CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020927, 020036/S015/S016

MEDICAL REVIEW(S)

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SEP 20 1998

Aredia Efficacy Supplement for Breast Cancer
(Two-year data on efficacy and safety in breast cancer)

1. General Information:

1.1 NDA# 20-927

1.1.2 Review: Type 6 NDA review
1.1.3 Submission date: September 22, 1997
1.1.4 Date of Review September 18, 1998
1.1.5 Related applications: IND
NDA 20,036

1.2 Drug Name

1.2.1 Generic name: Pamidronate disodium for injection
1.2.2 Trade name: Aredia

1.3 Applicant: Novartis

1.4 Pharmacologic Category: Biphosphonate anti-hypercalcemia agent

1.5 Proposed Indication: Extension of treatment and follow-up from one year to two years in treatment of patients with osteolytic bone metastases from breast cancer.

1.6 Dosage Form:

Available in vials each containing 30, 60, or 90 mg of lyophilized pamidronate disodium and varying amounts of mannitol, USP for i.v. infusion

1.7 Recommended Dose and schedule:

90 mg diluted in 250 ml sterile saline or D5W intravenously over 2 hours repeated every 2-3 weeks.

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ON ORIGINAL

2.0 TABLE OF CONTENTS

3.0 Material Reviewed

The following are the locations of the most important documents utilized in review of the submission:

Proposed Labeling:	Volume 1
Study report, patients receiving chemotherapy (P19)	Volume 30
Study report, patients receiving hormones (P18)	Volume 18
Integrated summaries of Safety and Efficacy	Volume 55

4.0 Introductory comments

Aredia was approved for treatment of patients with osteolytic lesions from breast cancer in 1996 based on 1-year data from 2 studies, Study P19, a study in patients receiving chemotherapy, and P18, a study in patients receiving hormone therapy. This supplement is submitted to update the labeling with data extending followup and treatment to 2 years. The reviewer will briefly review the design of the trials, the efficacy data, the safety data, and the proposed labeling.

5.0 Design of Protocol 19 (Chemotherapy)

COMPARATIVE TRIAL OF AREDIA VERSUS PLACEBO IN THE PREVENTION OF SKELETAL-RELATED COMPLICATIONS IN PATIENTS WITH BREAST CANCER AND LYTIC BONE LESIONS TREATED WITH CHEMOTHERAPY. PROTOCOL 19

STUDY DATES

FIRST PATIENT TREATED:	JANUARY 3, 1991
STUDY CLOSED TO ENROLLMENT:	MARCH 1, 1994
PREVIOUS STUDY REPORT:	10/20/95
PHASE II END	MARCH 1996

Summary of design

The following are excerpts from the original medical officer review of the efficacy supplement for breast cancer.

Objective

- Primary: To determine whether patients treated with Aredia 90 mg IV monthly will have significantly fewer skeletal-related events at 12 months (the end of study 'Phase I') than patients treated with placebo (250 ml 5% dextrose in water). The primary efficacy variable is the mean number of SRE (excluding instances of hypercalcemia) per patient per month.

- Secondary -Assess differences in palliative treatment (pain relief, QOL, performance status) of patients with breast cancer being treated with chemotherapy.

  -Assess safety and tolerableness of repeated doses of Aredia during 'phase II' (second year follow-up of study patients).

Reviewer comment:
Note that the final analysis for efficacy was to occur after phase I. The phase II objective was only to evaluate safety and tolerableness. This design would not support additional efficacy claims being made at 2 years.

Design:

This was a multi-center, randomized, parallel, double-blind, placebo-controlled stratified trial comparing 90 mg Aredia in D5W to D5W alone (placebo). Drug or placebo were given intravenously over 2 hours at intervals of 4 wks in patients with breast cancer who at least one predominantly osteolytic lesion and were being treated with chemotherapy. Phase I of the trial, which was to assess efficacy, was to last 12 months while the safety phase (phase II) was to continue for 24 months.

Strata:

ECOG performance status 0,1 versus 2,3.

The anticipated trial duration was to be 36 months: 12 months accrual, 12 months treatment, and 12 months additional follow-up (for phase II).

Selected Inclusion Criteria

The most pertinent inclusion criteria are listed below:

- Osteolytic lesions:
  -2 osteolytic lesions, one of which is 1 cm2 and no radiation to lesion in past 3 months.
  or
  -One osteolytic lesion 1 cm2 which has never been treated with radiotherapy and presence of extra skeletal metastases.

- Must be receiving chemotherapy with marketed drugs.

Selected Exclusion Criteria

- Serum creatinine > 2.5 mg/dl.

- Clinically significant ascites or bilirubin > 2.5 mg/dl.

- Treatment for hypercalcemia or a corrected Calcium ≥ 12.0 mg/dl during the 14 days prior to visit 2 (date of first treatment).

- Pathologic fracture, spinal cord compression or radiation therapy for bone pain within 12 days of visit 2.

