CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20036/S-016

CHEMISTRY REVIEW(S)

C/PATTERSON

FEB 2 1998

DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-927

REVIEW DATE: January 29, 1998

CHEMISTRY REVIEW #: 1

SUBMISSION TYPE:	DOC. DATE	CDER DATE	ASSIGNED DATE
IND 30,145	Sep. 22, 1997 (HFD-510) Oct. 3, 1997 (HFD-150)	Oct. 6, 1997	Nov. 5, 1997

DUE DATE: March 21, 1998

NAME & ADDRESS OF APPLICANT:

Novartis
59 Route 10
East Hanover, NJ 07936
Tel: 973-503-8180 (E. Cutler)

DRUG PRODUCT NAME: Established Name: Pamidronate disodium for injection
Proprietary Name: Aredia® Ampuls

PHARMACOL. CATEGORY/INDICATION: Treatment of osteolytic bone metastases of breast cancer

DOSAGE FORM: lyophilized vial

STRENGTHS: 30 mg, 60 mg, 90 mg.

ROUTE OF ADMINISTRATION: intravenous infusion

DISPENSED: _x_ Rx ____ OTC

RELATED DOCUMENTS:

Doc. type	Holder Name	Drug Name	Status	Date Reviewed	Reference in this review
IND	Novartis Phar,	Aredia,	AT	Jul. 11, 1990	Review by HFD-510
NDA 20,036	Novartis Phar,	Aredia, Pamidronate disoldium	AP	Oct. 31, 1991	Review by HFD-510
sNDA 20,036 SE1-009	Novartis Phar,	Aredia, Pamidronate disoldium	AP	Sep 1, 1995	Review by HFD-510
sNDA 20,036 SE1-011	Novartis Phar,	Aredia, Pamidronate disoldium	AP	Jul 16, 1996	Review by HFD-510

CONCLUSIONS & RECOMMENDATIONS:

The Expected introduction concentration (EIC) for pamidronate calculated from estimated production is much less than 1 ppb. It is qualified for a categorical exclusion requirements under 21 CFR 25.31(b). We, therefore, requests an approval for this New Drug Application.

cc:
Orig. NDA 20-927
HFD-150/Division File
HFD-150/LHsieh
HFD-150/RWood
HFD-150/DCatterson
filename: N20927.org

/S/ 1-29-98
Li-Shan Hsieh, Ph.D.
Review Chemist, HFD-150

/S/ 2-2-98
Rebecca H. Wood, Ph.D.
Team Leader, HFD-150

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20036/S-016

PHARMACOLOGY REVIEW(S)

Division of Oncology Drug Products, HFD-150

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Original Review

NDA No. 20,927 **Type** NDA **Date(s) of Submission** 09/22/97
Received by CDER: 10/06/97

Information to be Conveyed to Sponsor: Yes ( ), No (X)

Reviewer: Hua Zheng, Ph.D.

Date Review Completed: Aug 26, 1998

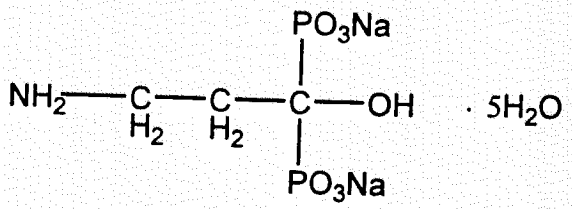
Sponsor: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

Drug Name: Pamidronate disodium for injection (Aredia®)

Chemical Name(s): Phosphonic acid (3-amino-1-hydroxypro-pylidene) bis-, disodium salt, Pentahydrate (ADP)

CAS Number: 57248-88-1

Structure:



Molecular Formula: $C_3H_9NO_7P_2Na_2 \bullet 5H_2O$

Molecular Weight: 369.1

Related INDs/NDAs/DMFs: IND NDA 20,036

Class: biphosphonate bone resorption inhibitor

Previous Indications: Hypercalcemia of Malignancy
Paget's Disease

Proposed Indication: "Aredia is indicated, in conjunction with standard antineoplastic therapy, for the treatment of osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma."

Clinical Formulation: Supplied as the sterile, lypholyzed powder available in 30-, 60- and 90-mg vials for intravenous administration; Aredia® is reconstituted by adding 10 ml of

sterile Water for Injection, USP, to each vial. The pH of the reconstituted solution is 6.0 – 7.4.

Quantitative composition of Aredia® lypholyzed powder for i.v. injection

	Unit Formula (mg/vial)		
Pamidronate disodium	30	60	90
Mannitol, USP	470	400	375
Phosphoric acid	For adjustment to pH6.5 prior to lyophilization		

Route of Administration: intravenous infusion

Dosage and Administration:

Starting Dose: for Moderate or Severe Hypercalcemia
60 mg (4-hr infusion) and/or 90 mg (24-hr infusion)

Repeat Dose: Paget's Disease: 30 mg qd × 3 (4-hr infusion)
Osteolytic Bone Lesions of Multiple Myeloma: 90 mg (4-hr infusion), monthly
Osteolytic Bone Metastases of Breast Cancer: 90 mg (2-hr infusion), q 3-4 w

Previous Review(s), Date(s), and Reviewer(s):
IND

NDA 20,036 Pharmacology Review A. Jordan 05/10/90

Studies previously reviewed under IND

I. Previous human experience none

II. Pharmacology

1. Relative effects on bone resorption and formation.
2. Studies on the mechanism of action.
3. Effects on tumor-induced acceleration of bone metabolism.
4. Evaluation in models of inflammation and arthritis and other predictors of clinical utility.
5. Activity profile of CGP23,339 A in the Koch Model.
6. Effects of CGP23,339 A on lymphocyte activation and models of lymphocyte/macrophage interaction *in vivo* and *in vitro*.
7. Effect of calcium supplement on pregnant rats treated with CGP23,339A.
8. Effects on rat neutrophil leukotriene B4 generation and action: the effects of CGP 57148B 23,339 A.
9. Effect of I.V. APD on the level of the mouse acute-phase reactant serum amyloid P component (SAP).
10. Immunopharmacological investigations.
11. Effects on serum calcium levels and blood glucose.

