

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

MEDICAL REVIEW

NDA 21-731

Supervisory Medical Officer's Memorandum

Date submitted: February 13, 2004

Date received: February 18, 2004

Memo draft completed: December 10, 2004

Drug product (tradename): ELIGARD® 45 mg

Drug product (non-proprietary): leuprolide acetate for injection

Dose: 45 mg every 6 months

Route: subcutaneous injection

Indication: palliative treatment of advanced prostate cancer

Sponsor: Atrix Laboratories, Fort Collins, CO

Related INDs/NDAs: IND #64,779 (6-month formulation) and NDAs 21-343 (1-month formulation), 21-379 (3-month formulation) and 21-488 (4-month formulation).

I. Executive summary:

The purpose of this medical team leader's memo is to provide a regulatory recommendation for NDA 21-731. I recommend that ELIGARD 45 mg should be approved for the indication of palliative treatment of advanced prostate cancer. There are no unresolved issues.

II. Clinical and regulatory background:

ELIGARD 45mg is the fourth drug product in this sponsor's leuprolide product line.

ELIGARD is a novel subcutaneous formulation of leuprolide intended for palliative treatment of men with advanced, hormonally-sensitive prostate cancer. The one-month formulation (7.5 mg) was approved in January 2002 under NDA 21-343. ELIGARD 22.5mg, the 3-month formulation, was approved in July 2002 under NDA 21-379. ELIGARD 30 mg, the 4-month formulation, was approved in February 2003 under NDA 21-488. Finally, the original IND for this newest formulation, ELIGARD 45 mg (every 6-month), was submitted to this Division on June 29, 2002.

This 6-month formulation will be the first commercially available 6-month depot leuprolide preparation. Leuprolide can be administered as a non-biodegradable one-year implant as either Duros (ALZA) or as Vantas (Valera Pharmaceuticals). However, ELIGARD 45mg would be the longest-acting biodegradable preparation that does not require removal from the body at the end of the dosing interval. Currently, the longest acting biodegradable preparations are for 4 months duration. For many prescribers and patients, this difference in dosing interval is an important benefit in terms of convenience and quality of life during palliative care for advanced cancer.

It should also be noted that Lupron Depot® (TAP) is an intramuscular injection and Zoladex® (AstraZeneca) is a subcutaneous "implant". Atrix contends that ELIGARD may be an improvement upon these formulations since it is a subcutaneous suspension able to be delivered with a fine-gauge, fairly short needle. The volume of this 45mg formulation is 0.375 mL, actually a smaller volume than the ELIGARD 22.5 mg, 4-month formulation. This new formulation of ELIGARD differs from the approved 4-month formulation primarily in the ratio of lactide to glycolide subunits in the polymer (now 85:15), a small change in the molecular weight of the polymer (now slightly greater), and a larger total amount of leuprolide acetate.

Leuprolide is a leutinizing hormone releasing hormone analogue (LHRH) that acts by initially stimulating the production of LH from the pituitary and later downregulating this production. Ultimately, testosterone secretion from the testes is reduced to "castrate levels". Currently, the Division accepts a total serum testosterone concentration of less than or equal to 50 ng/dL as evidence of medical "castration". The Division uses this surrogate marker to determine efficacy for these types of products.

Given the extensive clinical experience with leuprolide in the treatment of prostate cancer, this Division has recommended that clinical drug development programs for this type of product (for this indication) may consist of a single Phase 3 trial with some supporting evidence. The pivotal trial usually consists of approximately 100 to 120 patients and is supported by a small pharmacokinetics study or by a pharmacokinetic "sub-study" within the body of the larger protocol. Atrix conducted the clinical development program for ELIGARD 45mg in accordance with such guidance from DRUDP. In that regard, Phase 3 protocol AGL 0205 was discussed at a Pre-IND meeting on June 10, 2002 and was submitted with the original IND on June 29, 2002. The first person to enter the trial occurred on August 13, 2002 and last person completed the trial on October 21, 2003. The study report was dated January 19, 2004 and the NDA was submitted on February 13, 2004.

The clinical results submitted included: data from the single, multicenter, open-label, Phase 3 study (AGL 0205) in approximately 111 men with prostate cancer treated for 12 months (two dosage administrations), from a pharmacokinetic "sub-study" conducted in 27 patients, and from the previous study reports submitted for the other ELIGARD formulations.

III. Clinical results in brief:

1. Efficacy

Study AGL0205 enrolled a total of 111 patients. Five patients had Jewett's stage A disease, 43 had stage B disease, 19 had stage C disease and 44 patients had stage D disease. This study evaluated the achievement and maintenance of castrate serum testosterone suppression over 12 months of therapy (2 doses). A total of 106 patients received two injections of ELIGARD® 45 mg given once every six months and 103 patients completed the entire study.

Of the original 111 patients, two were withdrawn from the study prior to the Month 1 blood draw.

- Patient #0313 experienced a myocardial infarction resulting in death one day after the first injection (Day 1). This adverse event was judged as not related to treatment by the investigator.
- Patient #2704 withdrew from the study prior to the Day 28 blood draw as a consequence of complications of metastatic liver cancer. However, this patient had a castrate T level of 6.1 ng/dL recorded on Day 21.

Serum testosterone was suppressed to below the castrate threshold (< 50 ng/dL) by Day 28 in 108 of the 109 (99%) patients remaining in the study at Day 28. One patient (< 1%) did not achieve castrate suppression and was withdrawn from the study on Day 85, as follows:

- Patient #2002 did not achieve castrate serum T suppression at any time prior to withdrawing from the study on Day 85.

Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, only one patient (< 1%) demonstrated breakthrough (concentration above 50 ng/dL) during the study, as follows:

- Patient #1402 achieved castrate level suppression on Day 21 and remained suppressed through Day 301. On Day 308, his serum testosterone level rose to

112 ng/dL. On Day 336, his final testosterone level was 210 ng/dL. It may be of interest to note that his serum PSA at baseline was 8.5 ng/mL, which decreased to 0.3 ng/mL at Day 168, then subsequently increased to 0.4 ng/mL on Day 308 and to 1.3 ng/mL on Day 336.

Therefore, of 103 evaluable (per-protocol) patients in the study at its endpoint (at Month 12), 102 patients had testosterone concentrations of ≤ 50 ng/dL. In addition to the three patients described above (Patient #0313 -MI on Day 1, Patient #2704 -metastatic liver cancer, and Patient #2002 - failure to reach castrate T level), another five patients withdrew prior to completing the trial. In all five cases, the patient had attained castrate serum T by Day 28 and remained castrate until the final blood draw prior to their discontinuation. These five patients are described in detail below:

- Patient #1106 discontinued due to a rising serum PSA. He was placed on bicalutamide (Casodex) for biochemical progression. After attaining castrate suppression, all subsequent serum T values were castrate including his early termination visit (6.8 ng/dl) and his next to last visit on Day 217 (7.6 ng/dL).
- Patient #1501 discontinued after “malignant soft tissue masses” were noted. After attaining castrate suppression, all subsequent serum T values were castrate including his early termination visit (13 ng/dl) and his next to last visit on Day 133 (6.6 ng/dL).
- Patient #1902 discontinued to due a rising serum PSA beginning on Day 225. He was also placed on bicalutamide (Casodex) for biochemical progression. After attaining castrate suppression, all subsequent serum T values were castrate including his early termination visit (5 ng/dl) and his next to last visit on Day 294 (5.6 ng/dL)
- Patient #2904 discontinued after suffering a stroke on Day 159. He subsequently elected to stop his study participation. After attaining castrate suppression, all subsequent serum T values were castrate including his last visit on Day 147 (8 ng/dL)
- Patient #0513 was lost to follow-up after missing a number of visits following his second injection. After attaining castrate suppression, all subsequent serum T values were castrate including his last visit on Day 308 (17 ng/dL)

Therefore, none of the premature discontinuations were related to failure of the formulation to induce or maintain medical castration.

Of note, there was no evidence of acute rises in the serum testosterone upon repeated dosing (the so-called “acute-on-chronic” phenomenon).

In terms of mean serum testosterone concentrations, the mean serum testosterone concentration increased from 367.7 ng/dL at Baseline to 588.6 ng/dL at Day 2 following the initial subcutaneous injection. The mean serum testosterone concentration then decreased to below Baseline by Day 14 and was 16.7 ng/dL on Day 28. At the conclusion of the study (Month 12), mean serum testosterone concentration was 12.6 ng/dL (see Figure 1 below).

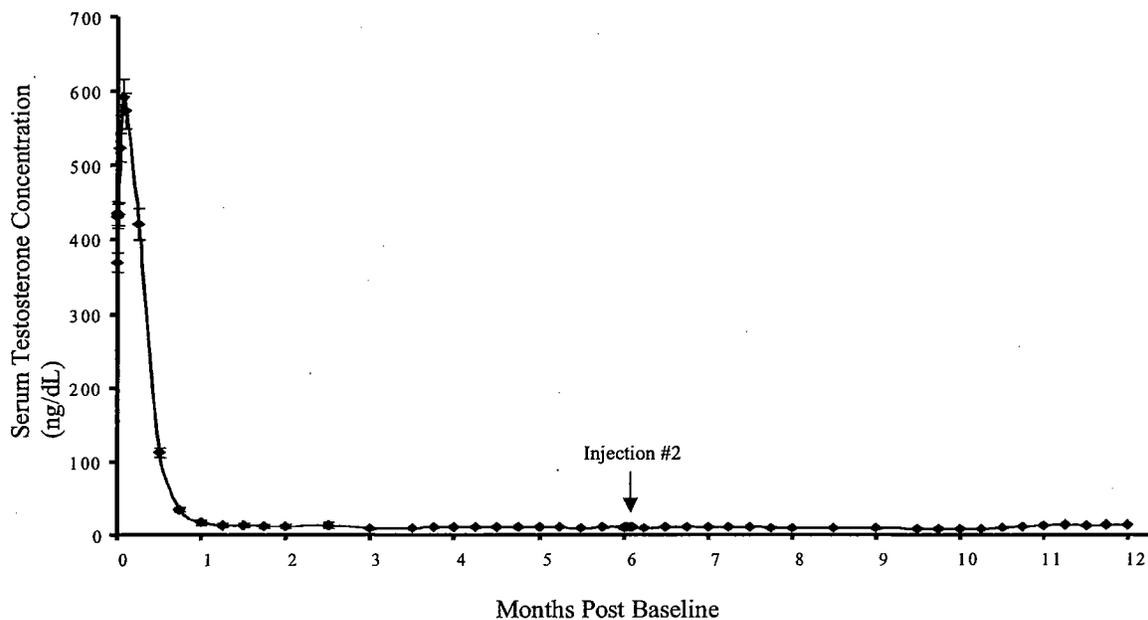


Figure 1. ELIGARD® 45 mg Mean Serum Testosterone Concentrations (n = 103 per-protocol patients)

Finally, Study AGL 0205 also measured several secondary efficacy parameters including the following: serum PSA, WHO Performance Status, bone pain, “urinary pain” and “urinary signs and symptoms”.

Reviewer’s comment: Acknowledging the limitations in study design and in these specific endpoints, this reviewer still believes that the results from these secondary endpoints provide support for the clinical utility of Eligard 45mg. The results are consistent with the clinical effects that one expects in this population following androgen deprivation therapy.

Serum PSA decreased in all patients whose Baseline values were elevated above the normal limit. At Month 12, PSA levels had decreased to within normal limits in 95% of patients who presented with elevated levels at Baseline.

In terms of the WHO Performance Status, at Baseline, 90% of patients were classified as “fully active” by the WHO performance status scale (Status=0), 7% as “restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature” (Status=1), and 3% as “ambulatory but unable to carry out work activities” (Status = 2). At Month 12, the percentage of fully active men was 94%, the percentage of men classified as “restricted” was 5%, and one patient (1%) remained classified as unable to carry out work activities.

At Baseline, patients experienced little bone pain, with a mean score of 1.38 (range 1-7) on a VAS pain scale of 1 (no pain) to 10 (worst pain possible). At Month 12, the mean bone pain score was essentially unchanged at 1.31 (range 1-8). Urinary pain, scored on the same VAS scale, was similarly low, with a mean of 1.22 at Baseline (range 1-8) and was essentially unchanged at Month 12, with a mean score of 1.07 (range 1-5). Finally, “Signs and symptoms on

urination” was scored on a VAS scale from 1 to 10, where 1 was defined as no difficulty and 10 defined as very difficult. Overall, urinary difficulty was scored as very low at Baseline with a mean score of 1.49 (range 1 to 7). At Month 12, the mean score was 1.18 (range 1 to 6).

The sponsor notes that there was “little if any” increase in the mean scores for bone pain, urinary pain, or urinary difficulty in the three days following each dose, suggesting no clinically meaningful flare symptoms occurred in this study.

2. Safety

Medical castration by GnRH analogue is usually accompanied by an initial rise in serum T level for 1-2 weeks followed by a decline to castrate levels in about three or four weeks. This initial rise can occasionally cause a clinical “flare” phenomenon whereby the patient might experience transient worsening of symptoms (bone pain, obstructive urinary symptoms). In rare instances, ureteral obstruction and spinal cord compression have been reported. While no “flares” were reported in this NDA, the potential for this adverse reaction is a labeled warning for all drugs of this class.

GnRH analogues can also potentially induce antibody formation and hypersensitivity reactions. These were not reported in this NDA but they are also labeled for the class.

Finally, decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density. This potential adverse reaction is described in the label for all drugs in this class.

In this specific NDA, for this novel 6 -month subcutaneous preparation of leuprolide, such known drug-class adverse events as hot flashes, fatigue/lethargy/weakness, urinary frequency, testicular atrophy/pain, gynecomastia, night sweats and diminished libido were reported. The incidences and severity of these events were generally in line with that expected for the class. For example, a total of 89 hot flash adverse events were reported in 64 patients (58% of all patients). Of these, 62 events (70%) were mild and 27 (30%) were moderate. Adverse Events are clearly described in the Adverse Reactions section of the label. There were no unexpected adverse reactions reported.