Visit schedule

The following table was created from selected elements from the follow-up schema in the protocol:

Tests	Phase I (year 1)	Phase II (year 2)
Bone Scan and Skeletal Radiographs	0,6,9,12 months	18, 24 months
Recording Skeletal-Related Events and interim physical exam	Monthly	Monthly
Routine labs (CBC,calcium,serum chemistries)	Monthly	Monthly
CEA	0,2,4,6,9,12 months	15,19,24 months
QOL Assessments (Pain, Narcotic, QOL index, and ECOG PS)	-14 to 0d; 0,3,4,6,9,10,12 months	15,16,18,21,22,24 months

Starting with visit number 4, scheduled visits were at 28 day intervals. Visit 1 and Visit 3 (occurring 2 weeks before and 2 weeks after the first treatment, respectively) were for recording baseline information whereas visit 2 and all visits after visit 3 were for both treatment and information gathering.

At visits 6,9,15,21, and 27, Bone Lesion Response of bone surveys was to be determined by the central radiologist. At visit 12 a study termination form (for efficacy phase) was to be completed for each patient.

Details of Data Collection for Specific Endpoints

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Skeletal Related Event:

At Visit 1 (baseline), the number of SRE's in the previous 3 months were to be noted. At visit 2, any patient with an SRE in the previous 14 days was to be excluded from the trial. SRE's were also to be recorded at each monthly visit. A skeletal related event was defined as any of the following:

1. Hypercalcemia: need for treatment of hypercalcemia (symptoms or a corrected

calcium ≥12 mg/dl).

2. Pathologic Fracture

3. Spinal cord compression/collapse

4. Radiation to bone for Pain Relief (expanded in 3/94 to include use of Strontium)

5. Radiation to Prevent spinal cord compression

6. Radiation to prevent pathologic fracture

7 Surgery to prevent spinal cord compression

8 Surgery to prevent pathologic fractures.

Reviewer Comment
Terms such as 'pathologic fracture' are not defined.

Toxicity Criteria:

NCI common toxicity criteria were used. Special criteria were utilized for some laboratory tests not included in those criteria.

Off-study Criteria

Unlike most oncology studies, patients were to remain onstudy regardless of disease progression. The only reasons for going offstudy were to be patient or investigator assessment that it was in the patient's best interest to do so. Any time a patient went off-study, the final visit data form was to be filled out.

Efficacy Considerations

Primary Endpoint:

The primary efficacy analysis was declared to be an intent to treat analysis of the 'Skeletal Morbidity Rate, excluding hypercalcemia [SMR(-HCM)]' during the first 12 months of the trial (phase I). SMR(-HCM) is defined as the number of SRE's, excluding hypercalcemia, divided by the number of months a patient participated in Phase I.

Reviewer comments:

The calculation and comparison of rates seems to suggest that rates are constant over a patient's time on-study. If there is significant dropout, and if event rates differ according

to time on-study, differential dropout between the 2 arms could produce spurious differences in rates.

Prognostic factors prospectively defined for use with the efficacy analyses included:

-Renal function (Cr < 2.0 vs ≥2.0)
-PS (ECOG 0-1 vs >1))
-age (≤50 vs >50)

Secondary Efficacy endpoints

The protocol specified analysis of several endpoints at 3, 6, 9, 12 months, and at last visit ('endpoint visit') as secondary analyses. These endpoints included the SMR (+/-HCM), proportion of patients with any SRE (+/-HCM), time to first occurrence of first SRE, evaluation of each individual type of SRE, pain and narcotic scores, quality of life index, performance status, response measurements from radiologic results on lytic lesions, and serum CEA measurements.

Pain score and Narcotic score were calculated as follows:

Pain score = (pain severity) X (Pain frequency)

For severity:
none = 0
mild = 1
moderate = 2
severe = 3

For frequency:
none = 0
occasional= 1
intermittent (at least once a day) = 2
Constant (most of the time) = 3

Reviewer comments:
Multiplication by the frequency category seems just as likely to obscure as to clarify the meaning of the pain severity.

Narcotic score = (medication type) X (medication frequency)

For medication type:

0 = none
1 = mild analgesic (OTC)
2 = mild narcotic (30 mg codeine, oxycodone, meperidine.)

3 = Strong narcotic (60 mg codeine, morphine, hydromorphone, etc.)

The quality of life index is from Spitzer (Spitzer, W.D. Measuring the quality of life of cancer patient,. A concise QL-index for use by physicians. J Chron Dis 34: 585-597, 1981.) The categories are rated 0-2 and include:

Activity
Daily Living
Health
Support
Outlook

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Statistical Issues (protocol, p 39)

The trial was initially designed to have 80% power to detect a 15% difference in proportion of patients with any SRE (including hypercalcemia) during the first 12 months. 268 patients were needed; 300 were to be enrolled assuming a 5% loss to follow-up rate. Analyses were to be intent-to-treat analyses. The sample size calculation was based on this endpoint rather than the SMR endpoint since only data on proportions of patients were available for estimation.

