Pharmaceuticals Division

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Ciba-Geigy Corporation
Summit, New Jersey 07901

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I.
CSO INITIALS DATE

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September 2, 1993

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Draft Labeling
for Supplement S-004

NDA 20-036
Aredia®
pamidronate disodium for injection

CENTER FOR DRUG
REC'D
SEP 07 1993
HFD-510
EVALUATION AND RESEARCH

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

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

Dear Dr. Sobel:

On September 23, 1992 we submitted a supplement (S-004) to NDA 20-036 for Aredia which provided for a reduced infusion time.

On May 17, 1993 you informed us that the supplement is approvable for the 60 mg over 4 hour dosing regimen, but not the 90 mg over 4 hour dosing regimen. At that time you recommended that we revise our labeling, and you also suggested that we consider undertaking long-term clinical and animal studies with Aredia.

At this time we wish to respond to your comments regarding our product labeling. We have attached a revised version of the draft package insert which incorporates your recommendations as outlined in your May 17, 1993 correspondence, with some modifications. The latest version of the package insert, C92-48, which was approved on May 6, 1993 was used as the base copy for making the revisions.

Items 1.a. and b. - The DOSAGE AND ADMINISTRATION section of the package insert was changed according to your recommendations with one exception. The "at least" in the sentence "The 90 mg dose must be given by an initial single-dose intravenous infusion over at least 24 hours." was deleted based upon the data in the approved original NDA. Those data support an infusion time of no more than 24 hours for the 90 mg dose of Aredia, and "at least" would erroneously suggest that safety and efficacy have been established with infusions of longer duration.

Items 2.a. through d. - The following changes were made to the CLINICAL PHARMACOLOGY section of the package insert as recommended in Items 2.a. through d.

a. The number of subjects (n=36) and study design (parallel) used in Protocol 09 were incorporated into the first sentence of the revised text.

b. The reference to peak plasma levels and AUC values being linearly related to dose was deleted from the second sentence of the revised text.

c. All reference to AUC data was deleted from the revised text.

d. Mean ± standard deviation values instead of ranges (minimum-maximum) were provided for all the pharmacokinetic data included in the revised text.

We cannot address Item 2.e. because studies to elucidate the effects of renal impairment and hepatic dysfunction on the pharmacokinetics of Aredia are underway, and no data are currently available. At the completion of these studies the package insert will be revised accordingly and submitted to you for review and approval.

We have taken this opportunity to revise the package insert in accordance with your April 29, 1993 correspondence, and also to correct an erroneous statement that was uncovered during our review.

As suggested in your April 29, 1993 letter, we printed the dosing instructions within the DOSAGE AND ADMINISTRATION section in bold letters in an effort to prevent overdosing.

We replaced the erroneous fourth sentence of the Preparation of Solution subsection of the DOSAGE AND ADMINISTRATION section with the following accurate statement, "The daily dose must be administered as an intravenous infusion over at least 4 hours for the 60-mg dose, and over 24 hours for the 90-mg dose."

We also elected to revise the package insert as outlined in the following two paragraphs.

In order to provide physicians with some explanation as to why 60 mg can be administered over 4 hours but not 90 mg, the following sentence was added to the end of the Clinical Trials subsection of the CLINICAL PHARMACOLOGY section, "Unlike Aredia 60 mg, the drug has not been investigated in a controlled clinical trial employing a 90-mg dose infused over a 4-hour period."

We changed the last sentence of the Pregnancy Category subsection of the PRECAUTIONS section from, "...it [Aredia] should not be given to women of childbearing potential" to "...it [Aredia] should not be given to women during pregnancy." Although the revised wording is less restrictive than the previous wording, it is still more restrictive than the recommended wording in 21 CFR § 201.57 (f)(6)(i)(c) entitled "Pregnancy Category C."

In addition to the package insert we are also submitting draft versions of the Aredia 30 mg, 60 mg and 90 mg cartons. On the back panel of each carton the sentence "The daily dose must be administered as an intravenous infusion over 24 hours." was replaced with "60 mg is given as an intravenous infusion over at least 4 hours. 90 mg must be given as an intravenous infusion over 24 hours." Also, "For intravenous infusion." which is currently printed on the front and back panels of each carton, was deleted from the back panels.

If you have any questions or comments regarding this submission, please contact Mr. Michael J. Macalush, Associate Director, Drug Regulatory Affairs, at (908) 277-4851.

Sincerely yours,

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation

Michael J. Macalush

for Ronald M. Califre
Executive Director
Drug Regulatory Affairs

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MED REVIEW

ORIGINAL

DEC 17 1992

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NDA # 20-036
NDA SUPPLEMENT: Four Hour Infusion

Sponsor: Ciba Pharmaceutical Company
CIBA-GEIGY Corporation
Summit, NJ 07901
(908) 277-4851

Date Review Completed: December, 1992

Submission Dated: September 23, 1992

RESUME

This NDA Supplement is a revision of a previously approved NDA for Aredia® (pamidronate disodium for injection). This revision provides for a reduction in the infusion time for administration from 24 to 4 hours.

The studies previously presented in support of the approved NDA are reviewed and an additional study is presented to support the use of a 4-hour intravenous infusion of Aredia® for the approved indication.

