

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-731

Trade Name: Eligard 45 mg Injectable Suspension

Generic Name: leuprolide acetate

Sponsor: Atrix Laboratories, Inc.

Approval Date: December 14, 2004

Indications: For palliative treatment of advanced prostate cancer.

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APPLICATION NUMBER:

21-731

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-731

Atrix Laboratories, Inc.
Attention: Cheri Jones, MS, RAC
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Dear Ms. Jones:

Please refer to your new drug application (NDA) dated February 13, 2004, received February 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIGARD[®] 45mg (leuprolide acetate for injectable suspension).

We acknowledge receipt of your amendments dated: May 20, August 11, September 17, November 23 (2), December 3 and 7, 2004.

This new drug application provides for the use of ELIGARD[®] 45mg for the palliative treatment of advanced prostate cancer.

We completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted labeling (package insert submitted December 7, 2004, **and** immediate container and carton labels submitted August 11 and November 23, 2004). Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-731.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling for PI

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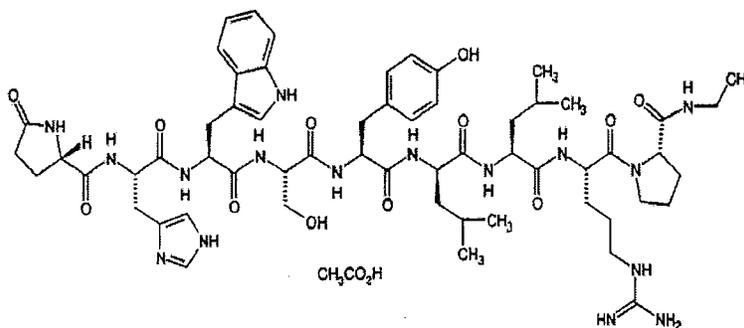
APPROVED LABELING

ELIGARD® 45 mg
(leuprolide acetate for injectable suspension)

DESCRIPTION

ELIGARD® 45 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 45 mg of leuprolide acetate at a controlled rate over a six-month therapeutic period.

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. The analog possesses greater potency than the natural hormone. The chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate with the following structural formula:



ELIGARD® 45 mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. ELIGARD® 45 mg is administered once every six months subcutaneously, where it forms a solid drug delivery depot.

One syringe contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. 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). PLG is a copolymer with an 85:15 molar ratio of DL-lactide to glycolide with hexanediol. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 45 mg of leuprolide acetate at the time of subcutaneous injection.

ELIGARD® 45 mg delivers 45 mg of leuprolide acetate (equivalent to approximately 42 mg leuprolide free base) dissolved in 165 mg *N*-methyl-2-pyrrolidone and 165 mg poly(DL-lactide-co-glycolide). The approximate weight of the administered formulation is 375 mg. The approximate injection volume is 0.375 mL.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprolide acetate results in suppression of testicular and ovarian steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold (≤ 50 ng/dL). These decreases occur within two to four weeks after initiation of treatment.

PHARMACODYNAMICS

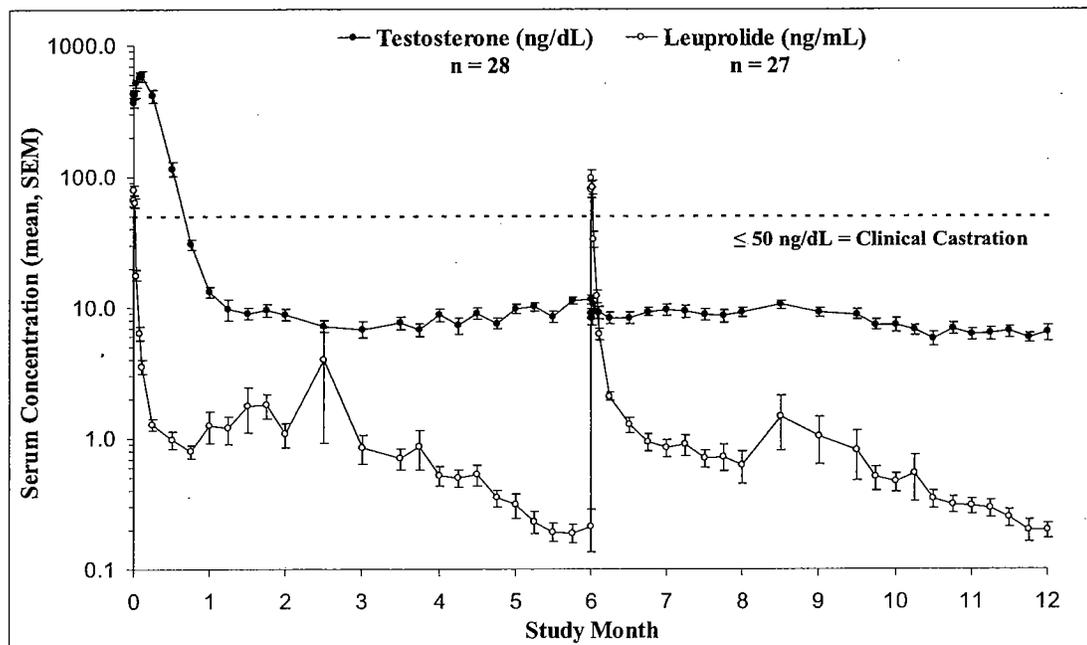
Following the first dose of ELIGARD® 45 mg, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold (≤ 50 ng/dL) within three weeks (Figure 1). One patient at Day 1 and another patient at Day 29 were withdrawn from the study before the Month 1 blood draw. Of the 109 patients remaining in the study, 108 (99.1%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). One patient did not achieve castrate suppression and was withdrawn from the study at Day 85. Once castrate testosterone suppression was achieved, one patient ($< 1\%$) demonstrated breakthrough (concentrations above 50 ng/dL after achieving castrate levels).

Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption: The pharmacokinetics/pharmacodynamics observed during injections administered initially and at six months (ELIGARD® 45 mg) in 27 patients with advanced carcinoma of the prostate is shown in Figure 1. Mean serum leuprolide concentrations rose to 82 ng/mL and 102 ng/ml (C_{max}) at approximately 4.5 hours following the initial and second injections, respectively. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.2 – 2.0 ng/mL). There was no evidence of significant accumulation during repeated dosing. Nondetectable leuprolide plasma concentrations have been occasionally observed during ELIGARD® 45 mg administration, but testosterone levels were maintained at castrate levels.

Figure 1 Pharmacokinetic/Pharmacodynamic Response (N = 27) to ELIGARD® 45 mg - Patients Dosed Initially and at Month 6



Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L.¹ In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism: In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination half-life of approximately three hours based on a two compartment model.¹

No drug metabolism study was conducted with ELIGARD® 45 mg. Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-1) metabolite.

Excretion: No drug excretion study was conducted with ELIGARD® 45 mg.

Special Populations:

Geriatrics: The majority (72%) of the 111 patients studied in the clinical trial were age 70 and older.

Pediatrics: The safety and effectiveness of ELIGARD® 45 mg in pediatric patients have not been established (see **CONTRAINDICATIONS**).

Race: In patients studied (17 White, 7 Black, 3 Hispanic), mean serum leuprolide concentrations were similar.

Renal and Hepatic Insufficiency: The pharmacokinetics of ELIGARD® 45 mg in hepatically and renally impaired patients have not been determined.

Drug-Drug Interactions: No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD® 45 mg.

CLINICAL STUDIES

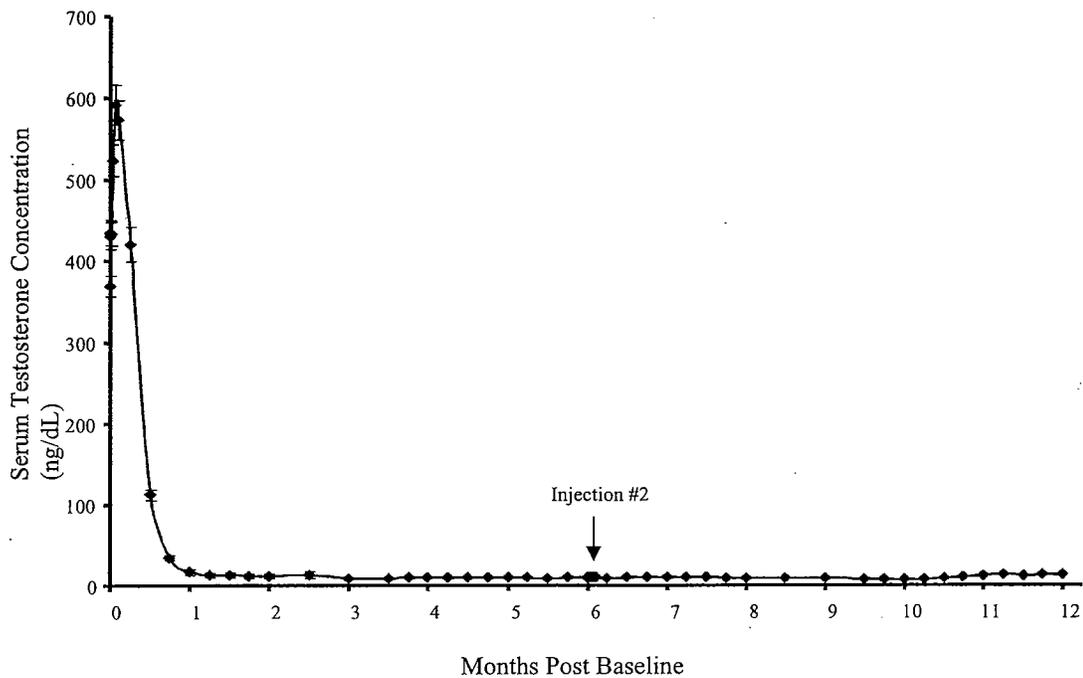
In one open-label, multicenter study (AGL0205), 111 patients with advanced prostate cancer were treated with at least a single injection of study drug. Of these, 106 patients received a total of two injections of ELIGARD® 45 mg given once every six months. Five patients had Jewett stage A disease, 43 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. A total of 103 patients completed the study.

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 (Figure 2).

Of the original 111 patients, two were withdrawn from the study prior to the Month 1 blood draw. Serum testosterone was suppressed to below the castrate threshold (≤ 50 ng/dL) by Day 28 in 108 of 109 (99.1%) patients remaining in the study. One patient ($< 1\%$) did not achieve castrate suppression and was withdrawn from the study on Day 85. 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 reached castrate suppression at Day 21 and remained suppressed until Day 308 when his testosterone level rose to 112 ng/dL. At Month 12 (Day 336), his testosterone was 210 ng/dL. Of 103 evaluable patients in the study at Month 12, 102 had testosterone concentrations of ≤ 50 ng/dL.

All five non-evaluable patients who had achieved castration by Day 28 maintained castration at each timepoint, up to and including the time of withdrawal.

Figure 2 ELIGARD® 45 mg Mean Serum Testosterone Concentrations
(n = 103)



Serum PSA decreased in all patients whose Baseline values were elevated above the normal limit. Individual mean values were reduced an average of 97% from Baseline to Month 12. At Month 12, PSA levels had decreased to within normal limits in 95% of patients who presented with elevated levels at Baseline.

Other secondary efficacy endpoints evaluated included WHO performance status, bone pain, urinary pain and urinary signs and symptoms. 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 increased slightly to 94%, the percentage of men classified as restricted decreased slightly to 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 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 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). Urinary signs and symptoms were similarly low at Baseline and decreased modestly at Month 12. In addition, there was a reduction in patients with prostate abnormalities detected during physical exam from 89 (80%) at Screening to 60 (58%) at Month 12.

INDICATIONS AND USAGE

ELIGARD® 45 mg is indicated for the palliative treatment of advanced prostate cancer.

CONTRAINDICATIONS

1. ELIGARD® 45 mg is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD® 45 mg. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.²
2. ELIGARD® 45 mg is contraindicated in women and in pediatric patients and was not studied in women or children. Moreover, leuprolide acetate can cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

WARNINGS

ELIGARD® 45 mg, like other LH-RH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. Patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, or bladder outlet obstruction. Isolated cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been observed in the palliative treatment of advanced prostate cancer using LH-RH agonists (see **PRECAUTIONS**).

If spinal cord compression or ureteral obstruction develops, standard treatment of these complications should be instituted.

PRECAUTIONS

General: Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** section).

Laboratory Tests: Response to ELIGARD® 45 mg should be monitored by measuring serum concentrations of testosterone and prostate specific antigen periodically.

In the majority of patients, testosterone levels increased above Baseline during the first week, declining thereafter to Baseline levels or below by the end of the second week. Castrate levels were generally reached within two to four weeks. One patient (<1%) failed to achieve castrate levels. Once suppressed, only one patient (< 1%) experienced a testosterone breakthrough with testosterone levels exceeding 50 ng/dL.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

Drug Interactions: See **PHARMACOKINETICS**.

Drug/Laboratory Test Interactions: Therapy with leuprolide acetate results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide therapy may be affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted with leuprolide acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. No carcinogenicity studies have been conducted with ELIGARD® 45 mg.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems and with ELIGARD® 7.5 mg in bacterial systems. These studies provided no evidence of a mutagenic potential.

Pregnancy, Teratogenic Effects: Pregnancy category X (see **CONTRAINDICATIONS**).

Pediatric Use: ELIGARD® 45 mg is contraindicated in pediatric patients and was not studied in children (see **CONTRAINDICATIONS**).

ADVERSE REACTIONS

The safety of ELIGARD® 45 mg was evaluated in 111 patients with advanced prostate cancer. ELIGARD® 45 mg, like other LH-RH analogs, caused a transient increase in serum testosterone concentrations during the first two weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS** and **PRECAUTIONS**).

In Study AGL0205, 111 patients were dosed with ELIGARD® 45 mg every six months for up to 12 months and injection sites were closely monitored. 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 (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.

These localized adverse events were non-recurrent over time. No patient discontinued therapy due to an injection site adverse event.

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 $\geq 2\%$ of patients (Table 1). Often, causality is difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

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%

In addition, the following possibly or probably related systemic adverse events were reported by 1% of the patients using ELIGARD® 45 mg in the clinical study.

General: Lethargy

Reproductive: Penile shrinkage*

Renal/Urinary: Nocturia, nocturia aggravated

Psychiatric: Loss of libido*

* Expected pharmacological consequences of testosterone suppression. In the patient population studied, a total of 89 hot flash adverse events were reported in 64 patients. Of these, 62 events (70%) were mild; 27 (30%) were moderate.

Changes in Bone Density: 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.³ It can be anticipated that long periods of medical castration in men will have effects on bone density.

OVERDOSAGE

In clinical trials using daily subcutaneous injections of leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

The recommended dose of ELIGARD® 45 mg is one injection every six months. The injection delivers 45 mg of leuprolide acetate, incorporated in a polymer formulation. It is administered subcutaneously and provides continuous release of leuprolide for six months.

Once mixed, ELIGARD® 45 mg should be discarded if not administered within 30 minutes.

As with other drugs administered by subcutaneous injection, the injection site should vary periodically. The specific injection location chosen should be an area with sufficient soft or loose subcutaneous tissue. In clinical trials, the injection was administered in the upper- or mid-abdominal area. Avoid areas with brawny or fibrous subcutaneous tissue or locations that could be rubbed or compressed (i.e., with a belt or clothing waistband).

Mixing Procedure

IMPORTANT: Allow the product to reach room temperature before using. **Once mixed, the product must be administered within 30 minutes.**

FOLLOW THE INSTRUCTIONS AS DIRECTED TO ENSURE PROPER PREPARATION OF ELIGARD® 45 MG PRIOR TO ADMINISTRATION:

ELIGARD® 45 mg is packaged in either thermoformed trays or pouches. Each carton contains:

- One sterile Syringe A pre-filled with the ATRIGEL® polymer system
- One Syringe B pre-filled with leuprolide acetate powder
- One long white plunger rod for use with Syringe B
- One sterile 19-gauge, 5/8-inch needle
- Desiccant pack(s)

1. On a clean field, open all of the packages and remove the contents. Discard the desiccant pack(s).

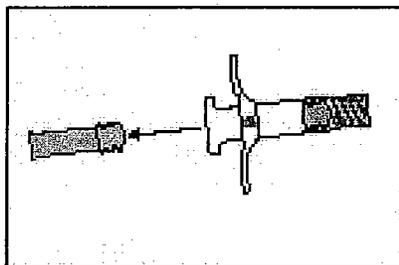


Figure 3

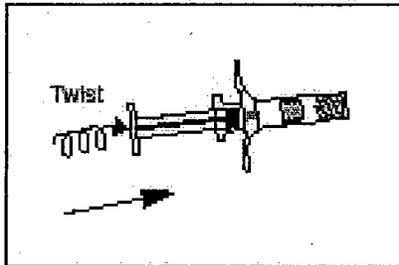


Figure 4

2. **Pull out the blue-tipped short plunger rod and attached stopper from Syringe B and discard (Figure 3).** Gently insert the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B by twisting it in place (Figure 4).