The following tests were to be used for endpoints discussed above under Efficacy:

-The primary analysis method is ratio of occurrences divided by time of exposure in each patient and was to be compared between arms by Wilcoxon Rank Sum test.

-Proportions of patients with any SRE (including and excluding hypercalcemia) were to be compared at 3, 6, and 9 months on-study using the chi-squared statistic. Time to occurrence of SRE was to be compared using Kaplan-Meier plots and the logrank test.

-Between-treatment comparisons for change in the various QOL scores were to use the Wilcoxon Rank Sum Test. Within-treatment differences from baseline were to be analyzed using the Wilcoxon signed-rank statistics. Survival was to be analyzed using the logrank test at the end of Phase I (12 months) and Phase II (24 months).

Summary points from review of Protocol P 19:

In general, this is a well-designed, double-blind, placebo-controlled trial to evaluate the occurrence of morbid events associated with bone destruction caused by metastatic breast cancer.

- The primary endpoint specified by the sponsor was Skeletal Morbidity Rate. Underlying assumptions of using this endpoint should be considered:

-Is event rate constant over time? Do drop-outs occur at similar times on the 2 arms?

-In the proposed modified Wilcoxon rank sum test, patients with no events are ranked the highest, and of these, those with the longest time of followup the highest. If there were an imbalance of dropouts, with numerous dropouts of short-follow-up on one arm, such an analysis might not be appropriate. Such an analysis would place higher value on a dropout followed for a short time than on a patient with a single event followed for the full time. Such a value-judgment would have to be re-examined in light of the actual frequency and timing of events in the data.

-Analysis of time to first event could demonstrate whether these findings are robust.

Design of P18

A COMPARATIVE TRIAL OF AREDIA® VERSUS PLACEBO FOR THE PREVENTION OF SKELETAL-RELATED COMPLICATIONS IN PATIENTS WITH BREAST CANCER AND LYTIC BONE LESIONS TREATED WITH HORMONAL THERAPY

STUDY DATES

FIRST PATIENT TREATED:	DECEMBER 21, 1990
STUDY CLOSED TO ENROLLMENT:	MAY 2, 1994
LAST STUDY REPORT:	10/20/95
PHASE II COMPLETE	JULY 1996

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Objective

Same as P19 for this population.

Design:

Same as P19.

Selected Inclusion Criteria

- Must be receiving hormonal therapy with marketed drugs.

Selected Exclusion Criteria

- No chemotherapy was allowed for 3 months prior to first treatment visit. Patients changing to chemotherapy during the trial were to be continued in the study. Originally, these patients were not to be included in the primary analysis. However, the 3/94 amendment specified that all patients were to be included in the primary analysis.

- Study design was essentially identical to that of the chemotherapy trial (P19) except that hormonal therapy was required instead of chemotherapy.

6.0 Updated Efficacy Data

6.1 Patient Disposition

382 patients were treated in Protocol 19 (chemotherapy patients) as outlined in the following table from the submission:

Distribution of patients by treatment group

Number of patients	Aredia	Placebo	Total
Randomized	185	197	382
Received	185	197	382
Excluded from Intent-To-Treat	0	2	2
Included in Intent-To Treat Analysis:	**185**	**195**	**380**
Stratum 1	121 (65%)	128 (66%)	249 (66%)
Stratum 2	64 (35%)	67 (34%)	131 (34%)
Completed Phase I +	99 (54%)	82 (42%)	181 (48%)
Completed Phase II	47 (25%)	35 (18%)	82 (22%)

+ Include patients who discontinued at Visits 15

Similarly, 372 patients were enrolled in protocol 18 (hormone patients):

Distribution of patients by treatment group

Number of patients	Aredia	Placebo	Total
Randomized	180	192	372
Received	182	190	372
Excluded from Intent-To-Treat	0	1	1
Included in Intent-To-Treat Analysis:	**182**	**189**	**371**
Stratum 1	144 (79%)	139 (74%)	283 (76%)
Stratum 2	28 (21%)	50 (26%)	88 (24%)
Completed Phase I	113 (62%)	98 (52%)	211 (57%)
Completed Phase II	68 (37%)	65 (34%)	133 (36%)

Notice that only about a third of the hormone-treated patients and less than a forth of the chemotherapy-treated patients finished 2 years of Aredia or placebo therapy.