The original NDA for Aredia® was approved on October 31, 1991. Aredia®, in conjunction with adequate hydration, is indicated for the treatment of moderate or severe hypercalcemia occurring in malignancy with or without bone metastases. The recommended dose of Aredia® for treatment of moderate hypercalcemia (serum calcium, corrected for albumin, of 12-13.5 mg/dl) is 60-90 mg, and for severe hypercalcemia (corrected serum calcium > 13.5 mg/dl) is 90 mg, administered as a single dose over the course of 24 hours, prepared by dilution of Aredia® brand of pamidronate disodium for injection (manufactured as a vial containing 30 mg of pamidronate disodium and 470 mg of mannitol, USP) with 1 liter of 0.9% saline, 0.45% saline, or 5% dextrose. Decrease in serum calcium after administration of Aredia® was noted in 24-48 hours and was considered as a positive response when noted by seven days to have occurred to an extent greater than had occurred with saline infusion alone.

The present Supplemental NDA submission is based on three studies collectively comparing 4 hour and 24 hour infusions. Two of these, Protocols 01 and 03, had been presented previously in support of the original NDA; the third, Protocol 02, was in progress at the time of the initial submission.

Protocol 01 compared the effects of three doses of pamidronate disodium, 30, 60, and 90 mg, administered as single 24 hour infusions, in an open protocol design, to three groups of patients (totalling 50) with cancer and hypercalcemia recruited

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by four centers, randomized to treatment groups, with a parallel, double-blind design. The range of serum calcium (corrected for serum albumin) at the start was 11.7-18.4 mg/dl. Of the 50 patients studied, 34 had confirmed bone metastases. About half of the patients (23/50) received furosemide, orally or intravenously, at some point in the first seven days after pamidronate administration. A dose-response relationship was observed in this study. By Day 7, 40% of those who had received 30 mg of drug showed "complete response" (return of serum calcium to normal values) as compared with 61% for the 60 mg group and 100% for the 90 mg group. If "partial responders" (decrease of serum calcium by at least 15%) were included, the numbers were 47%, 78%, and 100% respectively.

Protocol 03, also previously reported, compared the effects of a single dose of pamidronate disodium of 60 mg infused over 24 hours in 30 patients with three days of treatment with etidronate disodium (EHDP), 7.5 mg/kg/day in 35 patients in a randomized, parallel, double-blind, double-dummy design in nine centers. All patients had hypercalcemia secondary to a variety of cancers. Bone metastases were present in 70% of the patients receiving pamidronate and in 50% of those treated with etidronate. Concomitant furosemide treatment was used in about 53% of the pamidronate group and in 29% of the etidronate group. Complete response of serum calcium was seen by 7 days in 70% of the Aredia® group as compared to 41% in the EHDP group. When partial responders were added to the groups, there was only one patient who had not responded to Aredia® by 7 days as compared to 12 non-responders in the EHDP group.

Protocol 02, being reported in this SNDA, was designed to compare duration of infusion as the variable for effectiveness of therapy for hypercalcemia with Aredia®. In a randomized, parallel, double blind, double dummy design, 69 patients with hypercalcemia and cancer in 8 centers were divided into three groups to receive 0.9% saline, 60 mg Aredia® over 4 hours, or 60 mg Aredia® over 24 hours. As in the two previous protocols, a variety of cancer diagnoses were represented; between 29 and 53% of each group received concomitant furosemide therapy. The response pattern seen was similar to that reported in the two previous studies at the 60 mg/day dose level. In the four hour infusion group, 78% showed complete response and 87% complete plus partial response by day 7 after the infusion as compared to 61% and 74% respectively for the 24 hour infusion. These responses were not significantly different from each other but were significantly different from the saline group (22% and 35% respectively).

NUMBER OF RESPONDERS BY TREATMENT GROUP BASED ON CORRECTED SERUM CALCIUM BY DAY 7 POOLED DATA FROM PROTOCOLS 01, 02, 03						
TREATMENT GROUP	COMPLETE RESPONSE N	%	COMPLETE PLUS PARTIAL RESPONSE N	%	NON-RESPONDERS N	%
Aredia 30mg/24	6	40	7	47	8	53
Aredia 60mg/24	46	65	60	85	11	15
Aredia 90mg/24	17	100	17	100	0	0
Aredia 60 mg/4	18	78	20	87	3	13
EHDP	14	41	22	65	12	35
Saline	5	22	8	35	15	65

The number of patients achieving the principal end-point, normalization or 15% decline in hypercalcemia, thus appeared to be the same whether Aredia® was administered for 4 or 24 hours. Similar results are quoted from the published literature; In five studies, hypercalcemia was corrected with intravenous administration of pamidronate over 2 to 8 hrs, but no comparisons were made with 24 hour infusion intervals. Ralston found that in 22 patients with malignancies, no difference in response was noted when a low dose (45 mg) was infused over 3, 6, or 24 hours. Dodwell observed a similar response when 60 mg of Aredia® was infused over 2 hours (9 patients), 4 hours (11 patients), 8 hours (15 patients), or 24 hours (15 patients). In still another study, Sawyer found no difference in response rate or degree between administration of Aredia® at 1 mg/kg as either a 4 hour (12 patients) or 24 hour (13 patients) infusion.

OTHER OBSERVATIONS

In addition to observations of the effects of pamidronate infusion on serum calcium, additional observations are reported. Serum parathyroid hormone (PTH) levels were measured in Protocols 01, 02, and 03 during the baseline studies and were found, as expected, to be suppressed. In Protocol 01, despite the observed fall in serum calcium, serum PTH did not rise significantly with the infusion of 30 or 60 mg/day although median levels rose when 90 mg/day were infused. (Only median values for PTH are shown.) In Protocols 02 and 03, however, appropriate, significant changes in serum PTH were seen with administration of pamidronate at 60 mg/day, whether infused over 4 hours or 24 hours. Secondary hyperparathyroidism was not noted in any of the studies. There is no evidence in the SNDA of the number of patients studied for PTH effects.