Additionally, since ELIGARD 45 mg is a subcutaneous preparation, the sponsor conducted extensive injection site assessments. In all, 217 injections of ELIGARD® 45 mg were administered. Transient burning/stinging was reported at the injection site following 35 (16%) injections, with 32 of 35 (91.4%) of these events reported as mild and three of 35 (8.6%) reported as moderate. Mild pain was reported following nine (4.1%) study injections and moderate pain was reported following one (<1%) study injection (in a total of 2.7% of patients). Mild bruising was reported following five (2.3%) study injections and moderate bruising was reported following two (< 1%) study injections. Neither pruritis nor erythema was reported in any patient. All of the reported application site adverse events resolved spontaneously without sequelae. No patient was discontinued for a local adverse event.

IV. Relevant issues from other disciplines

1. Chemistry

The finalized chemistry review recommends the following:

"From chemistry, manufacturing and controls point of view, this NDA may be approved."

From a product quality standpoint, it is important to note that Eligard is supplied in two separate syringes. Syringe A contains the Atrigel Delivery System. This delivery system consists of grams of a sterile polymer (85:15 lactide-co-glycolide [PLG] and N-methyl-2-pyrrolidone [NMP]). Syringe B contains 45 mg of lyophilized leuprolide acetate. Prior to drug administration, these syringes are connected and the contents are mixed by pushing the contents back and forth for 45 seconds using the syringe plungers. The mixed suspension is then injected into the patient, delivering a leuprolide dose of 45 milligrams.

The relevant chemistry sections of the label are acceptable to the Chemistry team. The container and carton labeling, as revised, are now acceptable. The in vitro release specifications, as revised, are now acceptable. According to Chemistry and Clinical Pharmacology, the Atrix site is determined to be acceptable for manufacturing of Syringe B. The drug substance supplied by both sites is acceptable. Based on the stability data, 24 months expiry date was granted. All manufacturing sites were deemed acceptable by the Office of Compliance.

The Microbiology consultant ultimately recommended approval (see Dr. Riley's final review dated November 24, 2004).

Therefore, the major chemistry review issues have been fully discussed with sponsor and all have been acceptably resolved.

2. Clinical Pharmacology

OCPB found the submission "acceptable". Minor labeling comments were conveyed to sponsor and sponsor made the necessary revisions. There were no unresolved review issues noted in the written review and none were brought up at the time of the OCPB Briefing.

In her review, Dr. Apparaju noted the following:

In terms of Clinical Pharmacology:

1. The pharmacokinetics and pharmacodynamics of leuprolide after each of two dose administrations were evaluated in a subset of 28 patients in AGL 0205. Pharmacokinetics were available for 27 of these patients and pharmacodynamics for all 28 patients. The procedures for these assessments were acceptable.
2. Leuprolide is rapidly and completely absorbed when delivered by ELIGARD 45 mg. Bioavailability is >97%. Following initial absorption, ELIGARD 45mg demonstrates a slow and sustained release of leuprolide acetate over a period of 6 months. There is no evidence of accumulation.
3. The pK profiles for leuprolide reveal a distinctive "burst phase" followed by a "plateau phase", consistent with the release mechanism of this product. In the burst phase, serum leuprolide concentrations peaked and declined "rapidly" (T max approximately 4-5 hours and burst phase = 0-3 days). In the plateau phase, serum concentrations were generally maintained between 0.2-2.0 n/mL (plateau phase = Days 3-168).
4. In some patients, the minimum serum leuprolide concentrations were found to be less than 0.1 ng/mL and in several instances, the levels were even below the limit of quantification. Since all serum T levels remained suppressed in these patients, this suggests that even very low serum leuprolide concentrations in the plateau phase may be all that is needed to result in adequate T suppression.

5. The mean pharmacokinetic profiles for leuprolide following each of the two individual doses were similar. The only notable difference was a higher Day 0-3 AUC for the second dose compared to the first, and this was attributable to a high C_{max} following the second dose in one specific patient (#2401). In this patient, serum leuprolide concentrations remained stable and low for the rest of the dosing interval and serum testosterone was always suppressed to castrate levels.
6. In the pK subset, medical castration was achieved by all 28 patients by Day 28 and was sustained through both doses without breakthrough. No acute-on-chronic responses were seen in these 28 patients after the second dose administration.
7. Serum testosterone levels were measured using a validated radioimmunoassay (RIA) with a limit of quantification of 3ng/dL. Serum leuprolide concentrations were measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The method was found to be specific for leuprolide with a range of 0.05 ng/mL to 50 ng/mL.
8. In terms of QT assessment, Dr. Apparaju wrote:
 “The sponsor has not evaluated the QT interval prolongation potential of ELIGARD 45mg. However, it has been observed with leuprolide and other drugs in this class that a prolongation of the QT interval is caused by these drugs. This effect is however, attributed to the androgen ablation caused by these drugs (several literature citations suggest that androgens have a cardiac protective effective effect; also suggested by the presence of longer cardiac repolarization intervals in females, compared to males) and not due to the direct action of these drugs on ion channels.”

Reviewer’s comment: There is no evidence that leuprolide itself acts directly on cardiac tissues to alter cardiac repolarization. There have been suggestions made in the literature that androgen ablation (by any means) may affect the QT interval, but this remains an area of continued research. Regardless, there is a wealth of safety experience with leuprolide when used for the palliative treatment of patients with advanced prostate cancer, with a very good overall safety record.

9. There was a trend for decreasing C_{max} with increasing body weight. Dr. Apparaju notes: “However, due to the wide safety margin of leuprolide, these observed differences in initial exposure may not be clinically significant.” Body weight did not have an influence on total observed exposure by AUC_{0-6 months}.
10. There was a slight increasing trend for C_{max} with increasing age; however, there was no influence of age on total observed AUC.
11. There was no significant impact of race on leuprolide pharmacokinetics.

In terms of Biopharmaceutics:

1. The product is supplied in two syringes whose contents must be mixed immediately prior to administration. Syringe B delivers approximately 45mg of the drug substance leuprolide (equivalent to 42mg leuprolide free base). Syringe B contains the ATRIGEL polymeric delivery system containing — 85:15 poly-(DL-lactide-co-glycolide) (PLG) polymer, dissolved in — biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The approximate weight of the administered formulation is 375mg and the approximate volume is 0.375 mL.
2. NMP is also used in the other ELIGARD formulations; it is rapidly metabolized, it is eliminated in the urine, and it does not accumulate after repeated dosing.
3. There were two lots used in AGL 0205 (Lot 1522 for the first dose and Lot 1582 for the second dose). Both of these lots are the same as the to-be-marketed formulation.
4. The leuprolide acetate used for these lots was from two different manufacturers [—] . Dr. Apparaju notes that sufficient bridging information is available to

demonstrate comparable release and pK profiles whether using leuprolide from [redacted]

5. The sponsor ultimately accepted the DRUDP-proposed acceptance criterion for the polymer molecular weight (19-26 kda). This is particularly important for maintaining product quality and consistent release characteristics.
6. Sponsor sought approval for the manufacturing of Syringe B (the lyophilized leuprolide) at both Atrix Labs [redacted] even though all clinical trial material came from [redacted]. Sponsor used bridging techniques to show that drug product with Syringe B from either Atrix versus drug product with Syringe B from [redacted] were comparable. The Division concurred that "there was acceptable similarity between release profiles for lots manufactured at Atrix versus [redacted]" Further, sponsor provided lot-to-lot comparisons of the Atrix batches with the lots manufactured at [redacted]. Dr. Apparaju states: "Considering the most relevant lots as above (i.e. Clinical lots 1522 and 1582) and the new Atrix facility lots, overall it appears that the lots manufactured at the two proposed sites have acceptable similarity."

3. Pharmacology/toxicology (P/T)

Pharmacology recommended "approval" of NDA 21-731 for ELIGARD 45 mg for the palliative treatment of prostate cancer. There were no unresolved P/T issues. The product was considered safe for the proposed indication.

The reviewer noted that the sponsor submitted two 6-month animal studies: one in rat and one in dog. Both demonstrated acceptable pharmacodynamics (testosterone suppression) for the proposed formulation. Four other short-term, pre-clinical studies were submitted with this NDA.

The reviewer noted that there was a long regulatory and clinical usage history for leuprolide. The reviewer also noted the previous approvals of three other ELIGARD formulations, each of which revealed no P/T safety concerns for the drug substance (leuprolide) or for the drug product, including the excipient, N-methyl-2-pyrrolidone (NMP).

NMP is approved as an excipient in the drug Atridox, used for the treatment of periodontal disease, as well as an excipient in all four previous ELIGARD formulations. In Atridox, NMP is delivered as a single dose of 450 mg. ELIGARD 45mg contains NMP as a component of Syringe A, also called the ATRIGEL Delivery System. This delivery system consists of 410mg of 85:15 Poly(DL lactide-co-glycolide) and NMP by weight. Therefore, the total amount of NMP in the Syringe is [redacted] but the actually amount delivered is approximately 150mg. This is much lower in total and on a daily dose basis as compared to ATRIDOX. In fact, it is a lower amount than that delivered by the approved 4-month Eligard formulation [redacted] of NMP). Also, the amount of NMP used safely in toxicology and toxicokinetic studies far exceeds the daily amount to be given to patients in ELIGARD 45mg.

4. Biometrics

No Biometrics review was required for the efficacy analysis of this open-label, single-arm study.

5. Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

ODS/DMETS consultation was obtained for purposes of tradename and container/carton and insert labeling review. There was no objection to the use of the proprietary name "ELIGARD".

It should be noted, however, that DMETS identified one postmarketing report in which a concern was expressed about the potential for confusion between the proprietary names "Eligard" and "Elidel". DMETS determined that the potential for confusion between Eligard and Elidel did not warrant action at this time and that they would continue to monitor for potential confusion between these two names.

Reviewer's comment: I agree that no action is required based upon this potential tradename concern.

DMETS had several recommendations relevant to revising the carton/container labels, including:

1. Making the words "ATRIGEL Delivery System" more prominent on the Syringe A label.
2. Adding verbiage to both syringe labels to inform that the two syringes must be combined to constitute the product.
3. Revising these same items (#1 and #2) on the Syringe A pouch.
4. Making the words "For subcutaneous injection" more prominent on the pouch labeling.
5. Adding the route of administration ("subcutaneous") to the dose statement on the carton.
6.
7. Selecting a "more contrasting color" to better differentiate the Eligard 22.5mg and 45mg formulations.

Reviewer's comments: Items 1 through 5 have been revised in accordance with DMETS recommendations. In regard to item #6:

In regard to item #7, the review team agreed that there was sufficient contrast in color between cartons for each of the Eligard formulations and again no action is necessary.

Therefore, I am of the opinion that all ODS container/carton comments have been adequately managed.

6. Division of Scientific Investigations (DSI)

Clinical site inspections were not considered necessary and none were inspected of DSI. First, ELIGARD 45mg is a new formulation of a drug product approved on three separate occasions. Second, the 3 previous NDAs had been inspected without any notable findings. Finally, the group of investigators, data collection methods, and sponsor were either the same or virtually the same as the previous NDAs. In addition, there were no issues regarding clinical trial design or efficacy results that required clinical site inspections

7. Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC provided a detailed review of the proposed ELIGARD 45mg label. Each of the DDMAC labeling comments were carefully reviewed. Those that required action were enacted through successful labeling negotiations with sponsor.

V. Other relevant issues

1. Financial Disclosure

There were 22 investigators in the pivotal trial of 111 patients. Complete financial disclosure information was received for all the investigators. None had any disclosable information. Therefore, there was no disclosure of financial interests that could bias the outcome of the trial.

2. Pediatrics

ELIGARD 45 mg will be indicated for the palliative treatment of advanced prostate cancer. A waiver for conducting pediatric studies is considered appropriate.

3. Phase 4 commitments

No Phase 4 commitments were requested and none are considered necessary.

VI. Medical team leader's summary statement

ELIGARD 45 mg is considered safe and effective for the palliative treatment of advanced prostate cancer and should be approved for marketing. It offers another option for patient care in this population.

Mark S. Hirsch M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Arch NDA 21-731
cc: HFD-580/Div File
HFD-580/DShames/ABatra/JKim

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NDA 21-731

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW OF NDA 21-731

SPONSOR:	Atrix Laboratories, Inc. 2579 Midpoint Drive Fort Collins, CO 80525
DRUG PRODUCT:	Eligard® 45 MG
DOSE:	45 MG
ROUTE OF ADMINISTRATION:	Subcutaneous Injection
PHARMACOLOGICAL CLASS:	Gonadotropic Releasing Hormone (GnRH) Agonist
INDICATION:	Palliative Treatment of Advanced Carcinoma of the Prostate.
DATES:	
SUBMITTED:	February 18, 2004
PDUFA GOAL:	December 17, 2004
RELATED IND/NDA's:	IND# 64,779, NDA 21-343, NDA 21-488, NDA 21-379
MEDICAL OFFICER:	Ashok Batra MD
DATE REVIEW COMPLETED:	December 2, 2004

I. Executive Summary

1. Recommendations

1.1. Approvability

This reviewer recommends that ELIGARD® 45 mg, administered once every six months, should be approved for the proposed indication of palliative treatment of advanced prostate cancer. Minor labeling changes were requested to more accurately convey the product information to the prescriber.

1.2. Basis for recommendation regarding approvability (risk/benefit assessment)

Benefits

Androgen ablation is a current standard of care in the palliative management for advanced prostate cancer patients as the majority of prostate cancers are androgen sensitive. This is achieved either by surgical (orchiectomy) or medical means. The goal of therapy is to suppress serum testosterone (T) levels to at least below 50ng/dL. Medical therapies directed towards this goal achieve castrate T levels in approximately one month's time.

In support of its claim, the sponsor conducted one pivotal trial: AGL 0205 that enrolled 111 patients. The results from this trial demonstrated that after receiving two doses of ELIGARD® 45 mg (given every 6 months), 108 of 111 (97.3%) patients in the intent to treat (ITT) population reached castrate suppression of T concentration, defined as T concentration of ≤ 50 ng/dL for two consecutive time points approximately one week apart. One breakthrough (patient #1402) was noted. Patient #1402 initially suppressed at Day 21 following the first injection and remained suppressed up to and following the second injection. At Day 308, this patient's testosterone level rose to 112 ng/dL, and continued to rise to the end of the study (210 ng/dL at Day 336). The patient completed the study and was started on alternate therapy.