Reasons for dropout are listed in the following tables:

Protocol 19 (chemotherapy)

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Protocol 19

Summary of Reason for Premature Discontinuation

	Phase I		Phase I and II	
	Aredia	**Placebo**	**Aredia**	**Placebo**
For Adverse experience	28 (15%)	28 (14%)	45 (24%)	45 (23%)
Unsatisfactory Therapeutic Response	14 (8%)	25 (13%)	18 (10%)	36 (19%)
Use of Unacceptable Medication	3 (2%)	3 (2%)	5 (3%)	9 (5%)
Failure to Follow Appointment Schedule	3 (2%)	5 (3%)	4 (2%)	5 (3%)
Therapy Refusal	20 (11%)	23 (12%)	26 (14%)	28 (14%)
Lost to Follow-up	1 (<1%)	3 (2%)	2 (1%)	4 (2%)
Administrative Problem	1 (<1%)	5 (3%)	2 (1%)	6 (3%)
Abnormal Lab Values	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Death	26 (14%)	25 (13%)	38 (20%)	31 (16%)
Total Discontinued	96 (52%)	117 (60%)	140 (76%)	165 (85%)

Protocol 18(hormone therapy)

Summary of Reason for Premature Discontinuation

	Phase I		Phase I and II	
	Aredia	**Placebo**	**Aredia**	**Placebo**
For Adverse experience	19 (10%)	24 (13%)	36 (20%)	31 (16%)
Unsatisfactory Therapeutic Response	8 (4%)	14 (7%)	10 (6%)	19 (10%)
Use of Unacceptable Medication	1(<1%)	4 (2%)	6 (3%)	8 (4%)
Failure to Follow Appointment Schedule	2 (1%)	4 (2%)	3 (2%)	6 (3%)
Therapy Refusal	21 (12%)	24 (13%)	26 (14%)	33 (18%)
Abnormal Laboratory Value	0 (0%)	2 (1%)	0 (0%)	2 (1%)
Lost to Follow-up	0 (0%)	1 (<1%)	0 (0%)	2 (1%)
Administrative Problem	0 (0%)	2 (1%)	0 (0%)	4 (2%)
Death	18 (10%)	16 (9%)	34 (9%)	21(11%)
Total Discontinued	69 (38%)	91 (48%)	115(63%)	126(67%)

There has been no appreciable change in the reasons for going offstudy in either study from the phase I analysis (year 1) to the phase II analysis (year 2).

6.2 Efficacy: SMR

The results for skeletal morbidity rate are outlined in the following table from the submission:

Mean SMR (#SRE/year)

	Protocol 18 Phase I	Protocol 18 Phases I and II	Protocol 19+ Phase I	Protocol 19 Phase I and II
	SRE(-HCM)	SRE (-HCM)	SRE(-HCM)	SRE(-HCM)
Aredia	2.4	2.4	2.1	2.5
Placebo	3.5	3.6	3.3	3.7
P-value	0.051	.021	.004	<0.001

+ Exclude the Patient M6746B/116

The applicant also lists the morbidity rates for each of the components of the scale outlined in the following table from the application:

Mean SMR (#SRE/year)

	N	Pathologic Fractures	Vertebral Fractures	Non-Vertebral Fractures	Radiation To Bone	Surgery To Bone	Spinal Cord Compression	HCM
Protocol 19 (Phase I)								
Aredia	185	1.4	0.7	0.7	0.6	.10	.02	.09
Placebo	195	2.0	0.8	1.2	1.1	.17	.03	.56
P-Value		.368	.416	.037	.003	.025	.659	.024
Protocol 19 (Phase I and II)								
Aredia	185	1.6	0.7	0.9	0.8	.11	.04	.09
Placebo	195	2.2	0.9	1.3	1.3	.17	.05	.58
P-Value		.018	.778	.002	<0.001	.013	.419	.007
Protocol 18 (Phase I)								
Aredia	182	1.7	0.6	1.0	0.6	.10	.04	.05
Placebo	189	2.1	0.8	1.4	1.1	.12	.09	.14
P-Value		.108	.581	.744	.005	.570	.980	.143

Protocol 18 (Phase I and II)								
Aredia	185	1.6	0.7	0.9	0.6	.10	.05	.06
Placebo	189	2.2	0.9	1.4	1.2	.13	.10	.17
P-Value		.040	.429	.359	.013	.241	.734	.037

The next analysis is the proportions of patients with events. The following analysis summarizes the proportions of patients with any SRE (-HCM):

		Phase I		Phase I and II	
	N	SRE(-HCM)		SRE (-HCM)	
Protocol 19					
Aredia	185	79 (43%)		86 (46%)	
Placebo	195	110 (56%)		126 (65%)	
P-Value		.008		<0.001	
Protocol 18					
Aredia	182	85 (47%)		100 (55%)	
Placebo	189	104 (55%)		120 (63%)	
P-Value		.109		.094	

The following table derived from a table in the submission summarizes the proportions analysis of the individual components of the SRE endpoint:

	N	Pathologic Fractures	Vertebral Fractures	Non-Vertebral Fractures	Radiation To Bone	Surgery To Bone	Spinal Cord Compression	HCM
Protocol 19 (Phase I)								
Aredia	185	63 (34%)	42 (23%)	37 (20%)	36 (19%)	7 (4%)	4 (2%)	11 (6%)
Placebo	195	76 (39%)	37 (19%)	59 (30%)	65 (33%)	19 (10%)	3 (2%)	24 (12%)
P-value		.320	.371	.021	.002	.021	.651	.032
Protocol 19 (Phase I and II)								
Aredia	185	67 (36%)	47 (25%)	42 (23%)	51 (28%)	9 (5%)	4 (2%)	13 (7%)
Placebo	195	95 (49%)	51 (26%)	74 (38%)	88 (45%)	24 (12%)	7 (4%)	30 (15%)
P-value		0.014	.868	.001	<0.001	0.010	.407	.010

