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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-488

Medical Review(s)

NDA 21-488

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Medical Officer Review

Sponsor:	Atrix Laboratories 2579 Midpoint Drive Fort Collins, CO 80525
Drug:	Generic: leuprolide acetate Trade: Eligard™ 30mg
Route of administration:	Subcutaneous
Dosage form:	Depot suspension
Strength:	30 mg
Proposed indication:	Treatment of advanced prostate cancer
Related INDs/NDAs	IND# [redacted] NDA 21-343- Treatment of advanced prostate cancer NDA 21-379- Treatment of advanced prostate cancer

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Executive Summary:

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, the safety and efficacy of Eligard 30 mg has been established and this product should be approved for the indication "palliative treatment of advanced prostate cancer". No phase 4 requirements are recommended, and no changes are recommended for the proposed labeling (which is essentially the same as that for the currently marketed innovator product Lupron Depot 30 mg).

II. Summary of Clinical Findings

II A. Brief overview of the clinical program.

Orchiectomy or the administration of estrogens have been the primary mode of treatment of advanced prostate cancer. More recently, LH-RH agonists are offered as an alternative to these primary treatments when they are either not indicated or unacceptable to the patient.

Eligard, as a synthetic analog of the naturally occurring gonadotropic releasing hormone, LH-RH, is being proposed as a 30 mg subcutaneous injection given at 4-month intervals.

In support of NDA 21-488, the sponsor submitted a single phase 3, open-label, fixed-dose, study to evaluate the pharmacokinetics, safety, tolerance, and endocrine efficacy of two doses of Eligard 30 mg in 90 patients with advanced prostate cancer.

Reviewer's Comment: This reviewer believes that in view of the fact that existing data on both safety and efficacy are available from an essentially identical marketed product (Lupron), the data from a single trial, as is hereby submitted, is regarded as being sufficient for this NDA.

II B. Efficacy

The primary efficacy endpoint for this clinical trial was the reduction of baseline levels of testosterone to castrate levels, and maintenance of castrate levels for the duration of the two administered doses of drug. Castrate levels of testosterone were achieved by Day 28 in 85/89 remaining patients (96%) and by Day 42 in 89/89 (100%) remaining patients. Breakthrough of testosterone levels above castrate was seen in 3 patients. One patient, castrate by Day 14, exhibited breakthrough on Day 113 (serum T of 53 ng/dL) and was castrate from Day 115 through Day 224. Two patients who failed to attain castrate levels by Day 28 also had breakthroughs on Days 112 and 113. One of these 2 patients was castrate again by Day 115 through Day 224, and the other had breakthrough levels from Day 112 to Day 133 and again on Day 224.

The pharmacokinetics and pharmacodyamics of the Eligard formulation were similar to those seen with the commercially available Lupron formulation.

The data from this clinical trial demonstrated that Eligard 30 mg administered at 4-month intervals to patients with advanced prostate cancer could reliably achieve the primary efficacy endpoint, i.e., attaining and maintaining castrate levels of total serum testosterone.

II C. Safety

Data regarding clinical adverse events (AE's) were derived from the single phase-3 clinical trial enrolling 90 patients who received at least one dose of drug. Eighty-five patients received 2 doses of drug. There were no reported deaths, and of the 195 treatment related AE's seen in 77 patients, only 4 were regarded as severe. Two patients withdrew from study due to AE's; one on Day 105 because of hot flashes and fatigue, and the other on Day 115 because of hot flashes, night sweats, and decreased libido. The most common treatment related AE's were hot flashes (74%), administration site reactions (44%), fatigue (21%), and dizziness (14%). There were no clinically significant changes in vital signs, and hematology and clinical chemistry values were generally within normal limits.

Reviewer's Comment: In the reviewer's opinion, the commonly reported AE's reflect the pharmacologic activity of the drugs in this class. Other reported AE's were comparable to those reported with similar drugs. The safety profile of Eligard 30 mg is not of concern.

II D. Dosing, Regimen, and Administration Issues.