By study Month 1 (Day 28), 108 of 109 (99%) of the observed cases (OC) population achieved castrate suppression. One patient never reached suppression and was withdrawn from the study at Day 85. The median time to castrate suppression for both populations was 21 days and the mean time was 21.2 days.

Risks

Medical castration by GnRH agonist is usually accompanied by an initial rise in serum T level for 1-2 weeks followed by a decline to castrate levels in about one month. This initial rise can occasionally cause a "flare" phenomenon whereby the patient might experience transient worsening of symptoms (bone pain, spinal cord compression, obstructive urinary symptoms). While no "flares" were reported in this NDA, this potential adverse reaction is a labeled warning for all drugs in this class.

The sponsor of this NDA also reported such known drug-related adverse events as hot flashes, dizziness/giddiness, malaise/fatigue, testicular discomfort/atrophy, diminished

libido, and impotence. The incidences of these events were in line with expected incidences in the class.

GnRH analogs can also potentially induce antibody formation and hypersensitivity reactions. These were not reported in this NDA but they are labeled for the class.

Additionally, since ELIGARD is a subcutaneous preparation, local pain, itching, swelling, erythema, induration, and rarely ulceration may occur. While pain, itching, and swelling was a commonly reported adverse reaction, most events were reported as mild in severity and short in duration. All of the reported events resolved spontaneously without sequelae. No patient was discontinued for a local adverse event.

In summary, based on safety and efficacy information contained in NDA 21-731, this reviewer believes that the sponsor has demonstrated that ELIGARD® 45mg is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

1.3. Specific recommendations to the sponsor

A few minor labeling revisions were requested and sponsor was amenable and appropriately responsive.

II. Summary of clinical findings

2.1. Brief overview of the clinical program

2.1.1 Drug product

The drug product used in the clinical trials (ELIGARD® 45 mg) was manufactured by Atrix Laboratories. The lot numbers used in the study were 1522 and 1582. The injection volume was approximately 0.375 ml. ELIGARD is designed to deliver 45 mg of leuprolide acetate over a six-month therapeutic period.

ELIGARD 45 mg was supplied in two, separate, sterile syringes and was mixed immediately prior to administration. One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of 85/15 Poly (DL-lactide-co-glycolide) (PLG) and N-methyl-2-pyrrolidone (NMP). The other syringe contained 45 mg lyophilized leuprolide acetate. The syringes were joined via the syringe connections, and the delivery system was passed between syringes until it was thoroughly mixed with the leuprolide acetate. The study drug was manufactured by Atrix Laboratories.

2.1.2. Brief overview of the clinical trials conducted

Atrix Inc. has already received FDA approval for three subcutaneous (SC) leuprolide acetate depot injections:

1. One-month ELIGARD® 7.5 mg (NDA 21-343; 2002),
2. Three-month ELIGARD® 22.5 mg (NDA 21-379; 2002)
3. Four-month ELIGARD® 30 mg (NDA 21-488; 2003)

All three products are indicated for the palliative treatment of advanced prostate cancer. The sponsor developed and evaluated a six-monthly, extended-release formulation, ELIGARD® 45mg. ELIGARD® 45 mg contains 45 mg leuprolide acetate in the ATRIGEL® Delivery System and is highly similar to the ELIGARD® 7.5 mg, ELIGARD® 22.5 mg, and ELIGARD® 30 mg products.

The dose for the six-month ELIGARD® 45 mg formulation was selected by proportionally increasing the leuprolide acetate dose of the four-month ELIGARD® 30 mg formulation to 45 mg, along with modification of the formulation co-polymer to provide a six-month release profile. In non-clinical studies, the sponsor verified that by proportionally increasing the dose of ELIGARD® 30 mg (four-month) to 45 mg and modifying the co-polymer formulation, six-month duration of activity could be achieved in animal models. Non-clinical pharmacology, toxicology and irritation studies conducted to characterize the ELIGARD® products indicate that the products are effective LH-RH agonists with adequate safety profile.

Essential elements of the AGL0205 Phase 3 study design were agreed upon with the Agency.

The objectives of this study were:

1. To evaluate the safety and tolerance of two doses, delivered as single injections, six months apart, in patients with advanced prostate cancer.
2. To evaluate serum T and LH levels following two doses of LA-2580 45 mg in patients with advanced prostate cancer.
3. To determine the pharmacokinetic (PK) profile of serum leuprolide acetate following two subcutaneous injections with LA-2580 45 mg in a subset of patients with advanced prostate cancer.

The sponsor submitted data from one pivotal study (AGL 0205) in support of NDA 21-731. This study was a 12-month, open-label, fixed-dose study to evaluate the safety, tolerance, pharmacokinetics, and efficacy of two consecutive doses of Eligard® 45 mg in patients with advanced prostate cancer. Ninety-nine percent (99%) of the patients remaining in the study reached castrate testosterone suppression levels (< 50 ng/dL) by Month 1 (Day 28) following the baseline injection. One patient did not suppress, and was subsequently withdrawn from the study at Day 85 due to lack of efficacy. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, one patient (< 1%) demonstrated breakthrough (concentration above 50 ng/dL) during the study. This patient achieved castrate suppression by Day 28 and remained suppressed through Day 301. At Day 308, the patient's testosterone level rose above 50 ng/dL, and continued to rise to 210 ng/dL at Month 12 (Day 336).

The observed safety profile of ELIGARD® 45 mg was similar to other products containing leuprolide acetate. Common systemic adverse events (AE's) in treatment related categories were hot flashes, fatigue, testicular atrophy, myalgia, weakness, gynaecomastia, pain in limb and night sweats. The majority of these events are associated with testosterone suppression to castrate levels. Injection site AE's were typical of those associated with similar SC injection products. Analysis of performance status, bone and urinary pain and urinary symptoms suggest there was an adequate symptom control over the course of the study with no flare response in the patient

population tested. Overall, ELIGARD® 45 mg was found to have a reasonable safety profile.

2.2 Efficacy

2.2.1. Primary efficacy assessments and efficacy endpoints

For this NDA, the Division agreed that the attainment of castration levels of testosterone (<50 ng/dL) by treatment Day 28 and maintenance of these levels through 2 dosing cycles would constitute the primary measure for success.

Therefore, the efficacy objectives in Study AGL 0205 (the single Phase 3 trial) were to determine:

1. The proportion of patients with a serum testosterone of < 50 ng/dL (i.e., medically castrate) on Day 28.
2. The proportion of patients maintaining castrate levels of serum testosterone from Day 29 through Day 336.
3. The proportion of patients exhibiting "acute-on-chronic" phenomenon upon repeated dosing.

2.2.2. Efficacy Results (primary endpoints)

The results of AGL 0205 revealed that by Day 28, 108 of 111 (97.3%) of patients in the ITT population and 108 of 109 (99%) patients in the OC population had achieved castrate (< 50 ng/dL) T suppression. The median time to castrate suppression for both the ITT and OC populations was 21 days. One castrate suppression breakthrough was observed during the study (Patient #1402) beginning at Day 308. One patient (#2002) failed to suppress and was withdrawn from the study on Day 85.

2.2.3. Other efficacy issues

There was no evidence of acute rises in the serum testosterone upon repeated dosing (the so-called "acute-on-chronic" phenomenon). Little change was observed throughout the study in terms of WHO performance status, bone pain, urinary pain, and urinary signs and symptoms. All measures were low at Baseline and remained low during the study indicating an adequate symptom control was maintained during the twelve months of the study.

2.2.4. Proposed label indication

The data provided by the sponsor in this NDA, especially the data regarding post-dosing serum testosterone levels, are sufficient to support the claim that "ELIGARD™ 45 mg is indicated in the palliative treatment of advanced prostate cancer."

2.3. Safety

2.3.1. Exposure to study drug

One hundred eleven patients were enrolled and received at least one study injection. Of those, 106 patients (95.5%) received two study injections. Of the five that received only one study injection;

- Patient #0313 experienced myocardial infarction resulting in death at Day 1 of the study.
- Patient #1501 exited the study after malignant soft tissue masses were noted.
- Patient #2002 discontinued the study at Day 85 due to lack of efficacy of the study therapy.
- Patient #2704 voluntarily withdrew from the study and subsequently died as a result of metastatic liver cancer.
- Patient #2904 experienced a stroke and subsequently elected to discontinue participation in the study.

As a class, GnRH agonists have been found to be safe and well tolerated. Based on the data in the present application and the overall experience with leuprolide acetate, the exposure to the ELIGARD® 45mg is considered adequate to assess its general safety for the indication of management of advanced prostate cancer. Additionally the data regarding local site reactions is also considered sufficient to make a determination of the local tolerability of the drug.

2.3.2. General safety findings

The drug-related adverse reactions reported in this NDA for ELIGARD® 45 mg were comparable to those reported in the currently approved other leuprolide acetate products.

2.3.3. Patient deaths

There were two reported deaths in the studies conducted for this NDA. These were unrelated to the treatment:

1. Patient #0313 experienced a myocardial infarction resulting in death one day after his first injection.
2. Patient #2704 voluntarily withdrew from the study and subsequently died as a result of metastatic liver cancer.

2.4. Formulation and dosing

ELIGARD is designed to deliver 45 mg of leuprolide acetate over a six-month therapeutic period. It is supplied in two separate, sterile syringes and was mixed immediately prior to administration. One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of $\frac{1}{2}$ w/w 85/15 Poly (DL-lactide-co-glycolide) (PLG) and $\frac{1}{2}$ w/w N-methyl-2- pyrrolidone (NMP). The other syringe contained 45 mg lyophilized leuprolide acetate. The syringes were joined via the syringe connections, and the delivery system was passed between syringes until it was thoroughly mixed with the leuprolide acetate.

2.5. Special Populations

1. Women and children: No women and no children were studied for this indication. The package insert contraindicates use of ELIGARD in these populations.
2. Renal and hepatic impairment: There were no special investigations in patients with renal or hepatic impairment and these patients were excluded from the single Phase 3 trial. The label notes these issues.
3. Racial differences in efficacy and safety were similar across all races studied.

III. Clinical Review

3. Introduction and background

3.1. Drug established and proposed tradename, drug class, proposed indication(s), dose, regimen

Drug product:	Eligard® 45 mg
Drug substance	Leuprolide acetate
Dose:	45 mg
Dosing Regimen	Administered once every six months
Route of administration:	Subcutaneous injection
Pharmacological class:	Gonadotropic releasing hormone (GnRH) agonist
Indication:	Palliative treatment of advanced carcinoma of the prostate

3.2. Overview of disease and treatment options

3.2.1 Carcinoma of the prostate and medical therapy

Adenocarcinoma of the prostate is one of the most common cancers affecting the male population in the United States. Treatment strategies for the patients with advanced disease are focused on amelioration of symptoms and controlling disease sufficiently to increase survival. As a vast majority of prostate cancers are dependent on circulating androgens and are responsive to hormone manipulation, the mainstay of therapy is androgen deprivation or withdrawal. Testosterone (T) withdrawal is usually produced by orchiectomy (surgical) or by "medical castration" (via diethylstilbestrol or synthetic GnRH agonists) and is associated with a symptomatic improvement in 60-80% of patients. Chronic administration of GnRH agonists has a biphasic action, acutely increasing gonadotropin and T levels, and then paradoxically suppressing LH release from the anterior pituitary. Physiological secretion of GnRH is pulsatile and the continuous presence of GnRH down-regulates GnRH receptors and diminishes LH release. This lack of LH stimulation then reduces T production from Leydig cells in the testes. GnRH agonist therapy has equivalent efficacy to surgical castration.

Leuprolide acetate (LA) is a synthetic GnRH agonist which has been available in the US and Europe for a number of years as a daily subcutaneous (SC) injection or various depot intramuscular (IM) injections, for treatment of advanced prostate cancer. Synthetic analogues of GnRH have a longer half-life and higher potency than naturally occurring GnRH secreted by the hypothalamus. The pharmacological effects of T suppression commonly reported as side effects include hot flashes, sweating, impotence/decreased

libido, and gynecomastia. The adverse events (AE's) most frequently reported by recipients of leuprolide acetate in published studies are: hot flashes (35-64%), impotence/decreased libido (2-100%), sweating (11-17%), gynecomastia (16%), nausea/vomiting (13%), peripheral edema (13%) and disease flare (10-20%). Disease flare is characterized by an acute and temporary exacerbation of disease related symptoms during the first week of leuprolide acetate therapy. Flare occurs in susceptible patients consequent to the initial increase in T and LH stimulated by early leuprolide acetate therapy.

ELIGARD® is a SC injection formulation that delivers LA as a suspension in a biodegradable polymeric delivery system of Poly-(DL-lactide-co-glycolide) (PLG) or Poly (DL lactide-co-glycolide) COOH (PLGH) and the liquid carrier N-methyl- 2-pyrrolidone (NMP). The sponsor has already submitted and received FDA approval for three ELIGARD® products that deliver GnRH:

1. ELIGARD® 7.5 mg is a one-month formulation of LA.
2. ELIGARD® 22.5 mg is a three-month formulation of LA.
3. ELIGARD® 30.0 mg is a four-month formulation of LA.

This submission by the sponsor is in regards to a six-monthly formulation to deliver LA (45 mg) for the treatment of adenocarcinoma of the prostate. It is intended for SC dosing once every six months.

3.2.2. Important issues with pharmacologically related agents

As noted above, a superactive GnRH analog (Lupron) was first approved by the FDA for the treatment of advanced prostate cancer in 1985. Numerous other GnRH analogs have been subsequently approved for the same indication. Currently, GnRH agonists are widely used in urology with an acceptable safety record. The adverse events (AE's) most frequently reported by recipients of leuprolide acetate in published studies are: hot flashes (35-64%), impotence/decreased libido (2-100%), sweating (11-17%), gynecomastia (16%), nausea/vomiting (13%), peripheral edema (13%) and disease flare (10-20%).