Figure 5

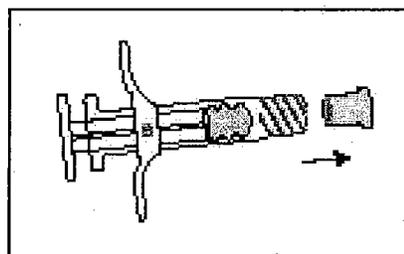


Figure 6

3. Unscrew the clear cap from Syringe A (Figure 5). Remove the gray rubber cap from Syringe B (Figure 6).

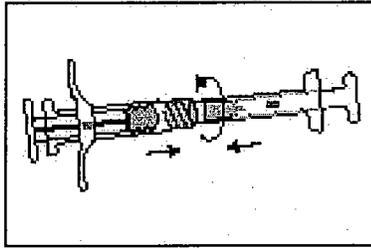


Figure 7

4. Join the two syringes together by pushing in and twisting until secure (Figure 7).

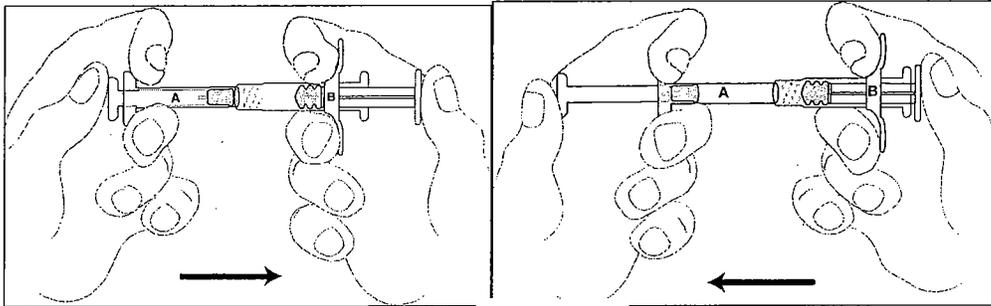
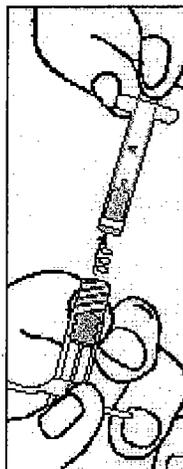


Figure 8

5. Inject the liquid contents of Syringe A into Syringe B containing the leuprolide acetate. Thoroughly mix the product by pushing the contents of both syringes back and forth between syringes (approximately 45 seconds) to obtain a uniform suspension (Figure 8). When thoroughly mixed, the suspension will appear colorless to pale yellow in color. **Please note: Product must be mixed as described; shaking will not provide adequate mixing of the product.**



6. Hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (short, wide syringe) by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger. Uncouple Syringe A while continuing to push down on the Syringe A plunger (Figure 9). **Please note: Small air bubbles will remain in the formulation – this is acceptable.**

Figure 9

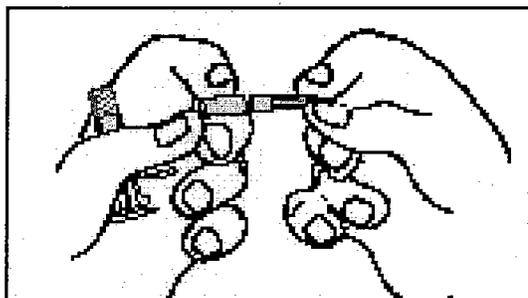


Figure 10

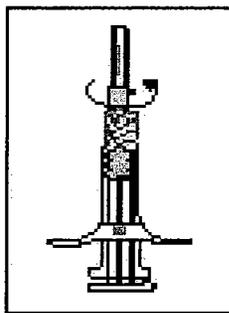


Figure 11

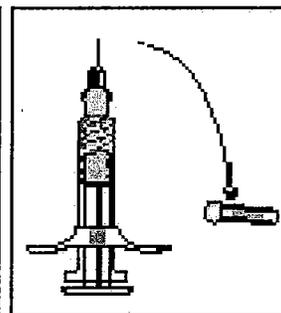


Figure 12

7. Hold Syringe B upright. Remove the yellow cap on the bottom of the sterile needle cartridge by twisting it (Figure 10). Attach the needle cartridge to the end of Syringe B (Figure 11) by pushing in and turning the needle until it is firmly seated. Do not twist the needle onto the syringe until it is stripped. Pull off the clear needle cartridge cover prior to administration (Figure 12).

Administration Procedure

IMPORTANT: Allow the product to reach room temperature before using. **Once mixed, the product must be administered within 30 minutes.**

1. Choose an injection site on the abdomen, upper buttocks, or anywhere with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Since you can vary the injection site with a subcutaneous injection, choose an area that hasn't recently been used.
2. Cleanse the injection-site area with an alcohol swab.



3. Using the thumb and forefinger of your nondominant hand, grab and bunch the area of skin around the injection site.



4. Using your dominant hand, insert the needle quickly. The approximate angle you use will depend on the amount and fullness of the subcutaneous tissue and the length of the needle.



5. After the needle is inserted, release the skin with your nondominant hand.

6. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.
7. Withdraw the needle quickly at the same angle used for insertion.
8. Discard all components safely in an appropriate biohazard container.

HOW SUPPLIED

ELIGARD® 45 mg is available in a single use kit. The kit consists of a two-syringe mixing system, a 19-gauge 5/8-inch needle, a silicone desiccant pouch to control moisture uptake, and a package insert for constitution and administration procedures. Each syringe is individually packaged. One contains the ATRIGEL® Delivery System and the other contains leuprolide acetate. When constituted, ELIGARD® 45 mg is administered as a single dose.

(NDC xxxxx-xxx-xx)

Rx only

Store at 2 - 8 °C (35.6 – 46.4 °F)

<Sanofi-Synthelabo logo>

Manufactured for Sanofi-Synthelabo Inc.
New York, NY 10016
by Atrix Laboratories, Inc.
Fort Collins, CO 80525

04318, Rev 0 12/04

Printed in USA

Revised MM/YYYY

¹ Sennello LT et al. Single-dose pharmacokinetics of leuprolide in humans following intravenous and subcutaneous administration. J Pharm Sci 1986; 75(2): 158-160.

² MacLeod TL et. al. Anaphylactic reaction to synthetic luteinizing hormone releasing hormone. Fertil Steril 1987 Sept; 48(3): 500-502.

³ Hatano T et. al. Incidence of bone fracture in patients receiving luteinizing hormone-releasing hormone agonists for prostate cancer. BJU International 2000 86: 449-452.

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Daniel A. Shames
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

MEDICAL REVIEW

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).

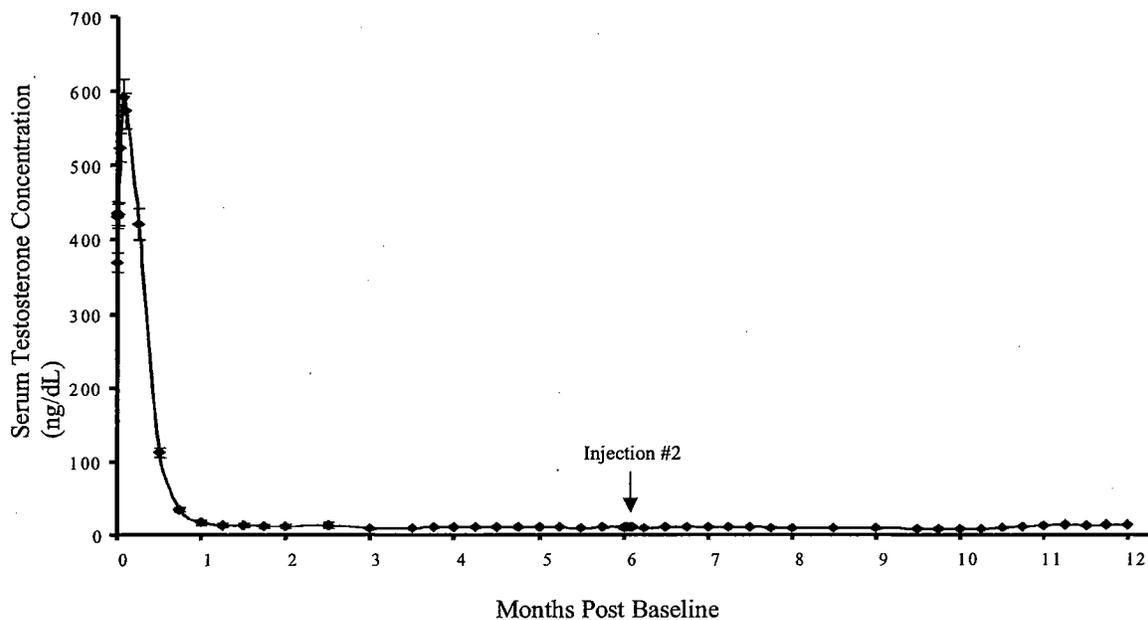


Figure 1. ELIGARD® 45 mg Mean Serum Testosterone Concentrations (n = 103 per-protocol patients)

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 are 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 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 (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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this page is the manifestation of the electronic signature.**

/s/

Mark S. Hirsch
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MEDICAL OFFICER

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12/10/04 02:32:07 PM
MEDICAL OFFICER

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.

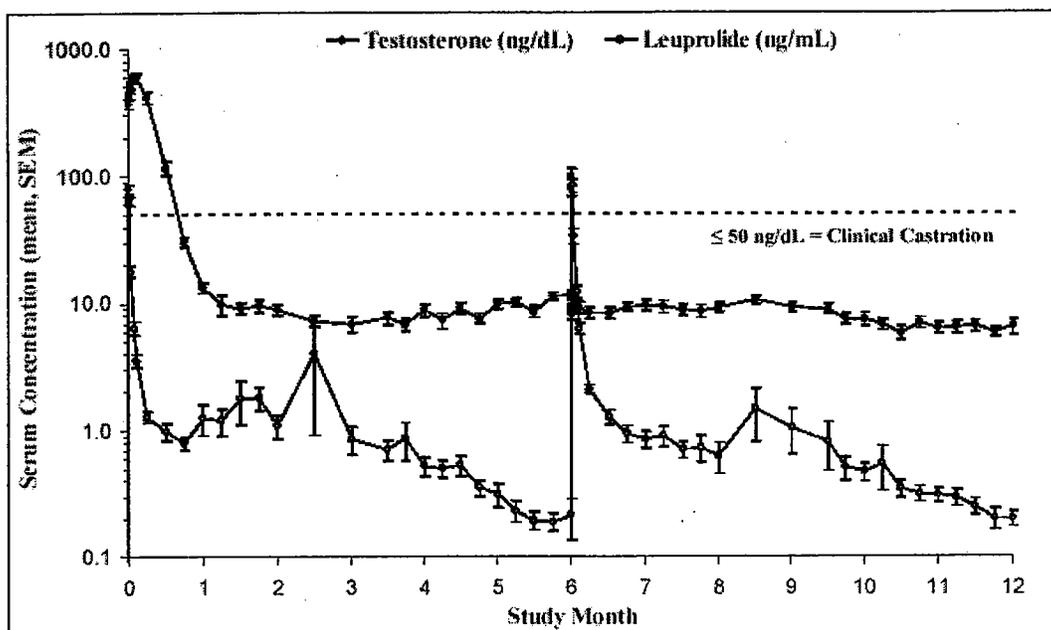
5. Human pharmacokinetic and pharmacodynamic

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 40	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.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

CHEMISTRY REVIEW(S)

NDA 21-731

**ELIGARD™, 45 mg
(Leuprolide acetate for Injectable suspension)**

ATRIX LABORATORIES INC.

SWAPAN K. DE

**DIVISION OF REPRODUCTIVE & UROLOGIC DRUG
PRODUCTS (HFD-580)**



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Chemistry Review Data Sheet

1. NDA 21-731
2. REVIEW # 1
3. REVIEW DATE: 20-NOV-2004 (revised)
4. REVIEWER: Swapan K. De
5. PREVIOUS DOCUMENTS:

Previous Documents

None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment #001 (response to IR letter dated
April 28, 2004)

Amendment #002 (labeling amendment)

Amendment #003 (updated stability data)

Amendment #004 (updated specifications)

Document Date

18-FEB-2004

20-MAY-2004

11-AUG-2004

17-SEPT-2004

23-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.

Address: 2579 Midpoint Drive
Fort Collins, CO 80525-4417

Representative: Cheri L. Jones

Telephone: (970) 212-4901

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ELIGARD™ 45 mg
- b) Non-Proprietary Name (USAN): Leuprolide acetate for Injectable suspension
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

11. DOSAGE FORM: Injectable suspension

13. ROUTE OF ADMINISTRATION: Subcutaneous

12. STRENGTH/POTENCY: 45 mg leuprolide acetate

14. Rx/OTC DISPENSED: Rx OTC

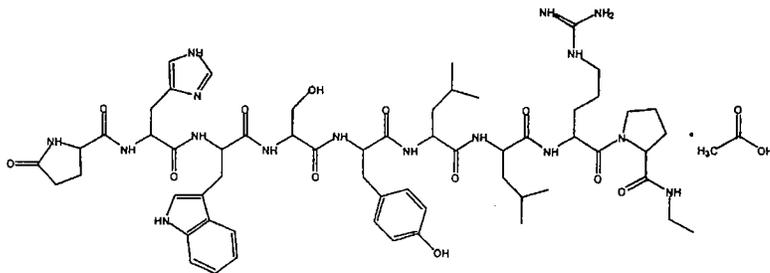
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

- SPOTS product – Form Completed
- Not a SPOTS product
- Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical names: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Chemical Structure:



Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide acetate

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Molecular formula: $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$

Relative molecular mass: 1269.48 Daltons (Leuprolide acetate)

CAS Registry number: 74381-53-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	II	[]	Drug substance (Leuprolide acetate)	3	Adequate	01/17/2000	Reviewed by S.K.De
	II		Drug substance (Leuprolide acetate)	3	Adequate	11/29/01	Reviewed by S.K.De
	II		Polymer (85/15 Poly(D,L-lactide-co-glycolide)		Adequate	12/08/04	Reviewed by S.K.De
	II		N-methyl-2-Pyrrolidone (excipient)	3	Adequate	1/03/02	Reviewed by S.K.De
	III		[]	3	Adequate	12/12/01	Reviewed by S.K.De
	III		[]	3	Adequate	1/22/04	Reviewed By G.W. Holbert

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7	III	3	Adequate	7/14/00	Reviewed By Young-de Lu
	III	3	Adequate	2/17/98	Reviewed by E.G.Pappas
	III		Adequate	9/21/04	Reviewed by Swapan K. De
	III		Adequate	9/23/04	Reviewed by Swapan K. De

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND 64-779, NDA 21-343, NDA 21-379 and NDA 21-488

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	29-NOV-2004	Office of Compliance
Pharm/Tox	Adequate	17-MAY-2004	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	06-DEC-2004	Sandhya Apparaju, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	5-OCT-2004	Denise Toyer, Drug safety reviewer
EA	Categorical exclusion granted	14-JAN-2004	Swapan K. De, Ph.D.
Microbiology	Adequate	24-NOV-2004	Bryan Reily, Ph.D.

