NDA 20-036

SUPPL 004

AP LETTER

NDA 20-036/S-004

APR 15 1994

Ciba-Geigy Corporation
Attention: Mr. Ronald M. Califre
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Califre:

Reference is made to your supplemental new drug application dated September 23, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Aredia (pamidronate disodium for injection).

The supplement provides for a reduction in infusion time from 24 to 4 hours for the 60 mg dose.

We also refer to our letter dated May 17, 1993, stating that the supplement is approvable for the 60 mg over 4 hour dosing regimen, but not the 90 mg over 4 hour dosing regimen and your letter dated September 2, 1993, providing draft labeling incorporating the changes requested in our approvable letter.

We have completed the review of your supplemental application 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 September 2, 1993, draft labeling. Accordingly, the supplemental application is approved, effective on the date of this letter.

Please submit twelve (12) copies of final printed labeling (FPL) identical to the draft labeling as soon as available. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved NDA 20-036/S-004". Approval of the submission by FDA is not required before the labeling is used. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug.

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

If you have any questions, please contact Mr. Randy Hedin at (301) 443-3520.

Sincerely yours,

4-14-94

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

RH 4/14/94

cc: NDA Arch
HFD-510
HF-2/with draft labeling
HFD-80/with draft labeling
HFC-130/JAllen
HFD-240/with draft labeling
HFD-730/with draft labeling
HFD-510/LLutwak/GTroendle/YChiu/AJordan
HFD-511/RHedin/4.1.94/ft/lp/4/14/94/N20036SA.LT4

Concurrences: Lutwak 4/5/Troendle 4/7/Galliers 4/11/Chiu 4/12/94

SUPPLEMENT APPROVAL (S-004)

MAY 17 1993

NDA 20-036/S-004

Ciba-Geigy Corporation
Attention: John R. Hanagan, M.D.
Pharmaceuticals Division
556 Morris Avenue
Summit, NJ 07901

Dear Dr. Hanagan:

Reference is made to your supplemental new drug application dated September 23, 1992, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act and to the provisions of 21 CFR 314.70(c) for Aredia (pamidronate disodium for injection).

The supplement provides for a reduction in the infusion time from 24 to 4 hours.

We have completed the review of your supplemental application and it is approvable for the 60 mg over 4 hour dosing regimen, but not the 90 mg over 4 hour dosing regimen. However, before the 60 mg over 4 hour dosing regimen may be approved, final printed labelling (FPL) must be submitted. The FPL should be identical to the draft labelling except for the following revisions:

1. Labelling changes for the DOSAGE AND ADMINISTRATION section of the package insert are as follows:

   a. Please change the second sentence of the first paragraph to read, "The recommended dose of Aredia in moderate hypercalcemia (corrected serum calcium of approximately 12-13.5 mg/dl) is 60 to 90 mg, and in severe hypercalcemia (corrected serum calcium, greater than 13.5 mg/dl) is 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 at least 24 hours.

   b. Please change the second sentence of the third paragraph to read, "Retreatment with Aredia, in patients who show complete or partial response initially, may be carried out if serum calcium does not return to normal or remain normal after initial treatment".

2. The labelling changes for the CLINICAL PHARMACOLOGY section of the package insert are as follows:

a. The number of subjects and design (parallel) used in Clinical Protocol 09 should be included in the labelling (i.e., "Cancer patients (36) who had minimal or no bony involvement were given an intravenous infusion of 30, 60, or 90 mg of Aredia using a parallel design over 4 or 24 hours.").

b. The plasma data presented in Clinical Protocol 09 do not support a conclusive establishment of linearity for the 30, 60, and 90 mg doses of pamidronate disodium after either 4 or 24 hours infusion. However, urine data support the linear relationship for the 3 doses. Therefore, the labelling statement "Peak plasma concentrations, AUC values, and cumulative urinary excretion were linearly related to dose", should be modified to indicate that based on urine data, linearity was established for the 30, 60, and 90 mg doses of pamidronate disodium after either 4 or 24 hours infusion (i.e., cumulative urinary excretion was linearly related to dose).

c. The estimated AUC values for the three doses and two infusion rates do not follow a linear relationship. This discrepancy in the AUC results, especially for the 60 mg dose, could be due to (i) a parallel study design that was used, (ii) there is high subject and drug variability, and (iii) the analytical method is not sensitive enough to detect low concentrations. Therefore, to avoid misleading information, it is recommended to delete the AUC data from the labelling.

d. It is recommended to include mean ± standard deviation values instead of ranges (minimum-maximum) for all the pharmacokinetics data included in the labelling.

e. It is recommended to include the effect of renal impairment and hepatic dysfunction on the pharmacokinetics of pamidronate if information is available.

However, we cannot approve the requested change in the infusion rate for the 90 mg dose because no controlled data were submitted for the 90 mg/4 hour dosing regimen. Data to support the 4 hour dosing regimen for the 90 mg dose should be submitted in a new supplement. In addition, when the safety/efficacy clinical trials to support the change in infusion rate for the higher 90 mg dose are conducted, it is recommended that some pamidronate blood levels be obtained (i.e., ideally peak and trough levels, so that a possible pharmacokinetic/pharmacodynamic relationship can be assessed from both an efficacy and safety prospective).

Further, we suggest that you consider undertaking the following studies:

1. Additional long-term follow-up studies are needed to evaluate the effect of renal disease and hepatic dysfunction on the pharmacokinetics of pamidronate.

2. Additional long-term clinical and animal studies are needed to evaluate the mechanism of action and long-term skeletal effects of pamidronate.

3. Since the biological half-life of pamidronate is long and the drug is released slowly over possibly years, additional data should be collected to evaluate possible long term toxicity on liver, kidney, and possibly other tissues where calcium binding may influence biological function.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

If you have any questions, please contact Mr. Randy Hedin at (301) 443-3510.

Sincerely yours,

5/14/93

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

RHedin
5/14/93

cc: NDA Arch
HFD-510
HFC-130/JAllen
HFD-80
HFD-510/LLutwak, RPierce, JHunt, AJordan
HFD-511/RHedin/4.30.93/ft/dj/5.13.93/N20036SA.LT2
Concurrences: Lutwak/Pierce5.4.93/Galliers4.6.93/Jordan5.10.93

SUPPLEMENT APPROVABLE (S-004)

Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, New Jersey 07901

CIBA - GEIGY

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
SEP 2 4 1992
HFD-510

September 23, 1992

NDA 20-036
Aredia ●
pamidronate disodium for injection

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II (HFD-510)
Document Control Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

NDA NO.______REF. NO.________
NDA SUPPL FOR____________

Attention: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

Dear Dr. Sobel:

We are submitting a supplement to our NDA for Aredia® (pamidronate disodium for injection) which provides for a reduction in the infusion time from 24 to 4 hours. In support of this change we have assembled a total of 117 volumes which contain relevant clinical, pharmacokinetic and toxicological data and summaries.

Any questions that may arise during your review of this supplement should be directed to Michael J. Macalush, Drug Regulatory Affairs, at (908) 277-4851.

Very truly yours,

Pharmaceuticals Division
CIBA-GEIGY Corporation

for John R. Hanagan, M.D.
Vice President
General Drug Development

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93abl

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I.

5/17/93
CSO INITIALS DATE

10/17/92