

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20036/S-016

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAR - 5 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-927 **Submission Date:** September 22, 1997
December 3, 1997

Drug Name: Aredia (pamidronate disodium for injection)

Formulation: Lyophilized vial

Sponsor: Novartis
59 route 10
East Hanover, NJ 07936

Reviewer: Z. John Duan, Ph.D.

Type of Submission: Supplemental New Drug Application

I. SYNOPSIS

Aredia, pamidronate disodium (APD), is a bone-resorption inhibitor available in 30-mg, 60-mg, or 90-mg vials for intravenous administration. The original NDA for Aredia was approved on October 31, 1991 for hypercalcemia of malignancy. A sNDA for treatment of osteolytic bone lesions of multiple myeloma was approved on September 1, 1995. A sNDA for treatment of osteolytic bone metastases of breast cancer was approved on July 16, 1996.

This sNDA contains the results of the one year extension period of the two Phase III, randomized, placebo-controlled trials in patients with breast cancer. The objective of the extension phase was to continue patients on the same double-blind treatment as in Phase I for an additional 12 months to evaluate survival, skeletal related episodes and long-term safety and to confirm the safety and efficacy of Aredia in the treatment of osteolytic bone metastases of breast cancer in patients treated with hormonal therapy and in patients treated with chemotherapy. Revised labeling reflecting the data from 24 cycles of monthly therapy is included in this submission.

No additional human pharmacokinetics and bioavailability information was submitted in this sNDA. Cross reference is made to the current New Drug Application and all approved Supplements for it.

There were no specific change made in package insert relevant to Clinical Pharmacology and Biopharmaceutics.

RECOMMENDATIONS

There were no specific issues relevant to Clinical Pharmacology and Biopharmaceutics in this submission. Therefore, no action is needed from Division of Pharmaceutical Evaluation I perspective.

IS/

Atiqur Rahman, Ph.D

Team Leader
Division of Pharmaceutical Evaluation I

3/5/98

Date

IS/

Z. John Duan, Ph.D.

Reviewer
Division of Pharmaceutical Evaluation I

3/4/98

Date

CC: NDA 20-927 original
HFD-150 Division File
HFD-150 DCatterson
HFD-150 GWilliams
HFD-850 LLesko, SHuang
HFD-860 HMalinowski, MMehta, ARahman, JDuan
HFD-340 Vishwanathan
CDR Barbara Murphy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20036/S-016

ADMINISTRATIVE DOCUMENTS

Bone Metastases Supplement

NDA 20-036

Aredia

(pamidronate disodium for injection)

Patent Information

No new patent information is included in this supplement outside of the information from the present investigation

EXCLUSIVITY SUMMARY for NDA # 20-927 SUPPL # —

Trade Name AREDIA® INJECTION Generic Name (PAMIDRONATE DISODIUM)

Applicant Name NOVARTIS PHARMACEUTICALS CORP. HFD- 150

Approval Date, if known 9/22/98

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 question about the submission.

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

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

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 / /

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 / /

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / / OTC Switch / /

If yes, NDA # 20-036 (HFD-510) Drug Name AREDIA® (PAMIDRONATE DISODIUM)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 / / NO / /

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

NDA# _____
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 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

- (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 8:

YES /___/ NO /___/

(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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.

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:
Title: Consumer Safety Officer

Date: Sept. 18, 1998

Signature of Division Director: Robert L. Justice, M.D.

Date: 9/22/98

cc: Original NDA
20-927

Division File
HFD-150

HFD-93 Mary Ann Holovac

AREDIA® (pamidronate sodium) FOR INJECTION
Supplemental New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity their services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

Date

9/18/97

Ellen Cutler
Ellen Cutler
Assistant Director
Drug Regulatory Affairs

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

(NDA) PLA # 20-927 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-150 Trade (generic) name/dosage form: AREDIA® Action: **(AP)** AE NA
(PAMIDRONATE DISODIUM FOR INJECTION)

Applicant NOVARTIS Therapeutic Class 6

Indication(s) previously approved HYPERCALCEMIA OF MALIGNANCY, PAGES 1-3 Pediatric labeling of approved indication(s) is adequate ___ inadequate ___ OSTEOLYTIC BONE METASTASES OF BREAST CANCER, + DISEASE

Indication in this application THIS NDA PROVIDES THE RESULTS OF THE (For supplements, answer the following questions in relation to the proposed indication.) ONE-YEAR EXTENSION PERIOD OF THE TWO PHASE 3 STUDIES THAT WERE SUBMITTED TO SUPPORT THE OSTEOLYTIC LESIONS OF MULTIPLE MYELOMA

1. PEDIATRIC LABELING IS ADEQUATE. 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 subgroups. Further information is not required.
2. 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. 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, explain the status of discussions on the back of this form.
- c. 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.
3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. BREAST CANCER AND MULTIPLE MYELOMA ARE NOT CHILDREN'S DISEASES.
4. EXPLAIN. If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

/S/ Signature of Preparer and Title (PM, CSO, MO, other) 9/21/98 Date

cc: Orig NDA/PLA # 20-927
HFD-150 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

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.

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CORRESPONDENCE



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Robert DeLap, M.D.
Director
Division of Oncology Drug Products/ HFD-150
FDA/Office of Drug Evaluation I
1451 Rockville Pike
Rockville, Maryland 20852

February 4, 1998

NDA 20-927
AREDIA® (pamidronate disodium for
injection) for intravenous infusion

Amendment to Pending
New Drug Application

Dear Dr. DeLap,

Reference is made to our New Drug Application (NDA) submitted September 22, 1997 for Aredia (pamidronate disodium for injection).

Reference is also made to a January 21, 1998 facsimile from Debbie Catterson on behalf of Dr. Sue Jane Wang regarding an electronic data request. This amendment provides data and documentation in response to Dr. Wang's request.

For ease of review, we have provided the requested data (diskettes) and documentation for Protocols 18E and 19E in volumes 1 and 2 of this submission, respectively. Each volume is preceded by an information sheet relevant to the contents of that particular volume and protocol.

Please refer any questions or comments concerning the content of this submission to Dr. Kathleen Mellars, Associate Director, Oncology at (908) 277-5192. If you have any questions or comments regarding the NDA please contact me at (973) 781-8180.

Sincerely yours,

Ellen Cutler
Assistant Director

Attachments

Submitted: 1 Archival (with diskettes)
1 Clinical, 1 Statistical (with diskettes)
desk copy: Sue Jane Wang, Ph.D. (letter only)
Debbie Catterson (letter only)