The application submission(s) covered by this review was taken in the date order of receipt. Yes No If no, explain reason(s) below:

The Chemistry Review for NDA 21-731

The Executive Summary

I. Recommendations

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

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance(s):

Dosage form: Injectable suspension
Strength: 45 mg Leuprolide acetate
Route of Administration: Subcutaneous

Description:

The drug product, ELIGARD™, 45 mg is a polymeric matrix formulation of leuprolide acetate intended for controlled delivery of the drug product over a six-month period for the palliative treatment of prostate cancer. The drug product consists of a two syringe mixing system, a 19 gauge 5/8-inch needle, and a silicone desiccant pouch to control moisture uptake. One syringe (Syringe A) contains the ATRIGEL® Delivery System. This delivery system consists of _____ of a sterile, polymeric delivery system solution of _____ 85:15 Poly(DL lactide-co-glycolide) (PLG) and _____ N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains _____ filled, lyophilized leuprolide acetate.

The ATRIGEL® Delivery System (85:15 PLG and NMP; Syringe A) is compounded, filled into syringes, and pouched at Atrix Laboratories Inc. in Fort Collins, CO. This subassembly is then

_____ An aqueous solution of leuprolide acetate _____ lyophilized in syringes (Syringe B) and packaged at Atrix Laboratories Inc. in Fort Collins, CO

_____ The final assembly occurs at Atrix Laboratories Inc., in Ft. Collins, CO and either consists

_____ The quality is controlled by tests of both parts of the drug product, Syringe A and Syringe B. Syringe A tests include color, appearance, polymer identification (by NMR), polymer molecular weight, polydispersity, water content, NMP content, sterility (USP <71>) and endotoxin (USP <85>). Syringe B tests include color, appearance, identification (IR and HPLC), related substances (HPLC), sterility (USP <71>) and endotoxin (USP <85>). Furthermore, the reconstituted product is released by regulatory specifications and is controlled by tests that include color, appearance, leuprolide acetate content and drug release.

CHEMISTRY REVIEW

Executive Summary Section

The primary packaging of the two syringes that constitute the drug product are performed separately and individually packaged. The ATRIGEL Delivery System is filled into _____ syringes

The required DMF's (DMF — DMF — DMF — and DMF —) for the packaging components are found adequate. From Microbiologist's point of view, container/closure integrity is deemed satisfactory.

Based on the stability data provided, a 24-month expiry date is granted. The tradename, ELIGARD™, 45 mg has been accepted by DMETS, and adequate chemistry information is presented in the labeling and labels of the primary as well as the secondary packaging.

Leuprolide is a synthetic analog of the hormone, leuteinizing hormone releasing hormone (LH-RH). Leuprolide is a nonapeptide and acts as an agonist of naturally-occurring gonadotropin releasing hormone (GnRH). After a short period of up-regulation of the steroidogenesis, sustained leuprolide treatment desensitized anterior pituitary and results in low steroid blood levels. The analog possesses greater potency than the natural hormone.

The sponsor has provided data to show the comparability of the drug substances among the two suppliers and they are deemed satisfactory. Toxicology and clinical studies qualifies the above impurities and is deemed acceptable.

Executive Summary Section

Leuprolide has the chemical designation 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt). It is white to off-white powder, soluble in water and acetic acid and hygroscopic in nature. The characterization and proof of structure of leuprolide acetate has been determined by mass spectrometry and amino acid analysis.

B. Description of How the Drug Product is Intended to be Used

Six month ELIGARD™, 45 mg is supplied as two prefilled sterile syringes and a sterile needle. The product should come to room temperature before use. Prior to administration of the drug product the two syringes are coupled and the contents of the two syringes are mixed by passing the contents from syringe to syringe. It should be mixed for approximately 45 seconds to achieve a uniform suspension. When thoroughly mixed, the suspension will appear as a light tan to tan color. Following mixing, the contents are transferred into syringe B and the syringes are decoupled. A sterile needle is then affixed to the syringe B for patient injection. The total deliverable injection weight is 375 mg including 45 mg of leuprolide acetate. Once mixed the drug product should be administered within 1 hour.

The drug product is administered subcutaneously and provides continuous release of leuprolide for six months.

The drug product has an 24-month expiry date, when stored at 2-8°C.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate data to demonstrate product quality. Therefore, from a CMC point of view, the data support approval of the NDA.

The sponsor submitted the original submission of this NDA following their other approved products (ELIGARD™, 7.5 mg, ELIGARD™, 22.5 mg and ELIGARD™, 30 mg) and thus, had minor deficiencies. These deficiencies were sent to the sponsor on April 28, 2004. The sponsor's submission of amendment #001 (20-May-2004) includes the response to the deficiencies and was found adequate. Amendment #003 (17-Sept-2004) includes the updated information on stability (to provide more stability data) and revised specifications. Amendment #004 dated 23 Nov, 2004 includes response on PLG polymer specification and extended release specification based on the recommendation forwarded through t-con dated Nov 9-2004 and Nov 12-2004. Some of the major issues and their resolution for this NDA include submission of information for the justification of drug product overage, adjustment of PLG molecular weight and extended release acceptance criteria based on qualification and batch record. Thus, considering the provided information, this NDA is deemed satisfactory regarding CMC and may be approved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/S. K. De, Ph.D.
HFD-580/M.J. Rhee, Ph.D.
HFD-580/J. Kim

C. CC Block

HFD-580/Division File/NDA 21-488
HFD-580/S. K. De, Ph.D.
HFD-580/M.J. Rhee, Ph.D.
HFD-580/ J. Kim

69 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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

/s/

Swapn De
12/9/04 10:51:24 AM
CHEMIST

Moo-Jhong Rhee
12/9/04 01:30:07 PM
CHEMIST
I concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-731

Applicant: ATRIX LABORATORIES INC.

Stamp Date: 18-FEB-2004

Drug Name: ELIGARD, 45 mg

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes_X_ No_)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		DMF number and authorization letter has been provided
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

NDA is fileable from a manufacturing and controls perspective.

Review Chemist: Swapan K. De, Ph. D.

Date: 26-MAR-2004

Team Leader: Moo-Jhong Rhee, Ph. D.

Date: 26-MAR-2004

cc:

Original NDA 21-731

HFD-580/Division File

HFD-580/Chem/De/Rhee

HFD-580/PM/Kimj

HFD-580/DivDir/DShames

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

PHARMACOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-731
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 2/13/04
DRUG NAME: ELIGARD 45mg
INDICATION: Advanced Prostate Cancer
SPONSOR: ATRIX Laboratories
DOCUMENTS REVIEWED: Vols. 2.1, 2.18 – 2.27.1
REVIEW DIVISION: Division of Reproductive and Urologic Drug
Products (HFD-580)
PHARM/TOX SUPERVISOR: Krishan Raheja, Ph.D.
DIVISION DIRECTOR: Daniel Shames, M.D.
PROJECT MANAGER: John Kim

Date of review submission to Division File System (DFS): 05/17/04

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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability: Pharmacology will recommend approval of NDA 21-731 for Aligard (Leuprolide acetate) 45 mg injectable indicated for the palliative treatment of prostate cancer.
- B. Recommendation for nonclinical studies: none
- C. Recommendations on labeling: Labeling will be similar to the sponsor approved 1- month formulation (Eligard 7.5 mg), 3-month formulation (Eligard 22.5 mg) and 4-month formulation (Eligard 30 mg) approved respectively under NDAs 21-343, 21-379 and 21-488.

II. Summary of nonclinical findings

- A. Brief overview of nonclinical findings: Sponsor has submitted a rat and a dog non-GLP P/K studies of 196 days duration and demonstrated that in rats a dose of 4.5 mg/0.08 ml in 85/15 PLG (IV 0.27)/ NMP + LA and 4.5 mg/0.04 ml in 85/15 PLG (IV 0.7)/ NMP + LA suppressed serum testosterone to castrate levels for a period of 6 months.

Sponsor has submitted a rat and a dog non-GLP P/K studies of 196 days duration and demonstrated that in rats a dose of 4.5 mg/0.08 ml in 85/15 PLG (IV 0.27)/ NMP + LA and 4.5 mg/0.04 ml in 85/15 PLG (IV 0.7)/ NMP + LA suppressed serum testosterone to castrate levels for a period of 6 months.

Similarly in dogs Eligard 45 mg formulations (85/15 PLG , NMP + LA (IV) suppressed serum testosterone to castrate levels for a period of 6 months. A formulation made with lower molecular weight polymer and a lower NMP content to simulate the effect of aging was also effective.

- B. Pharmacologic activity: The pharmacologic activity of leuprolide acetate for the treatment of prostate cancer is related to its suppression of serum testosterone to castrate levels.
- C. Nonclinical safety issues relevant to clinical use: none

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-731

Review number: 001

Sequence number/date/type of submission: 000/2-13-04/original submission

Information to sponsor: Yes () No (*)

Sponsor and/or agent: ATRIX Laboratories, Inc. Fort Collins, CO

Manufacturer for drug substance:

Manufacturer for polymer:

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.

Division name: Reproductive and Urologic Drug Products

HFD #: 580

Review completion date: 4-11-04

Drug:

Trade name: ELIGARD 45 mg

Generic name (list alphabetically): Leuprolide acetate for injectable suspension

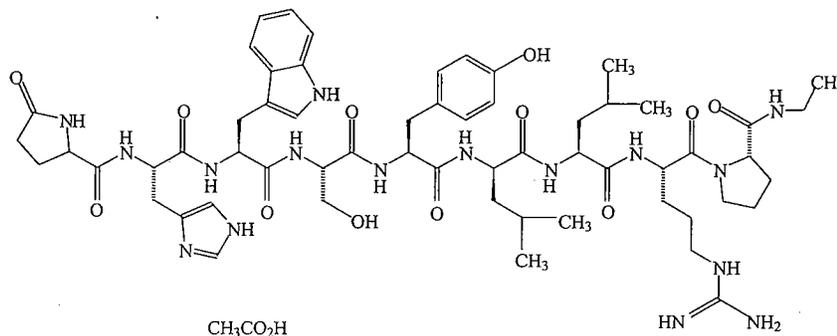
Code name: -

Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl- L-seryl- L-tyrosyl-D-leucyl-
L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

CAS registry number: 74381-53-6

Molecular formula/molecular weight: $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2/1269.48$ Daltons

Structure:



Excipient: 1-methyl-2-pyrrolidone

Synonyms/codes: N-methylpyrrolidone

NMP

N-methylpyrrol

H-20417

CAS registry No.: 872-50-4

Molecular weight: 99.13

Relevant INDs/NDAs/DMFs: INDs 57,413; 59,771; 60,050; 64,779

NDA 21-343; 21-488

DMFs _____ (for Leuprolide acetate);

— for poly (D,L-lactide) and its copolymers. _____

Drug class: GnRH agonist

Indication: For the palliative treatment of advanced prostate cancer

Clinical formulation: Eligard 45 is designed as a parenteral drug product that consists of a sterile syringe containing lyophilized active drug substance, leuprolide acetate, a sterile syringe containing the polymeric ATRIGEL Delivery system, and a sterile needle for injection. The ATRIGEL Delivery System is composed of poly (D-L-lactide-co-glycolide) dissolved in N-methylpyrrolidone (NMP). The drug product is mixed immediately prior to patient administration as a subcutaneous injection. The drug product is designed to deliver a nominal 45-mg of leuprolide acetate over a period of 6-months. The total injection mass is 375 mg. As administered it is a biodegradable and bioabsorbable polymeric formulation consisting of — 85:15 poly (DL-lactide-co-glycolide), — N-methyl-2-pyrrolidone and — leuprolide acetate.

Route of administration: Subcutaneous

Proposed use: For the palliative treatment of advanced prostate cancer. The recommended dose of Aligard 45 mg is one injection every 6 months.

Drug history: The safety of leuprolide acetate is well established as it has been approved by the FDA as leuprolide acetate for injection and Lupron Depot as leuprolide acetate depot suspension under various NDAs for the treatment of both malignant and benign conditions. Eligard is currently approved at doses of 7.5, 22.4 and 30 mg leuprolide acetate for the palliative treatment of advanced prostate cancer. Lupron injection is approved for the palliative treatment of the advanced prostate cancer and for the treatment of precocious puberty. Lupron Depot 3.75 is approved for the treatment of endometriosis, Lupron Depot 7.5 mg and Lupron Depot-3 month 22.5 mg for the palliative treatment of prostate cancer, and Lupron Depot-PED 7.5, 11.5, and 15 mg for the treatment of children with central precocious puberty.

[Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.]

Results showed no treatment effect on body weight. No overt toxicity or test site tissue reaction was recorded. Almost all recovered implants were located SC and were firm in consistency. Testosterone was no longer suppressed in group 1 at Day 140 and in group 2 at Day 168. Testosterone levels in groups 3 and 4 were suppressed throughout the study. By Day 154, 95%-100% and by Day 196, 99%-100% of leuprolide had been released. It was concluded that the more hydrophobic polymer with a molar ratio of lactide to glycolide of 85:15 gave the best testosterone suppression. Increased loading to — did not decrease the efficacy of polymer formulation. Formulations did not cause lasting tissue reaction.

2. Evaluation of the 24-hour release kinetics of ten Atrigel formulations containing — and — leuprolide acetate injected subcutaneously in rats. Protocol No. ATRS-465 — 129.431.

Ten formulations were tested. The % of polymer in various groups was — with lactide/glycolide ratio of 75/25 or 85/15, the remainder being NMP. The leuprolide concentration was — or — The drug dosage was 15 mg or 30 mg in 0.250 ml formulation. There were 5 male rats/g.

Results: Irritation at the test sites was considered mild with bruising seen at test sites in all groups. This was attributed to increased amount of NMP than previously used or due to the large volume of injection and higher LA concentration. The 24-hour release ranged from — leuprolide with no difference between — drug load. Serum leuprolide which was determined in group 1 (— 75/25 PLG (IV 0.31), — NMP w — LA) and group 2 (— 75/25 PLG (IV 0.31), — NMP w — LA) was 210 ng/ml and 101 ng/ml respectively.

3. Evaluation of the 24-hour release of sixteen Atrigel formulations containing — leuprolide acetate when delivered subcutaneously in the rat. Protocol No. ATRS-486, — 129.452.

In this study the ratio of polymer/NMP was 45/55, 50/50, 55/45, 60/40 and 65/35 and the ratio of lactide:glycolide was 75:25 or 85:15. The drug dosage was 6 mg or 12 mg in formulation volumes of 0.1 ml. There were 5 male rats/g.

Results: Some redness and bruising was observed in groups 1 and 2, which had — NMP in formulation. There was minimal tissue reaction observed during implant retrieval. No formulation gave over — release in the first 24 hours, the highest being — by group 1 (— 75/25 PLG (IV 0.31) w — LA). The lowest burst was seen in the group with — 85/15 PLG (0.22) w — LA, which was difficult to inject through 18 gauge needles. The trend was that higher polymer concentration formulations gave lower initial bursts and leuprolide loading of — had lower initial burst than those with a loading of — did.

4. Evaluation of three Atrigel formulations containing — leuprolide acetate when delivered subcutaneously in the dog. Protocol No. ATRS-499. — 129.465.

This study was designed to determine the six month release and efficacy of three Atrigel formulations containing — leuprolide acetate by analyzing serum leuprolide acetate levels and testosterone suppression. The test site reactions were also monitored. There were 6 male dogs in each treatment group. The formulations were as follows:

- | | | | |
|-----|----------------------|----------|---------------------------------|
| 1 - | 85/15 PLG (IV0.27)/ | NMP with | leuprolide acetate, 18 G needle |
| 2 - | 85/15 PLG (IV 0.22). | NMP with | leuprolide acetate, 18G needle |
| 3 - | 85/15 PLG (IV0.22)/ | NMP with | leuprolide acetate, 18 G needle |

The formulation was administered SC as 0.250 ml single injection (containing 60 mg LA) to deliver 25.6 ug leuprolide acetate/kg/day.

Blood was collected from each dog before dosing and then at various time intervals up to Day 210 for testosterone and drug level analysis. After Day 210 blood collection, all dogs received a SC injection of 1 mg leuprolide acetate in saline and blood was collected at 3, 6 and 24 hours post injection for testosterone determination. This was done to establish that if the production of testosterone were still suppressed there would be no surge in testosterone level after challenging pituitary with additional leuprolide acetate.