The dose used in this clinical trial was 30 mg of Eligard administered as a subcutaneous injection at 4-month intervals. A total of 2 doses were administered per patient. This dose is the same as that of the marketed innovator product (Lupron Depot 30 mg) which is administered as an intramuscular injection.

II E. Use in Special Populations

Gender: Eligard is indicated in the palliative treatment of advanced prostate cancer and should not be used in women.
Pediatric: Safety and effectiveness of Eligard have not been established in pediatric patients. A full waiver from pediatric use labeling information has been requested by the sponsor. In the opinion of the reviewer, this waiver should be granted.
Elderly: The inclusion criteria for the study population in this phase-3 trial called for patients between the ages of 40 and 85. There are no data to suggest concern using this product in the elderly.
Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of Eligard 30 mg was studied in 18 White, 4 Black, and 2 Hispanic patients. The mean serum leuprolide concentrations were similar.
Renal and Hepatic Insufficiency: The pharmacokinetics of Eligard 30 mg in liver and kidney impaired patients have not been determined.

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Clinical Review

1. Introduction and Background

1.1. Proposed trade name of drug, class, proposed indication, dose and regimen.

Eligard is a synthetic analog of the naturally occurring gonadotropic releasing hormone LH-RH being proposed as palliative treatment for advanced prostate cancer. It is classified as a LH-RH agonist and administered every 4 months as a 30 mg subcutaneous injection.

1.2. State of armamentarium for indication.

Orchiectomy or the administration of estrogens had been the primary mode of treatment for advanced prostate cancer, and LH-RH agonists are offered as an alternative to these primary treatments when they are either not indicated or un-acceptable to the patient.

1.3. Milestones in product development.

IND [redacted] was originally filed on March 20, 2000. The sponsor requested a CMC pre-NDA teleconference which was held on March 13, 2002 and was basically devoted to issues of product stability. This product represents the third formulation for leuprolide acetate that the sponsor has submitted, the others being 7.5mg (submitted December1998) and 22.5 mg (submitted March, 2000).

1.4. Foreign marketing history.

Eligard 30 mg has not been marketed outside of the United States.

1.5. Important issues with pharmacologically related agents.

A transient rise in serum testosterone levels during the first week of treatment may cause a worsening of symptoms or the occurrence of additional signs and symptoms of prostate cancer. Additional adverse events reported in 5% or more of patients treated with leuprolide acetate include vasodilation (flushes), nausea, weight gain, myalgia, decreased libido, urinary frequency, erectile dysfunction, asthenia, and pain on injection.

2. Significant findings from Chemistry, Pharmacology, Toxicology, and Statistics.

There are no unresolved chemistry, pharmacology, toxicology or statistical issues.

3. Human Pharmacokinetics and Pharmacodynamics.

3.1. Pharmacokinetics

An evaluation of both the pharmacokinetics and pharmacodynamics of Eligard 30 mg was performed in a subset of 24 patients under treatment and monitored over 2 consecutive 4 month intervals. Following the first dose, serum leuprolide was measured by a validated [redacted] assay at hours 2, 4, and 8, and Days 1, 2, 3, 7, and weekly for 15 weeks. Identical monitoring followed the second dose (Day 112). During the initial ("burst") phase, leuprolide concentrations rapidly rose to levels > 100 ng/mL and then rapidly declined over the next several days. During the second ("plateau") phase, mean leuprolide concentrations remained between 0.1 and 1.0 ng/mL throughout most of each dosing interval. Individual levels ranged from <0.05 to 5.8 ng/mL. Bioavailability was >90% and there was no evidence of accumulation after repeated dosing. Leuprolide concentrations and AUCs were similar after each dose, and mean concentrations at the end of each interval were 0.08 ng/mL and 0.07 ng/mL, respectively.

