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

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 Placebo P-Value	 185 189	 1.6 2.2 .040	 0.7 0.9 .429	 0.9 1.4 .359	 0.6 1.2 .013	 .10 .13 .241	 .05 .10 .734	 .06 .17 .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 Placebo P-Value	 185 195	 79 (43%) 110 (56%) .008		 86 (46%) 126 (65%) <0.001	
Protocol 18 Aredia Placebo P-Value	 182 189	 85 (47%) 104 (55%) .109		 100 (55%) 120 (63%) .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 Placebo P-value	 185 195	 63 (34%) 76 (39%) .320	 42 (23%) 37 (19%) .371	 37 (20%) 59 (30%) .021	 36 (19%) 65 (33%) .002	 7 (4%) 19 (10%) .021	 4 (2%) 3 (2%) .651	 11 (6%) 24 (12%) .032
Protocol 19 (Phase I and II) Aredia Placebo P-value	 185 195	 67 (36%) 95 (49%) 0.014	 47 (25%) 51 (26%) .868	 42 (23%) 74 (38%) .001	 51 (28%) 88 (45%) <0.001	 9 (5%) 24 (12%) 0.010	 4 (2%) 7 (4%) .407	 13 (7%) 30 (15%) .010

Protocol 18 (Phase I) Aredia Placebo P-value	182 189	66 (36%) 83 (44%) .133	37 (20%) 42 (22%) .656	56 (31%) 59 (31%) .926	39 (21%) 63 (33%) .010	10 (6%) 13 (7%) .581	4 (2%) 4 (2%) .957	5 (3%) 11 (6%) .145
Protocol 18 (Phase I and II) Aredia Placebo P-value	182 189	81 (45%) 103 (55%) .054	50 (28%) 58 (31%) .496	66 (36%) 75 (40%) .498	56 (31%) 76 (40%) .058	13 (7%) 20 (11%) .245	7 (4%) 6 (3%) .725	8 (4%) 19 (10%) .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 Placebo P-Value	13.1 7.0 .005		13.9 7.0 <0.001	
Protocol 18 Aredia Placebo P-Value	10.9 7.4 .163		10.9 7.4 .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

with

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

6.4 Sponsor's efficacy conclusions:

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

"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:

Page 9 Proposed change in table

Updated numbers are added to the efficacy table, and a new column of 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
This is deleted, and the sponsor added:

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) from 1.17 to 1.14 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

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

	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:

> "Many patients in these trials received chemotherapy. Of the toxicities commonly associated with chemotherapy, vomiting and anorexia were noted to occur slightly more frequently in the Aredia patients."

	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

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 51-65 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:

	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:

The applicant proposes the following statement in the adverse reactions section of 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

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