3.3. Important milestones in product development

The first GnRH agonist approved by the FDA for this indication was leuprolide acetate (Lupron™, TAP Pharmaceuticals) in 1985. Other superactive GnRH agonists approved by the FDA for this indication include goserelin acetate (Zoladex™, Astra Zeneca Pharmaceuticals) and triptorelin pamoate (Trelstar™ Depot, Debio Recherche Pharmaceutique). Because these peptide agonists are rapidly metabolized and not pharmacologically active if taken orally, they are administered parentally by means of long-acting biodegradable formulations. These long-acting formulations are currently administered at intervals ranging from 4 to 52 weeks.

The sponsor developed ELIGARD®, a SC injection formulation that delivers LA as a suspension in a biodegradable polymeric delivery system of Poly-(DL-lactide-co-glycolide) (PLG) or Poly (DL lactide-co-glycolide) COOH (PLGH) and the liquid carrier N methyl- 2-pyrrolidone (NMP). A Pre-IND meeting for this new formulation was held with sponsor on June 10, 2002. The IND (#64,779) was submitted on June 29, 2002. The first patient enrolled in the pivotal study AGL 0205 on August 13, 2002 and the last

patient completed the study on October 21, 2003. The study report is dated January 19, 2004, and the NDA was submitted on February 18, 2004. Of note, the sponsor has previously received FDA approval for three ELIGARD® products that deliver GnRH:

1. ELIGARD® 7.5 mg is a one-month formulation of LA
2. ELIGARD® 22.5 mg is a three month formulation of LA.
3. ELIGARD® 30.0 mg is a four-month formulation of LA.

Each formulation contains the same drug (LA) in varying amounts and the same biocompatible solvent (NMP). The polymer formulations are somewhat different in the ELIGARD® 7.5 mg and ELIGARD® 22.5 mg formulations to allow for the appropriate length of delivery of LA. The lactide/glycolide subunit ratios and the mean molecular weights are adjusted to achieve the desired drug release rates. In addition, the amount of drug delivered is adjusted to achieve the length of treatment desired with each injection. The ELIGARD® 30.0 mg and ELIGARD® 22.5 mg formulations are identical. To extend the delivery to four months with ELIGARD® 30.0 mg a larger injection volume is given (500 mg versus 375 mg) which results in more drug being delivered (30.0 mg versus 22.5 mg).

The sponsor conducted pharmacology studies in rats and dogs to verify that the treatment with LA2580 45mg resulted in T suppression for at least six months with no overt systemic toxicity and no irritation or minimal erythema after subcutaneous injection. The result of these animal studies supported the clinical administration of subcutaneous LA-2580 45 mg injections to adult human males once every six months. The sponsor also conducted a Phase III pivotal study AGL 0205 (8-13-2002 to 10-23-2003) in support of ELIGARD® 45mg product.

LA-2580 45 mg is a six-month formulation that delivers LA (45 mg) for the treatment of adenocarcinoma of the prostate. The polymer formulation is somewhat different and the amount of drug delivered larger (45 mgs) to allow for six-month delivery. The injection volume in LA-2580 45 mg is ~0.375 mL. This compares to an injection volume of ~0.500 ml with ELIGARD® 30.0 mg and ~0.375 ml with ELIGARD® 22.5 mg.

3.4. Other relevant information

Three preparations of ELIGARD® are approved by the FDA.

1. ELIGARD® 7.5 mg is a one-month formulation of LA.
2. ELIGARD® 22.5 mg is a three month formulation of LA.
3. ELIGARD® 30.0 mg is a four-month formulation of LA.

4. Clinically relevant findings from chemistry, animal pharmacology and toxicology, microbiology, biopharmaceutics, statistics and/or other consultant reviews

4.1. Toxicology review

According to the primary reviewer (Dr. K. Raheja), there are no Pharmacology/toxicology findings that would preclude the approval of the 6-monthly formulation of ELIGARD® 45mg for the proposed indication of advanced prostate cancer.

4.2. Clinical pharmacology and bio-pharmaceutics review

According to the primary reviewer (Dr. S. Apparaju), there are no Bio-pharmaceutical findings that would preclude the approval of the 6-monthly formulation of ELIGARD® 45mg for the proposed indication of advanced prostate cancer. The pharmacokinetics/pharmacodynamics data is supportive of approval.

4.3. Chemistry review

According to the primary chemistry reviewer (Dr. S. De), there are no chemistry findings that would preclude the approval of the 6-monthly formulation of ELIAGR® 45mg for the proposed indication of advanced prostate cancer.

4.4. Microbiology review

According to the Microbiology reviewers, there are no Microbiology findings that would preclude the approval of the 6-monthly formulation of ELIAGR® 45mg for the proposed indication of advanced prostate cancer.

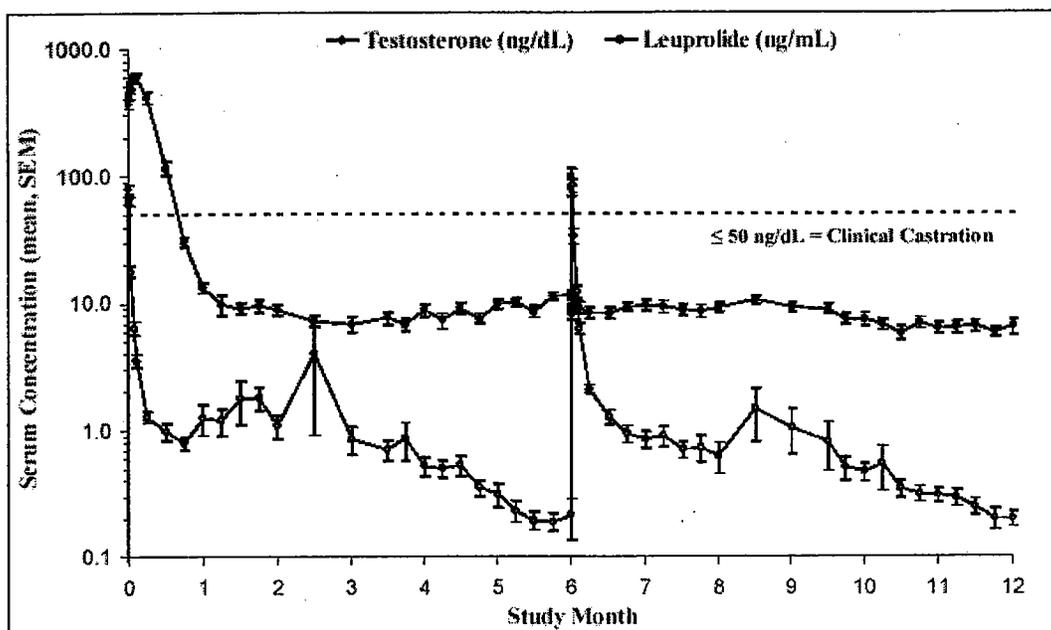
5. Human pharmacokinetic and pharmacodynamic

5.1. Pharmacokinetics:

Twenty-eight (28) patients were enrolled in the PK subset. Of these, 26 received both doses of LA-2580 45-mg and provided a complete set of PK parameters. One patient (#1501) received the first dose and provided PK samples through Day 140 only. All 27 patients for whom complete or partial PK data are available were included in the PK analysis.

The pharmacokinetics of leuprolide after administration of LA-2580 45 mg were multiphasic (Figure 1). Following the initial burst ($C_{max} > 80$ ng/ml), the concentrations of leuprolide declined rapidly over the first 3 days, then declined more gradually over the remainder of the dosing interval (3 days to 6 months). During the "plateau" phase the concentrations of leuprolide were maintained between 0.2-2.0 ng/ml. During the plateau phase the average rate of drug delivery from the depot was estimated to be 138 - 163 µg/day. There was no evidence of accumulation after repeated dosing with ELIGARD® 45 mg in the pivotal phase 3 study. Serum leuprolide concentrations and AUC's following the second dose were similar to those observed after the first dose.

Figure 1. Pharmacokinetic and Pharmacodynamic of LA-2580 45 mg. Mean Serum Leuprolide and Testosterone after Two Consecutive SC Doses, at Baseline (Day 0) and Month 6 (Day 168)



*Source Figure1: Figure 1 AGL 0205 Study Report.

5.2. Pharmacodynamics

The pharmacodynamic response to ELIGARD 45mg, as reflected in serum T concentrations was quite consistent after both the doses (Figure 1). Following the first dose of ELIGARD® 45 mg, mean serum testosterone concentrations transiently increased, then fell to levels (< 50 ng/dL) associated with medical castration in 99.1% of subgroup patients by Day 28. ELIGARD® 45 mg then maintained testosterone suppression during the remainder of the first six-month dosing interval. There were no acute-on-chronic testosterone responses during the burst phase after the second dose of ELIGARD® 45 mg. One patient did not achieve castrate suppression and one patient demonstrated breakthrough (T > 50 ng/dL after achieving castrate levels).

Medical officer's comment:

The pK/pD profile is adequate for the indication sought.

6. Description of clinical data and sources

Complete study report for one pivotal clinical trial was submitted in NDA 21-731, Volumes 2.118 – 2.155. The case report form tabulations were provided in Volumes 2.119 and 2.120, and the case report forms were provided in Volumes 2.138– 2.154. The AGL 0205 report included:

1. PK study in a subset of 27 patients.

2. AGL 0205: single pivotal Phase 3 trial.

Previously reviewed (and re-submitted) study reports included:

- AGL0001 Volumes 2.156 – 2.167
- AGL9909 Volumes 2.168 – 2.184
- AGL9904 Volumes 2.185 – 2.197
- AGL9802 Volume 2.198

7. Clinical review methods

7.1 How the review was conducted

The review conducted by this medical officer focused on Study AGL 0205.

The accuracy of the sponsor's primary efficacy analyses for maintenance of testosterone suppression and acute changes in serum LH and testosterone levels after repeat dosing were reviewed. Analyses and summary tables relating to major protocol violations, deaths, serious adverse events, and routine adverse events were reviewed using the data listings or case report forms provided by the sponsor.

7.2. Overview of materials consulted in review

All submissions to NDA 21-731 were reviewed.

7.3. Overview of methods used to evaluate data quality and integrity

7.3.1 DSI audits of clinical sites

The Division decided that a DSI consult and audit were not required for this NDA because of the sufficient experience with this sponsor, research sites, the trial conducted and the other ELIGARD® products.

7.3.2 Site monitoring

According to the Final Report for AGL 0205, the investigators allowed representatives of Atrix to inspect all phases of the study at any time throughout the study. The Atrix monitor kept a record of each visit to the study site. The record included the monitor's name, date of visit, purpose of visit, and study personnel who were present during the visit.

The Atrix CRA responsible for each center reviewed the completed CRF's at the study center and sent them to Atrix. Receipt of the CRF's was documented. Data entry was initiated following the validation of data entry screens developed specifically for the protocol. Accuracy of data entry into the system was audited by an independent contractor.

Audited patients were randomly selected, and the case reports for each were compared to data in printouts generated from the database. Discrepancy logs were used to verify changes to the case report forms and/or database content. This audit confirmed the accurate entry of data into the database

Medical officer's comment:

The monitoring process, data entry, and auditing procedures were adequate. The sponsor could not confirm the validity of data collected from the _____ site [] that included data for three patients (#3201, #3202, and #3203). However, this validation issue should not preclude the approval of this product as the data from this site was in line with rest of the data in the study.

7.3.3. Central laboratories

7.3.3. []

[] was responsible for all laboratory tests with the exception of T, LH and leuprolide acetate. At _____ the database was constantly monitored to insure that the specifications of the protocol were met. Any modifications or amendments made to the database post launch were validated in a similar manner to the pre-study validation. _____ Quality Control Departments conducted periodic internal audits of ongoing studies as well as hosting external audits by independent agencies and sponsors. An accreditation certificate for [] Limited was submitted in the NDA.

7.3.3.2 _____ Center for Clinical Trials

[] was utilized for T and LH analyses. The laboratory is supervised by PhD level chemists who have been involved with the development of assays and laboratory management for many years. Section supervisors review assays before any results are reported. All the antisera used in the assays were developed at [] and were selected because their high sensitivity and low cross reactivity allow for specific results on small volumes of samples.

The laboratory has a written Quality Assurance/Preventive Maintenance program which encompasses: calibration of equipment and instruments; preventive maintenance of equipment; inventories of critical reagents; schedules for purification of isotopes; calibration of measuring devices; and other systems which are necessary for long-term maintenance of laboratory performance. The sponsor submitted validation reports for T and LH respectively.

7.3.3.3 [] - Leuprolide Acetate Assay

Leuprolide concentrations in serum were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method in which samples were purified using []

Medical officer's comment:

The overall quality control data submitted by [redacted] were adequate to obtain a general impression of the quality of the laboratories. Based on the quality control data included in this application, the testosterone data submitted in support of NDA 21-731 appears to be acceptable to assess suppression of serum testosterone to values below 50ng/dl.

7.4 Were trials conducted in accordance with accepted ethical standards?

Based on the IRB documents, the protocol design, the conduct and analysis of the trial and the reports of DSI audits and sponsor's internal auditing, it appears that this study was conducted within norms of current standards.

7.5 Evaluation of financial disclosure

Based on information submitted by the sponsor there were no financial conflict-of-interest issues.

8. Integrated review of efficacy

8.1. Efficacy endpoints

The primary efficacy assessment measure in the pivotal Phase III Study, AGL 0205, was serum total testosterone concentration at various sampling time points. Descriptive statistics (e.g., mean, standard error, minimum, maximum) were used to summarize the concentrations at each time point as well as to determine the mean and median time to testosterone suppression. Descriptive statistics were also used to evaluate testosterone data for acute-on-chronic and breakthrough responses following initial suppression.

8.1.1. Primary efficacy endpoints

The primary efficacy endpoint was:

The proportion of patients achieving castrate levels of serum testosterone (testosterone < 50ng/dl) on Study Day 28 (i.e., within 28 days following the initial injection of Study Drug).