3.2. Pharmacodynamics

As a LH-RH agonist, Eligard acts as a potent inhibitor of gonadotropin secretion. Following an initial increase of luteinizing hormone (LH) and of follicle stimulating hormone (FSH), continuous exposure to drug results in castrate levels of testosterone within 2-4 weeks. In response to the "burst" and "plateau" phases describe above, mean serum testosterone levels rose to 588 ± 40 ng/dL on Day 3, fell to 31.7 ± 4.2 ng/dL on Day 21, and remained between 6-12 ng/dL for the duration of the study. Individual testosterone levels fell below castrate levels (≤ 50 ng/dL) by Day 21 in 18/24 patients, and castrate levels were achieved in the remaining 6 patients by the time of the next sampling (Day 28). Except for a single patient who had a breakthrough value of 53 ng/dL was, all patients in this pK subgroup remained clinically suppressed once castrate levels were achieved.

4. Description of Clinical Data and Sources.

The following materials were reviewed: 1) Integrated summary of pharmacokinetic and pharmacodynamic aspects of the pivotal phase 3 clinical study from the NDA, including the bioanalytic methods. 2) Description and analysis of the single clinical study (AGL0001) in the treatment of prostate cancer, integrated summary of safety, and the integrated summary of efficacy from the NDA. 3) Documentation of statistical methods from the NDA. 4) Adverse events data from the NDA.

5. Clinical Review Methods.

The pharmacokinetics in the 24-patient pK subgroup were reviewed in detail and is attached as appendix A. Additional pharmacodynamic information from this subgroup is attached as appendix B. The pivotal phase 3 clinical trial (AGL0001) was reviewed in detail and is attached as appendix C.

There were no issues requiring a DSI audit.

Adequate documentation was submitted to comply with financial disclosure by the sponsor and the clinical investigators.

6. Integrated Review of Efficacy.

6.1. Introduction:
The sponsor presented evidence of efficacy from an open-label phase 3 clinical trial of this Eligard 30 mg formulation's ability to suppress serum testosterone levels.

6.2. General Approach:
The efficacy database consists of a single open-label trial at 22 centers in the United States, conducted from January through November 2001, and enrolling 90 patients.

6.3. Review of the Clinical Trial:
The objective of the trial and the primary efficacy endpoint was attaining a reduction of baseline testosterone levels to castrate levels (≤ 50 ng/dL) by Day 28, and maintaining castrate levels for the duration of treatment. The patients enrolled (age range 53-84) had either histologically or cytologically confirmed prostate cancer (stages A2, B, C, or D) or a rising PSA after failed local therapy, and were candidates for androgen ablative therapy. Study entry criteria included a baseline testosterone > 150 ng/dL and a WHO/ ECOG performance status of 2 or less. All patients signed an informed consent form, and were required to have adequate renal and hepatic function by defined standard laboratory values. Exclusion criteria included patients with any prior prostate cancer therapy within 2 months of baseline, life-threatening renal, hepatic or cardiovascular disease, evidence of brain metastasis, and symptoms of spinal cord compression or ureteral obstruction. Treatment began with a dose of Eligard 30 mg on Day 0 and repeated on Day 112, with scheduled follow-up visits for efficacy measures of serum testosterone and LH levels, clinical laboratory measurements, and collection of adverse event information. A subset (24 patients) participated in a pharmacokinetic study of leuprolide. Data were analyzed on the intent-to-treat population using SAS statistical software.

Except for one patient who withdrew from the study on Day 14 because of severe depression and suicidal intent (Patient **#0401**), 85 of the remaining 89 were castrate by Day 28 (96%), and the other 4 were castrate by Day 42 (100%). "Castrate" was defined as testosterone levels ≤ 50 ng/dL for at least 2 consecutive timepoints 1 week apart. An additional 6 patients withdrew from study; **#1602** (Day 168, moved away), **# 1606** (Day 154, liver metastasis), **#1710** (Day 105, hot flashes and fatigue), **#1802** (Day 98, study interfered with vacation plans), **#2304** (Day 112, status post heart valve surgery), **#1909** (Day 112, ho5t flushes, night sweats). One patient (**#1004**) was lost to follow-up as of Day 182.

