

**“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 ( $\geq 15\%$ ) by Treatment Group and Body System<br>whether or Not Trial Drug Related |            |              |            |              |
|--|------------|--------------|------------|--------------|
|  | Aredia     |              | Placebo    |              |
|  | N          | %            | N          | %            |
| <b>Total Patients</b>  | <b>367</b> | <b>100.0</b> | <b>386</b> | <b>100.0</b> |
| <b>With Experiences</b>  | <b>364</b> | <b>99.2</b>  | <b>380</b> | <b>98.4</b>  |
| 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 ( $\geq 15\%$ ) by Treatment Group and Body System<br>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:

| <b>Severe Adverse Experiences by Body System</b> |                                   |          |                |          |
|--|-----------------------------------|----------|----------------|----------|
|  | <b>Protocols 18 and 19 Pooled</b> |          |                |          |
|  | <b>Aredia</b>                     |          | <b>Placebo</b> |          |
|  | <b>N</b>                          | <b>%</b> | <b>N</b>       | <b>%</b> |
| 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:

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|                                    | Aredia |       | Placebo |       |
|------------------------------------|--------|-------|---------|-------|
|                                    | N      | %     | N       | %     |
| <b>Total Patients</b>              | 367    | 100.0 | 386     | 100.0 |
| <b>Deaths</b>                      | 128    | 34.9  | 115     | 29.8  |
| <b>Body as a Whole</b>             |        |       |         |       |
| Sudden Death                       | 0      | 0     | 1       | 0.3   |
| Trauma                             | 0      | 0     | 1       | 0.3   |
| <b>Cardiovascular System</b>       |        |       |         |       |
| 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     |
| <b>Digestive System</b>            |        |       |         |       |
| Hepatic Failure                    | 1      | 0.3   | 0       | 0     |
| GI Hemorrhage                      | 0      | 0     | 1       | 0.3   |
| <b>Infections and Infestations</b> |        |       |         |       |
| Sepsis                             | 1      | 0.3   | 1       | 0.3   |
| <b>Nervous System</b>              |        |       |         |       |
| Neurologic Disorder (NOS)          | 1      | 0.3   | 0       | 0     |
| Suicide (Accomplished)             | 1      | 0.3   | 0       | 0     |
| <b>Respiratory System</b>          |        |       |         |       |
| Respiratory Failure                | 3      | 0.8   | 0       | 0     |
| Pneumonia                          | 1      | 0.3   | 0       | 0     |
| <b>Urogenital System</b>           |        |       |         |       |
| 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.

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