Protocol 18 (Phase I)								
Aredia	182	66 (36%)	37 (20%)	56 (31%)	39 (21%)	10 (6%)	4 (2%)	5 (3%)
Placebo	189	83 (44%)	42 (22%)	59 (31%)	63 (33%)	13 (7%)	4 (2%)	11 (6%)
P-value		.133	.656	.926	.010	.581	.957	.145
Protocol 18 (Phase I and II)								
Aredia	182	81 (45%)	50 (28%)	66 (36%)	56 (31%)	13 (7%)	7 (4%)	8 (4%)
Placebo	189	103 (55%)	58 (31%)	75 (40%)	76 (40%)	20 (11%)	6 (3%)	19 (10%)
P-value		.054	.496	.498	.058	.245	.725	.036

Time to first SRE is updated in the following table derived from a table in the submission:

Median Time to First SRE (months)

	Phase I		Phase I and II	
	SRE (-HCM)		SRE (-HCM)	
Protocol 19				
Aredia	13.1		13.9	
Placebo	7.0		7.0	
P-Value	.005		<0.001	
Protocol 18				
Aredia	10.9		10.9	
Placebo	7.4		7.4	
P-Value	.163		.118	

Notice that the difference between the arms became more significant from phase I to phase II in the chemotherapy group (Protocol 19) but the difference was still not significant in the hormonal group (Protocol 18).

6.3 Quality of life

Updated analyses of quality of life are summarized in the following 2 tables from the application.

Protocol 19 (Phase I and II)

	Mean Change from Baseline at the Last Measurement				
	N	Aredia	N	Placebo	Between-Treatment P-Value
Pain score	175	+0.93	183	+1.69	.050
Analgesic score	175	+0.74	183	+1.55	.009
ECOG	178	+0.81	186	+1.19	.002
Spitzer QOL	177	- 1.76	185	-2.21	.103

Protocol 18 (Phase I and II)

	Mean Change from Baseline at the Last Measurement				
	N	Aredia	N	Placebo	Between-Treatment P-Value
Pain score	173	+0.50	179	+1.60	.007
Analgesic score	173	+0.90	179	+2.28	<.001
ECOG	175	+0.95	182	+0.90	.733
Spitzer QOL	173	-1.86	181	-2.05	.409

Reviewer comment
The sponsor wishes to reword the section of the labeling by replacing

This last statement seems misleading since only of the patients actually completed phase II.

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6.4 Sponsor's efficacy conclusions:

The following are the sponsor's efficacy conclusions copied from page 42 of the ISE:

"These large well-controlled trials (Protocol 18 and 19) have demonstrated that:"

- "monthly intravenous infusions of 90 mg of Aredia, in addition to antineoplastic therapy, prevent skeletal-related episodes (SREs) in patients with osteolytic bone metastases.

- "the skeletal morbidity rate of having any SRE(±HCM) was significantly lower in Aredia patients compared to placebo patients in Protocols 18 and 19.

"Skeletal Events

- "By 24 cycles of monthly therapy, the skeletal morbidity rate (SMR) of having any SRE(±HCM) was significantly lower in patients in the Aredia treatment groups of both Protocol 18 (hormonal therapy) and 19 (cytotoxic chemotherapy) compared to patients in the respective placebo treatment groups.

- "By 24 cycles of monthly therapy, the proportions of Aredia patients having any SRE(±HCM), non-vertebral pathologic fractures, radiation to bone, surgery to bone, and events of hypercalcemia were significantly lower than those of placebo patients in Protocol 19. The proportion of patients having any SRE (+HCM), pathological fractures, radiation to bone, and events of hypercalcemia were lower ($p < .06$) on Aredia than placebo in Protocol 18.

- "By 24 cycles of monthly therapy, the times to first SRE(±HCM), pathological fractures, non-vertebral pathologic fractures, radiation treatments to bone, surgery to bone, and events of hypercalcemia were significantly longer for patients in the Aredia treatment group compared to patients in the placebo treatment group in Protocol 19. The time to first SRE (+HCM), radiation to bone and events of hypercalcemia was significantly longer for patients in the Aredia group compared to patients in the placebo group in Protocol 18.

"Quality of life variables

"In both Protocols 18 and 19, at the last measurement in Phase I and II, the changes from baseline in the bone pain score and analgesic score was significantly worse for placebo patients than for Aredia patients. Generally, mean changes from baseline in ECOG performance scores and quality of life scales were worse for placebo patients than Aredia patients in these trials."