III. Safety Pharmacology

12. General pharmacology

13. Effect of I.V. APD on body temperature.

IV. Toxicology

Acute Toxicity Studies

14. CD-1 mouse-Oral
15. CD-1 mouse-Intravenous
16. CD-1 mouse-I.P.
17. C.O.B.S. rat-Oral
18. C.O.B.S. rat-I.V.
19. C.O.B.S. rat-I.P.
20. NZW rabbit-Oral
21. NZW rabbit-I.V.
22. NZW rabbit-I.P.

Subacute Toxicity Studies

23. 26-Weel oral toxicity study in C.O.B.S. rats
24. One month subcutaneous injection toxicity study in Tif:RAIF(SPF) rats
25. Thirty-two week oral toxicity study in the beagle dogs
26. One month oral tolerability study in the beagle dogs
27. 28-Day intravenous study in beagle dogs
28. One month I.V. injection toxicity study in beagle dogs

Subchronic and Chronic Toxicity Studies

25. 6/12 month oral toxicity study in beagle dogs

V. Toxicokinetics/ADME

26. Absorption (rat)
27. Distribution and persistance (rat)
28. Distribution and excretion of ^{14}C-labeled substrance after I.V., S.C. and peroral administration to rats.
29. Distribution and kinetics in the dog
30. Metabolism (rat)
31. Excretion (rat)
32. Urinary excretion of CPG 23,339A in dog after a single oral or intravenous administration.
33. Whole-body autoradiography in rats after intravenous administration of ^{14}C-labeled substance.
34. Distribution, accumulation and elimination of ^{14}C-labeled substance in the body of rats after single and repeated I.V. administration.
35. Distribution and excretion of ^{14}C-CGP23,339 A after single intravenous administration to mice.

VI. Special Toxicology

36. Eye irritation (NZW rabbit)
37. Primary skin irritation (NZW rabbit)
38. Intravenenous local tolerability (Chinchilla rabbit)
39. Intramuscular local tolerability (Chinchilla rabbit)
40. Delayed dermal sensitization (Guinea pig)

Reproductive Toxicity

41. Segment I study (C.O.B.S. rat)
42. Segment II study (C.O.B.S. rat)
43. Segment I study (Dutch rabbit)
44. Segment III study (C.O.B.S. rat)

Genetic Toxicity

45. Mutagenicity Study 1980 (Ames Test) (IND
46. Genetic Toxicology Test No. 876291: CGP23339A: sister chromatid exchange studies on somatic cells of the Chinese hamster. (NDA20,036, Vol. 17)
47. Genetic Toxicology Test No. 876290 CGP23339A: Nucleus anomaly test in somatic interphase nuclei of Chinese hamster. (NDA20,036, Vol. 18)
48. Genetic Toxicology Test No. 876292 CGP23339A Point mutation test with Chinese hamster cells V79. (NDA20,036, Vol. 18)
49. Experimental Pathology Report 850385 ADP Salmonella/mammlian-microsome mutagenicity test. (NDA20,036, Vol. 18)
50. Genetic Toxicology Test No. 896237 Micronucleus Test, Rat (IND

Carcinogenesis Studies

51. 80-Week carcinogenicity study in the CD-1 mouse 1979-1981.
52. 104-Week carcinogenicity study in the WI strain rat 1979-1981.

Studies previously reviewed for NDA 20,036

I. Previous human experience none
II. Pharmacology none
III. Safety Pharmacology none
VI. Toxicology

Subchronic Toxicity Studies

53. 3-Month IV toxicity study in rats.
54. 3-Month IV toxicity study in dogs

IV. Pharmacokinetics/ADME none
V. Special Toxicology none

Overall Summary and Evaluation

Introduction: This NDA for Aredia® is submitted to this Division for the treatment of osteolytic bone metastases of breast cancer in patients treated with hormonal therapy and in patients treated with chemotherapy. Aredia® has been studied under IND (in the Division of Metabolism and Endocrine Drug Products/HFD-510). The original NDA for Aredia® was approved on 10/31/91 for hypercalcemia of malignancy. It was later on approved for treatment of osteolytic bone lesions of multiple myeloma (09/01/95) and osteolytic bone metastases of breast cancer (07/16/96). This NDA contains the results of the one year extension period of the two phase III trial, which are being used to update the labeling, particularly with the efficacy statement regarding the patients

In the draft package insert of this NDA under

The studies supporting this statement could not be found in the pharmacology review for NDA20,036. With the assistance of Novartis the original studies were located and confirmed to support this label statement. There is no need to change the labeling for this part.

Recommendations: This NDA is approved from the pharm/tox perspective. No pharm/tox changes are needed for the proposed insert labeling.

Draft Letter, Request for Sponsor: No

/S/ 8/26/97

Hua Zheng, Ph.D. Date
Pharmacologist/Toxicologist

/S/ 8/26/97

Paul Andrews, Ph.D
Pharm/Tox Team Leader

cc: NDA 20,927 and Div. File
/HFD-150
/P Andrews
/G Williams
/D Catterson
/H Zheng