Results: Serum leuprolide levels in all the groups showed a very high initial concentration followed by rapid decrease. The data indicated that a higher molecular weight polymer was necessary to maintain sufficient circulating leuprolide to suppress testosterone levels for 6 months. Macroscopic tissue evaluations did not show any lasting tissue reactions due to the test articles. It was concluded that formulation 1, suppressed and maintained testosterone levels at human castration levels for at least 6 months.

5. Evaluation of the effect of drug loading and polymer concentration on the 24-hour release of the 6-month leuprolide acetate product. Protocol No. ATRS-628, — 129.598.

Four Atrigel 6-month formulations containing — leuprolide acetate were administered SC in 5 male rats/g. The volume for the — drug load formulation was about 0.5 ml containing 45 mg LA, while it was 0.375 ml for the — drug load formulation containing 45 mg LA.

The 4 formulations were as follows:

- | | | | |
|-----|----------------------|-------|----|
| 1 - | 85/15 PLG (IV 0.27)/ | NMP w | LA |
| 2 - | 85/15 PLG (IV 0.27)/ | NMP w | LA |
| 3 - | 85/15 PLG (IV0.27)/ | NMP w | LA |
| 4 - | 85/15 PLG (IV 0.27)/ | NMP w | LA |

Results showed minimal to marked external redness and mild to moderate macroscopic tissue reactions in all animals from all groups during necropsy/implant retrieval. It was

stated that formulations 1 and 3 were difficult to inject through an 18 G needle. Formulation 2 had the highest initial burst (37.9%) and formulation 3 had the lowest (22.1%) The average initial bursts were higher in the formulations with higher NMP and lower polymer content for both the _____ drug doses. Sponsor concluded that the 85/15 PLG (IV 0.27) at a 50:50 polymer to solvent ratio by weight percent would be developed for the 6-month delivery of LA.

6. ATRS-676: Evaluation of the efficacy of ATRIGEL formulations with varying molecular weights and NMP concentrations containing leuprolide acetate when delivered subcutaneously in the dog. — # 129.647

The purpose of this non-GLP study was to determine the efficacy of 8 ARIGEL formulations containing — leuprolide acetate (LA) with varying MW and NMP concentrations for the 6-month leuprolide acetate product over 196 days in dogs (6 dogs/g). The primary objective was to determine efficacy of eight 85/15 poly (DL-lactide-co-glycolide) ATRIGEL formulations with varying MW and NMP concentrations containing LA. The secondary objective was to compare polymers from different suppliers. The efficacy was determined by measuring suppression of testosterone levels. Blood was collected on days -7, -3, 0 (pre-injection) 1, 7, 14, 28, 42, 56, 85, 98, 112, 126, 140, 154, 168, 183, and 196 from all dogs.

The composition of the 8 formulations and supplier information is provided in table below:

1.	85/15 PLG (InV 0.25) /	NMP with	LA drug load, APT
2.	85/15 PLG (InV 0.31) ,	5 NMP with	LA drug load, APT
3.	85/15 PLG (InV 0.25) ,	5 NMP with	LA drug load, APT
4.	85/15 PLG (InV 0.31) ,	5 NMP with	LA drug load, APT
5.	85/15 PLG (InV 0.25),	h / 42% NMI	LA drug load, APT
6.	85/15 PLG (InV 0.25),	/ 52% NMI	LA drug load, APT
7.	85/15 PLG (InV 0.28) ,	5 NMP with	LA drug load, —
8.	85/15 PLG (InV 0.26) ,	5 NMP with	LA drug load, —

Note: Six of the formulations were gamma irradiated at a dose of _____, while 2 of the formulations (i.e. # 5 and 6) were irradiated at a high dose _____ to obtain MWs expected at the end of the shelf life (termed as “aged” formulation)

All dogs were administered a single SC injection via an 18 gauge, 1 inch needle. Approximately 375 mg of ATRIGEL polymer formulation containing 45 mg of LA was the anticipated dose. The dog dose in this study averages 20 ug/kg/day. The human dose of 45 mg equals 3.57 ug/kg/day. The study was started on 3-4-02.

Results: On day 1, minimal edema at the injection site was reported in 2 dogs in group 1 and one dog in group 3. On day 14, one dog in group 5 had slight edema around the injection site. On day 80, one dog in group 7 had both ears very red and swollen and had scabs and patches of hair missing due to persistent scratching. It was considered due to

idiopathic, chronic otitis externa and was treated with topical antibiotic and steroid. On day 88, one dog in group 1 had several seizures and was treated with diazepam and phenobarbital.

Serum testosterone levels: All 8 groups had the expected initial increase in testosterone levels followed by a decrease below the human castration level of 0.5 ng/ml by day 14. Groups 1, 2, 5 and 6 sustained testosterone suppression below the human castration level through 154 days. Group 5 continued below this level through 183 days. At day 168 due to higher values for one or two dogs, the average above the human castrate level resulted in groups 1, 2, and 6. Sponsor stated that considering that testosterone suppression is more difficult in dogs than in humans, groups 1, 2, 5 and 6 can be considered to have shown effective testosterone suppression through 6 months. Groups 7 and 8 had the desired testosterone profile initially but did not maintained suppression as long. Levels above the human castrate limit were detected on day 126 and 140, respectively. These 2 groups had test article with polymers from alternate suppliers. Groups 2 and 4 had the same profile as the other groups through 14 days but the levels were erratic and generally above the human castrate limit for rest of the study. These formulations had higher NMP content than nominal.

From these data it was concluded that — LA formulations made at a nominal — polymer / — NMP ratio with 85/15 PLG and an InV range of 0.25 – 0.31 from APT are effective in suppressing testosterone in dogs for 6 months. A formulation made with lower MW polymer and a lower NMP content to simulate the effect of aging was also effective. Formulations made with — NMP did not maintain testosterone levels below human castrate limit. Also formulations made with polymers from — did not maintain testosterone levels below the human castrate limit for as long as the comparable formulations made with APT polymer. The polymers from — however, showed comparable in vitro performance (i.e., color, appearance, solubility, MW and polydispersity).

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not Submitted

2.6.6 TOXICOLOGY

General toxicology: None submitted

Genetic toxicology: None submitted

Carcinogenicity: None submitted

Reproductive toxicology: None submitted

Special toxicology: None submitted

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not Submitted

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on extensive nonclinical toxicity and clinical safety and efficacy data available along with sponsor's conducted P/K studies in rats and dogs demonstrating that the proposed Eligard 45 mg formulation is effective for a period of 6 months, From a Pharmacology prospective Eligard 45 mg formulation appears to be safe for the proposed indication.

Unresolved toxicology issues (if any): None

Recommendations: From a pharmacology/toxicology perspective, we recommend approval of NDA 21-731 for Eligard 45 mg for the palliative treatment of advanced prostate cancer.

Suggested labeling: Labeling will be similar to the other Eligard products.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

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

/s/

Krishan L. Raheja
5/17/04 10:34:09 AM
PHARMACOLOGIST

Lynnda Reid
5/17/04 03:08:14 PM
PHARMACOLOGIST

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

MICROBIOLOGY REVIEW

Product Quality Microbiology Review

Review for HFD-580

19 NOVEMBER 2004

NDA: 21-731

Drug Product Name

Proprietary: Eligard 45 mg

Non-proprietary: leuprolide acetate injectable suspension

Drug Product Priority Classification: S

Review Number: 1

Subject of this Review

Submission Date: 13 February 2004

Receipt Date: 18 February 2004

Consult Date: 27 April 2004

Date Assigned for Review: 28 April 2004

Submission History (for amendments only)

Date(s) of Previous Submission(s): N/A

Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor

Name: Atrix Laboratories

Address: 2579 Midpoint Drive, Fort Collins, CO 80525

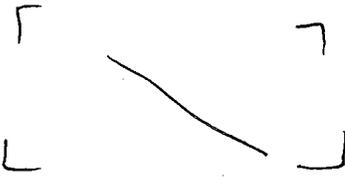
Representative: Cheri Jones

Telephone: 970-212-4901

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUPPLEMENT:** N/A
 2. **SUPPLEMENT PROVIDES FOR:** N/A
 3. **MANUFACTURING SITES:** Atrix Laboratories
701 Centre Avenue
Fort Collins, CO 80526

 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Lyophilized powder in a Pre-filled syringe for subcutaneous administration, 45 mg
 5. **METHOD(S) OF STERILIZATION:** _____
 6. **PHARMACOLOGICAL CATEGORY:** Treatment of prostate cancer
- B. **SUPPORTING/RELATED DOCUMENTS:** Product quality microbiology reviews of NDA 21-343 dated 11/19/01, 12/13/01 and 12/26/01. NDA 21-731 amendment #003 (17 September 2004)
- C. **REMARKS:** A different strength of the same drug product and delivery system is currently approved for manufacture at _____ The applicant would also like to manufacture this drug product at it's own facility in Fort Collins, CO. This review deals primarily with the manufacturing facility and process at Atrix. The process at _____ is identical to the approved process for the other strengths of the drug product.

filename: N021731R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** – This submission is recommended for approval on the basis of product quality microbiology
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is _____ filled.
- B. Brief Description of Microbiology Deficiencies** – N/A
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Microbiology Supervisor
- C. CC Block**
N/A

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

**This is a representation of an electronic record that was signed electronically and
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/s/

Bryan Riley
11/24/04 08:39:07 AM
MICROBIOLOGIST

David Hussong
11/24/04 10:09:54 AM
MICROBIOLOGIST
Microbiology recommends APPROVE

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-731	Submission Date(s): 02/13/2004
	PDUFA Goal Date: 12/17/2004
Brand Name	ELIGARD® 45 mg
Generic Name	Leuprolide acetate
Reviewer	Sandhya Apparaju, Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	DPE II
OND division	Division of Reproductive and Urology Drug Products
Sponsor	Atrix Laboratories, Inc.
Relevant IND(s)	64,779
Submission Type; Code	Standard
Formulation; Strength(s)	Injectable suspension, 45 mg
Indication	Palliative treatment of advanced prostate cancer

OCPB briefing: Optional intra-division level briefing was conducted on November 15th, 2004; Attendees: Drs'. Henry Malinowski, John Hunt, Mark Hirsch, Ameeta Parekh, Julie Bullock, and Sandhya Apparaju.

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1 Executive Summary

ELIGARD[®] 45mg (Atrix laboratories; NDA 21-731) is a six-month, controlled release polymeric depot injection of leuprolide acetate intended for the palliative treatment of advanced prostate cancer. Leuprolide acetate is a synthetic agonist of the gonadotropin releasing hormone (GnRH or LH-RH). The agency had previously approved the Eligard[®] 7.5 mg, 22.5 mg and 30 mg formulations for sustained release of leuprolide over one, three and four months, respectively for the prostate cancer indication. The sponsor conducted a pivotal clinical trial in 111 prostate cancer patients dosed with two subcutaneous ELIGARD[®] 45 mg injections at six month intervals. The PK/PD subgroup of this study involved 27/28 patients with intensive pharmacokinetic sampling. As intended by its design, the ELIGARD[®] 45mg formulation demonstrated a slow and sustained release of leuprolide acetate over a period of 6 months. There was no evidence of significant accumulation after the second injection. The testosterone suppression (to below castration) was achieved in 100% of the PK/PD patients following the first dose and was maintained at these low levels by the second dose. In vitro release testing method and release specifications have been proposed and reference has been made to previously approved ELIGARD[®] NDAs to support the safety and efficacy of ELIGARD[®] 45mg.

1.1 Recommendation

NDA 21-731 is acceptable from a clinical pharmacology and biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of clinical pharmacology and biopharmaceutics findings

The sponsor has conducted a phase 3 (pivotal) clinical trial to investigate the safety, pharmacokinetics and efficacy of ELIGARD[®] 45 mg in prostate cancer patients. Summarized below are the important aspects of this study in the clinical pharmacology & biopharmaceutics perspective:

Pivotal clinical trial (AGL0205): A 12-month, open-label, fixed-dose phase 3 clinical trial was conducted in 111 advanced prostate cancer patients (mean age: 73.2 years) to evaluate the safety, tolerance, pharmacokinetics and endocrine efficacy of two consecutive (six months apart) doses of ELIGARD[®] 45 mg formulation. The PK/PD subset consisted of 27/28 patients who had intensive blood sampling for the determination of pharmacokinetics (serum leuprolide)/ pharmacodynamics (serum testosterone) following the first and second injections of the drug product.

Pharmacokinetics: ELIGARD® 45 mg injections resulted in a multiphasic leuprolide concentration versus time profiles characterized by a distinctive burst phase and a plateau phase, consistent with the release mechanism of this polymeric drug product. Following the first and second SC injections of ELIGARD® 45 mg formulation, maximum leuprolide concentrations (C_{max}) of 82.0 and 102.4 ng/ml, respectively were observed at a T_{max} of ~ 4.5 hours post-dose. After the initial “burst phase” in which drug concentrations peaked and declined at a rapid rate (0- 3 days), serum leuprolide concentrations then declined gradually and were generally maintained between 0.2-2.0 ng/ml during the “plateau” phase (days 3-168) of the release. The total systemic exposures ($AUC_{0-6\text{ months}}$) following the first and second doses of ELIGARD® 45 mg SC injection were comparable (5922 versus 5573 ng.hr/ml, respectively) suggesting absence of leuprolide accumulation upon repeated injections.

Pharmacodynamics: Within the PD subset of 28 patients, clinical castration (Testosterone ≤ 50 ng/dL) was achieved in 100 % of patients by day 28. In response to leuprolide exposure, mean baseline testosterone levels in these patients rose initially to 584.5 ± 48.6 ng/dl on day 3, fell to 30.4 ± 3.0 ng/dL on day 21, and then remained between 5.8 – 11.6 ng/dL for the remainder of the study period. The second injection did not cause acute increases in serum testosterone but in fact maintained the testosterone suppression that was achieved by the first dose. Serum testosterone remained suppressed in all patients for the entire study duration (12-months).

In addition to the changes in serum testosterone concentrations, reduction in serum luteinizing hormone (LH) concentrations and serum prostate specific antigen (PSA) to the desired threshold (secondary measures of efficacy) during the two six month dosing periods provided additional evidence of the pharmacodynamic effect of ELIGARD® 45 mg formulation.

Intrinsic factors: No subpopulation analysis was conducted for ELIGARD® 45 mg. Elderly patients made up a substantial portion of the patients whose pharmacokinetics were evaluated in the pivotal clinical trial of ELIGARD® 45 mg, which included patients between the ages of 50 and 85 years. The clinical pharmacokinetic subset in the ELIGARD® 45 mg phase 3 study included patients identified as white, black, and Hispanic, who ranged in weight from 56 to 121 kg. These patients had a variety of concomitant disease states, took various medications, and exhibited a range of clinical chemistry and hematologic abnormalities during the study. ELIGARD® 45 mg provided sustained leuprolide release and sustained testosterone suppression in all pharmacokinetic subgroup patients.

2 QBR

2.1 General Attributes

2.1.1 Regulatory background

ELIGARD® (leuprolide acetate) formulations for subcutaneous injection have been previously approved by FDA for the palliative treatment of prostate cancer at three different strengths: 7.5 mg, 22.5 mg and 30 mg formulations designed to cause controlled drug release over 1 month, 3 months and 4 months, respectively. The NDA numbers for

these three previously approved formulations are 21-343, 21-379 and 21-488, respectively. The current submission for ELIGARD[®] 45 mg (NDA 21-731) is fourth in this series and represents the first 6-month formulation of leuprolide acetate for the prostate cancer indication.