8.1.2. Secondary (supportive) efficacy endpoints

The Secondary efficacy endpoints were:

- The proportion of patients maintaining castrate levels of serum testosterone from the day they actually achieved castrate levels to study end.
- The proportion of patients showing acute-on-chronic and breakthrough responses following initial suppression:
- WHO performance status, patient assessments of bone pain, urinary pain and urinary signs and symptoms.

- Serum PSA levels.
- Serum leuprolide concentrations.

8.2. Populations analyzed

Analyses were performed for both the intent-to-treat (ITT) and observed-cases (OC) data-sets. These populations were defined as follows:

8.2.1. ITT population

The ITT population included all efficacy data for patients enrolled in the study who received at least one dose of study drug, with one exception: patients with baseline data only (e.g., patients who discontinued before any efficacy information was collected) were not included in the ITT data-set. In addition, in the analysis of testosterone suppression, the intent-to-treat analysis involved carrying forward data to the end of the study for three patients who were withdrawn prior to completing the study.

8.2.2. "Observed-cases" population

The observed cases data-set is similar to the ITT data-set used to analyze testosterone suppression, except that the data for the withdrawn patients was not carried forward past the time that they were withdrawn.

8.3 Handling of dropouts or missing data

Missing data were handled as follows for the intent-to-treat population: Patients with baseline data only (i.e., no on-study efficacy data) were not included in the analysis. In addition, for any missing interim visits, the value from the previous visit was carried forward to the missing visit (e.g., last observation carried forward). For all other data, no corrections or adjustments were made for missing data.

8.4. Principal clinical trial to support efficacy claim (AGL 0205)

8.4.1. Study dates: 8/13/2002 to 10/23/2003

8.4.2. Design

This was a 12-month, multi-center (21 centers), fixed-dose investigation of two consecutive doses of LA-2580 45 mg administered to patients with Jewett Stage A2, B, C, or D adenocarcinoma of the prostate at six-month intervals. A total of 111 patients received at least one, SC injection of LA-2580 45 mg. The first was given at Baseline and the second at Month 6 (Day 168). Patients were male, between 50 and 86 years of age. No blinding, randomization or stratification procedures were performed, and no concurrent controls were used.

The Screening visit took place within 3-16 days prior to initial LA-2580 45mg administration. Patients who met all eligibility criteria were given a patient number on Day 0 (Baseline), prior to treatment, and entered into the study. On Day 0 patients received a single dose of LA-2580 45 mg SC between 6:00 a.m. and 10:00 a.m. Blood samples for hormone and PK determinations were collected at specific time points.

During participation in the study, patients were monitored by physical examinations, vital signs, clinical laboratory values, and AE's. At Month 6 (Day 168), patients were given a second dose of LA-2580 45 mg. Final assessment and evaluation took place at Month 12 (Day 336). The reader is also referred to Table 1.

8.4.3. Patient Selection Criteria

8.4.3.1. Inclusion Criteria

The inclusion criteria were intended to select a reasonably healthy study population of men with advanced prostate cancer. Patients entered the study based upon an initial screening ensuring the following conditions:

1. Patient read and signed the informed consent agreement. If the patient required someone to read and/or interpret any or all of the informed consent, a statement of this fact was included. If a patient was unable to read or if a legally acceptable representative was unable to read, an impartial witness was present during the entire informed consent discussion to ensure accurate representation of the informed consent document was given verbally. If a patient did not understand English, a validated translated informed consent was provided.
2. Patient was male between 40-85 years of age, inclusive.
3. Patient was an outpatient, not hospitalized.
4. Patient had histologically or cytologically proven adenocarcinoma of the prostate.
5. Patient had Jewett Stage A2, B, C, or D adenocarcinoma of the prostate or a rising PSA after failed local therapy for prostate cancer.
6. Patient was a candidate for androgen-ablative therapy. Hormone refractory patients were excluded from the study.
7. Patient had a World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) performance status of 0, 1, or 2.
8. Patient had a life expectancy of at least one year.
9. Patient had adequate renal function. Adequate was defined by a serum creatinine <1.6 times the ULN (upper limit of normal) for the clinical laboratory, and adequate and stable hepatic function as defined by bilirubin <1.5 times the ULN and transaminases (i.e., SGOT, SGPT) <2.5 times the ULN for the clinical laboratory at Screening.
10. Patient was willing to complete all phases and all procedures of the study.

8.4.3.2. Exclusion criteria

Disease-specific Criteria

1. Patient could not have evidence of brain metastases, in the opinion of the Investigator, taking into account medical history, clinical observations, and symptoms.
2. Patient could not have evidence of spinal cord compression, in the opinion of the Investigator, taking into account medical history, clinical observations, and symptoms.
3. Patient could not have evidence of urinary tract obstruction where a flare in disease could have put the patient at significant risk, in the opinion of the Investigator, taking into account medical history, clinical observations, and symptoms.

4. Patients could not have serum T levels below 150 ng/dL at Screening.

Therapy Criteria

5. Patient could not be under the effects of any of the following treatments for prostate cancer within two months of Baseline: immunotherapy (e.g. antibody therapies, tumor-vaccines), external radiotherapy, brachytherapy, chemotherapy, or biological response modifiers (e.g. cytokines). There had to have been at least a two month washout period between the end of the physiological action of their therapy and the Baseline visit.
6. Patient could not have undergone any prostatic surgery (e.g. transurethral resection of the prostate (TURP), radical prostatectomy) within two weeks of Baseline.
7. Patient could not be under the effects of any hormonal therapy, including anti-androgens, (e.g. Lupron®, Zoladex®, Megace®, etc.) for treatment of prostate cancer within three months of Baseline. There had to be at least a three-month washout period between the end of the action of their last hormonal therapy and the Baseline visit.
8. Patient could not have received LA-2500 7.5 mg, LA-2550 22.5 mg, or LA-2575 30 mg previously.
9. Patient must not have had orchiectomy, adrenalectomy, or hypophysectomy.
10. Patient must not have used any investigational drug, biologic, or device within five half-lives of its physiological action or three months, whichever was longer, before Baseline.
11. Patient could not have received finasteride (i.e., Proscar® or Propecia®) within two months of Baseline.
12. Patient must not have been anticipated to need concomitant hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer throughout the duration of the study.
13. Patient must not have used over-the-counter or alternative medical therapies that have an estrogenic or anti-androgenic effect (i.e., PC-SPES, saw palmetto, Glycyrrhiza, Urinozinc, DHEA) within the three months prior to Baseline.

Other Clinical Criteria

14. Patients could not have received ketoconazole or glucocorticoids within two months of Baseline.
15. Hematological parameters could not be outside 20% of the upper and lower limits of normal (ULN, LLN) for the clinical laboratory at Screening.
16. Patient could not have a cancer diagnosis without a history of stability/remission for greater than 5 years, with the exception of non-metastatic basal and/or squamous cell carcinomas of the skin. Enrollment into the study of patients with basal and/or squamous cell carcinomas was discussed with the Atrix Study Director on a case by case basis.
17. Patient could not have uncontrolled congestive heart failure within six months before Baseline.
18. Patient could not have experienced a myocardial infarction or a coronary vascular procedure (e.g., balloon angioplasty, coronary artery bypass graft) within six months before Baseline.
19. Patient could not have significant symptomatic cardiovascular disease within six months of Baseline.

20. Patient could not have experienced venous thrombosis within six months of Baseline.
21. Patient could not have experienced resting uncontrolled hypertension ($\geq 160/100$ mmHg) or symptomatic hypotension within three months before Baseline.
22. Patient could not have insulin-dependent diabetes mellitus.
23. Patient could not have a history of drug and/or alcohol abuse within six months of Baseline.
24. Patient could not have other serious intercurrent illness(es) or disease(s) (e.g., hematological, renal, hepatic, respiratory, endocrine, psychiatric) that might have interfered with, or put him at additional risk for, his ability to receive the treatment outlined in the protocol.

Medication Criteria

25. Patient could not have prothrombin and partial thromboplastin times outside of the normal range for the laboratory assays. Patients who were on anticoagulation or antiplatelet medications (e.g., dipyridamole, ticlopidine, warfarin derivatives) must have been receiving a stable dose for three months before baseline. Patients who were receiving warfarin-derivative anticoagulants must have had an International Normalized Ratio (INR) in the therapeutic range for the clinical indication for which the anticoagulant had been prescribed.
26. Patient could not have a known hypersensitivity to GnRH, GnRH agonists, ATRISORB® Barrier product, ATRIDOX® product, or any excipients of the study drug (NMP, PLG).
27. Patient with a history of the following prior to the study was excluded:
 - Immunization (within four weeks of Baseline).
 - Flu shots (within two weeks of Baseline)
 - Donation or receipt of blood or blood products (within two months of Baseline).
 - Anaphylaxis.
 - Skin disease which would interfere with injection site evaluation.
 - Dermatographism.

Medical officer's comment:

The study design, patient selection (including the rationale provided for each patient selection criterion), and the laboratory measurements are adequate and acceptable.

8.4.4. Study drug and dose selection

Three formulations of ELIGARD® have been developed by this sponsor and approved by FDA for treatment of advanced prostate cancer. LA-2500 7.5 mg (ELIGARD® 7.5 mg) is a one-month formulation of LA; LA-2550 22.5 mg (ELIGARD® 22.5 mg) is a three month formulation and LA-2575 30.0 mg (ELIGARD® 30.0 mg) a four-month formulation. LA-2580 45 mg is a six-month formulation developed by the sponsor following preclinical safety and tolerability studies, to deliver LA (45 mg) every six months. The formulation contains the same drug (LA) and the same biocompatible solvent (NMP) as the other ELIGARD® formulations.

Medical officer's comment:

Clinical laboratory measurements, including hematology, coagulation, and serum chemistry, were assessed at Screening, Baseline (Day 0), Days 1, 3, 7, 14, 28, 42, 56, 70, 84, 98, 112, 140, 168 (Month 6); Days 169, 171, 175, 182, 196, 210, 224, 238, 252, 266, 280, 308, and 336 (Month 12/Early Termination visit). Performance status (WHO/ECOG) was assessed at Screening, Baseline, and Days 28, 56, 84, 112, 140, Month 6 (Day 168), 196, 224, 252, 280, 308, and Month 12 (Day 336).

Patient assessments, including bone pain, urinary pain and urinary signs and symptoms, were collected at Baseline, Days 1, 2, 3, 7, 14, 28, 56, 84, 112, 140, 168 (Month 6), 169, 170, 171, 175, 182, 196, 224, 252, 280, 308, and 336 (Month 12). Blood samples for PSA and total acid phosphatase were collected at Screening, Baseline and Days 14, 28, 56, 84, 112, 140, 168 (Month 6), 182, 196, 224, 252, 280, 308, and 336 (Month 12). Vital signs including heart rate, blood pressure, respiratory rate and temperature were documented at Screening, Baseline (Day 0), and Days 7, 14, 28, 56, 84, 112, 140, 168 (Month 6), 175, 182, 196, 224, 252, 280, 308, 336 (Month 12/Early Termination visit).

8.5.3. Pharmacokinetic assessments

8.5.3.1 Special pharmacokinetic and pharmacodynamic assessments

Blood samples for PK analysis (serum leuprolide acetate) were taken at Baseline (Day 0), and each visit thereafter for Group A patients only. The reader is referred to the Clinical Pharmacology review for further details. Blood samples for evaluation of the efficacy variables T and LH were drawn at each visit.

8.5.3.2 Laboratory procedures for efficacy and pharmacokinetic assessments

To standardize clinical laboratory measurements, samples obtained from the patients at the investigational center were prepared and shipped to the central clinical laboratory for analyses. Samples for evaluation of leuprolide acetate, T and LH were then forwarded to central reference labs for analysis. The leuprolide analyses were performed by [] and the T and LH analyses were performed by []

When duplicate samples demonstrated differing testosterone levels beyond the established range of variability of the assay, the samples were re-run to determine the appropriate testosterone level for that sample time point.

Serum leuprolide was determined using a validated assay. This method involved solid-phase extraction (SPE) of leuprolide from human serum. The extract was further purified by high performance liquid chromatography (HPLC) which separated leuprolide from potential cross-reacting compounds. Analysis for leuprolide was by radioimmunoassay. This method was validated with a minimum quantifiable level of 100 pg/mL for leuprolide.

Medical officer's comment:

All of these assays are commercially available procedures, verified and monitored by a standard laboratory. Other supportive efficacy assessments are also considered adequate.

8.6 Efficacy results

8.6.1 Demographics

The mean age of the 111 patients enrolled in the study was 73.2 years (± 7.5), ranging from 50-86 years. The majority of patients (49.6%) were 70-79 years of age, while 22.5% were ages 80-86, 22.5% were in the 60-69 age group, and 5.4% were in the 50-59 age group. Over seventy-five percent (75.7%) of patients were White, 17.1% were Black, 5.4% were Hispanic, 0.9% were Asian, and 0.9% were Other. The mean height of patients was 68.9 (± 3.2) inches (5'9") and ranged from 62 to 76 inches. The mean weight of patients was 190.1 (± 36.7) pounds, ranging from 109-321 pounds. Demographics were similar across centers.

Nearly 77% (85/111) enrolled in the study reported a history of vascular disorders. 74.8% (83/111) of patients reported a history of musculoskeletal and connective tissue conditions, 73% (81/111) reported a history of urinary and renal conditions, 71.2% (79/111) reported surgical and medical procedures, 69.4% (77/111) reported reproductive and breast disorders, 49.6% (55/111) reported immune system disorders, 48.7% (54/111) metabolism and nutrition disorders, 43.2% (48/111) reported infections and infestations, 38.7% (43/111) reported a history of eye disorders, 36% (40/111) reported nervous system disorders, 36% (40/111) reported investigations, 35.1% (39/111) reported cardiac disorders, 32.4% (36/111) reported neoplasms benign, malignant and unspecified, 28.8% (32/111) reported respiratory, thoracic and mediastinal disorders, 27% (30/111) reported psychiatric disorders, 27% (30/111) reported general disorders, 23.4% (26/111) reported injury, poisoning and procedural complications, 18% (20/111) reported skin and subcutaneous tissue disorders, 16.2% (18/111) reported ear and labyrinth disorders, 9.9% (11/111) reported hepatobiliary disorders, congenital, familial or genetic disorders, and blood and lymphatic system disorders were each reported by 6.3% of patients (7/111), 4.5% (5/111) reported endocrine disorders.