Breakthrough (defined as a single level of testosterone > 50 ng/dL after castrate) was seen in three patients: # 0201 was castrate on Day 42, and from Day 112 through Day 115 testosterone levels were > 50 ng/dL, then returned to castrate for the remainder of the

study. # 1002 was castrate on Day 14, had a breakthrough on Day 113, then remained castrate from Day 115 to end of study. # 1604 was castrate on Day 35, had a breakthrough on Day 112 which lasted 21 days, was again castrate until Day 224 (end of study) when there was another breakthrough.

Reviewer's comment: *Despite the breakthroughs seen in three patients, the attainment of castration in 94% of patients by Day 28 and maintenance of castration by 96% of patients at the end of study suggests satisfactory efficacy, at least comparable to similar available products.*

6.4 Efficacy Conclusions.
This single open-label trial has demonstrated that Eligard 30 mg depot suspension administered at 4-month intervals could reliably achieve the primary efficacy endpoint of reducing baseline testosterone levels to castrate levels of serum testosterone in patients with advanced prostate cancer. It is the opinion of this reviewer, that from an efficacy standpoint, Eligard 30 mg should be approved.

7. Integrated Review of Safety

7.1. Brief Statement of Findings.
Adverse events (AE's) data were derived from all 90 patients who received at least one dose of study drug. The severity of the event was determined by the patient. Thje relationship of the event to treatment was determined by the investigator. Of the195 treatment-related AE's reported by 77 patients, 4 were classified as severe and the remainder as mild or moderate. No deaths were reported. Two patients withdrew from study due to AE's: one (decreased libido, night sweats and hot flashes) on Day 115 without receiving the second dose, and the other (hot flashes and fatigue) on Day 105. There were no clinically significant changes noted in vital signs. The most common treatment-related AE's were hot flashes (74%), administration site reactions (44%), fatigue (21%), and dizziness (14%). Hematology and clinical chemistry values were generally within normal limits for all study timepoints.

Reviewer's comment: *In the reviewer's opinion, the reported AE's reflect the pharmacologic activity of the compounds in this class of drugs. The safety profile of Eligard 30 mg is not of concern.*

7.2 Materials Utilized in the Review.
As previously noted, all materials available for review were derived from the single phase-3 clinical trial including the pharmacokinetic and pharmacodynamic data from the initial 24 patients, and the integrated summaries of safety and efficacy data.

7.3 Extent of Exposure.
Drug exposure in study AGL0001 was in 90 patients for one injection, of whom 85 received a second injection per protocol.

7.4 Safety Findings from the Clinical Study.

7.4.A. Clinical Safety Data

Clinical AE's have been described previously. The safety profile from this trial did not reveal any outstanding concerns, and the safety data is further described in Table 1 below:

Table 1. Adverse Events seen in >5% of Patients. (all causalities)	Total #	%
System Organ Class		
Vascular disorders		
Hot flushes	67	74
Hypertension	9	10
General disorders and injection site conditions		
Injection site burning	31	34
Fatigue	19	21
Injection site paresthesia	5	6
Fever	5	6
Musculoskeletal and connective tissue disorders		
Back pain	16	18
Arthralgia	12	13
Limb pain	10	11
Muscle cramps	5	6
Peripheral swelling	5	6
Gastrointestinal disorders		
Diarrhea	8	9
Nausea	6	7
Constipation	5	6
Dyspepsia	5	6
Pharyngeolaryngeal pain	5	6
Renal and urinary disorders		
Urinary frequency	9	10
Nocturia	8	9
Bacteruria	6	7
Hematuria	6	7
Infections		
Nasopharyngitis	11	12
Upper respiratory infection	6	7
Urinary tract infection	5	6

Nervous system disorder		
Dizziness	14	16
Headache	10	11
Paresthesia	5	6
Insomnia	5	6
Skin disorder		
Rash	6	7
Hematology and blood chemistry		
Elevated creatinine phosphokinase	6	7
Neoplasms		
Basal cell carcinoma	5	6

Reviewer's comment: *It should be noted that the above listed AE's represent both treatment-related and unrelated events. Many of these were not causally related.*

7.4.B. Safety Update

Safety Update Report (November 27, 2002) involved one patient who was diagnosed with two bladder tumors on the day following study completion. He underwent transurethral resection of the tumors. The event was categorized as mild, and unrelated to study drug.