2.1.2 Physicochemical properties

The active ingredient of ELIGARD[®] 45 mg is leuprolide acetate [C₅₉H₈₄N₁₆O₁₂•C₂H₄O₂; MW of free base: 1209.4]. Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LHRH). Replacement of glycine in position 6 by a D-isomer of leucine renders the GnRH analog resistant to enzymatic cleavage and greatly increases its circulating half-life (around 3.5 hours) compared to native GnRH that has a short half-life of less than 15 minutes. The analog is approximately 80-100 times more potent than the natural hormone. The chemical name of leuprolide acetate is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate with the following structural formula:

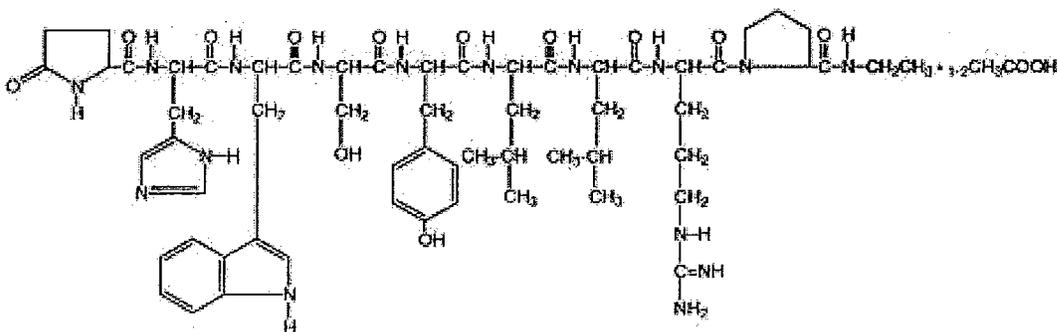


Figure 1: Leuprolide (Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide) acetate.

2.1.3 Formulation characteristics

ELIGARD[®] 45 mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration. One syringe (syringe A) contains the ATRIGEL[®] Delivery System and the other (syringe B) contains the active drug, 45 mg leuprolide acetate (equivalent to approximately — leuprolide free base). ATRIGEL[®] is a biodegradable polymeric delivery system consisting — of 85:15 poly-(DL-lactide-co-glycolide) (PLG) polymer dissolved in — of biocompatible solvent, N-methyl-2-pyrrolidone (NMP). The approximate weight of the administered formulation is 375 mg. The approximate injection volume is 0.375 mL.

— Upon subcutaneous injection of the delivery system containing the suspended drug, the water-miscible NMP diffuses into the surrounding tissue as aqueous extracellular fluid permeates into the implant. This process leads to coagulation of the water-immiscible PLG to form an implant in situ. Rapid release of a portion of the leuprolide acetate (LA) solute during the initial diffusion of NMP is termed the burst phase (C_{max}). The remaining LA stays within the PLG implant by physical entrapment, non-polar binding forces and weak hydrogen bonding. Longer-term release (plateau phase) of this portion of the drug content from the implant occurs at a slower, steadier rate via two mechanisms: dissolution and erosion. The dissolution phase involves LA

Because of the compositional and therapeutic similarities of the four ELIGARD® formulations, clinical data on the ELIGARD® 30 mg (four-month), ELIGARD® 22.5 mg (three-month) and ELIGARD® 7.5 mg (one month) formulations that support the safe and effective use of ELIGARD® 45 mg are included in this application.

Table 1: A comparison of the ELIGARD® 45 mg to other ELIGARD® formulations.

Table 2 Comparison of ELIGARD® Formulations for SC Administration				
Formulation	ELIGARD® 45 mg	ELIGARD® 30 mg	ELIGARD® 22.5 mg	ELIGARD® 7.5 mg
NDA Reference	21-731	21-488	21-379	21-343
Frequency of Administration	Once every six months	Once every four months	Once every three months	Once per month
Active drug (Dose)	Leuprolide acetate (45 mg)	Leuprolide acetate (30 mg)	Leuprolide acetate (22.5 mg)	Leuprolide acetate (7.5 mg)
Drug loading (w/w)	[]			
Polymer type (lactide/glycolide ratio)	PLG (85/15)	PLG (75/25)	PLG (75/25)	PLGH (50/50)
Polymer Mol. Wt. Acceptance Criteria	16-26 kDa	15-21 kDa	15-21 kDa	23-45 kDa
Polymer (% by wt.)	[]			
NMP Solvent (% by wt.)	[]			
Injection mass	0.375 g	0.500 g	0.375 g	0.250 g

Although the formulations have qualitatively similar components, they differ in the drug load, lactide/glycolide subunit ratio and molecular weight ranges of the polymer in order to achieve the desired rate of drug release.

2.1.4 Mechanism of action

In males, acute administration of leuprolide acetate causes an initial increase in circulating levels of luteinizing hormone (LH) due to the sensitization of the pituitary gonadotropin receptors. The LH surge leads to a transient increase in the gonadal steroids testosterone and dihydrotestosterone. However, continuous release of leuprolide acetate from a long-acting depot formulation such as ELIGARD® 45 mg results in desensitization and down regulation of the receptors, thereby decreasing the production of LH and consequently testosterone, which is reduced below castrate threshold (< 50 ng/dL). This androgen depletion can occur within two to four weeks after initiation of treatment and is reversible upon discontinuation of drug therapy.

2.1.5 Therapeutic indication

The proposed indication for ELIGARD[®] 45 mg is palliative treatment of advanced prostate cancer. Testosterone is necessary for prostate growth and development, and it also serves as a profound stimulator of malignant progression. Decrease in testosterone to castrate levels (< 50 ng/dL) helps in reducing pain, urinary problems and other symptoms associated with prostate cancer.

2.1.6 Proposed dose and route of administration

ELIGARD[®] 45 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 45 mg of leuprolide acetate at a controlled rate over a 6-month therapeutic period.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

- Pivotal clinical trial (AGL0205): Atrix laboratories, Inc., has conducted a pivotal phase 3 study entitled: A 12-month, open-label, fixed-dose study to evaluate the safety, tolerance, pharmacokinetics and endocrine efficacy of two doses of LA-2580 45 mg in patients with advanced prostate cancer.

This multi-center study was conducted in 111 male patients (aged 50-86 years; mean 73.2 yrs) with Jewett stage A2, B, C, or D adenocarcinoma of the prostate. The racial distribution of these patients was as follows: White (75.7 %), Black (17.1 %), Hispanic (5.4 %), Asian (0.9 %), other (0.9 %). While all 111 patients received at least one injection, 106 patients received a SC injection of ELIGARD[®] 45 mg once every six months for twelve months, for a total of two injections. Pharmacodynamics was assessed in a subgroup of 28 patients and pharmacokinetic data was available and evaluated in 27 patients in this subset during each of the two six-month (168-day) dosing intervals.

- Supportive information: In addition, data from clinical pharmacokinetic studies of ELIGARD[®] 30 mg (4 months; NDA 21-488), ELIGARD[®] 22.5 mg (3 months; NDA 21-379) and ELIGARD[®] 7.5 mg (1 month; NDA 21-343) formulations is also provided in the submission. These formulations have been approved by FDA for use in the palliative treatment of prostate cancer. Because of compositional and therapeutic similarities of these three previously approved ELIGARD[®] formulations with the proposed formulation (ELIGARD[®] 45 mg), data from those clinical trials was referenced in the submission as supporting information.

What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

- The primary efficacy endpoint for this study was the proportion of patients in whom the serum testosterone concentration was suppressed to castrate levels by month 1 (day 28). In addition the efficacy was also assessed in terms of the cumulative proportion of patients maintaining castrate testosterone suppression through out the dosing interval (in this case 6 months).

- Because prostate cancers are dependent on circulating androgens, hormonal manipulation using GnRH analogs is the mainstay of symptomatic treatment in contrast to surgical castration that may be undesirable to many patients. Testosterone concentration ≤ 50 ng/dL is generally accepted as castrate level needed to achieve adequate symptomatic control. The agency accepts a 4-week time frame for the achievement of clinical castration in patients. This has been based upon the fact that most people receiving Lupron depot (“gold standard” for LHRH agonist therapy) achieve castration level by week 4 and also because 4 weeks is a reasonable amount of time for these patients to wait for purposes of treatment.
- Serum testosterone concentrations were determined at screening, and baseline (day 0) before injection of study drug. Post injection testosterone concentrations were determined at day 0: Hours 2, 4 and 8, Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 (month 6): Hours 0 (pre-second dose), 2, 4, 8 following the second injection, days 169, 170, 171, 175, 182, 189, 196, 203, 210, 217, 224, 238, 252, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, and 336 (month 12). Serum testosterone levels were measured employing a validated radioimmunoassay (RIA) method with a LOQ of 3 ng/dL.
- Other secondary measures of efficacy include serum luteinizing hormone (LH) concentrations (obtained at the same time points as testosterone measurements, except for the screening sample) and serum prostate specific antigen (PSA). While decrease in serum testosterone and LH demonstrate leuprolide-mediated suppression of steroidogenesis (thus confirming the drug-response relationship), PSA levels act as surrogate marker for disease progression. In addition to these surrogate endpoints, direct evidence of efficacy was derived from clinical efficacy endpoints including measures of bone pain, urinary pain and urinary signs & symptoms, and WHO performance status scores.

Are the active moieties in the serum appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Serum leuprolide (PK) and serum testosterone (PD) concentrations following SC injection of ELIGARD[®] 45 mg were determined using validated analytical methods in order to obtain relevant exposure-response information.

- Concentrations of leuprolide in blood serum, from a subset of patients designated as Group A (n = 27), were assessed from the samples taken at the following scheduled visits: Day 0 (prior to dosing, and hours 2, 4 and 8 post-dosing), Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 98, 105, 112, 119, 126, 133, 140, 147, 154, 161, 168 (month 6: prior to dosing and hours 2, 4 and 8 post-dosing), days 169, 170, 171, 175, 182, 189, 196, 203, 210, 217, 224, 238, 252, 266, 273, 280, 287, 294, 301, 308, 315, 322, 329, and 336 (month 12).
- Leuprolide concentrations in serum were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method in which samples were purified using liquid-solid phase extraction. The assay lower limit of quantitation was 50 pg/ml (0.05 ng/ml). The LC-MS/MS assay employed is specific for leuprolide. Four known metabolites of leuprolide (M-I, M-II, M-III and M-IV) were shown not to interfere with a similar LC/MS/MS assay.

- Concentration-response relationship was assessed by correlating the changes in the pharmacodynamic endpoint i.e. testosterone serum concentrations, with serum leuprolide concentrations obtained at the same time points following SC injection of ELIGARD® 45 mg.

2.2.1 Exposure-Response

What are the characteristics of the exposure-response relationships for efficacy?

- Concentration-response relationship: The serum leuprolide concentrations following the first and second doses of ELIGARD® 45 mg administered at six month interval are tabulated below, along with the corresponding changes in serum testosterone concentrations.

Table 2: Serum leuprolide and testosterone concentrations in PK/PD subgroup patients (n = 27/28) following the 1st dose of Eligard® 45 mg. Concentrations are provided as mean ± S.E.M

Time (days)	Leuprolide (ng/ml)	Testosterone (ng/dL)
0 (1 st dose)	0.063 ± 0.01	367.7 ± 12.98
0.08 (2 h)	66.54 ± 7.81	431.0 ± 16.1
0.17 (4 h)	79.45 ± 7.10	434.2 ± 15.4
0.33 (8 h)	63.97 ± 5.11	432.3 ± 14.5
1	17.85 ± 1.68	522.7 ± 18.7
2	6.42 ± 0.74	588.6 ± 23.9
3	3.56 ± 0.40	569.9 ± 23.7
7	1.28 ± 0.12	420.8 ± 20.7
14	0.97 ± 0.15	114.6 ± 6.79
21	0.79 ± 0.08	34.78 ± 3.38
28 (M1)	1.25 ± 0.34	16.73 ± 3.35
35	1.19 ± 0.28	13.11 ± 2.73
42	1.77 ± 0.67	12.83 ± 3.37
49	1.79 ± 0.39	11.94 ± 2.75
56 (M2)	1.08 ± 0.23	11.54 ± 2.73
70	3.64 ± 2.72	12.23 ± 4.12
84 (M3)	0.85 ± 0.21	8.29 ± 0.49
98	0.71 ± 0.13	8.75 ± 0.49
105	0.87 ± 0.29	9.58 ± 0.51
112 (M4)	0.53 ± 0.09	10.05 ± 0.49
119	0.50 ± 0.08	9.83 ± 0.59
126	0.53 ± 0.10	10.04 ± 0.57
133	0.35 ± 0.05	9.39 ± 0.53
140 (M5)	0.31 ± 0.06	10.08 ± 0.52
147	0.23 ± 0.04	9.94 ± 0.49
154	0.19 ± 0.03	8.5 ± 0.43
161	0.19 ± 0.03	9.4 ± 0.50
168 (Month 6)	0.21 ± 0.08	10.4 ± 0.54

Table 3: Serum leuprolide and testosterone concentrations in PK/PD subgroup patients (n = 27/28) following the 2nd doses of Eligard® 45 mg. Concentrations are provided as mean ± S.E.M

Time (days)	Leuprolide (ng/ml)	Testosterone (ng/dL)
168.08 (2 nd dose)	80.39 ± 11.15	8.17 ± 0.47
168.16 (4h)	98.16 ± 14.35	8.74 ± 0.48
168.33 (8h)	83.5 ± 9.73	8.2 ± 0.49
169	33.5 ± 4.78	9.94 ± 0.6
170	12.2 ± 1.45	9.68 ± 0.65
171	6.28 ± 0.66	9.51 ± 0.6
175	2.09 ± 0.15	8.69 ± 0.49
182	1.27 ± 0.17	9.47 ± 0.51
189	0.94 ± 0.14	10.37 ± 0.53
196 (M7)	0.85 ± 0.13	9.48 ± 0.49
203	0.9 ± 0.17	9.56 ± 0.64
210	0.71 ± 0.11	10.05 ± 0.63
217	0.74 ± 0.19	9.04 ± 0.48
224 (M8)	0.63 ± 0.17	8.74 ± 0.47
238	1.48 ± 0.65	8.35 ± 0.43
252 (M9)	1.05 ± 0.41	8.35 ± 0.48
266	0.82 ± 0.34	7.97 ± 0.56
273	0.51 ± 0.11	6.93 ± 0.4
280 (M10)	0.47 ± 0.08	7.48 ± 0.48
287	0.55 ± 0.21	7.72 ± 0.55
294	0.35 ± 0.05	8.87 ± 0.75
301	0.32 ± 0.04	9.63 ± 0.75
308 (M11)	0.31 ± 0.04	10.79 ± 1.18
315	0.29 ± 0.04	12.4 ± 1.69
322	0.25 ± 0.04	11.35 ± 1.84
329	0.2 ± 0.04	12.17 ± 1.82
336 (M12; End of study)	0.2 ± 0.03	12.56 ± 2.06

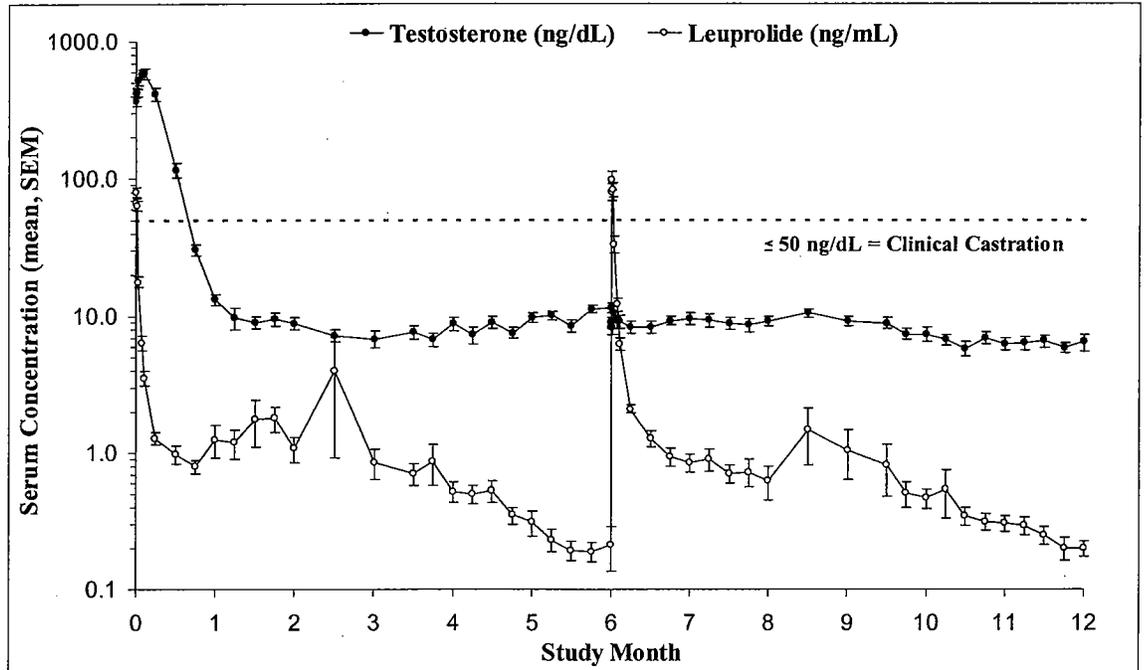


Figure 2: Mean serum Leuprolide and Testosterone after two consecutive SC doses, at baseline (Day 0) and month 6 (Day 168) in patients with advanced prostate cancer (n = 23-28).