Medical officer's comment:

The demographics included in this trial are generally representative of this patient population.

8.6.2. Disposition of patients

One hundred eleven patients were enrolled and received at least one study injection. Of those, 106 patients (95.5%) received two study injections. Eight patients discontinued during the study:

1. Patient #0513 was lost to follow up, having missed a number of visits following the second injection due to being out of town.
2. Patient #2002 was withdrawn from the study at Day 85 due to lack of efficacy, having failed to achieve testosterone suppression.
3. Patient #2704 voluntarily withdrew from the study due to metastatic liver cancer. After withdrawal from the study, the patient died as a result of metastatic liver cancer.

Five patients discontinued due to adverse events:

1. Patient #0313 experienced a myocardial infarction resulting in death one day after the first injection.
2. Patient #1106 discontinued due to rising PSA values and concomitant treatment with Casodex.
3. Patient #1501 exited the study after malignant soft tissue masses were noted.
4. Patient #1902 discontinued due to rising PSA starting at Day 225 and concomitant treatment with Casodex.
5. Patient #2904 experienced a stroke at Day 154 and subsequently elected to discontinue the study.

Medical officer's comment:

Although there were eight discontinuations, these did not significantly impact on the approvability of the product.

8.6.3. Major protocol violations

There were 278 protocol deviations attributable to 81 patients during the study (Table 2 below). The majority of protocol deviations (43%) were due to the timing of patient visits outside of the visit window.

Table 2: Summary of Protocol Deviations

Deviation	Frequency	
1. Outside of visit window	120/278	(43%)
2. Visit not conducted	81/278	(29%)
3. Incomplete collection of examination data	47/278	(17%)
4. Abnormal laboratory value at Baseline	15/278	(5%)
5. Other admission failure	8/278	(3%)
6. Other	5/278	(2%)
7. Prohibited medication during the study	2/278	(<1%)

*Source: Table A, AGL 0205 study report.

Medical officer's comment:

Although there were a notable number of protocol deviations, these did not significantly impact the approvability of the product.

Primary efficacy variable

8.6.4 Achievement of castrate T levels on Day 28

Intent-To-Treat population:

Testosterone suppression to castrate levels was first observed on Day 14, in 13 of 111 patients in the ITT population. The number of patients with castrate suppression increased rapidly over the next two weeks. By Month 1 (Day 28), 108 of 111 patients (97%) had achieved castrate suppression. Only three patients were not suppressed on Day 28. Two of these (#0313 and #2704) withdrew from the study before the Day 28 time point. For patient #0313, serum T data were obtained only on Day 1. For patient #2704, serum T data were obtained through Day 21, at which time the patient's T level had fallen to 6.1 ng/dl. The third patient (#2002) did not achieve T suppression at any time prior to withdrawing from the study on Day 85.

A high proportion of ITT patients (83% at Day 28 and 94% at Day 42) achieved the more stringent criteria of T suppression using a threshold of ≤ 20 ng/dl for at least two consecutive time points approximately one week apart. Of the 108 patients who achieved castrate level T suppression, none experienced breakthrough during the first six-month dosing interval and only one experienced breakthrough during the second dose period. This patient (#1402) achieved castrate level suppression on Day 21 and remained suppressed through Day 301. On Day 308, his T levels rose above 50 ng/dl, and remained so through the end of the study on Day 336 (Table 3). At Baseline, this patient's PSA level was 8.5, decreasing to 0.3 at Day 168; at break through the level was 0.4, rising to 1.3 at the end of study.

Table 3: Measures of Testosterone Suppression - Intent-to-Treat Population

Testosterone		M1		M2	M3	M4	M5	M6
Suppression	Day 14	Day 28	Day 42	Day 56	Day 84	Day 112	Day 140	Day 168
	N=111	N=111	N=111	N=111	N=111	N=111	N=111	N=111
≤ 50 ng/dL	13 (12%)	108 (97%)						
Breakthrough								
Above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≤ 20 ng/dL	0 (0%)	92 (83%)	104 (94%)	106 (96%)	106 (96%)	106 (96%)	102 (92%)	102 (92%)

Testosterone		M7	M8	M9	M10	M11	M12
Suppression	Day 182	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336
	N=111						
≤ 50 ng/dL	108 (97%)	108 (97%)	108 (97%)	108 (97%)	108 (97%)	107 (96%)	107 (96%)
Breakthrough							
above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
≤ 20 ng/dL	105 (95%)	105 (95%)	107 (96%)	104 (94%)	105 (95%)	101 (91%)	95 (86%)

*Source: Table B, AGL 0205 study report.

Observed Cases Population:

For the OC population, 108 of the 109 (99%) patients remaining in the study achieved castrate T suppression by Day 28. A high proportion of patients (84% at Day 28 and 95% at Day 42) achieved the more stringent criteria of T suppression to ≤ 20 ng/dL. At the end of the study (Day 336), 90 of 103 (87%) of the measured T levels were ≤ 20 ng/dL. Of the 103 patients whose serum T levels were measured on Day 336, all but one remained suppressed after achieving initial suppression. Details of this patient's breakthrough are given in Table D. For all cases (ITT and OC), the median time to castrate suppression was 21 days while the mean time to castrate suppression was 21.2 days. In addition, no acute-on-chronic responses were observed in any patients following the second treatment on Day 168 of the study.

Table 4: Measures of Testosterone Suppression - Observed Cases Population

Testosterone		M1		M2	M3	M4	M5	M6
Suppression	Day 14	Day 28	Day 42	Day 56	Day 84	Day 112	Day 140	Day 168
	N=110	N=109	N=109	N=108	N=106	N=104	N=105	N=105
≤ 50 ng/dL	13 (12%)	108 (99%)	108 (99%)	107 (99%)	106 (100%)	104 (100%)	105 (100%)	105 (100%)
Breakthrough								
above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
≤ 20 ng/dL	0 (0%)	92 (84%)	104 (95%)	105 (97%)	104 (98%)	102 (98%)	99 (94%)	99 (94%)

Testosterone		M7	M8	M9	M10	M11	M12
Suppression	Day 182	Day 196	Day 224	Day 252	Day 280	Day 308	Day 336
	N=103	N=105	N=103	N=104	N=97	N=101	N=103
≤ 50 ng/dL	103 (100%)	105 (100%)	103 (100%)	104 (100%)	97 (100%)	100 (99%)	102 (99%)
Breakthrough							
above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
≤ 20 ng/dL	100 (97%)	102 (98%)	102 (99%)	100 (96%)	94 (97%)	94 (93%)	90 (87%)

*Source: Table C, AGL 0205 study report.

8.6.5 Maintenance of castrate T levels

Of those patients who achieved castrate testosterone suppression (<50 ng/dL), all but one remained suppressed throughout their participation in the study. That is, one castrate suppression breakthrough was observed during the study (Patient #1402) beginning at Day 308. One patient (#2002) failed to suppress and was withdrawn from the study on Day 85.

8.6.6 Acute increases in serum T levels following repeat dosing

No acute-on-chronic responses were observed in any patients following any of the post-Baseline study injections.

Medical officer's comments:

1. A GnRH agonist has a potential to increase serum testosterone concentrations on repeat dosing, even in the face of apparent prior suppression of testosterone (the acute-on-chronic phenomenon). Such increases may be of a source of clinical symptoms. This study did not demonstrate this phenomenon.
2. The pharmacodynamic effects of ELIGARD® 45mg are similar to those reported following long-term administration of other GnRH agonists.
3. These efficacy results show that the end-points were achieved.

8.6.7 Overall changes in T concentrations

According to the sponsor's submission the Testosterone mean \pm SEM concentration at Baseline was 367.7 ± 13.0 ng/dL, with the middle 50% of the data ranging from 286 - 441 ng/dL. The mean concentration increased to a maximum of 588.6 ± 23.9 ng/dL on Day 2. By Day 21, the mean concentration (34.8 ± 3.4 ng/dL) had fallen below the medical castrate threshold. The mean concentration continued to decline, reaching 16.7 ± 3.4 ng/dL at Month 1 (Day 28).

Mean T levels were 10.4 ± 0.53 ng/dL prior to the second injection at Month 6 (Day 168), and remained at 10 ng/dL or less from Day 168 to Day 308. Mean T levels then increased slightly, to 12.6 ± 2.1 ng/dL at Month 12 (Day 336).

Medical officer's comment:

Review of data-sets submitted affirmed the T profile outlined above by the sponsor.

Secondary efficacy variables

8.6.8 Changes in serum LH concentrations

Serum LH concentrations, at Baseline, the mean \pm SEM concentration was 6.98 ± 0.48 MIU/mL, with the middle 50% of the data ranging from 3.8 to 9 MIU/mL. After the first treatment, LH increased to a maximum mean concentration of 37.9 ± 2.43 MIU/mL at

Hour 8 post-Baseline. By Day 7, the mean LH concentration (6.86 ± 0.34 MIU/mL) had decreased below the Baseline concentration, and LH concentrations fell consistently through the first 19 weeks to 0.095 ± 0.01 MIU/mL at Day 133. The mean LH concentration remained at 0.112 ± 0.024 MIU/mL on Day 168 prior to the second treatment.

Following the Day 168 (Month 6) injection, LH levels rose transiently to reach 0.206 ± 0.019 MIU/mL on Day 169, and then remained relatively steady throughout the remainder of the study. At Month 12 (Day 336) the mean LH concentration was 0.229 ± 0.14 MIU/mL.

Medical officer's comments:

The pivotal study showed that ELIGARD® 45mg achieved constant suppression of testosterone secretion by maintaining serum leuprolide exposures at levels above the minimum required for complete inhibition of gonadotropic hormone release.

8.6.9. PSA Levels

Serum PSA is considered elevated at levels above 4 ng/mL. At Baseline, the mean PSA was 39.8 ± 21.3 ng/mL, and 83 of the 110 patients (75.5%) tested at Baseline had elevated PSA readings. By Month 2 (Day 56) the mean PSA level had been reduced to 3.59 ± 1.00 ng/mL. By Month 6 (Day 168) the mean PSA level was 1.36 ± 0.32 ng/mL and only 6 of 105 (5.7%) remained elevated. Four of these 6 elevations had levels of <6 ng/mL. The two remaining patients had PSA levels (20-26 ng/mL) that were substantially reduced from their Baseline values (120-579 ng/mL).

Day 336 mean PSA levels were 1.15 ± 0.32 ng/mL and 4 of 103 (4%) of the PSA levels were elevated. Of the 77 patients who had elevated PSA levels at Baseline and also had a Month 12 (Day 336) PSA measure, 73 (95%) had achieved normal levels by the end of the study. All patients who had normal PSA levels at Baseline remained at normal PSA levels at the end of the study.

8.6.10. WHO patient performance status

At Screening, Baseline (Day 0), Days 28, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308 and Month 12 (Day 336), patient performance status was evaluated using a WHO performance scale. The scale consisted of three categories, ranging from 0 to 2 with the following definitions: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = Ambulatory and capable of self care but unable to carry out any work activities.

At Baseline, 100 (90.1%) patients were classified as fully active (Status = 0), eight patients (7.2%) were classified as restricted (Status=1), and three patients (2.7%) as unable to carry out work activities (Status=2). by Month 12 (Day 336) the percentage of fully active men increased slightly to 94%, and the percentage of men classified as restricted decreased slightly to 5%. One patient (< 1%) (#2402) remained classified as unable to carry out work activities at the end of the study (Status=2).

8.6.11 Patient assessments of bone pain and urinary symptoms

Bone pain and "urinary pain" were assessed by patient visual assessment scales (VAS) ranging from 1 to 10 and collected at Baseline, Days 1, 2, 3, 7, 14, 28, 56, 84, 112, 140, 168, 169, 170, 171, 175, 182, 196, 224, 252, 280, 308 and 336. On these scales, pain e ranged from 1 (no pain) to 10 (worst pain possible). "Urinary signs and symptoms" were also assessed on a VAS scale ranging from 1 to 10, with 1 defined as no difficulty and 10 defined as very difficult.

Overall at Baseline, patients experienced limited to no bone pain, with a mean score of 1.39 ranging from 1 to 7. This score remained low throughout the study with a mean score of 1.31 at Month 12 (Day 336), ranging from 1 to 8. "Urinary pain" was similarly low, with a mean of 1.22 at Baseline (range 1-8). By Month 12 (Day 336), the mean decreased slightly to 1.07 (range 1-5). Likewise, "urinary signs and symptoms" were low at baseline and throughout the study.

At Baseline, the mean symptom score was 1.49 (range 1-7), and 1.18 at Month 12 (Day 336) (range 1-6). Clinically, it is well recognized that brief symptomatic flare may occur following therapy with leuprolide acetate or other LH-RH agonists, sometimes necessitating concomitant medication or other treatment. However, there was little if any increase in the means of these symptom scores in the three days post-dosing, suggesting no flare symptoms.

Medical officer's comment:

The secondary efficacy assessments demonstrate changes similar to those reported following long-term administration of other superactive GnRH agonists. This finding reflects the fact that majority of patients in this population have hormone-sensitive tumors. While these were not truly validated endpoints, and they were not rigorously built into the statistical analyses, and this was an open-label, uncontrolled study, still these results are consistent with the reported pharmacodynamics and the palliative effect expected with this drug class in this patient population.

8.7 Conclusions regarding demonstrated efficacy

8.7.1 Achievement of protocol defined primary efficacy endpoints

Following 2, six-monthly doses of Eligard® 45 mg, 108 of 111 (97.3%) of patients in the ITT population and 108 of 109 (99%) patients in the OC population had achieved castrate T suppression. The median time to castrate suppression for both the ITT and OC populations was 21 days, and the mean time to castrate suppression was 21.2 days. All but one patient who achieved castrate T suppression (≤ 50 ng/dL) remained suppressed throughout the study. One castrate suppression breakthrough (defined as a T concentration of > 50 ng/dL after achieving suppression) was observed during the study (Patient #1402) beginning at Day 308.