8. Dosing, Regimen, and Administration Issues.

The dose used in this clinical trial was 30 mg of Eligard administered as a subcutaneous injection at 4-month intervals. A total of 2 doses were administered per patient. This dose is the same as that of the marketed innovator product (Lupron Depot 30 mg) which is administered as a intramuscular injection.

9. Use in Special Populations

Gender: Eligard is indicated in the palliative treatment of advanced prostate cancer and should not be used in women.
Pediatric: Safety and effectiveness of Eligard have not been established in pediatric patients. A full waiver from pediatric use labeling information has been requested by the sponsor. In the opinion of the reviewer, this waiver should be granted.
Elderly: The inclusion criteria for the study population in this phase 3 trial called for patients between the ages of 40 and 85. There are no data to suggest concern using this product in the elderly.

Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of Eligard 30 mg was studied in 18 White, 4 Black, and 2 Hispanic patients. The mean serum leuprolide concentrations were similar in the 3 groups.
Renal and Hepatic Insufficiency: The pharmacokinetics of Eligard 30 mg in liver and kidney impaired patients have not been determined.

10. Conclusions, Recommendations, and Labeling

10.1 Conclusions Regarding Safety and Efficacy.

This reviewer concludes that the submitted clinical data support the safety and efficacy of Eligard 30 mg for the palliative treatment of patients with advanced prostate cancer.

10.2 Recommendations on Approvability.

From a clinical perspective, Eligard 30 mg could be approved for the clinical indication "palliative treatment of advanced prostate cancer". However, the reviewer acknowledges that chemistry , manufacturing , and controls deficiencies may preclude approval.

10.3 Labeling

The proposed labeling is essentially the same as that for the currently marketed innovator product (Lupron Depot 30 mg), and no changes are recommended.

11. Appendices.

11A. Pharmacokinetic Study (within Study AGL0001)

A subset of 24 patients, all of whom received both doses of drug, underwent pharmacokinetic (PK) analyses. Patients were 75% white, 17 % black, and 8 % Hispanic. They had a mean age of 72 and a mean weight of 196. Serum samples were obtained at 40 intervals throughout the study and drug concentrations were measured by a validated method using [redacted] PK parameters were calculated using standard PK methods. Areas under the serum drug concentration vs. time curve (AUC) were determined by linear trapezoidal integration.

The PK profile of leuprolide after each administration of drug was multiphasic. Mean serum concentrations rose rapidly after each dose, then declined rapidly over the next several days (burst phase). Drug levels then declined more slowly for the balance of each dosing interval (plateau phase), from Day 3 to Day 112.

Levels of <0.05 ng/mL were observed one or more times in 11/24 patients after the first dose, and in 18/24 patients after the second dose. The mean (median) Day 112 levels in 19/24 patients were 0.066 ± 0.004 ng/mL (0.057 ng/mL), and the mean (median) Day 224 levels in 14/22 patients were 0.059 ± 0.006 ng/mL (0.05 ng/mL).

Further PK details and discussion may be seen in the biopharmacologist's section of this NDA review.

11 B. Pharmacodynamic Information from the pK subgroup

In AGL0001, serum testosterone (T) levels were measured concomitantly by a validated RIA assay performed after sample extraction and —— —— . This assay had a lower limit of quantitation of .– ıg/dL.

Of note, following the first dose of drug, the mean serum T levels rose to 588 ± 40 ng/dL on Day 3, fell to 31.7 ± 4.2 ng/dL on Day 21, and remained between 6-12 ng/dL for the remainder of the study.

Serum T was suppressed to below castrate levels by Day 21 in 18/21 patients in which a Day 21 sample was obtained. All other patients in this subgroup attained T suppression below castrate at the time of the next sample on Days 28, 35, or 42. Serum T did not increase in response to the second dose of drug, and castrate levels continued for the second dose interval in all but one patient (#1002) whose level was 53 ng/dL one day after the second dose. T levels returned to castrate for the balance of the dosing interval. This patient also had the lowest observed plateau phase AUC after the first dose, and represents the only breakthrough in this subset of patients.