Urinary hydroxyproline excretion was measured over 24 hour periods and corrected for creatinine excretion only in Protocol 01. Significant decreases are reported (but no data presented) in the groups receiving 30 or 90 mg/day, but not in the 60

mg/day group. Since diet was not controlled in this study, it is suggested that the variations noted were dietary in origin.

In Protocol 01, urinary calcium/creatinine ratio was measured in 24 hour samples and showed consistent decreases at Day 4, and more pronounced at Day 7 and at the Endpoint. The presented data do not have any indices of variability. In Protocol 02, calcium/creatinine ratios were measured in two hour urine collections performed while the subjects were inpatients. Decreases were noted in all three groups, the two regimens of Aredia® infusion and the saline group, but were much greater in the active drug groups and somewhat greater in the 4 hour group than in the 24 hour group. Only median values for calcium/creatinine ratios are reported, thus not allowing for evaluation of the magnitude of significance. Similar semi-quantitative observations have been reported in published clinical studies. More precise observations of calcium clearance might aid in interpreting mechanisms of action of the bisphosphonates.

MEDIAN 2-HOUR URINE CALCIUM AND CALCIUM/CREATININE RATIO AT 7-DAY END-POINT (PROTOCOL 02)

MEASUREMENT	Saline	Aredia 60 mg/4 h	Aredia 60 mg/24
URINE CALCIUM			
Baseline (mg)	57.0	44.5	50.0
Decrease (mg)	3.6	38.8	36.5
% Decrease	12.3	79.4	66.4
n	16	14	17
URINE CA/CREATN			
Baseline	1.0	0.8	1.0
Decrease	0.2	0.5	0.6
% Decrease	17.0	85.0	62.0
n	15	14	17

ONSET OF ACTION

The onset of action of Aredia®, as determined by a fall in serum calcium, was noted within the first 24 hours of administration of the drug at all three dosage levels (30, 60, and 90 mg/day) and whether administered for 4 hours or 24 hours. By Day 4, in all three protocols, complete or partial response was noted in all active groups, with data suggesting a dose-response relationship. Once again, the mean values reported suggest a somewhat better response in Protocol 02 in those receiving treatment over 4 hours as compared with the 24 hour infusions. However, only means are reported for each of the groups in all three protocols.

DURATION OF ACTION

Table A (page 095 of the SNDA) indicates that Protocols 01 and 02 each lasted 60 days and Protocol 03, 28 days. However, Table H (page 104) contains data for relatively few subjects at days 10 and 14. The total number of responders (complete plus partial) on those days is reported for the different regimens (53 of the original 183 on day 14), but how many of the 133 patients not reported were true non-responders and how many had been lost to follow up is not reported. Statistical analyses based on Confidence Intervals for duration of complete response for Time to Relapse suggest significant response relative to saline, but the numbers of subjects are insufficient to determine the clinical significance of this response.

NUMBER OF COMPLETE PLUS PARTIAL RESPONDERS BASED ON CORRECTED SERUM CALCIUM AT DAYS 10 AND 14

Treatment Group	Day 10 N	(%)	Day 14 N	(%)
Protocol 01				
Aredia 30 mg/24 h (N = 15)			2	13
Aredia 60 mg/24 h (N = 18)			6	33
Aredia 90 mg/24 h (N = 17)			9	53
Protocol 02				
Aredia 60 mg/24 h (N = 23)	12	52	6	26
Aredia 60 mg/ 4 h (N = 23)	11	48	9	39
Saline (N = 23)	2	9	2	9
Protocol 03				
Aredia 60 mg/24 h (N = 30)	14	47	13	43
EHDP (N = 34)	5	15	6	18

**DURATION OF COMPLETE RESPONSE* AND TIME TO RELAPSE†
BASED ON CORRECTED SERUM CALCIUM**

Treatment Group (N)	Complete Response* Duration (Days) Median (N)	95% C.I.	Time to Relapse† (Days) Median	95% C.I.
Protocol 01				
Aredia 30 mg/24 h (15)	4 (6)	1 - 30	0	0 - 13
Aredia 60 mg/24 h (18)	5 (11)	3 - 19	6	1 - 28
Aredia 90 mg/24 h (17)	6 (17)	5 - 11	11	6 - 15
Protocol 02				
Aredia 60 mg/24 h (23)	6.5 (14)	3 - 12	7§	1 - 14
Aredia 60 mg/ 4 h (23)	4 (18)	2 - 9	7§	2 - 13
Saline (23)	6 (5)	0 - ∞	0	0 - 1
Protocol 03				
Aredia 60 mg/24 h (30)	7 (21)	1 - 14	9.5 ‖	4 - 14
EHDP x 3 days (34)	5 (14)	2 - 29	4	0 - 6

* Duration of complete response is time from complete response to that of last serum calcium above upper limit of normal.
† Time to Relapse is time from occurrence of a complete or partial response to that of last serum calcium less than 11.5 mg/dl; non-responders assigned a time of 0.
§ $P < 0.05$ for Aredia vs. saline.
‖ $P < 0.05$ for Aredia vs. EHDP

When we compare the two previous tables, however, there appear to be some discrepancies. For instance, the number of complete plus partial responders in Protocol 02 for those who received Aredia 60 mg over 24 hours was reported as 12 by Day 10 and 6 by Day 14. However, in the data reported for duration of complete response for this same group, the number of patients showing complete response was listed as 14, Similar discrepancies exist for all the groups in Protocols 01, 02, and 03.