6.5 Reviewer evaluation of proposed changes in labeling related to efficacy

Page 7 Proposed new wording:

Reviewer comment
The following wording should be substituted:

The efficacy results of the two double-blind cancer trials are shown in the table below:"

Page 9 Proposed change in table

Updated numbers are added to the efficacy table, and a new column of "fractures" is added.

Reviewer comment
The footnote needs to read:

In addition, the footnote should be marked at the corresponding p value rather than at the column heading.

Page 10 Proposed change in text and table

Previously the text describing the Pain, ECOG PS, etc. tests used the phrase '

Reviewer comment
This is misleading since, at most, one third of the patients finished the 2-year trial. The original wording in this paragraph should be retained.

Page 11 Removal of clause from indications section

During the 1996 ODAC deliberation of the breast cancer indication, it seemed that the was on the verge of voting against approval of Aredia for patients who were receiving hormonal therapy. The committee asked for a commitment from the FDA that a strong message would be placed in the label that the effect in patients receiving hormones seemed less than the effect in patients receiving chemotherapy. A clause was inserted in the INDICATIONS section of the label:

The applicant thinks this should be removed since the primary analysis (SRE-HCM) is now statistically significant for the hormonal group.

Reviewer Comment
If there had been a question of whether or not Aredia worked for the group receiving hormonal therapy, this indication would not have been approved. The question, however, was whether the small effect documented was worth the trouble and discomfort of monthly injections. The

additional events leading to detection of statistical significance now does not change the central point. My examination of the data and the evaluation by the Agency statistician, Sue-Jane Wang, PhD, do not demonstrate any change in the evidence regarding the relative treatment effect of Aredia in patients receiving hormonal therapy versus the effect in women receiving chemotherapy. This is most easily demonstrated in the more conservative analyses of 'proportions of patients with at least one event' and in analysis of 'time to first SRE.'

PROPORTIONS ANALYSIS						
	ONE YEAR			TWO YEARS		
	AREDIA	PLACEBO	RATIO (P/A)	AREDIA	PLACEBO	RATIO (P/A)
CHEMORX	43%	56%	1.30	46%	65%	1.41
HORMONE	47%	55%	1.17	55%	63%	1.14

The ratio of the number of patients with an event on placebo versus the number with an event on Aredia increases (more treatment effect) from 1.30 at the end of year one to 1.41 at the end of year two on the chemotherapy study, whereas this ratio slightly decreases (less treatment effect) going from year one to year two in patients receiving hormonal therapy. More simply, the difference between placebo and Aredia increased from 13% after year one to 19% after year two on the chemotherapy study. On the hormone therapy study the difference between placebo and Aredia was the same, 8%, after one year and after 2 years.

The time to SRE was highly significant for the chemotherapy study (difference in medians of 6.9 months and $p < 0.001$) but was still not significant for the hormone therapy study (difference in medians of 3.5 months and $p = 0.118$).

At the suggestion of the Oncologics Drugs Advisory Committee, a clause was required in the INDICATIONS section noting that the treatment benefit appeared to be less in patients receiving hormone therapy for breast cancer compared to patients receiving chemotherapy. The data presented above suggest that the difference in the benefit between these 2 groups after 2 years of treatment was as least as great as the difference noted after one year. This same conclusion was reached by the statistical reviewer. The clause in the indications section should be retained.

7.0 Safety

In the integrated summary of safety, the applicant updates safety data from the 2 pivotal trials. One important consideration bearing on reported toxicities was the type of anticancer treatment which patients received. Such therapy was balanced as outlined in the table in V 55, p 18 of the submission. The most common adverse experiences are outlined in the following table from the ISS:

Summary of Adverse Experiences (≥ 15%) by Treatment Group and Body System whether or Not Trial Drug Related				
	Aredia		Placebo	
	N	%	N	%
Total Patients	**367**	**100.0**	**386**	**100.0**
With Experiences	**364**	**99.2**	**380**	**98.4**
Pain Skeletal	257	70.0	291	75.4
Nausea	233	63.5	228	59.1
Vomiting	170	46.3	151	39.1
Fatigue	148	40.3	111	28.8
Anemia	145	39.5	142	36.8
Fever	140	38.1	124	32.1
Constipation	132	36.0	149	38.6
Dyspnea	129	35.1	94	24.4
Metastases	115	31.3	94	24.4
Anorexia	114	31.1	96	24.9
Diarrhea	108	29.4	118	30.6
Headache	100	27.2	91	23.6
Myalgia	97	26.4	87	22.5
Asthenia	94	25.6	74	19.2
Coughing	93	25.3	76	19.7
Insomnia	92	25.1	75	19.4
Pain Abdominal	89	24.3	70	18.1
Urinary Tract Infection	74	20.2	68	17.6
Upper Resp Tract Infection	72	19.6	78	20.2
Granulocytopenia	71	19.3	79	20.5
Dyspepsia	67	18.3	58	15.0
Anxiety	66	18.0	65	16.8
Dizziness	61	16.6	43	11.1
Sinusitis	59	16.1	40	10.4

