROUTE OF ADMINISTRATION: IV Infusion

DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1) Disodium dihydrogen (3-amino-1-hydroxypropylidene) diphosphonate
2) Phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt
Empirical formula (anhydrous salt): $C_3H_9NP_2O_7Na_2$
Molecular Weight (anhydrous): 279.1



CAS # (anhydrous) 57248-88-1

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
[redacted]	[redacted]	[redacted]	Deficiency letter sent	4-25-00	5-10-00
[redacted]	[redacted]	[redacted]	Acceptable	2-4-94	NA
[redacted]	[redacted]	[redacted]	Acceptable	2-26-96	NA

RELATED DOCUMENTS : NDA 20-036; ANDA 75-290

CONSULTS: None

REMARKS/COMMENTS:

This application was originally submitted as an ANDA, but was subsequently reclassified as an NDA under Section 505 (b)(2) of the Federal, Food Drug, and Cosmetic Act. [The 3mg/ml and 9mg/ml dosage forms correspond to reconstituted solutions of the referenced drug, Aredia (NDA 20-036), marketed by Novartis.] A generic version of this drug, submitted to the office of Generic Drugs by the applicant (ANDA 75-290), for a lyophilized powder is also currently under review.

The responses to the Chemistry deficiencies described in Chemistry Review #1, and communicated to the applicant in a letter dated 12-15-99, are the subject of Bedford's 2-28-00 amendment. The amendment, dated 7-26-00, provides a minor correction to these responses. This Review (#2) discusses these responses. This Review (#2) also makes reference to Chemistry Review #3 of [redacted] for the drug substance, which indicated that satisfactory responses from the DMF holder, for a number of deficiencies, are still pending.

The NDA is still deficient in the following areas: Drug Substance [redacted] Drug Product stability with respect to levels of [redacted] Environmental Assessment, and labeling in the Package Insert. Furthermore, an acceptable cGMP status has been withheld for one of the analytical testing laboratories for the drug substance.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry point of view, this submission is approvable pending satisfactory responses to the chemistry deficiencies in the NDA and in [redacted] for the drug substance. An acceptable cGMP status from a testing facility has been withheld. Issue an Approvable Letter (See Draft List of Deficiencies).

cc:
Orig. NDA 21-113
HFD-510/Division File
HFD-510/Sheldon Markofsky/(Review Chemist)
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)

/S/

/S/

Sheldon Markofsky, Review Chemist

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

13 pages

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 21-113 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 12-7-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NDA (Original)	2-26-99	3-2-99	3-10-99
Amendment	5-21-99	5-24-99	5-28-99
Amendment	7-30-99	8-2-99	8-4-99
Amendment	9-7-99	9-8-99	9-14-99

NAME & ADDRESS OF APPLICANT:
Bedford Laboratories (A Division of Ben Venue Laboratories, Inc)
300 Northfield Road
Bedford, Ohio 44146

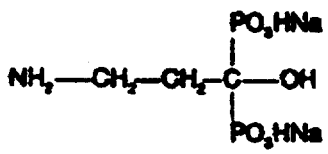
DRUG PRODUCT NAME:
Proprietary: Not yet provided
Nonproprietary: Pamidronate Disodium Injection
Chem. type/Ther. Class: 3 S

PHARMACOL.CATEGORY/INDICATION:
Treatment of hypercalcemia associated with malignancy
DOSAGE FORM: Injectable Solution
STRENGTHS: 3mg/ml & 9mg/ml (both in 10ml vials)

ROUTE OF ADMINISTRATION: IV Infusion

DISPENSED: X **Rx** _____ **OTC**

CHEMICAL NAMES, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
1) Disodium dihydrogen (3-amino-1-hydroxypropylidene) diphosphonate
2) Phosphonic acid (3-amino-1-hydroxypropylidene) bis-, disodium salt
Empirical formula (anhydrous salt): $C_3H_9NP_2O_7Na_2$
Molecular Weight (anhydrous): 279.1



CAS # (anhydrous) 57248-88-1

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
[redacted]			Deficiency letter sent	11-12-99	11-19-99
			Acceptable	2-4-94	NA
[redacted]			Acceptable	2-26-96	NA

RELATED DOCUMENTS : NDA 20-036; ANDA 75-290

CONSULTS: Microbiology (HFD-805)

REMARKS/COMMENTS:

This application was originally submitted as an ANDA, but was subsequently reclassified as an NDA under Section 505 (b)(2) of the Federal, Food Drug, and Cosmetic Act. [The 3mg/ml and 9mg/ml dosage forms correspond to reconstituted solutions of the referenced drug, Aredia (NDA 20-036), marketed by Novartis.] A Generic version of this drug, submitted to the office of Generic Drugs by the applicant (ANDA 75-290), for a lyophilized powder is also currently under review.

The amendment of 5-21-99 provides for an additional strength (9mg/ml) of the drug product, revised specifications, revised labeling, up-dated stability data, and a revised stability protocol. The 7-30-99 amendment provides 1) for a reduction of the batch size from [redacted] 2) additional stability data, 3) a revised stability protocol, and 4) revised specifications. Finally, the amendment of 9-7-99 provides methods validation for the analysis of [redacted] in the drug product.

CONCLUSIONS & RECOMMENDATIONS:

From a chemistry point of view, this submission is approvable pending satisfactory responses to the chemistry deficiencies in the NDA and in [redacted] for the drug substance, as well as acceptable cGMP inspections. Issue an ~~Information Request~~ Letter (See Draft List of Deficiencies).

Approvable Now 12-7-99

SAN

cc:
Orig. NDA 21-113
HFD-510/Division File
HFD-510/Sheldon Markofsky/(Review Chemist)
HFD-510/R. Hedin (CSO)
HFD-510/D-G. Wu (Team Leader)

/S/

Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n21113d

/S/

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

28 pages

Bacterial Endotoxins are to be monitored from inverted vials, stored at 25 °C/60% RH, at the 18 month time point (Test Schedule D).

[The Post-Approval Stability Protocol is acceptable.]

C. INVESTIGATIONAL FORMULATION: (Satisfactory)
See Chemistry Review # 1.

D. ENVIRONMENTAL ASSESSMENT: [Satisfactory]

Agency Comment:

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).

Summary of Response:

Bedford Laboratories continues to claims a categorical exclusion for the Environmental Assessment, under 21 CFR.25.31(a). Thus, the introductory letter to the 12-5-00 amendment states:

> "The marketing of Pamidronate Disodium Injection will not increase the use of active moiety; since, the approvable application is for a different dosage form and not a new indication".

This response is satisfactory and is in accordance with the Environmental Assessment Guidance (issued 7/1998).

E. METHODS VALIDATION: (Satisfactory)
See Chemistry Review # 1.

F. LABELING: [Satisfactory]

Agency Comments:

Please change the pH range in the Description section of the Package Insert to reflect your revised pH specification.

Summary of Response:

The pH range in the Description section has been revised to reflect the current pH specifications.