The following Table attempts to combine the data from all three protocols, but direct comparisons are difficult to make because of the discrepancies noted and because data for duration of response are reported as median values, making pooling of data difficult.

COMPARISONS OF EFFECTS OF DIFFERENT LEVELS OF AREDIA COMBINING DATA FROM PROTOCOLS 01, 02, 03

TREATMENT GROUP (N) *(PROTOCOLS)*	NO. TOTAL RESPONDERS DAY 14 N	(%)	DURATION OF COMPLETE RESPONSE WTD. MEDIAN	(N)
Aredia 30 mg/24 hr (15) *(01)*	2	13	4	6
Aredia 60 mg/24 hr (71) *(01, 02, 03)*	25	35	8.4	46
Aredia 60 mg/ 4 hr (23) *(02)*	9	39	4	18
Aredia 90 mg/24 hr (17) *(01)*	9	53	6	17
EHDP (34) *(03)*	6	18	5	14
Saline (23) *(02)*	2	9	6	18

SEVERITY OF BASELINE

Efficacy data from Protocols 01 and 02 suggest a relationship between baseline serum calcium values and magnitude of response to different doses of Aredia®. In Protocol 01, when serum calcium at the start was < 13.5 mg/dl, response was noted at all three dosages used; when the level was greater, no effect was seen at 30 mg/day, but response occurred at 60 and 90 mg/day. In Protocol 02, complete response rate was greater with both saline and Aredia® when serum calcium was <13.5 mg/dl (100% at 60 mg/4 hr; 67% at 60 mg/24 hr; 30% with saline); at higher serum calcium levels, response was significant for the drug treatment groups only (67% for 60 mg/4 hr; 57% for 60 mg/24 hr; 15% for saline).

RESPONSE RATE BY SEVERITY OF HYPERCALCEMIA (PROTOCOL 02)

Response	Saline		Aredia 60 mg/24 h		Aredia 60 mg/4 h	
Serum Calcium→	<13.5	≥13.5	<13.5	≥13.5	<13.5	≥13.5
N =	10	13	9	14	8	15
Complete	3	2	6	8	8	10
Partial	0	3	0	3	0	2
None	7	8	3	3	0	3

RENAL FUNCTION

The sponsors do not recommend change in dosage of pamidronate from 60 mg over either 4 hour or 24 hours for serum creatinine levels below 5.0 mg/dl. However, data are admittedly scanty and the question of effect of renal clearance on dosage should remain an area of continuing surveillance.

RENAL FUNCTION TESTS - PROTOCOL 02

TREATMENT	TEST	BASELINE MEAN	(N)	VISIT 2 MEAN	(N)	VISIT 4 MEAN	(N)	VISIT 8 MEAN	(N)	VISIT 14 MEAN	(N)
APD 60/ 4 H	BUN	19.96	23	19.35	23	18.50	22	10.38	16	13.50	2
	Creatinine	1.45	23	1.37	23	1.34	22	1.05	16	0.95	2
	Creatinine Cl.	66.23	23	71.76	23	73.91	22	78.60	16	66.80	2
APD 60/24 H	BUN	17.00	22	15.23	22	14.44	18	10.81	16	17.25	4
	Creatinine	1.25	22	1.19	22	1.21	18	1.02	16	0.95	4
	Creatinine Cl.	59.21	22	63.94	22	60.43	18	69.72	16	88.15	4
Saline /24 H	BUN	15.09	22	13 55	22	12.15	20	8.00	9	14.00	2
	Creatinine	1.19	22	1.2	22	1.14	20	0.94	9	0.80	2
	Creatinine Cl.	70.52	21	71.96	21	67.29	19	70.96	8	72.00	2

PHARMACOKINETICS

Pharmacokinetic data were derived from another study in which 36 patients "at risk for developing bone metastases" were randomized into six treatment groups to receive a single intravenous infusion of Aredia® of 30, 60, or 90 mg over 4 or 24 hours.

SUBGROUPS

No clinical relationship of response to Aredia® was noted when patients were separated into groups on the basis of age, sex, race, or body weight.

FUROSEMIDE

Approximately half of the patients followed in Protocols 01, 02, and 03 received furosemide at some point during the observations after administration of intravenous Aredia®. No significant difference in response (as measured by urinary clearance of calcium or production of hypocalcemia) was seen as a result of the diuretic.

BONE METASTASES

About 60% of the patients reported in the three protocols were noted to have bony metastases; the data presented are inadequate to perform statistical analyses but appear to show no effect of the presence or absence of metastases on the response rate to Aredia® administered at 60 or 90 mg/day over 4 or 24 hours.

TYPE OF CANCER
Too few patients of any specific cancer type were studied to permit statistical analysis of a relationship between response and type of cancer.

DOSE-RESPONSE
No dose response was noted in patients with serum calcium values < 13.5 mg/dl. In Protocol 01, the highest dose of 90 mg/day produced the greatest fall in serum calcium in the patients with baseline values > 13.5 mg/dl.