Summary of Adverse Experiences (≥ 15%) by Treatment Group and Body System whether or Not Trial Drug Related (cont)				
	Aredia		Placebo	
	N	%	N	%
Arthralgia	56	15.3	49	12.7
Infection Viral	56	15.3	42	10.9
Pain	55	15.0	70	18.1
Pleural Effusion	55	15.0	35	9.1
Dehydration	54	14.7	61	15.8

Metastases were reported as an adverse event in 31% of the Aredia patients versus 24% of placebo. This difference was not statistically significant for the pooled results or for individual studies when evaluated by log rank test. Furthermore, this was not a prospective endpoint and it seems likely that there was informative censoring (i.e. patients likely to have documented metastases may have dropped out due to symptoms of those impending metastases). Fatigue (40% versus 29%) and dyspnea (35% versus 24%) were more common on Aredia.

As outlined in tables in volume 55 (not reproduced for this review), the incidences of cytopenias associated with chemotherapy, the incidences of infections and the incidences of renal problems were similar on the Aredia and placebo arms of the studies. Hypocalcemia was more common on Aredia (2.7% versus 1.3%) as were injection site reactions (5.4% versus 1.6%).

Conjunctivitis has been associated with Aredia use in the past. There was little evidence of an ophthalmic effect Aredia as summarized in the following table from the application:

	Protocols 18 and 19 Pooled			
	Aredia		Placebo	
	N	%	N	%
Vision Abnormal	20	5.4	13	3.4
Conjunctivitis	9	2.5	8	2.1
Xerophthalmia	5	1.4	5	1.3
Infection Ocular	4	1.1	0	0
Pain Eye	4	1.1	4	1.0
Corneal Keratopathy	1	0.3	0	0
Eye Abnormality	1	3.0	2	0.5
Edema Eye	1	0.3	2	0.5
Eye Complaints	0	0	2	0.5
Iritis	0	0	1	0.3
All Eye Complaints	38	10.4	33	8.5

Severe adverse reactions are listed in the following table from the application:

Severe Adverse Experiences by Body System				
	Protocols 18 and 19 Pooled			
	Aredia		Placebo	
	N	%	N	%
Body as a Whole	143	39.0	134	34.7
Musculoskeletal System	126	34.3	200	51.8
Digestive System	115	31.3	99	25.6
Hemic and Lymphatic System	96	26.2	96	24.9
Respiratory System	85	23.2	52	13.5
Cardiovascular	67	18.3	40	10.4
Nervous System	63	17.2	77	19.9
Infections and Infestations	28	7.6	25	6.5
Metabolic and Nutritional Disorders	26	7.1	27	7.0
Urogenital System	24	6.5	28	7.3
Skin and Appendages	18	4.9	26	6.7
Laboratory Abnormalities	15	4.1	19	4.9
Special Senses	4	1.1	5	1.3
Endocrine System	1	0.3	0	0

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These are broken down by category in the following table from the application:

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	Protocols 18 and 19 Pooled			
	Aredia		Placebo	
	N	%	N	%
Total Patients	367	100	386	100
Pain Skeletal	116	31.6	184	47.7
Metastases	62	16.9	43	11.1
Nausea	55	15.0	42	10.9
Anemia	50	13.6	43	11.1
Dyspnea	43	11.7	16	4.1
Vomiting	41	11.2	26	6.7
Granulocytopenia	39	10.6	50	13.0
Asthenia	37	10.1	33	8.5
Pleural Effusion	23	6.3	12	3.1
Fatigue	22	6.0	23	6.0
Dehydration	21	5.7	19	4.9
Headache	21	5.7	16	4.1
Thrombocytopenia	20	5.4	27	7.0
Constipation	18	4.9	22	5.7

The higher incidence of skeletal pain on the placebo arm is likely due to the treatment effect of Aredia. There was a higher incidence of severe dyspnea (12% vs 4%) on the Aredia arm. The reviewer evaluated the individual patient data for each these cases. In most cases the dyspnea appeared to be cancer related. Since patients stayed on the Aredia arms significantly longer (median of 421 days versus median of 327 days), the reporting of adverse events is expected to be biased against Aredia.

Toxicities associated with chemotherapy are outlined in the following excerpt from the submission:

	Protocols 18 and 19 Pooled			
Common Chemotherapy Toxicities				
	N	%	N	%
Vomiting	170	46.3	151	39.1
Anorexia	114	31.1	96	24.9
Stomatitis	49	13.4	48	12.4
Alopecia	45	12.3	57	14.8
Malaise	17	4.6	10	2.6
Cachexia	8	2.2	2	0.5

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ON ORIGINAL

The applicant analyzed adverse reactions by race and age. There were 324 whites, 21 blacks, and 22 other in the Aredia arms. There was no difference in event rates noted by race. There were 92 patients less than 50 years of age, 154 between years of age, and 121 greater than 65 years of age in the Aredia arms. The side effect profile was similar for the 3 age groups.