11 C. Clinical Trial AGL0001

This was an 8-month investigation of 2 doses of Eligard 30 mg administered at 4-month intervals to patients ages 53-84 with prostate cancer stages A2, B, C, or D. Ninety patients were enrolled in the trial, which had the primary objectives of 1) evaluating the safety and tolerance of the administered drug; 2) evaluating serum T levels as a measure of efficacy; and 3) determining the PK profile of drug in a subset of 24 patients.

The trial was a fixed-dose, open-label, non-comparative study. Twenty-two investigational centers participated.

Inclusion Criteria

1. Signed informed consent.
2. Outpatients between ages 40-85 with histologically or cytologically proven adenocarcinoma of the prostate, stages A2, B, C, or D, or a rising PSA after failed local therapy.
3. Candidates for androgen-ablative therapy.
4. Life expectancy of at least 1 year.
5. WHO/ECOG performance status of 0, 1, or 2.
6. Serum creatinine ≤ 1.6 times the upper limit of normal (ULN) for the laboratory at screening; and bilirubin ≤ 1.5 times the ULN, and SGOT and SGPT ≤ 2.5 times the ULN at screening.

Exclusion Criteria

1. No evidence of brain metastasis, spinal cord compression, or urinary tract obstruction.
2. Serum T levels below 150 ng/dL at screening.
3. Medical or radiological prostate cancer treatments within 2 months of baseline.
4. Surgical treatment of prostate cancer within 2 weeks of baseline.
5. Hormonal therapy for prostate cancer within 3 months of baseline.
6. Prior treatment with any Eligard formulation.
7. Prior orchiectomy, hypophysectomy, or adrenalectomy.
8. Prior use of investigational drug, device or biologic within 5 half-lives of its action or 3 months of baseline, whichever was longer.
9. Use of finasteride within 2 months of baseline.
10. Anticipated need for any other concomitant therapy for prostate cancer for the duration of the study.
11. Use of alternative medical therapies with estrogenic or anti-androgenic effects within 3 months of baseline.
12. Ketoconozole or glucocorticoids within 2 months of baseline.
13. Hematological parameters outside 20% of the upper and lower limits of normal for the laboratory at screening.
14. Diagnosis of any cancer without a history of stability/remission within 5 years of baseline, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin.
15. Significant cardiac or vascular disease within 6 months of baseline.
16. Uncontrolled hypertension of symptomatic hypotension within 3 months of baseline.
17. Insulin-dependent diabetes or other serious intercurrent illness that would pose unreasonable risk or interfere with compliance with the protocol.
18. History of drug and/or alcohol abuse within six moths of baseline.
19. Patients on anticoagulation or antiplatelet drugs must have been receiving a stable dose for 3 month of baseline, and not have a prothrombin or partial thromboplastn time outside of the normal laboratory range.
20. Known hypersensitivity to LH-RH agonists or drug formulation ingredient.
21. History of anaphylaxis, dermatographism, or skin disease that would interfere with injection site evaluation.
22. Any immunization within 4 weeks of baseline (flu shots within 2 weeks).
23. Receipt or donation of blood or blood products within 2 months of baseline.

Study Procedures

A medical history was obtained at the screening visit and a physical examination, including vital signs, was performed. The baseline visit occurred at a minimum of 3 days and a maximum of 16 days after screening. Baseline and all subsequent protocol scheduled evaluations and blood samplings included interviews concerning use of concomitant medications and reports of AE's.

PK analyses were performed on a subset of 24 patients.

The primary efficacy variable, serum T concentrations, and a secondary measure of efficacy, serum LH concentration, were determined at frequent protocol mandated intervals.

All clinical laboratory measurements were performed at an accredited central clinical laboratory, and evaluations of T, LH, and leuprolide samples were performed at specific central reference laboratories.