RETREATMENT
Of the 183 patients initially entered into the three protocols, 32 were re-treated with Aredia® in the extension studies, presumably because of failure of response, only partial response, or return of serum calcium to elevated levels. In Protocol 01 Extension, retreatment was with 60 mg/24 hour infusion; 9 of 19 resulted in normalization of serum calcium. In Protocol 02 Extension, patients were retreated with 60 mg/4 hour infusions; 3 of 7 initially treated with Aredia® responded on retreatment; 2 of 4 initially treated with saline showed complete response. Retreatment in Protocol 03 Extension was with 60 mg/24 hrs; 2 of 6 had partial or complete responses. These data are insufficient to draw firm conclusions concerning effectiveness of retreatment.

SAFETY
Safety data presented are derived from the three Protocols submitted with the present SNDA, as well as data from other non-blinded studies using single doses of Aredia® of 60 and 90 mg infused over 2, 4, and 24 hours, in patients with Paget's Disease, breast cancer, prostate cancer. None of the medical problems encountered were considered sufficiently severe to warrant discontinuation of treatment. The problems considered related to treatment with the drug included fever, bone pain, nausea, infusion site reaction, and fluid overload. None appeared to be dose related nor related specifically to the more rapid (4 hr vs. 24 hr) rate of administration of drug. Only two patients were removed from study in the three reported protocols: one who developed transient asymptomatic hypocalcemia as a result of pamidronate and one who experienced seizures but had been receiving saline alone. Of interest, however, was the observation of decrease in serum phosphate to "below 1.5 mg/dl in about one third of the patients"; this necessitated blood chemistry monitoring and "was readily reversed by administration of phosphate supplements." Data of actual values for serum phosphate and dosage of phosphate supplements required were not noted in the NDA volumes. Since reference to the hypophosphatemia occurs in several places in the NDA, as well as in the Proposed Labeling, I would like to see more detail of this finding, including time of onset of hypophosphatemia relative to infusions, whether or not this occurs on repeated treatment, amounts of phosphate required to reverse, relationship to dose of Aredia, mode of administration, relationship to diagnosis (e.g., Paget's disease vs. malignancy)..

Safety data from Protocols 01, 02, 02 Extended, 03, 05, 09 were reviewed and are summarized below for problems that may be of significance.

SELECTED MEDICAL PROBLEMS; POOLED DATA					
GROUP	NO.	FEVER	INFUSION SITE*	HYPOKALEMIA	HYPOMAGN.
Protocols 01,03					
APD 30	15	4	0	6	10
APD 60	50	20	5	22	17
APD 90	17	5	5	7	5
Protocol 02					
APD 60/4	23	6	§	1	1
APD 60/24	23	4	§	1	3
Saline	23	0	§	0	1
Protocol 02-Ext.					
APD 60	7	1	§	§	§
Saline	4	0	§	§	§
Protocol 05					
APD 60/4	10	1	2	§	§
APD 60/24	10	2	1	§	§
Protocol 09					
APD 30/4	6	1	0	§	§
APD 30/24	6	0	3	§	§
APD 60/4	6	1	1	§	§
APD 60/24	6	1	1	§	§
APD 90/4	6	2	2	§	§
APD 90/24	6	1	2	§	§
All APD 30	27	5	3/27	6/15	10/15
All APD 60	135	36	10/82	24/96	21/96
All APD 90	29	8	9/29	7/17	5/17
All APD	191	49	22/138	37/128	36/128
All Saline	27	0	0/27	0/23	1/23

* Infusion Site Problems include items listed in the NDA tables as pain, infusion site reaction, thrombophlebitis, vasculitis.

§ No data recorded

BENEFIT-RISK

Aredia® is effective in lowering hypercalcemia of malignancy to normal levels at a dosage of 60 to 90 mg/day administered in a single infusion. The data in the present SNDA submission indicates equal effectiveness when administered over 4 hours or 24 hours. Onset of hypocalcemic activity is noted within 24-48 hours, reaching maximal effectiveness in about 7 days, and persisting for 1 to 2 weeks. It was shown in a small number of patients that retreatment is often effective.

Aredia® was effective in hypercalcemia with and without bony metastases. Reduction of serum calcium was noted at moderate (<13.5 mg/dl) and severe (>13.5 mg/dl) hypercalcemia. Effectiveness was noted both below and above 65 years of age, in all races, and did not appear to be dependent on the type of cancer involved.

No evidence for deterioration of renal function was seen in any of the protocols; as serum calcium declined, serum creatinine returned to normal. The inhibition of serum PTH noted during baseline hypercalcemia disappeared as serum calcium decreased with no evidence for secondary hyperparathyroidism developing as a rebound phenomenon.

Approximately 50% of the intravenously administered dose used in these studies (30-90 mg) remains in the body after 24 hours. Animal studies show that "almost all" of this is in the bone. Clinical studies in published studies showed decreases in urinary excretion of hydroxyproline and calcium which are interpreted by the sponsor as supporting inhibition of bone resorption as the mechanism of action for pamidronate.

1. The duration of action of pamidronate is short, relative to the long half life in bone.
2. The urinary excretion data of bone constituent are sketchy and insufficient to lead to an unqualified conclusion that bone resorption has been inhibited.
3. The mechanism of action of pamidronate remains unknown and deserves additional study, both clinical and in animals.
4. If pamidronate remains in the bone for extended periods of time, without demonstrable action on serum calcium, does it or may it have other metabolic effects with time?

PROPOSED LABELING

In the section on pharmacodynamics, it is noted that "serum phosphorus levels have been noted to decrease after administration of Aredia." The possible magnitude of this decrease, its time of occurrence, its frequency, its significance, and guidelines for correction should be discussed here or subsequently.