About a third of the patients died during the trial or within 30 days. The causes of death are outlined in the following table from the application:

APPEARS THIS WAY
ON ORIGINAL

	Aredia		Placebo	
	N	%	N	%
Total Patients	367	100.0	386	100.0
Deaths	128	34.9	115	29.8
Body as a Whole				
Sudden Death	0	0	1	0.3
Trauma	0	0	1	0.3
Cardiovascular System				
Cardiac Failure	3	0.8	2	0.5
Cardiomyopathy	0	0	1	0.3
Cardiorespiratory Arrest	1	0.3	0	0
Circulatory Failure	1	0.3	0	0
Embolism Pulmonary	1	0.3	2	0.5
Fibrillation Atrial	1	0.3	0	0
Myocardial Infarction	1	0.3	0	0
Digestive System				
Hepatic Failure	1	0.3	0	0
GI Hemorrhage	0	0	1	0.3
Infections and Infestations				
Sepsis	1	0.3	1	0.3
Nervous System				
Neurologic Disorder (NOS)	1	0.3	0	0
Suicide (Accomplished)	1	0.3	0	0
Respiratory System				
Respiratory Failure	3	0.8	0	0
Pneumonia	1	0.3	0	0
Urogenital System				
Breast Cancer	112	30.5	104	26.9
Hemolytic Uremic Syndrome	0	0	1	0.3
Uremia	0	0	1	0.3

There were no clear differences in causes of death. Deaths associated with respiratory failure were from breast cancer or sepsis associated with neutropenia from chemotherapy.

Evaluation of laboratory abnormalities demonstrated that 16.2% of the Aredia patients versus 11.8% of placebo patients had a grade 4 hemoglobin value recorded. The per cent of patients with neutropenia (11.4% versus 7.4%) was slightly higher on Aredia, but there was no difference in grade 4 thrombocytopenia (3.0% versus 2.9%). Grade 1 creatinine elevations were more common with Aredia (18.5% versus 12.3%). There was no difference between the study arms in the incidences of liver function test abnormalities.

7.1 Conclusion

The following summary statements from the applicant should be considered for inclusion in the labeling:

Reviewer comment

This seems at odds with the applicant's own summary. Grade 4 granulocytopenia occurred in 11.4% versus 7.4% of patients. This difference is actually borderline statistically significant. Regardless, the study was not designed to evaluate such differences and I am not comfortable with the statement that cytopenias were the same on the study arms.

I propose the following:

8.0 Summary of Labeling Recommendations

Labeling recommendations have been discussed throughout this review. In appendix II of this review all recommended labeling changes have been incorporated into a copy of the proposed labeling which was submitted by the applicant. The major changes to the proposed labeling are listed separately in appendix I of this review. I recommend approval of this efficacy supplement with these changes in the proposed labeling.

/S/

9/18/98

Grant A. Williams, MD
Medical Team Leader
Division of Oncology Drug Products

APPEARS THIS WAY
ON ORIGINAL

/S/

9/20/98

Robert Justice, MD
Acting Division Director
Division of Oncology Drug Products

CC: ORIG. NDA 20-927
HFD-150 / DIV FILE
G WILLIAMS
DCATTERSON
HFD-510/R.HEDIN
HFD-510/BSCHNEIDER
ORIG. NDA 20-036
HFD-510 / DIV FILE

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ON ORIGINAL

28 Page(s) Redacted

DRAFT LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020927, 020036/S015/S016

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

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.

9/18/97
Date

Ellen Cutler
Ellen Cutler
Assistant Director
Drug Regulatory Affairs

ORIGINAL

NOVARTIS

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NDA NO 20036 REF. NO. 015

SUBMITTED PER SLR

June 4, 1998

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products/ HFD-510
Attn: Document Control Room 14 B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

JUN 08 '98
HFD-510

NDA 20-036

AREDIA® (pamidronate disodium for injection) for Intravenous Infusion

"SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED"

/S/
6-15-98

FINAL PRINTED LABELING

Dear Dr. Sobel:

Reference is made to our New Drug Application (NDA) for Aredia (pamidronate disodium for injection). In accordance with 21 CFR 314.70 (c)(2)(i), we hereby submit a "Special Supplement-Changes Being Effected" to provide for the following revision to the ADVERSE REACTIONS section of our package insert.

This revision is based on information received through spontaneous adverse reaction reports. Copies of the reports are included.

The ADVERSE REACTIONS Subsection heading **Clinical Studies** is added for clarification.

Enclosed are 15 copies of Final Printed Labeling. This change will be implemented at the next printing or within six months, whichever is sooner.

If you have any questions or comments, please contact me at (973) 781-8180.

acceptable

/S/
6-19-98

Sincerely,

/S/
6-22-98

Ellen Cutler
Assistant Director
Drug Regulatory Affairs

/S/
6-19-98

Attachments: 1 Archival (including 15 copies of FPL)
1 Duplicate
Desk copy: Grant Williams, MD HFD-150

REVIEWS COMPLETED

DSC ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

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