Patient #2002 failed to suppress and was withdrawn from the study on Day 85.

8.7.2 Medical officer's overall assessment of efficacy

The efficacy results from pivotal Study AGL 0205 indicated that the efficacy objectives of the trial were successfully met. The sponsor's study successfully achieved the principal criteria that DRUDP has used to evaluate the efficacy of GnRH analogs in the palliative management of prostate cancer.

8.7.3 Support of efficacy claims in proposed label

The results of Study AGL 0205 support the sponsor's proposed label indication (the palliative treatment of advanced prostate cancer). The reviewer believes that this novel six monthly formulation of leuprolide offers another resource for the medical community in treating these patients with advanced prostate cancer.

9. Integrated review of safety

9.1. Data sources

As previously noted, a complete study report for one pivotal clinical trial was submitted in NDA 21-731, Volumes 2.118 – 2.155. The case report form tabulations were provided in Volumes 2.119 and 2.120, and the case report forms were provided in Volumes 2.138– 2.154. The study report included:

- PK study in a subset of 27 patients.
- AGL 0205: Single pivotal Phase 3 trial.

9.2. Description of patient exposure

One hundred eleven patients were enrolled and received at least one study injection. Of those, 106 patients (95.5%) received two study injections. Of the five who did not receive the second injection; Patient #0313 experienced myocardial infarction resulting in death at Day 1 of the study. Patient #1501 exited the study after malignant soft tissue masses were noted; Patient #2002 discontinued the study at Day 85 due to lack of efficacy of the study therapy. Patient #2704 voluntarily withdrew from the study; after withdrawal from the study he died as a result of metastatic liver cancer. Patient #2904 experienced a stroke and subsequently elected to discontinue participation in the study.

Medical officer's comment:

The number of patients exposed to the six-monthly formulation of ELIGARD® and the duration of its exposure, in conjunction with the historical information relevant to other GnRH formulations (and very similar ELIGARD® formulations), is considered adequate to assess the general safety of ELIGARD® for the indication of management of advanced prostate cancer.

9.3. Safety assessments conducted in the primary safety study

9.3.1. Procedures for collecting safety data

At each clinical visit, patients were to be assessed for potential adverse events. At each visit, adverse events were recorded on a visit-specific adverse event case report form (CRF). Additional information about serious adverse events was provided to the sponsor on a separate serious adverse event (SAE) form.

9.3.2. Analysis and reporting of safety data.

9.3.2.1. Adverse events

Adverse events were classified into body system categories and summarized by the number of patients reporting an event and the percentage of patients with that event.

9.3.2.2. Vital signs

Vital signs including heart rate, blood pressure, respiratory rate and temperature were documented at various time points (Table 1)

9.3.2.3. Clinical laboratory tests

Individual laboratory values were listed by patient and by visit. Laboratory parameters before treatment, at each visit, and the change from pretreatment values to each on-treatment assessment were presented as summary statistics. Shift tables (change from baseline value to on-treatment values) based on laboratory normal ranges were presented for each laboratory measurement and each assessment time. Incidence rates of new on-treatment abnormal laboratory values, based on the shift tables, were calculated and listed by laboratory test and visit.

Blood samples for hematology, coagulation, and blood chemistry were collected at screening and at various visits (Table 1) visits. The specific assessments were:

- Hematology: hemoglobin, red blood cell count, and total leukocytes prothrombin time.
- Blood chemistry: Glucose, BUN, creatinine, SGOT/AST, SGPT/ALT, alkaline phosphatase, and bilirubin.

Medical officer's comment:

Safety assessments listed are adequate for this product.

9.4. Demographics for Pivotal Study AGL0205.

Please refer to section 8.6.1 of this review.

9.5. Adverse events

9.5.1. Overview of adverse events (Data from AGL 0205)

One hundred eleven men with carcinoma of the prostate received at least one SC injection of LA-2580 45 mg. The majority of patients were white, older males in their seventies.

1. Vital Sign Measurements: There were no clinically significant changes observed in vital sign measurements (temperature, heart rate, blood pressure and respiratory rate) during the study.
2. Deaths: Two deaths were reported in this study. Neither appeared to be drug-related.
3. Discontinuations Due to Adverse Events: Five patients discontinued the study due to adverse events.
4. Serious Adverse Events: No serious treatment-related AE's were reported. Thirty-four serious *non*-treatment-related AE's were reported by a total of 22 patients.
5. Overall, there were 949 all-causalities AE's, of which 846 were mild to moderate in severity. Sixty nine all-causalities AE's were classified as severe by the investigator.
6. Two hundred eleven (211) treatment-related AE's were reported by a total of 82 patients. Of the 211 treatment-related events, 210 were reported as mild to moderate, and one was reported as severe. The most common AE's (experienced by 3 or more patients) found in the treatment-related categories were: hot flashes, administration site conditions (burning, stinging, bruising and pain), fatigue, weakness, gynaecomastia, testicular atrophy, myalgia, limb pain, and night sweats. Many of these AE's are those typically associated with T suppression and consequent medical castration.
7. Injection site AE's were typical of those associated with similar SC injectable products. No patients discontinued the study due to these events. No injection site AE's raised a clinical concern.
8. Laboratory values: Mean values for hematology and clinical chemistry parameters were generally within normal limit ranges for all study time points. Mean values deviated from the normal range at sometime during the study period for the following analytes: RBC count, HCT, HGB, cholesterol, triglycerides, alkaline phosphatase, acid phosphatase, and PSA.

Medical officer's comment:

The reviewer believes that the adverse events reported in this trial are generally seen in this patient population that is treated with the GnRH agonists.

9.5.2. Premature discontinuations due to adverse events

Five patients discontinued the study due to adverse events:

1. Patient #0313 experienced a myocardial infarction resulting in death one day after the first injection.
2. Patient #1106 discontinued due to rising PSA values and concomitant treatment with Casodex.
3. Patient #1501 exited the study after malignant soft tissue masses were noted.
4. Patient #1902 discontinued due to rising PSA starting at Day 225 and concomitant treatment with Casodex.

2. **Vascular disorders:** 68 patients (61.3%) reported events in this category. Sixty-four patients (57.7%) reported hot flashes ("Hot flushes NOS"). Hypertension aggravated was reported by 10 patients (9.0%).
3. **Musculoskeletal and connective tissue disorders:** 59 patients (53.2%) reported events in the class. Twenty-six patients (23.4%) reported arthralgia and 22 patients (19.8%) reported limb pain. Myalgia was reported by 11 patients (9.9%), while 10 patients (9.0%) experienced back pain. Muscle cramps were reported by six patients (5.4%).
4. **Gastrointestinal disorders:** 49 patients reported events (44.1%) in this category. Seventeen patients (15.3%) reported nausea, and eleven patients (9.9%) reported diarrhea NOS. Constipation was reported by nine patients (8.1%). Dyspepsia and vomiting were each reported by five patients (4.5%).
5. **Infections and infestations:** 48 patients (43.2%) reported events in this category. The most common event was nasopharyngitis, reported by 18 patients (16.2%). Upper respiratory tract infection NOS and urinary tract infection NOS were each reported by seven patients (6.3%).
6. **Nervous system disorders:** 38 patients (34.2%) reported events in this category. The most common event, dizziness was reported by 17 patients (15.3%). Headache NOS was reported by nine patients (8.1%), while four patients (3.6%) experienced syncope.
7. **Renal and urinary disorders:** 35 patients (31.5%) reported events in this category. The most common event in this category was dysuria reported by 9 patients (8.1%). Urinary frequency was reported by eight patients (7.2%). Six patients (5.4%) reported nocturia. Four patients (3.6%) each experienced haematuria, micturition disorder and urgency.
8. **Respiratory, thoracic and mediastinal disorders:** 30 patients (27.0%) reported events in this category. Nine patients (8.1%) reported cough, while eight (7.2%) reported pharyngitis. Five patients (4.5%) reported dyspnea.
9. **Skin and subcutaneous tissue disorders:** 27 patients (24.3%) reported events in this category. Contusion and rash NOS were each reported by nine patients (8.1%). Four patients (3.6%) reported generalized pruritus.
10. **Reproductive system and breast disorders:** 20 patients (18.0%) reported events in this category. Ten patients (9.0%) experienced testicular atrophy, and four patients (3.6%) reported gynaecomastia.
11. **Psychiatric disorders:** 19 patients (17.1%) reported events in this category. Six patients (5.4%) reported anxiety, four patients (3.6%) reported insomnia, and three patients (2.7%) reported nervousness.
12. **Cardiac disorders:** 14 patients (12.6%) reported events in this category. Three patients (2.7%) each experienced congestive cardiac failure and myocardial

infarction. All other events in this class were each reported by no more than two patients.

13. **Metabolism and nutrition:** 12 patients (10.8%) reported events in this category. Five patients (4.5%) experienced hypercholesterolaemia and three patients (2.7%) reported hyperlipidaemia NOS.
14. **Neoplasms:** 10 patients (9.0%) experienced benign, malignant, and unspecified cysts and polyps. Four patients (3.6%) reported basal cell carcinoma events.
15. **Blood and lymphatic system disorders:** 6 (5.4%) reported events in this category. Four patients (3.6%) experienced lymphadenopathy.

Medical officer's comment:

The adverse event profile presented above does not raise any new safety issues with this product and appears similar to that seen with the other approved Eligard® products in this patient population.

9.5.5.2. Treatment related adverse events

The following possibly or probably related systemic adverse events occurred during clinical trials of up to 12 months of treatment with ELIGARD® 45 mg, and were reported in > 2% of patients.

Table 5. Incidence (%) of Treatment Related Systemic Adverse Events Reported by > 2% of Patients (n = 111) Treated with ELIGARD® 45 mg for up to 12 Months in Study AGL0205

Body System	Adverse Event	Number	Percent
Vascular	Hot flashes**	64	57.7%
General Disorders	Fatigue**	13	11.7%
	Weakness	4	3.6%
Reproductive	Testicular atrophy**	8	7.2%
	Gynecomastia**	4	3.6%
Skin	Night sweats**	3	2.7%
Musculoskeletal	Myalgia	5	4.5%
	Pain in limb	3	2.7%

*Source Table 19 ISS/PI - Treatment-related adverse events

**Associated with Low T levels

The following possibly or probably related systemic adverse events were reported by 1% of the patients (2/111) using ELIGARD® 45 mg in the clinical study.

- General: Lethargy
- Reproductive: Penile disorder
- Renal/Urinary: Nocturia
- Psychiatric: Loss of libido

Medical officer's comments:

Hot flashes, impotence, decreased libido, gynecomastia and testicular atrophy are frequently reported adverse events following androgen withdrawal. These are well-recognized pharmacological consequences of medical castration.

Overall, the types of adverse events reported and their frequencies are not unexpected considering the study population and treatment (e.g. older men with advanced prostate cancer).

9.5.5.3 Adverse events by race, age, weight, disease stage

9.5.5.3.1. Race:

All-Causalities Adverse Events by Race

Eighty-four patients were white, 19 were black, and eight were in other race categories (Hispanic/Asian/Other). Events were generally evenly distributed between the three race categories, and comparisons were non-significant except as noted below.

Within the General disorders and administrative site conditions class, fatigue was statistically more prevalent among other races (50.0% of patients) than among blacks (5.3% of patients). Injection site burning was significantly more prevalent among whites (22.6% of patients) than blacks (0.0% of patients). Peripheral edema was prevalent in other races than whites.

In the Musculoskeletal and connective tissue disorder class, arthralgia was statistically more prevalent among blacks (47.4% patients) than whites (17.9% of patients). Pain in limb was more prevalent among the other races (50.0% of patients) than blacks (10.5% of patients). No other statistically significant difference was noted across the categories.

Medical officer's comment:

There are not enough numbers in various race categories to draw definitive conclusions. Additionally, no significant associations were discovered between treatment-related adverse event rates and race.

9.5.5.3.2. Weight:

No significant associations were discovered between treatment-related adverse event rates and weight.

9.5.5.3.3. Disease Stage:

There were no significant associations noted between treatment-related adverse events and baseline disease stage by Jewett's classification system.

9.5.5.4 Localized injection site adverse events

Of the 217 injections administered, localized reactions were associated with 53 (24.4%). All reactions were mild, except the seven reported as moderate in intensity. The majority of the injections were not associated with any reported localized AE's. The most commonly reported AE was burning on injection. This event was reported during 28 of the 217 injections (12.9%). Burning severity was reported as mild for 26 of these events and moderate in two.

Stinging at the injection site was reported after 7 of 217 injections (3.2%). Stinging severity was reported as mild for six of seven events and moderate for one event. Pain at the injection site was reported during 10 of 217 injections (4.6%). Severity was reported as mild in 9 (90%) of 10 reported events. Bruising was reported following five (2.3%) study injections and moderate bruising was reported following two (<1%) study injections.

Medical officer's comments:

Localized injection site AE's were mild in intensity, short in duration and non-recurrent over time. This profile is similar to the other approved Eligard® products. No patient discontinued therapy and no new signals were uncovered in this NDA due to an injection site adverse event.

9.6 Laboratory assessments

9.6.1 Routine laboratory assessments

Hematology assessments included total WBC's, total RBC's, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and platelets.

Clinical chemistry assessments included serum glucose, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphorous, sodium, potassium, chloride, bicarbonate, triglycerides, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatine kinase, and lactate dehydrogenase.

Mean values for hematology, clinical chemistry, and coagulation parameters were generally within normal limit ranges for all study time points. No clinically significant excursions or trends were noted.

9.6.2. Special laboratory assessments

9.6.2.1. Prostate cancer markers

Serum PSA was elevated for 83 of 110 (75.5%) patients tested at Baseline, which is consistent with this study population of advanced prostate cancer patients awaiting androgen suppressive therapy. The incidence of patients with increased PSA declined steadily at each consecutive time point from Day 28 to Month 12.

5. Patient #2904 experienced a stroke at Day 154 and subsequently elected to discontinue the study.

Medical officer's comment:

The reviewer believes that the adverse events reported above are frequently seen in this patient population.