Hypophosphatemia is also discussed in the Precautions section; amplification is also recommended at this point.

Under Precautions, hypocalcemia is mentioned, with the caveat that it has been "asymptomatic" , but "short-term calcium therapy may be necessary." Under what circumstances is therapy recommended? What agents have been used, orally or intravenously? How frequently were they administered?

In the section on Laboratory Tests, it is recommended that serum calcium, phosphate, magnesium and creatinine be "closely monitored"; are there recommendations for frequency? The data presented suggest that possibly daily tests be done for a week after drug administration and possibly weekly thereafter for several weeks.

Under "Pregnancy Category C" I would recommend a change in writing style. The last sentence should be changed to: "Since it has been shown that Aredia..." (See Strunk and White; Fowler; i.a., for appropriate use of "as" and "since".)

Under "Dosage and Administration", the recommended dose for "severe" hypercalcemia is stated to be 90 mg administered over 4 hours; very few data have been submitted for this dosage; the few studies included in this NDA suggest increased incidence of adverse reactions at this dosage as compared with the 60 mg over 4 hours, which was evaluated to a greater extent.

Under "Preparation of Solution" it is emphasized that Aredia not be mixed with calcium containing solutions; however, is there any effect on availability of the drug due to calcium solutions administered before or after the Aredia?

RECOMMENDATIONS

1. Approval for use of Aredia® for the treatment of hypercalcemia of malignancy by intravenous infusion of up to 60 mg of active drug, diluted in 0.9% sodium chloride solution (500 ml) over a four hour interval.

2. Retreatment may be carried out if serum calcium does not return to normal or remain normal one week after initial treatment in patients who showed complete or partial response initially.

3. Additional controlled data are needed before approval of a 90 mg/4 hour dosage regimen.

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

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

6. 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 biofunction.

6. The Proposed Labeling should be rewritten as recommended above.

- L. Lutwak December 8, 1992

Excellent review. Concur = "approvable" rec.
for 60mg/4hr, but not 90mg/4hr. We may
request that sponsor provide the # and proportion
of subjects in controlled trials who experience
rises in serum creatinine by ≥ 0.5 mg/dL to
values ≥ 2.0 mg/dL at any time on treatment,
as well as those developing potentially
clinically significant hypocalcemia, hypophosphatemia,
hypomagnesemia, and hypokalemia, thresholds for
which must be defined. Sponsor should also report
rates of infusion site reactions for each arm of study 2.

L. K. Lewis, MD
12/17/92

cc
NDA
HFD-510
HFD-510/Lutwak/Pierce/Thaxton

FINAL

MEDICAL OFFICER'S REVIEW OF LABELLING

OCT 22 1993

NDA NO. 20-036: Draft labelling for Supplement S-004
DRUG: Aredia® pamidronate disodium for injection
SPONSOR: Ciba-Geigy Corporation
Summit, NJ 07901
DATE OF SUBMISSION: September 2, 1993
DATE RECEIVED CDER: September 7, 1993
DATE RECEIVED MO: September 10, 1993
DATE OF REVIEW: October 21, 1993

NDA Supplement S-004 to this NDA, dated Sept 23, 1992 concerned reduction of infusion time of Aredia from 24 to 4 hours in patients with hypercalcemia of malignancy. In a letter dated May 1, 1993, the Agency approved reduction in infusion time to 4 hours for doses of 30 and 60 mg, but not for 90 mg, since data in support of the shorter time for the highest dose had not been submitted. In addition, revision of labelling was recommended. The present submission contains the revised labelling, consisting of a revised package insert and cartons.

Changes are as follows:

1. Under **Clinical Pharmacology**, the section describing the studies in cancer patients with minimal or no involvement has been rewritten, eliminating reference to AUC data and expressing results as mean ± standard deviation instead of ranges.
2. The concerns of effects of renal impairment in patients have not been addressed directly, since the studies are still in progress; the section under **Warnings** expands the discussion of renal effects in rats and dogs.
3. A study of hypercalcemia in 69 patients studied in a multicenter, randomized, parallel double-blind trial is described in detail. It is emphasized that 60 mg may be given in a four hour infusion, but data are not available for 90 mg doses given in four hours.
4. The section on the effects on **Pregnancy** has been rewritten.
5. The **Adverse Reactions** section is updated.
6. The section on **Dosage and Administration** has been rewritten to reflect the 4 hour infusion for 60 mg and 24 hour for 90 mg. This is repeated in the section on **Preparation of Solution.**
7. Carton labelling has been revised to reflect the 4 and 24 hour infusion times.

MEDICAL OFFICER'S RECOMMENDATIONS:
The revised labelling is acceptable.

Leo Lutwak, M.D., Ph.D.
October 21, 1993
Gloria Troendle 10-22-93

cc: NDA Arch.
HFD-510
HFD-510/GTroendle/LLutwak

STAT

REVIEW

ORIGINAL

MAR 24 1993

STATISTICAL REVIEW AND EVALUATION

NDA#: 20-036/S-004

APPLICANT: Ciba-Geigy Corporation

NAME OF DRUG: Aredia (pamidronate disodium for injection)

INDICATION: Hypercalcemia associated with malignancy

DOCUMENTS REVIEWED: Volumes 1 and 20-29 of NDA 20-036 S-004 dated September 23, 1992

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Leo Lutwak, M.D. (HFD-510)

Relevant Issues Discussed In This Review:

1. Aredia 60 mg patients infused over 4 or 24 hours experienced significantly greater reductions in corrected serum calcium levels as well as significantly greater response rates than did saline patients.