Disposition of Study Patients

Ninety patients were enrolled and received at least 1 dose of drug. Eighty-five (85) of the original 90 received two doses as per schedule. Mean age was 73.5 (range, 53-84). Mean weight was 196 pounds (range 133-313). Seventy –nine percent (79%) were white, 11% were black, and 9 % were Hispanic.

One patient (#1909) was withdrawn from study on Day 112, prior to receiving the second dose, due to AE's considered related to drug (loss of libido, hot flashes, night sweats).

Six patients voluntarily withdrew from study (Patients # 0401, 1602, 1606, 1710, 1802, and 2304). Patient #0401 withdrew following Day 14 because of suicidal intentions and hospitalization. Patient #1602 withdrew after Day 168 because of moving from area. Patient #1606 withdrew after Day 154 following diagnosis of liver metastasis. Patient #1710 withdrew after Day 105 because of hot flashes, fatigue and interference with vacation plans. Patient #1802 withdrew after Day 95 because of interference with vacation plans. Patient #2304 withdrew after Day 112 because of poor health following heart valve surgery.

One patient was lost to follow-up (Patient #1004).

Efficacy Evaluation

Efficacy data was analyzed by the sponsor using an intent-to-treat dataset and an "observed cases" dataset. The ITT dataset uncluded all 90 patients enrolled, except for the those who withdrew prior to collection of any efficacy data. In the analysis of T suppression, the intent-to-treat principle involved carrying forth data to the end of study for patients who withdrew. The observed-cases dataset did not carry forth data past the time of withdrawal. Again, efficacy analysis was performed on both datasets, and is summarized in Table 2 (intent-to-treat) and Table 3 (observed-cases) below. These tables are derived from the sponsor's summary efficacy analyses tables in the NDA.

According to the sponsor, the primary endpoint for this study was the proportion of patient who attained castrate serum T concentrations by Day 28. Secondary endpoints included the cumulative proportion of patients maintaining castrate levels of T (no breakthroughs), proportion of patients not maintaining suppression, performance status, assessments of pain, and urinary signs and symptoms. Mean concentrations of T and LH were also summarized.

Table 2. Serum T Measures (Intent To Treat Dataset), All Centers

	Day 28 # / %	Day 42 # / %	Day 56 # / %	Day 84 # / %	Day112 # / %	Day 168 # / %	Day 224 # / %
# of patients	90	90	90	90	90	90	90
# suppressed	85 / 94.4	89 / 98.9	89 / 98.9	89 / 98.9	88 / 97.8	89 / 98.9	88 / 97.8
# cumulative suppression	84 / 93.3	86 / 95.6	86 / 95.6	86 / 95.6	86 / 95.6	88 / 97.8	88 / 97.8
# suppression not maintained	0 / 0	0 / 0	0 / 0	0 / 0	1 / 1.1	0 / 0	1 / 1.1

Table 3. Serum T Measures (Observed -Cases Dataset), All Centers

	Day 28 # / %	Day 42 # / %	Day 56 # / %	Day 84 # / %	Day 112 # / %	Day 168 # / %	Day 224 # / %
# of patients	89	89	89	89	88	84	82
# suppressed	85 / 95.5	89 / 100	89 / 100	89 / 100	87 / 98.9	84 / 100	81 / 98.8
# cumulative suppression	84 / 94.4	86 / 96.6	86 / 96.6	86 / 96.6	85 / 96.6	83 / 98.8	81 / 98.8
# suppression not maintained	0 / 0	0 / 0	0 / 0	0 / 0	1 / 1.1	0 / 0	1 / 1.1

***Reviewer's comment**: As seen in Tables 2 and 3, satisfactory efficacy endpoints were achieved when the data was analyzed in the ITT and observed-cases populations. The reviewer is of the opinion that the efficacy of Eligard 30mg is satisfactory.*

The reader is referred to pages 7 and 8 of this review where efficacy is described further.

A pK analysis of serum leuprolide was performed in a subset of 24 patients and has been summarized on pages 6 and 11 of this review.

Leutenizing Hormone (LH) Concentrations.