- After each SC injection of ELIGARD[®] 45 mg, mean serum leuprolide levels peaked during the first day (T_{max} ~ 4.5 hours), fell rapidly during the next three days, and then declined more slowly, maintaining levels between 0.2-2.0 ng/ml for the remainder of the six month dosing interval.
- In response to this pattern of leuprolide exposure, mean serum testosterone levels in the PK subset (n = 28) rose initially to 584.5 ± 48.6 ng/dl on day 3, fell to 30.4 ± 3.0 ng/dL on day 21, and then remained between 5.8 – 11.6 ng/dL for the remainder of the 336 day study.
- Serum testosterone did not increase in response to the second dose of ELIGARD[®] 45 mg, but remained suppressed in all patients in the PK subset during the entire second dose interval. This is because the sustained exposure of the pituitary gonadotropin receptors to leuprolide following the first injection has rendered them insensitive to further stimulation by GnRH or its analogs. Therefore a second dose was successful in maintaining the castration that was brought about by the first ELIGARD[®] 45 mg injection.
- Dose-response relationship: Pivotal study (AGL0205) was a fixed-dose, non-comparative, open-label study. All patients were to receive two identical injections of ELIGARD[®] 45 mg given once every six months. No dose response was performed with ELIGARD[®] 45 mg.

What is the time of onset and offset of the desirable pharmacological response or clinical endpoint?

- Within the PD subset of 28 patients, clinical castration (defined as Testosterone concentration of ≤ 50 ng/dL for two consecutive time points approximately one week apart) was achieved in 100 % of patients by day 28. Serum testosterone remained suppressed in all patients for the study duration (12-months).
- In the pivotal study patients, 108 of the 111 (97 %) enrolled patients who received the first injection achieved castrate suppression by Day 28. Of the three patients that did not achieve suppression, two patients had withdrawn prior to the 28 day assessment and one patient (# 2002) failed to achieve testosterone suppression at any time prior to withdrawing from the study on day 85.
- The median time to castrate suppression was 21 days while the mean time to castrate suppression was 21.2 days.
- No patient experienced breakthrough during the first 6 months of the study. Following the second injection at month 6, testosterone suppression was maintained throughout the study period i.e. month 12, in all but one patient (# 1402). This patient experienced breakthrough (defined as testosterone values above castration when they were previously below castration) on day 308 following the second dose and remained so through the end of the study period (T = 210 ng/dL on day 336).
- Leuprolide serum concentrations are not available for patients # 2002 and # 1402.

Table 4: The time of onset and duration of maintenance of the desired changes in the efficacy variables i.e. decrease in the serum concentrations of Testosterone and LH following two SC injections of ELIGARD® 45 mg given six months apart are tabulated below for all pivotal trial patients (n = 106-111; values indicate Mean \pm SEM)

	Testosterone (ng/dL) Desired Threshold for Testosterone: ≤ 50 ng/dL	Luteinizing hormone (LH; MIU/mL) Desired LH < 1 MIU/mL
Baseline (Before 1 st dose)	367.7 \pm 13.0	6.98 \pm 0.48
Initial Surge (C _{max})	588.6 \pm 23.9 (day 2)	37.9 \pm 2.43 (Hour 8)
Day 7	420.81 \pm 20.7	6.85 \pm 0.34
Day 14	114.56 \pm 6.8	2.54 \pm 0.13
Day 21	34.8 \pm 3.4	1.137 \pm 0.062
Day 28 (month 1)	16.7 \pm 3.4	0.538 \pm 0.026
Day 56 (month 2)	11.54 \pm 2.72	0.111 \pm 0.009
Month 6 (2 nd dose)	10.4 \pm 0.53	0.112 \pm 0.024
Month 12 (study end)	12.6 \pm 2.1	0.229 \pm 0.14

What are the characteristics of exposure-response relationships (dose-response or concentration-response) for safety?

- Common systemic adverse events found in this study were related to the normal physiological response following testosterone suppression and consequent medical castration including: hot flashes, fatigue, weakness, testicular atrophy, gynaecomastia, night sweats and myalgia.

- When testosterone was at its peak concentration during days 0-3 post-dose, no clinically significant increases in the mean scores for bone pain, urinary pain & symptoms etc were observed, suggesting that there were no flare symptoms.
- In general, the drug was well tolerated when given as two consecutive SC injections six-months apart.

Does this drug prolong the QT or QTc interval?

The sponsor has not evaluated the QT interval prolongation potential of ELIGARD[®] 45 mg. However, it has been observed with leuprolide and other drugs in this class that a prolongation of the QT interval is caused by the use of these drugs. This effect is however attributed to the androgen ablation caused by these drugs (several literature references suggest that androgens have a cardiac protective 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.

2.2.2 Pharmacokinetics:

What are the single dose and multiple dose PK parameters?

- Following the first dose of ELIGARD[®] 45 mg SC injection, mean serum leuprolide concentrations rose rapidly to a C_{max} of 82.0 ± 38.2 ng/ml (range 30.4 – 180 ng/ml) at 4.4 ± 1.7 hours (T_{max}). The concentrations then fell rapidly over the next three days, with a day 3 mean concentration of 3.56 ± 0.4 ng/ml. Following this initial “burst” phase, leuprolide concentrations declined slowly over the remaining duration of the dosing interval (day 3-day 168). The serum concentrations during this “plateau” phase (includes data on days 7 to 168) were generally maintained at 0.2-1.8 ng/ml, while individual levels in patients ranged from _____ i.e. BLOQ to _____ (subject # 0201).
- When a second dose of ELIGARD 45 mg SC injection was administered at month 6 (day 168), peak serum leuprolide concentrations of 102.4 ± 72.1 ng/ml (range 28.4 – 376 ng/ml) at a median T_{max} of 4.75 ± 2.0 hours. Concentrations then fell rapidly over the first three days (mean concentration on day 3 was 6.28 ± 0.67 ng/ml) following the second injection and then were maintained in the range of 0.2-2.1 ng/ml during the plateau phase, while individual values ranged from <

Table 5: Summary of PK parameters after the first (Day 0) and second (day 168 or month 6) ELIGARD® 45 mg SC injection

Subject Number	Burst Phase (Day 0-3)			Plateau Phase (Day 3-168)				Total (Day 0-168)		Subject Number	Burst Phase (Day 0-3) ^a			Plateau Phase (Day 3-168)				Total (Day 0-168)	
	AUC ng hr ml ⁻¹	C _{max} ng/ml	T _{max} hr	AUC ng hr ml ⁻¹	C _{max} ng/ml	C _{min} ng/ml	C _{last} ^a ng/ml	AUC ng hr ml ⁻¹	F ^b %		AUC ng hr ml ⁻¹	C _{max} ng/ml	T _{max} hr	AUC ng hr ml ⁻¹	C _{max} ng/ml	C _{min} ng/ml	C _{last} ^b ng/ml	AUC ng hr ml ⁻¹	F ^c %
0201	1932.9	64.6	4.08	31109.8				33042.7	5.83	0201	2926.7	84.4	7.58	8982.7				11909.4	2.10
0202	1431.2	84.8	4.08	2968.4				4399.6	0.78	0202	2765.0	111	2.08	2818.1				5583.1	0.98
0203	706.3	31.4	8.17	2087.9				3104.2	0.55	0203	2171.8	114	3.83	1695.9				3867.7	0.68
0301	2329.24	120	7.65	3744.4				6073.64	1.07	0301	2471.6	81	7.50	5251.6				7723.2	1.36
0302	1817.5	73.8	3.88	3844.1				5661.6	1.00	0302	1824.3	83.9	3.80	2680.7				4505.0	0.79
0303	747.5	40.2	3.83	3631.24				4378.74	0.77	0303	793.8	39.5	4.05	1826.7				2620.5	0.46
0304	1549.1	78.9	3.93	3696.56				5245.66	0.93	0304	599.6	28.4	4.03	3638.1				4237.7	0.75
0305	2460	160	4.13	2996.8				5456.8	0.96	0305	2793.0	119	3.98	1181.1				3974.1	0.70
0306	2970	116	3.87	6794.4				9764.4	1.72	0306	2944.4	106	8.07	6238.1				9182.5	1.62
0307	1858.9	96.2	3.80	3736.1				5595	0.99	0307	1949.4	88.3	7.97	8957.8				10907.2	1.92
0308	1329.5	62.4	4.00	4277.07				5606.57	0.99	0308	2582.7	96.9	7.85	4281.1				6863.8	1.21
0701	1317	60.3	3.92	2858.8				4175.8	0.74	0701	1068.4	39.9	7.92	2386.6				3455.0	0.61
0702	2306.3	132	3.67	1187.49				3493.79	0.62	0702	1531.8	52.7	3.75	3143.0				4674.8	0.82
1101	504.2	34	3.95	6861				7365.2	1.30	1101	1212.7	72.4	4.03	1737.3				2950.0	0.52
1401	1004.3	59.4	4.00	2374.64				3378.94	0.60	1401	1066.3	50.4	3.75	733.5				1799.8	0.32
1501	1816.3	122	2.00							1601	1712.2	75.8	4.00	3011.7				4723.9	0.83
1601	860.2	52.4	4.00	3339.55				4199.75	0.74	1602	2167.6	45.7	8.00	1939.2				4106.8	0.72
1602	856.3	30.4	8.00	3108.3				3964.6	0.70	2001	4172.0	167	3.75	4840.9				9012.9	1.59
2001	1725	70.1	7.75	5631.66				7356.66	1.30	2201	1550.5	41.1	4.00	3379.7				4930.2	0.87
2201	1049.3	41.9	7.17	2455.1				3504.4	0.62	2202	1628.6	68.1	4.00	1415.6				3044.2	0.54
2202	1565	105	4.08	1226.27				2791.27	0.49	2203	3826.0	185	2.00	2083.5				5909.5	1.04
2203	1790.2	99.7	3.83	4965.4				6755.6	1.19	2401	7237.0	376	3.53	3328.7				10565.7	1.86
2401	2861	180	1.83	2285.6				5146.6	0.91	2701	3402.0	210	2.00	1172.5				4574.5	0.81
2701	1140.8	88.7	2.00	1213.89				2354.69	0.42	2702	2425.8	107	4.00	2257.7				4683.5	0.83
2702	1438.1	71.6	4.08	1625.5				3063.6	0.54	2703	1590.1	74.1	3.92	1846.5				3436.6	0.61
2703	1603.7	81.2	4.00	1499.6				3103.3	0.55	2802	2867.0	144	4.00	2777.7				5644.7	1.00
2802	1082.6	56.1	3.83	3898.9				4981.5	0.88	Mean	2356.9	102.4	4.75	3215.6	3.37	0.12	0.20	5572.6	0.98
Mean	1557.5	81.97	4.43	4362.2	6.71	0.12	0.21	5921.7	1.04	SD	1345.6	72.14	2.01	2142.1	3.19	0.08	0.14	2715.5	0.48
SD	641.1	38.18	1.74	5667.7	14.75	0.10	0.39	5785.9	1.02	RSD	57.1	70.47	42.39	66.6	94.9	64.8	69.8	48.7	48.7
RSD	41.2	46.59	39.3	129.9	220.0	88.58	183.5	97.7	97.7	Median	2169.7	84.15	4	2729.2	2.43	0.111	0.16	4679.2	0.83
Median	1549.1	73.8	4	3223.9	2.75	0.072	0.102	4690.6	0.83	Min									
Min								2354.7	0.42	Max									
Max								33042.7	5.8										

^a Concentration 168 days after dosing. Bioavailability (F) based on reported AUC of intravenous leuprolide.

^b Bioavailability (F) based on reported AUC of intravenous leuprolide.

^c Could not be determined, patient withdrew after Day 140.

BLOQ, below assay limit of quantitation

^a Days after administration of second dose.

^b Concentration 168 days after dosing.

^c Bioavailability (F) based on reported AUC of intravenous leuprolide.

BLOQ, below assay limit of quantitation

Table 6: Comparison of the mean pharmacokinetic parameters of ELIGARD® 45 mg following two consecutive SC injections at six-month intervals in advanced prostate cancer patients.

Parameter ^b	Phase	Dose 1	Dose 2	P-Value ^c
		Mean (± SD)	Mean (± SD)	
AUC	Total	5922 (5786)	5573 (2716)	NS
	Burst	1558 (641)	2357 (1346)	<0.01
	Plateau	4362 (5668)	3216 (2142)	NS
T _{max}	Burst	4.43 (1.7)	4.75 (2.0)	NS
C _{max}	Burst	82.0 (38.2)	102.4 (72.1)	NS
	Plateau	6.7 (14.8)	3.37 (3.2)	NS
C _{min}	Plateau	0.12 (0.1)	0.12 (0.08)	NS
C _{last}	Plateau	0.21 (0.39)	0.20 (0.14)	NS

^a Patient 1501, who did not receive the second dose, is excluded.

^b The parameter F, which is a linear transformation of AUC_{total}, was not compared.

^c Determined using the Wilcoxon signed-rank test. NS = Not statistically significant using 2-tailed α=0.05.

Reviewer's comments:

- The ELIGARD[®] 45 mg formulation resulted in a multiphasic leuprolide concentration versus time profiles characterized by a distinctive burst phase and a plateau phase.
- The serum leuprolide concentrations and the associated pharmacokinetics following the first and second doses of ELIGARD[®] 45 mg suggest lack of significant accumulation with repeated dosing at 6 month intervals.
- Although the Day 0-3 AUC was about 50 % higher after the second dose in comparison to the first dose (due to high C_{max} in one individual as explained below), the overall AUC did not differ between the two doses.
- Following the second dose of ELIGARD[®] 45 mg, the C_{max} in patient # 2401 (376 ng/ml) was 4 times higher than the mean from the other patients (~ 91.5 ng/ml). Following this large initial C_{max}, the leuprolide concentrations in this patient remained in the range of 0.3-3.4 during the plateau phase (day 4-day 168). The testosterone levels in this patient remained suppressed below castration and did not exhibit any acute changes.

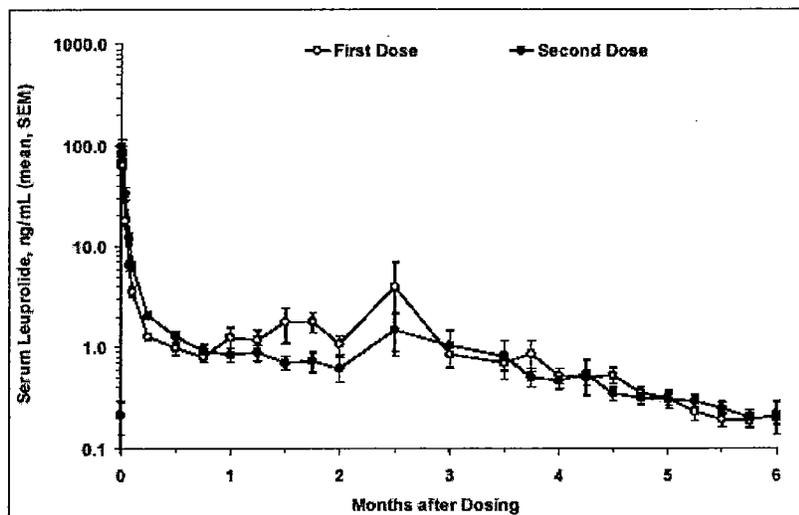


Figure 3: Pharmacokinetic profile of ELIGARD[®] 45 mg, showing serum leuprolide levels (mean, SEM) after two consecutive SC injections at six-month intervals in advanced prostate cancer patients (n = 26-27).