2. The efficacy and safety profiles were comparable between Aredia 60 mg patients regardless of the infusion time.

Background:

In a statistical review and evaluation dated June 4, 1990, I reviewed two (Studies 01 and 03) multi-center, double-blind, randomized studies which were conducted to assess the effect of Aredia in lowering serum calcium levels in patients who had persistent hypercalcemia (corrected serum calcium of at least 12 mg/dl) after adequate hydration.

It was concluded in the above mentioned review that Aredia 60 mg patients in Study 03 who received a single 60 mg 24-hour infusion experienced significantly greater reductions in corrected serum calcium (primary efficacy parameter) levels than did the control (etidronate sodium) patients. I also noted that the results of Study 01 were supportive of the Study 03 results.

The original NDA for Aredia was approved on October 31, 1991. The recommended dose of Aredia in moderate hypercalcemia (corrected serum calcium of approximately 12-13.5 mg/dl) is 60-90 mg, and in severe hypercalcemia (corrected serum calcium >13.5 mg/dl) is 90 mg, given as an initial, single-dose, intravenous infusion over 24 hours.

KEY WORDS: hypercalcemia, infusion time, serum calcium

Vol#20.1
5E2004

The current submission which is a supplement provides data (Study 02) to support a single 4-hour infusion of Aredia 60 mg compared to the above mentioned single 24-hour infusion of Aredia 60 mg.

Study 02

This multi-center, double-blind, randomized, study was conducted to assess the effects of 60 mg single doses of Aredia infused over either 4 or 24 hours in comparison to saline alone in lowering corrected serum calcium levels in patients with cancer. A secondary objective was to determine if Aredia 60 mg/4 hour was as efficacious and safe as Aredia 60 mg/24 hour in lowering corrected serum calcium levels.

Patients who had hypercalcemia (corrected serum calcium of at least 12 mg/dl) and a histologic diagnosis of malignancy were randomized to receive double-blind infusions. A "double dummy" design was used to maintain the blind.

Randomized patients were followed closely as inpatients for 7 days (inpatient phase) for effects on corrected serum calcium levels and for any adverse experiences associated with the infusion of Aredia. In a follow-up phase (days 10-60), patients were followed either as inpatients or outpatients for recurrence of hypercalcemia and for any long term adverse reactions associated with Aredia.

The primary efficacy variable was the reduction in corrected serum calcium levels. Patients whose corrected serum calcium level was reduced to within the patient's center's normal range were considered to have experienced a complete therapeutic response. A partial response was defined to be a decrease of at least fifteen percent in the corrected serum calcium level without attaining normalization.

The primary efficacy analysis was based on data obtained during the 7-day inpatient phase.

Reviewer's Comments on Study 02

A total of 69 patients (23 in each treatment group) were randomized to receive double-blind treatment. Forty-two (9 saline, 16 Aredia 60 mg/4 hour, 17 Aredia 60 mg/24 hour) of these patients completed the inpatient phase whereas thirty-four (4 saline, 15 Aredia 60 mg/4 hour, 15 Aredia 60 mg/24 hour) of these patients entered the follow-up phase. The most common (14 saline, 1 Aredia 60 mg/4 hour) reason for terminating the study during the inpatient phase was an unsatisfactory therapeutic response.

In examining the adverse reaction data submitted by the sponsor, I noted that each patient reported at least one adverse reaction during the study. Significant differences were detected (Table 1) in favor of saline over Aredia with regard to nausea, anemia, fever, anorexia, fluid overload, and hypophosphatemia. The only between active treatment group significant difference was with regard to anemia as a significantly greater proportion of Aredia 60 mg/24 hour patients experienced anemia than did Aredia 60 mg/4 hour patients (60.9% vs 30.4%, p=.038).

The sponsor compared the treatment groups with respect to responder proportions. Aredia versus saline pairwise comparisons were conducted at the .025 significance level whereas the Aredia 60 mg/4 hour - Aredia 60 mg/24 hour pairwise comparison was conducted at the .05 significance level.

The results of the sponsor's analyses which are displayed in Table 2 indicated that both Aredia treatment group patients statistically outperformed their saline counterparts with regard to complete (by day 5) and complete or partial (by day 5) response rates. No significant differences were detected between the 2 Aredia groups, although the 4 hour infusion patients experienced a greater ultimate response rate than did the 24 hour infusion patients.

However, as was noted in the June 4, 1990 statistical review of the original NDA submission dated December 20, 1989, once a patient was classified as a responder, that patient was considered a responder at all subsequent inpatient phase visits whether or not that patient still satisfied the responder definition.

In examining the patient responder data submitted by the sponsor, it was apparent that similar responder results are obtained if the responder classification is not automatically carried forward.

The results of this reviewer's endpoint (last observation carried forward) all patient corrected serum calcium analyses (similar results were obtained by the sponsor) are displayed in the upper portion of Table 3.

In examining these results, one notes that they are consistent with the responder results in that each active treatment group's patients experienced significantly greater reductions in corrected serum calcium levels than did saline patients whereas no such statistical significance was detected between the active treatment groups.

The middle and lower portions of Table 3 indicate that these results were consistent between patients with moderate and severe hypercalcemia.