The mean LH concentration at baseline was 7.5 ± 0.7 MIU/mL. Concentrations increased until a maximum mean concentration of 37.8 ± 2.8 MIU/mL was reached at hour 4 post-baseline By Day 7 the mean concentration had decreased to below baseline levels and consistently dropped to 0.1MIU/mL at Day 91. Concentrations rose slightly to 0.4 MIU/mL

at hour 4 on Day 112 (immediately following dose 2) and then decreased steadily for the remainder of the study to 0.1 MIU/ml on Day 224.

Prostate Specific Antigen (PSA) Levels
Mean PSA levels at baseline were 13.2 ± 2.0 ng/mL, and decreased to 1.3 ± 0.3 ng/mL on Day 224 (86% reduction). Of the 66/88 patients who had elevated serum PSA at baseline, only 4/81 still had elevations at Day 224. All patients who had a normal PSA level at baseline continued normal at end of study.

Safety Evaluation.
There were no deaths reported and all-causality AE's are described on pages 8-10 of this review. Treatment-related AE's are described in the following Table 4.

Table 4. Patients with Treatment-Related AE's by MedDRA System Organ Class

MedDRA Term	Number // %	
Vascular disorders		
Hot flashes	66 //	73
Hypertension	1 //	1
General and administration site disorders		
Injection site burning	20 //	22
Fatigue	12 //	13
Injection site paresthesia	5 //	6
Injection site pain	3 //	3
Injection site erythema	2 //	2
Injection site inflammation	1 //	1
Lethargy	1 //	1

Reproductive and breast disorders	Number //	%
Testicular atrophy	4 //	4
Gynecomastia	2 //	2
Testicular pain	2 //	2
Breast enlargement	1 //	1
Erectile dysfunction	1 //	1
Hydrocele	1 //	1
Penile size reduced	1 //	1
Skin and subcutaneous tissue disorders		
Clamminess	4 //	4
Night sweats	3 //	3
Alopecia	2 //	2
Hair growth abnormal	1 //	1
Sweating increased	1 //	1

(Table 4 continued)

	Number	//	%
Renal and urinary disorders			
Nocturia	2	//	2
Frequency	2	//	2
Urgency	1	//	1
Renal impairment	1	//	1
Incontinence	1	//	1
Nervous system disorders			
Dizziness	4	//	4
Paresthesia	1	//	1
Psychiatric disorders			
Libido decreased	2	//	2
Depression	1	//	1
Insomnia	1	//	1
Loss of libido	1	//	1
Suicidal ideation	1	//	1
Musculoskeletal disorders			
Myalgia	2	//	2
Muscle atrophy	1	//	1
Limb pain	1	//	1
Gastrointestinal disorders			
Nausea	2	//	2
Dry mouth	1	//	1
Laboratory investigations	Number	//	%
Alanine aminotransferase increased	1	//	1
Aspartate aminotransferase increased	1	//	1
Blood urea increased	1	//	1
Lymphocyte count decreased	1	//	1
White cell count decreased	1	//	1
Cardiac disorders			
Palpitations	1	//	1
Metabolism and nutrition disorders			
Appetite decreased	1	//	1
Respiratory disorders			
Dyspnea	1	//	1

***Reviewer's Comment**: As seen in Table 4, except for hot flashes and injection site reactions, AEs were relatively rare for most conditions reported. The majority were seen in only one patient each. In the opinion of this reviewer, there appear to be no safety concerns with the use of this formulation.*

For additional details relative to application site reaction, the reader may refer to the medical team leader's review.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Harry Handelsman
1/27/03 11:27:02 AM
MEDICAL OFFICER

Mark S. Hirsch
1/27/03 01:33:51 PM
MEDICAL OFFICER
I concur.

Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg
Atrix Laboratories, Inc.
NDA 21-488

Safety Update Review

The Medical Officer's review contains the safety update review.

AR 2/11/03

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NDA 21-488

Microbiology (Efficacy Review)

This new drug application did not require a microbiology efficacy review.

ak 2/11/03