- The apparent increases in mean plasma leuprolide concentrations observed at 2 to 3 months after the first and second injections were due to very high values in one patient (# 0201) [68.7 ng/ml on day 70 (first dose) and 16.1 ng/ml on day 238 (second dose)]. This patient also contributes to the high CV (> 100 %) observed for the plateau phase C_{max} and AUC, while moderate variability was observed for the burst phase (CV < 50 %). The variability associated with the overall AUC (0-6 months) was also very high after the first dose (CV 97.7 %) due to the inclusion of data from patient # 0201. Pharmacokinetic data following the second dose of ELIGARD[®] 45 mg was less variable compared to the first dose, especially with respect to the plateau phase and the overall AUC over six months. Although

data from patient # 0201 may suggest possible dose dumping from the sustained release formulation, it still doesn't explain why these sudden increases in leuprolide concentration occurred in this patient at around the same time (day 70) after both the doses. However, because the testosterone concentrations in this individual remained castrate at these time points and were not altered by the sudden increase in serum leuprolide concentrations, this observation is not clinically relevant.

- The average plateau phase serum leuprolide concentrations following the first and second doses were 0.69 and 0.81 ng/mL. Based on the reported clearance value of 139 ± 30 ml/min (or 8.3 ± 1.8 L/h) after intravenous injection of a single 1 mg bolus dose of leuprolide in humans, the estimated rate of drug release from the ELIGARD[®] 45 mg formulation during the plateau phase is 138 and 162 µg/day following the first and second injections (rate = concentration* clearance).
- A single 1 mg intravenous injection of leuprolide acetate in adult males results in an AUC of 126 ± 33 ng.hr/ml (Senello et al; J. Pharm. Sci., 1986). Therefore, the AUC following a 45 mg intravenous dose of leuprolide acetate would be approximately 5670 ng.hr/ml. Based on this estimation, the observed exposure of 5922 and 5573 ng.hr/ml following the first and second doses of ELIGARD[®] 45 mg SC injections in prostate cancer patients suggests extensive absorption and subsequent mean bioavailability of 104 % (median 83 %) and 98 % (median 83 %) following the first and second doses of the depot formulation.
- The C_{min} (minimum serum leuprolide concentration observed during any dosing interval) for many subjects was found to be less than 0.1 ng/ml and in several instances even below the detection limit (i.e. ——— suggesting that sustained exposure to leuprolide concentrations that are less than 0.1 ng/ml may result in adequate testosterone suppression.
- There is no pharmacokinetic data available for those patients who exhibited lack of response to treatment (failure; # 2002) and breakthrough following initial suppression (escape; # 1402).
- This reviewer has compared the PK/PD following the initial injection of Eligard 45 mg to those observed with other Eligard formulations;
 - It appears that the total AUC following the six-month formulation was roughly in the ballpark of what can be expected from administering 6 doses of the 1-month formulation or 2 doses of the 3-month formulation.
 - The C_{max} for the 6-month formulation was lower than the 3- or 4- month formulations (desirable from a clinical perspective) and T_{max} was similar.
 - In addition, the plateau concentrations were maintained between 0.2-2.0 ng/ml and are consistent with other strengths of Eligard.
 - The formulations also did not vary with respect to the initial surge concentrations of testosterone, the time for castration and the castrate levels during plateau phase.

Table 7: A comparison of leuprolide pharmacokinetics and pharmacodynamic endpoints (i.e. testosterone) following the initial injections of the 1, 3, 4 and 6 month formulations of Eligard.

	Eligard 7.5 mg (1 month)	Eligard 22.5 mg (3 months)	Eligard 30 mg (4 months)	Eligard 45 mg (6 months)
Leuprolide analysis method	RIA	RIA	HPLC/MS	LC-MS/MS
C _{max} (ng/ml)	25.3 ± 11.3	127 ± 39	149 ± 77	81.9 ± 38.2
T _{max} (hours)	4 to 8	4.6 ± 1.6	3.3 ± 1.2	4.4 ± 1.7
Plateau levels (ng/ml)	0.2 – 2.0	0.2 – 2.0	0.1 – 1.0	0.2 – 2.0
Total AUC (ng.hr/ml)	873 ± 229	3646 ± 1100	3551 ± 990	5922 ± 5786
Delivery rate (µg/day)	140	150 – 190	83-113	138-163
Testosterone peak (ng/dL)	600 ± 74	610 ± 246	588 ± 40	585 ± 49
Time of Testosterone Peak	Day 3	Day 2	Day 3	Day 3
Time for castration (Overall study)	Days 21-42	Days 21-35	Days 21-42	Day 21-28
Castrate levels (ng/dL)	7-18	7-13	6-12	6-12

2.2.2.1 Absorption

Leuprolide is inactive if given by oral route as it undergoes rapid enzymatic degradation by the gut proteases. It is therefore generally administered via subcutaneous or intramuscular routes. Leuprolide acetate is rapidly and completely absorbed after SC administration, as suggested by the observed bioavailability of > 97 % following SC injection of ELIGARD[®] 45 mg formulation.

2.2.2.2 Distribution

The mean volume of distribution (V_{dss}) after intravenous administration of leuprolide to healthy male volunteers is reported to be 26.5 ± 10.1 L. The *in vitro* binding of radio labeled leuprolide to human serum, as measured by _____, ranged from _____, suggesting that leuprolide is only weakly bound to plasma proteins after administration.

2.2.2.3 Metabolism

Metabolites of leuprolide were not assessed in this study. Leuprolide is known to be metabolized by cleavage of its serine-tyrosine peptide bond to form a pentapeptide metabolite (M-I), which is further degraded to several di- and tri-peptide metabolites (M-II, M-III and M-IV). All four metabolites are inactive. The principal metabolite, M-I, is present in serum and urine at lower concentrations than the parent drug.

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.3 ± 1.8 L/h (139 ± 30 ml/min), with a

terminal elimination $T_{1/2}$ of 2.9 ± 0.5 hours based on a two compartment model (Sennello *et al.* J Pharm Sci 1986;75:158-60).

2.2.2.4 Excretion

The sponsor did not conduct a drug excretion study with ELIGARD® 45 mg formulation.

Animal studies with ^{14}C -leuprolide showed that 49% to 68% of the radioactivity was recovered in the urine, mainly as parent drug and the M-I and M-II metabolites, suggesting that urinary excretion might play an important role in leuprolide elimination.

2.3 Intrinsic Factors

The PK subset of the pivotal trial patients in NDA 21-731 included subjects belonging to various subcategories based on demographic characteristics, disease state etc. However, no formal sub population analysis was conducted. The sponsor states that ELIGARD® 45 mg provided sustained leuprolide release and sustained testosterone suppression in all pharmacokinetic subgroup patients.

Body weight (BW): The clinical pharmacokinetic subset in the ELIGARD® 45 mg phase 3 study included patients who ranged in weight from 56 to 121 kg. When these patients were administered a fixed dose of 45 mg leuprolide acetate (ELIGARD® 45 mg), there was a trend for decreasing C_{max} values with increasing BW (significantly different with $p=0.002$). However, due to the wide safety margin of leuprolide, these observed differences in initial exposure may not be clinically significant. BW did not appear to have an influence on total observed exposure ($\text{AUC}_{0-6 \text{ months}}$) following a single dose of ELIGARD® 45 mg ($p = 0.5772$).

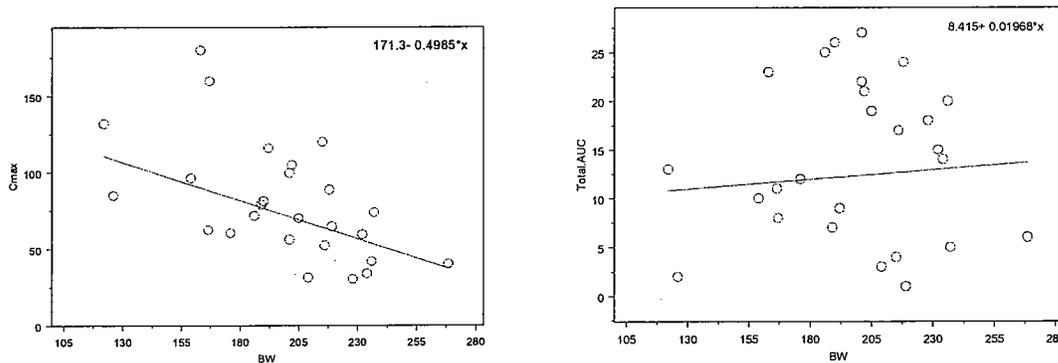


Figure 4: Effect of bodyweight (BW) on C_{max} and AUC of leuprolide from ELIGARD 45mg.

Age: Elderly patients made up a substantial portion of the patients whose pharmacokinetics were evaluated in the pivotal clinical trial of ELIGARD® 45 mg, which included patients between the ages of 50 and 85 years. Within the age group studied, C_{max} exhibits a slight increasing trend with age (not significant). However, there was no influence of age on total observed AUC ($p > 0.05$).

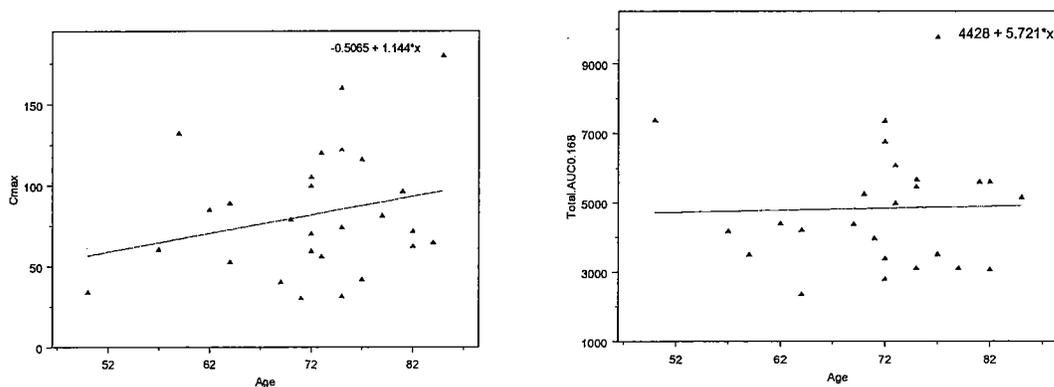


Figure 5: Effect of patient age on ELIGARD 45 mg pharmacokinetics; patient # 0201 was excluded from the right (AUC vs age) plot.

Race: There was no significant impact of race (7 blacks, 17 whites and 3 Hispanics) on leuprolide pharmacokinetics. The mean Cmax values in blacks, whites and Hispanics were 62 ± 24 , 89 ± 39 and 87 ± 51 ng/ml, respectively. The mean total AUC(0-6 months) was 4505 ± 1480 , 6763 ± 7247 and 4737 ± 1763 ng.h/ml, respectively in the black, white and Hispanic populations following the first dose. None of these differences were statistically significant.

No apparent relationship was observed between the various exposure parameters (Cmax, Cmin, AUC) and pharmacodynamic endpoints (testosterone peak, time for castration). In addition, these patients had a variety of concomitant disease states and exhibited a range of clinical chemistry and hematologic abnormalities during the study. However, the sponsor did not attempt to correlate the observed exposure or response parameters with any of these intrinsic factors.

Women and pediatric subjects were not included in the clinical studies described in this application, which seeks approval to market ELIGARD® 45 mg for the treatment of advanced prostate cancer in men.

2.4 Extrinsic Factors

Drug-drug interactions: No pharmacokinetic drug-drug interaction studies were performed with ELIGARD® 45 mg. No drug-drug interactions have been described for other preparations of leuprolide acetate, which does not appear to be metabolized by Cytochrome P450 or other phase I or phase II pathways that could lead to metabolic interactions with other drugs. Pharmacokinetic drug-drug interactions are unlikely to be observed with ELIGARD® 45 mg because leuprolide is primarily degraded by peptidase(s), and is less than 50% bound in the plasma.

2.5 General Biopharmaceutics

Dose selection:

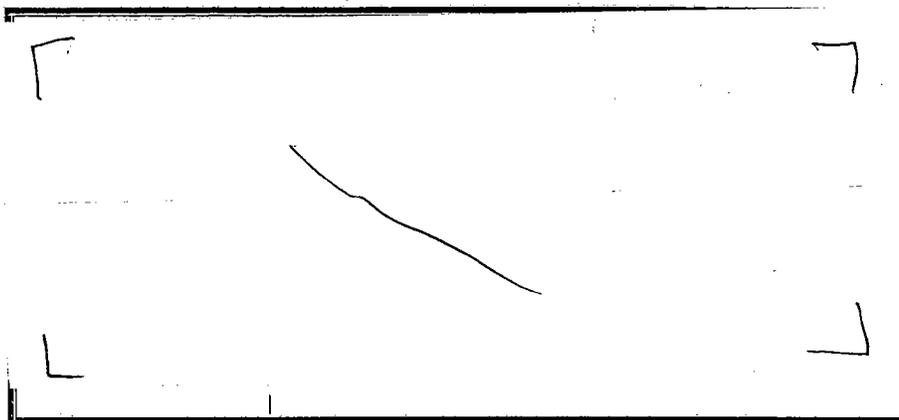
The sponsor provides the following rationale for dose selection in ELIGARD® six month formulation: The dose for the six-month ELIGARD® 45 mg formulation was selected by proportionally increasing the leuprolide acetate dose of the four-month ELIGARD® 30 mg formulation to 45 mg, along with modification of the formulation co-polymer that resulted in a six-month release profile. This resulted in six-month duration of activity in animal models and human clinical trials. Because serum levels below the assay limit of quantitation (0.05 ng/mL) might be associated with incomplete suppression of pituitary gonadotropin secretion, and the wide safety margin of leuprolide acetate, lower doses were not investigated for the ELIGARD® 45 mg. In addition, a review of the clinical literature found two dose-ranging studies that determined the objective response following monthly treatment with 3.75 mg and 7.5 mg leuprolide acetate. These studies suggested a trend (not statistically significant) toward a better objective response with the larger dose (Akaza et al. *J Int Med Res* 1990; 18(1):90-102 and Akaza et al. *Jpn J Clin Oncol* 1992; 22:177-184). These data supported the selection of a 45 mg dose of leuprolide acetate for the six-month product.

Formulation: The two lots (1522 & 1582) of ELIGARD® 45 mg used in the phase 3 clinical trial (AGL0205) represent the same drug formulation used in the to be marketed product, and no other formulation or significant manufacturing changes were implemented during the clinical trials (Page 221, Volume 2.1). Although the drug substance (leuprolide acetate) employed in the clinical trials and for the to-be-marketed formulations is from two different sources because the clinical trial employed two lots (1522 and 1582 for the first dose and second dose, respectively) that were manufactured using drug substance from each of the above sources, bridging information in the form of *in vitro* dissolution comparison and clinical (PK/PD) data is available to demonstrate comparable release and pharmacokinetic profiles.

In vitro release testing method (T667): The proposed release testing method for ELIGARD® 45mg is non-physiological in nature with no *in vivo* relevance and is meant strictly for ensuring quality control. Therefore the release specification setting is being handled by chemistry. Nevertheless a brief description of the method and important results together with CMC's recommendation is given below.

The T667 method employs accelerated release testing designed to produce close to release within a testing period. In method T667, the constituted ELIGARD® 45 mg product (375 mg) [

T667 Method Summary



Samples are taken at 6, 24 and 54 hours. All samples are assayed by HPLC to determine the cumulative amounts of leuprolide acetate released, which are reported as percentages of the finished product label claim of 45 mg leuprolide acetate. The proposed release specifications for ELIGARD 45mg are shown below:

Table 8: Proposed release specifications for ELIGARD® 45mg.

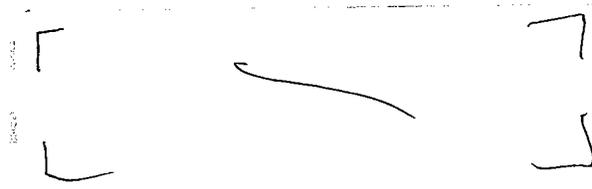
Extended Release (Cumulative % Release)	T667	Mean % of Theory 45 mg		Not less than individual unit results are within ± 10% of the acceptance criteria for mean results.		No individual unit result is more than ± 15% of the acceptance criteria for mean results.	
		Min.	Max.	Min.	Max.	Min.	Max.
6 hour			25		35		40
24 hour		27	62	17	72	12	77
54 hour		75		65		60	
Tier 1: If any acceptance criterion is not met, proceed to Tier 2.							
Tier 2: An additional 6 units are tested. Results from these units must meet all acceptance criteria.							