Reviewer's Concluding Comments

The results of Study 02 indicated that Aredia 60 mg patients infused over 4 or 24 hours experienced significantly greater reductions in corrected serum calcium levels as well as significantly greater response rates than did saline patients. Furthermore, the magnitude of the Aredia 60 mg corrected serum calcium reductions were comparable to those experienced by the Aredia 60 mg/24 hour Study 01 and Study 03 patients.

The results of Study 02 also indicated that Aredia 60 mg patients infused over 4 or 24 hours experienced comparable corrected serum calcium reductions and response rates.

Also the adverse reaction profiles of the 4 and 24 hour infusion treatment groups were comparable.

David N. Marticello

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius 3-24-93

Dr. Dubey 3-24-93

cc:
Original: NDA 20-036/S-004
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Lutwak
HFD-510/Ms. Galliers
HFD-344/ Dr. Lisook
HFD-713/Dr. Dubey[File:1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/Mr. Marticello
CHRON File

This review consists of 4 pages of text and 3 pages of tables.

AREDIA.REV./SRS/03/15/93

Table 1

Study 02

Adverse Reaction Frequencies +

Reaction	Saline	Aredia 60 mg/4hr	Aredia 60 mg/24hr	All Aredia
Constipation	14(60.9%)	16(69.9%)	18(78.3%)	34(73.9%)
Hypokalemia	11(47.8%)	11(47.8%)	14(60.9%)	25(54.3%)
Hypomagnesemia	11(47.8%)	9(39.1%)	12(52.2%)	21(45.7%)
Nausea	7(30.4%)	14(60.9%)*	9(39.1%)	23(50.0%)
Bone Pain	9(39.1%)	10(43.5%)	10(43.5%)	20(43.5%)
Anemia	7(30.4%)	7(30.4%)	14(60.9%)*#	21(45.7%)
Fever	4(17.4%)	9(39.1%)	10(43.5%)	19(41.3%)*
Anorexia	3(13.0%)	11(47.8%)*	9(39.1%)*	20(43.5%)*
Insomnia	4(17.4%)	4(17.4%)	9(39.1%)	13(28.3%)
Dyspnea	4(17.4%)	7(30.4%)	6(26.1%)	13(28.3%)
Abdominal Pain	7(30.4%)	6(26.1%)	4(17.4%)	10(21.7%)
Pain	2(8.7%)	7(30.4%)	6(26.1%)	13(28.3%)
Vomiting	8(34.8%)	6(26.1%)	4(17.4%)	10(21.7%)
Fluid Overload	1(4.3%)	8(34.8%)*	6(26.1%)	14(30.4%)*
Hypophosphatemia	1(4.3%)	7(30.4%)*	7(30.4%)*	14(30.4%)*

\+ Reported by at least 30% of the patients in at least one of the treatment groups. Twenty-three patients in each treatment group.

* p<.05 Aredia vs Saline

\# p<.05 Aredia 60mg/24 hours vs Aredia 60 mg/4 hours

Table 2
Study 02

Responder Proportions

Complete

Day#	Saline (N=23)	Aredia 60 mg/4hr (N=23)	Aredia 60 mg/24hr (N=23)
1	0	0	0
2	1 (4.3%)	2 (8.7%)	1 (4.3%)
3	2 (8.7%)	4 (17.4%)	8 (34.8%)
4	2 (8.7%)	9 (39.1%)	10 (43.5%)*
5	3 (13.0%)	14 (60.9%)**	12 (52.2%)*
6	5 (21.7%)	18 (78.3%)***	14 (60.9%)*
7	5 (21.7%)	18 (78.3%)***	14 (60.9%)*

Complete or Partial

Day#	Saline (N=23)	Aredia 60 mg/4hr (N=23)	Aredia 60 mg/24hr (N=23)
1	2 (8.7%)	1 (4.3%)	2 (8.7%)
2	3 (13.0%)	10 (43.5%)	6 (26.1%)
3	5 (21.7%)	19 (82.6%)***	12 (52.2%)
4	6 (26.1%)	19 (82.6%)***	14 (60.9%)
5	7 (30.4%)	20 (87.0%)***	17 (73.9%)**
6	8 (34.8%)	20 (87.0%)***	17 (73.9%)*
7	8 (34.8%)	20 (87.0%)***	17 (73.9%)*

\# Cumulative number of patients who respond by the given day
* p<.025 Aredia vs Saline
** p<.01 Aredia vs Saline
*** p<.001 Aredia vs Saline

No significant differences were detected between the active treatment groups.

Table 3
Study 02

Corrected Serum Calcium Means (mg/dl)

All Patients

Treatment Group	N	Baseline	Endpoint (a)	Reduction
Saline	22	13.74	12.88	.85
Aredia 60mg/4hr	23	14.18	10.55	3.62***
Aredia 60mg/24hr	22	13.71	10.56	3.15***

Patients with Baseline < 13.5 mg/dl

Treatment Group	N	Baseline	Endpoint (a)	Reduction
Saline	10	12.89	11.96	.93
Aredia 60mg/4hr	7	12.87	9.93	2.94**
Aredia 60mg/24hr	8	12.60	10.18	2.43*

Patients with Baseline > 13.5 mg/dl

Treatment Group	N	Baseline	Endpoint (a)	Reduction
Saline	12	14.44	13.65	.79
Aredia 60mg/4hr	16	14.74	10.83	3.92**
Aredia 60mg/24hr	14	14.34	10.78	3.56**

a last value carried forward
* p<.05 in favor of Aredia over saline
** p<.01 in favor of Aredia over saline
*** p<.001 in favor of Aredia over saline

No significant differences were detected between the active treatment groups.