9.5.3. Deaths: Two deaths were reported; one occurred while the patient was on-study and the second occurred after the patient discontinued their participation. Both were determined *unrelated* to the study treatment. Patient #0313 experienced a myocardial infarction resulting in death one day after the first injection; Patient #2704 voluntarily withdrew and subsequently died from metastatic liver cancer.

9.5.4. Serious Adverse Events: No serious treatment-related AE's were reported. Thirty-four serious *non-treatment-related* AE's were reported by a total of 22 patients. These included: worsening of rheumatoid arthritis requiring surgery (#0101); respiratory infection (#0201); chest pain and myocardial infarction (#0304); decreased motor function (#0310); myocardial infarction resulting in death (#0313); left femoral neck fracture (#0503); gastrointestinal bleeding (#0701); faintness, weakness and gastrointestinal bleeding (#0801); diverticulosis (#0806); "swollen glands" resulting in hospitalization (#0808); gallstones and abdominal pain (#1105); exacerbation of chronic obstructive pulmonary disease (#1107); radius fracture (#1901); hernia (umbilical, incisional and inguinal, #2201); myocardial infarction (#2401); pneumonia and cough (#2403); malignant neoplasm, nausea, constipation, dehydration and listeriosis bacteria resulting in death (#2704); stroke (#2904); bilateral shoulder pain requiring hospitalization (#3102); cerebral vascular accident and exacerbation of congestive heart failure (#3104); transient ischemic attack (#3106) and acute chronic obstructive pulmonary disease (#3203).

Medical officer's comment:

This reviewer believes that the adverse events reported above are frequently seen in this patient population. No deaths or serious adverse events described in the NDA were judged as causally related to the treatment.

9.5.5 Reported Adverse Events

9.5.5.1. All-causality adverse events

1. **General disorders and administration site conditions:** 69 patients (62.2%) reported events in this category. Local site reactions included: injection site burning reported by 19 patients (17.1%); seven patients (6.3%) reported injection site bruising, and injection site pain; six patients (5.4%) reported injection site reaction NOS. Systemic reactions included: Fatigue reported by 22 patients (19.8%). Peripheral edema reported by 12 patients (10.8%); nine patients (8.1%) reported weakness; seven patients (6.3%) reported influenza-like illness; six patients (5.4%) reported chest pain.

The mean acid phosphatase concentrations remained within normal range at all study time points, with a 35.5% increase from Baseline to Month 12.

9.6.2.2. Serum cholesterol

Mean total cholesterol values were within the normal range at Baseline and all time points up to Day 28. From Day 28 forward, mean values at all time points were elevated above the upper limit of normal (5.0% - 10.8%). There was a 7.7% increase in mean total cholesterol from Baseline to Month 12. At the individual patient level, 41 of 107 patients tested (38.3%) had minimally elevated cholesterol concentrations that were pre-existing at Baseline.

From Day 28, the number of patients with slightly elevated cholesterol increased above Baseline frequency to a peak of 50 of 101 patients tested (49.5%) at Day 84. The incidence of patients with mildly elevated cholesterol then fluctuated between 40 - 48% throughout the remainder of the trial.

Medical officer's comment: The result for serum cholesterol may or may not reflect the effect of testosterone suppression.

9.7. "Marked" laboratory abnormalities

Nineteen patients had values that were considered "markedly abnormal" at some point during the clinical study. Five patients had marked abnormalities noted for more than one parameter. No patient discontinued from the clinical program due to any clinical laboratory abnormality.

Medical officer's comments:

1. This reviewer agrees with the sponsor's assessment that the clinical laboratory changes were not clinically significant.
2. The data submitted describing "shifts" in laboratory values to (a) values below the lower limit of the normal range ("shift to low") or (b) to values above the upper limit of the normal range ("shift to high") were not notable for any clinically important drug-related changes.
3. Overall, all available laboratory data do not raise concerns about significant drug-induced toxicity associated with the use of the ELIGARD® 45mg for the treatment of advanced prostate cancer.

9.8 Safety issues of special concern

There are no safety issues of "special concern". As a class, clinical experience has shown that superactive GnRH agonists are generally safe and well tolerated in the treatment of advanced prostate cancer.

As noted previously, prescriber's should be aware of the rare potential for "clinical flare", rare systemic allergic reactions upon initiating therapy, and the clinical manifestations of T suppression.

In the particular case of ELIGARD® 45mg, it appears that local site reactions were mild in severity, brief in duration, and appeared to resolve without incident.

9.9 Safety consultations

No safety consultations were obtained.

9.10 Safety Update

On December 3, 2004, the sponsor notified the Division that there is nothing further to report in regard to safety since submission of the original NDA. There are no new deaths, SAE's, or medically significant AE's.

9.11 Safety findings and proposed labeling

The following sections of the proposed labels underwent minor labeling revisions:

- Clinical pharmacology
- Clinical Studies
- Adverse Reactions
- Dosage and Administration

Labeling negotiations with sponsor were conducted in a cooperative manner.

10. Package insert

The proposed package insert was reviewed in great detail. Overall, the PI was accurate and clear. However, minor modifications of the clinical and clinical pharmacology information were deemed necessary. These proposed changes in the PI were forwarded to sponsor. Labeling negotiations with sponsor transpired in cooperative fashion.

11. Use in special populations and Drug-Drug interactions.

Women and children were not studied for this indication (treatment of advanced prostate cancer). These groups are contraindicated in the package insert. Regarding race, pharmacokinetic data was available for 17 White, 7 Black and 3 Hispanic patients. Mean serum leuprolide concentrations were similar in these 3 groups. The overall number of non-White patients was too small to allow for definitive conclusions regarding differences in clinical adverse events.

The pharmacokinetics of ELIGARD® in patients with renal or hepatic insufficiency was not studied for this NDA. No drug-drug interaction studies were conducted. While this fact is noted in the package insert, it is not considered a safety issue because clinical experience has revealed leuprolide to be safe even at high concentrations and because

leuprolide is rapidly metabolized by peptidase(s) and is less than 50% bound in the plasma.

12. Conclusions and recommendations

12.1. Overall risk/benefit assessment

The reader is also referred to the Executive Summary section of this review.

Benefits: The goal of androgen suppression therapy for the palliative management of advanced prostate cancer is to reduce serum testosterone concentrations to levels comparable to those observed following orchiectomy (≤ 50 ng/dL). Superactive GnRH agonists that suppress serum testosterone to castrate levels have been shown to have comparable long-term efficacy to bilateral orchiectomy, as assessed by time to disease progression and survival. Achievement of castrate levels of serum testosterone is generally obtained by one month after the start of therapy with a superactive GnRH agonist. In the case of ELIGARD 45 mg, 108 of 109 evaluable patients obtained castrate suppression by Day 28 (99%).

Following two, once every six months, treatments with ELIGARD® 45 mg, 99% of patients completing the study maintained castrate suppression of T concentration, defined as T concentration ≤ 50 mg/dL for two consecutive time points approximately one week apart.

One patient did not reach castrate T suppression and was withdrawn from the study at Day 85. One patient achieving castrate T suppression did not remain suppressed throughout the remainder of the study. This patient had a breakthrough late in the study and did not resuppress. The median time to castrate T suppression was 21 days and the mean time was 21.2 days. In addition, there was no acute-on-chronic phenomenon seen during the course of the study. These findings are considered sufficient to support the efficacy of the ELIGARD® for the palliative treatment of advanced prostate cancer.

Risks: In contrast to surgical castration, treatment with a superactive GnRH agonist initially results in a temporary (1-2 weeks) increase in gonadal androgen secretion before reducing serum testosterone to castrate levels. The initial rise in serum testosterone may cause a temporary worsening of symptoms referred to as "a flare." Most commonly, the androgen-induced flare consists of an increase in bone pain in patients with advanced prostate cancer. Less frequently, more serious complications such as compression of the spinal cord with motor impairment can occur. This potential complication is a labeled warning for all superactive GnRH agonists. The likelihood of such serious complications is diminished with earlier diagnosis of prostate cancer, as is occurring today in the United States. The risk of a clinically serious complication resulting from the initial surge of testosterone at the onset of treatment with ELIGARD™ should be no different than that associated with the use of other presently approved superactive GnRH analogs.

Vast clinical experience had shown that GnRH agonists are safe and well tolerated for the treatment of prostate cancer.

Since GnRH analogs are small peptides, they have the potential to induce antibody formation and hypersensitivity reactions. Rare reports of systemic allergic reaction have been noted in the literature.

In addition, injection site adverse events such as local induration, pain, burning, erythema and pruritis were similar to those seen with the other approved Eligard® products.

In summary, based on safety and efficacy information submitted in NDA 21-731, this reviewer believes that ELIGARD® 45mg is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

12.2. Recommendations

It is recommended that the six-monthly formulation of ELIGARD®45mg should be approved for the proposed indication of "palliative treatment of advanced prostate cancer".

Ashok Batra, MD
Medical Officer
Division of Reproductive and Urologic Drug Products
Arch NDA 21-731
cc: HFD-580/Div File
HFD-580/DShames/MHirsch/JKim

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ashok Batra
12/6/04 09:56:40 AM
MEDICAL OFFICER

Mark S. Hirsch
12/6/04 11:46:32 AM
MEDICAL OFFICER
I concur.

NDA 21-731
March 16, 2004

Medical Officer's Memo – Filing Review for New IND

Date submitted: February 13, 2004
Date received CDER: February 20, 2004
Date memo completed: March 19, 2004

Drug product: Eligard™ (Luprolide acetate 45 mg for injectable suspension)
Dose: once every six months
Sponsor: Atrix Laboratories Inc.
Fort Collins, CO
Indication: Palliative treatment of advanced prostate cancer

1. Executive summary: The purpose of this memo is to provide my recommendation to the medical TL and the Division Director in regard to filing this NDA. **I recommend that the NDA should be filed.**

2. Scientific background

Drug product: ELIGARD® 45 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly(DL-lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The second syringe contains leuprolide acetate. Constituted product is designed to deliver 45 mg of leuprolide acetate at a controlled rate over a six-month therapeutic period.

Indication: Eligard™ is indicated for the palliative treatment of advanced prostate cancer.

3. Overview of clinical data in the original NDA:

The sponsor currently holds FDA approval for three subcutaneous (SC) leuprolide acetate depot injections for the palliative treatment of prostate cancer.

- One-month ELIGARD® 7.5 mg (NDA 21-343) in January 2002.
- Three-month ELIGARD® 22.5 mg (NDA 21-379) in July 2002
- Four-month ELIGARD® 30 mg (NDA 21-488) in February 2003.

All three have been shown to be effective in reducing testosterone levels to medical castrate levels (< 50 ng/dL) within three to four weeks. The sponsor now submits this NDA in regards to, a six-month, extended-release formulation, ELIGARD® 45 mg. The sponsor conducted one pivotal phase III study (AGL0205) in the development of this NDA. Essential elements of study AGL0205 were agreed upon with the Agency. Study AGL0205 was a 12-month, open label, non controlled, fixed-dose (2 doses) study. This study investigated the safety and hormonal efficacy in 111 patients, and the pharmacokinetics of leuprolide in a subset of 28 patients.

Results from the pivotal Study AGL0205:

Efficacy:

Over the 12-month study period, 106 patients (95.5%) received two study injections. A total of eight patients discontinued during the study. 108 of 111 (97.3%) patients, between 50 and 86 years, in the ITT population reached castrate suppression of T concentration, defined as T concentration of ≤ 50 ng/dL for two consecutive time points approximately one week apart. A high proportion of ITT patients (83% at Day

28 and 94% at Day 42) achieved the more stringent criteria of T suppression using a threshold of ≤ 20 ng/dL. Three patients failed to suppress during the study. One breakthrough was noted.

Safety:

Local site adverse events

Of the 217 injections administered, localized reactions were associated with 53 (24.4%). These included, injection site burning (15.3%), injection site stinging (5.4%), injection site bruising (2.7%), injection site pain (4.6 %). All reactions were mild, except the seven reported as moderate in intensity.

Deaths, Dropouts Due to Adverse Events, and Other Serious AE's:

Two deaths were reported in this study. One death occurred during the study and one death within 30 days following patient discontinuation. There were five cases of premature discontinuations. None of these events were considered associated by the investigator.

Systemic AE's

The most common AE's (experienced by 3 or more patients) found in the treatment-related categories were: hot flashes (58%), administration site conditions (burning, stinging, bruising and pain), fatigue (12%), weakness (4%), gynecomastia, testicular atrophy, myalgia, limb pain, and night sweats(See table). No serious treatment-related AE's were reported. Thirty-four serious non-treatment-related AE's were reported by a total of 22 patients.

Table: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by > 2% of Patients (n = 111) Treated with ELIGARD® 45 mg for up to 12 Months in Study

Body System	Adverse Event	Number	Percent
Vascular	Hot flashes*	64	57.7%
General Disorders	Fatigue	13	11.7%
	Weakness	4	3.6%
Reproductive	Testicular atrophy*	8	7.2%
	Gynecomastia*	4	3.6%
Skin	Night sweats*	3	2.7%
Musculoskeletal	Myalgia	5	4.5%
	Pain in limb	3	2.7%

4. Other aspects of filability

Proposed label:

Preliminary review of label, including the subsections, shows that it is organized appropriately for the claims sought.

Legibility and formatting:

The NDA document is adequately formatted and legible to allow for a substantive clinical review.

Case report forms:

Case report forms for deaths, SAE's and discontinuations due to AE's were submitted as required.

5. Summary statement

Preliminary review shows that the sponsor has conducted an acceptable pivotal study. The supporting data is acceptable. In brief, the submission is organized adequately to lend itself to a substantive review. In view of this reviewer, the NDA is fileable.

Ashok Batra, M.D.
Medical Officer
Division of Reproductive and Urologic Drug Products
Arch NDA 21-731
Cc: HFD-580/Div File
HFD-580/DShames/MHirsch/NCrisostomo

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ashok Batra
4/27/04 11:41:00 AM
MEDICAL OFFICER

Mark S. Hirsch
4/27/04 06:11:20 PM
MEDICAL OFFICER
I concur.