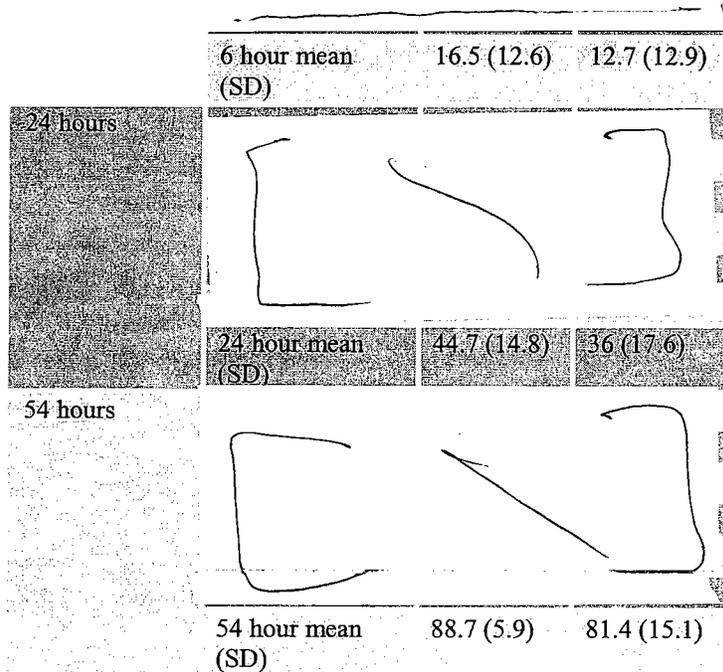
The release rates from constituted products of clinical lots 1522, 1582 and 1582A using method T667 are shown below. Note that while the mean release rate was within the acceptance criteria at all time points, individual units fell out of specification at one or more time points during testing. Testing allows for testing of 6 additional individuals and all individuals need to be within the acceptance criteria to qualify a lot. Although testing was not done for these initial lots, stability lots that failed testing have been shown to pass testing.

Table 9: In vitro release profiles for the clinical lots employed in pivotal trial.

Sampling time	Units	Lot 1522	Lot 1582
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6 hours





The following changes to the mean elution specifications for ELIGARD 45 mg proposed by CMC were accepted by the sponsor:

6 hours: NMT —

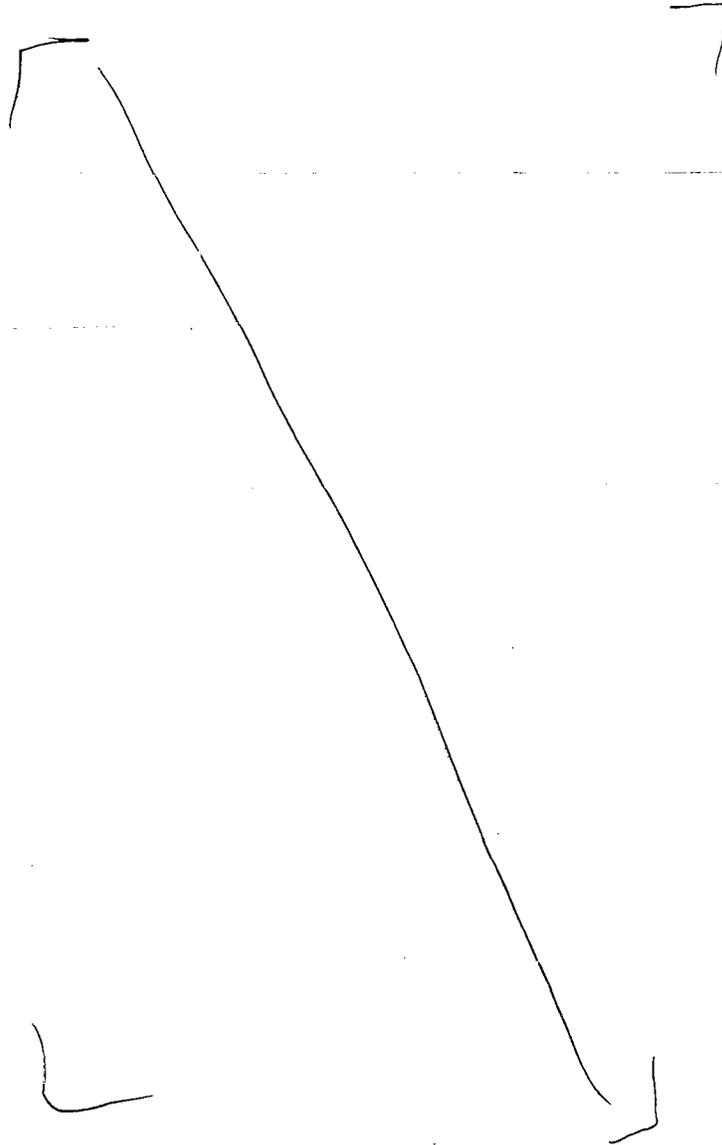
24 hours: —

54 hours: NLT —

Additional comments: During the method development it was observed by the sponsor that this method was unable to adequately discriminate between acceptable lots and unacceptable lots i.e. those with polymer MW and solvent content (NMP specifications) outside pre-specified ranges, thereby raising a concern regarding the usefulness of the method in maintaining product uniformity. Changes in polymer molecular weight, lactide-glycolide ratio and solvent content may alter the density, viscosity, porosity characteristics of the delivery system and thereby impact the release characteristics of the final product. The sponsor acknowledges that the method does not discriminate adequately but maintains that this should not be a concern as the method is anticipated to be used in conjunction with other analytical methods that can identify out-of-range polymer and solvent specifications. Because drug release profile from this controlled release long-acting formulation is dependent on the performance of the delivery system, this apparent lack of sensitivity in the release testing method should be adequately addressed by the sponsor. These observations have been conveyed to the CMC reviewer. **The sponsor has accepted Chemistry's recommendation to tighten the acceptable range of polymer MW to** —

Manufacturing site considerations (issue identified during filing)

- Eligard® 45 mg final product is comprised of two syringes, A and B. SYRINGE A consists of ATRIGEL polymeric delivery system comprised of poly (DL-lactide –co-glycolide) (PLG) and N-methyl 2-Pyrrolidone (NMP). Atrix Laboratories is the proposed primary site of manufacturing for Syringe A. SYRINGE B consists of the active ingredient, leuprolide acetate. The



The results of dissolution profile comparison (f2 factor calculations) in general demonstrate acceptable similarity between the release profiles of lots manufactured at Atrix. Although the above presented information constitutes the most relevant information for this comparison, the sponsor also provided lot to lot comparisons of the Atrix batches with the primary stability lots manufactured in. Some of the f2 values for release comparison were less than — but the sponsor notes that this is likely because the lots from Atrix and — were all not tested for release within the same time frame which would normally take care of potential bias due to assay method variability. The sponsor also notes that for lots manufactured and tested within the same time frame in — the similarity factors were less than — on a few occasions suggesting apparent difference between product lots manufactured at the same site. However, considering the most relevant lots as seen above i.e. the 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.

Delivered mass: ELIGARD® 45 mg formulation is designed to deliver 45 mg of leuprolide acetate subcutaneously within a nominal delivered mass of 375 mg of constituted product. The mean delivered mass for the two phase 3 study lots was determined at various time points during stability testing (Table 11). These studies demonstrated that the mean delivered mass was maintained at approximately 375 mg for both phase 3 clinical lots (# 1522 and 1582) with an individual unit range between 337.3 mg and 387.6 mg and acceptable variability, as judged by USP mass content uniformity criteria. These data demonstrate the reproducibility of the total mass delivered by the ELIGARD® 45 mg dosing system, and suggest that the actual doses administered to patients in the pivotal study were accurate and consistent.

Table 12: Delivered mass data for phase 3 study lots.

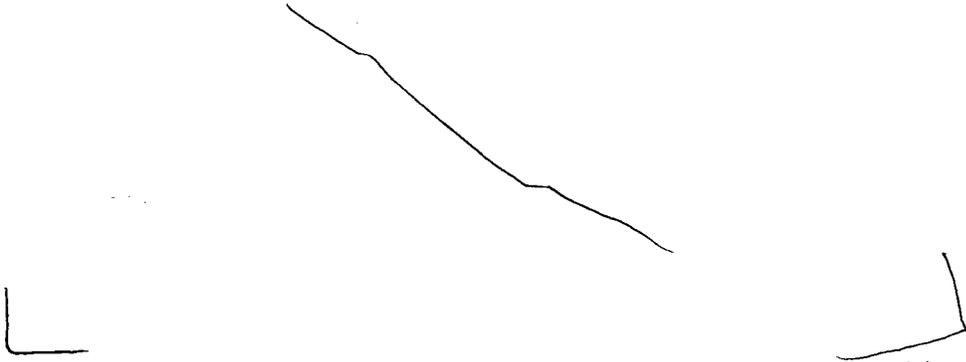
Table 10 Delivered Mass Data for Phase 3 Study Lots								
Method	Lot	Time Point (months)*	Mean Delivered Mass (mg)	Delivered Mass (% of Nominal)	RSD (%)	Min (mg)	Max (mg)	N
Constitute, Dispense and Weigh ¹								
Constitute, Dispense and Weigh ¹								

2.6 Analytical methods

2.6.1 Leuprolide analysis

Leuprolide (C₅₉H₈₄N₁₆O₁₂.CH₃COOH; MW: _____ Retention Time: _____) concentrations in serum samples obtained during the phase 3 _____ pharmacokinetic evaluation of ELIGARD® 45 mg (AGL0205) were measured by a validated LC-MS/MS method in which samples are purified by solid-phase extraction, separated by HPLC and detected by tandem mass spectrometry. The method uses _____ leuprolide or Leuprolide-D₁₀ (C₅₉H₇₄N₁₆O₁₂D₁₀.CF₃COOH; MW: _____ Retention Time: _____) as the internal standard and monitors _____ Calibration was accomplished by weighted linear regression of the ratio of the peak area of leuprolide to that of the added internal standard. The method was found to be specific for leuprolide with no interference from any of the molecules endogenous to serum. No interference was observed for leuprolide with the internal standard.

Validation results:

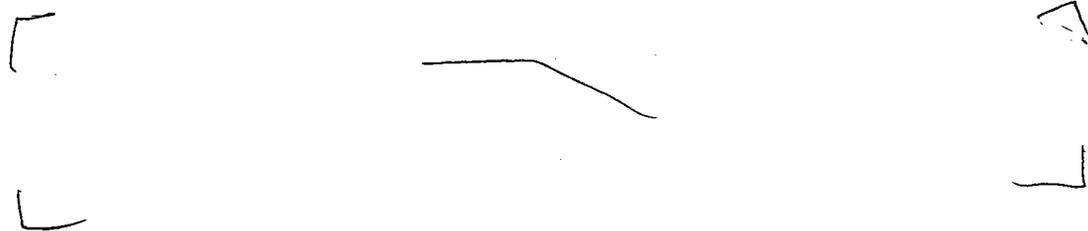


Reviewer's comments:

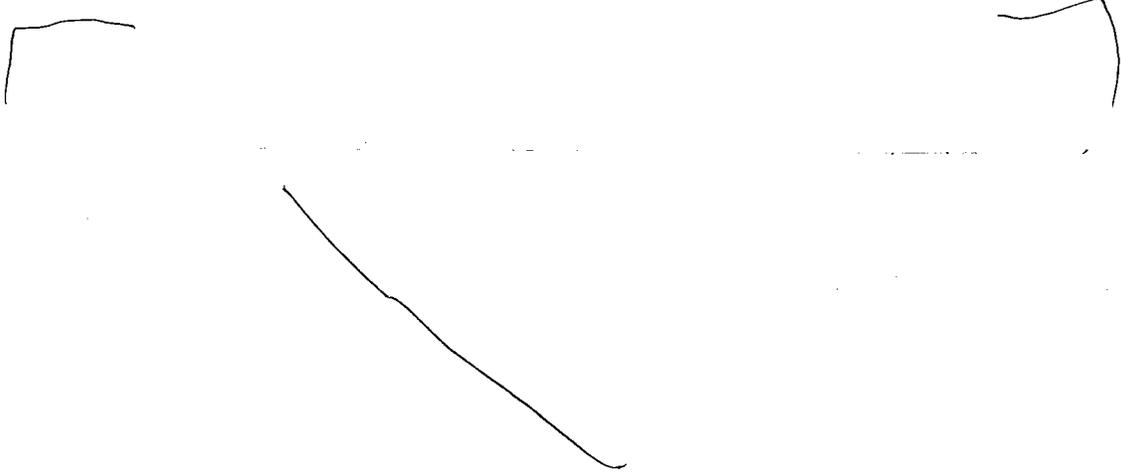
The LC-MS/MS method employed for leuprolide analysis in human serum samples appears adequately validated with accuracy and precision values within agency recommended boundaries ($\pm 15\%$ for all samples, except at LLOQ, where $\pm 20\%$ is acceptable).

2.6.2 Testosterone analysis

Serum testosterone levels were measured in samples from the pivotal phase 3 study (AGL0205) by an RIA (radioimmunoassay) method.



Reviewer's comments:



1 Page(s) Withheld

 ✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

3 Labeling recommendations

Labeling recommendations have been communicated to the sponsor. The final approved labeling for Eligard 45 mg can be found in DFS.

4 OCPB Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
<i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
	Information		Information	
NDA Number	21-731	Brand Name	Eligard® 45 mg	
OCPB Division (I, II, III)	DPE2	Generic Name	Leuprolide acetate	
Medical Division	DRUDP	Drug Class	GnRH agonist	
OCPB Reviewer	Dr. Sandhya Apparaju, Ph.D	Indication(s)	Palliative treatment for Pancreatic cancer	
OCPB Team Leader	Dr. Ameeta Parekh, Ph.D	Dosage Form	Suspension(extended release)	
		Dosing Regimen	Once every 6 months	
Date of Submission	02/20/04	Route of Administration	Subcutaneous	
Estimated Due Date of OCPB Review	12/03/04	Sponsor	Atrix laboratories	
PDUFA Due Date	12/17/04	Priority Classification	3S	
Division Due Date	12/10/04			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X			
PK/PD:				

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

/s/

Sandhya Apparaju
12/3/04 03:46:17 PM
BIOPHARMACEUTICS

Ameeta Parekh
12/6/04 01:22:43 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-731	Brand Name	Eligard® 45 mg
OCPB Division (I, II, III)	DPE2	Generic Name	Leuprolide acetate
Medical Division	DRUDP	Drug Class	GnRH agonist
OCPB Reviewer	Dr. Sandhya Apparaju, Ph.D	Indication(s)	Palliative treatment for Pancreatic cancer
OCPB Team Leader	Dr. Ameeta Parekh, Ph.D	Dosage Form	Suspension(extended release)
		Dosing Regimen	Once every 6 months
Date of Submission	02/20/04	Route of Administration	Subcutaneous
Estimated Due Date of OCPB Review	12/03/04	Sponsor	Atrix laboratories
PDUFA Due Date	12/17/04	Priority Classification	3S
Division Due Date	12/10/04		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:	X			
gender:				
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:	X			
Population Analyses -	X			
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X			
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies	5			
<ul style="list-style-type: none"> The clinical trial and the to-be-marketed formulations for Eligard 45 mg are reported to be identical. Although the drug substance (leuprolide acetate) employed in the clinical trials and for the to-be-marketed formulations is from two different sources, bridging information (<i>in vitro</i> and clinical) is provided to demonstrate comparable release and pharmacokinetic profiles. A specific LC-MS/MS method is used for analysis of leuprolide. The validation report is provided and appears adequate. Testosterone analysis was carried out employing RIA method that shows cross-reactivity with _____ Sponsors claim that _____ chromatography procedures prior to RIA increase the specificity of the method for testosterone analysis. The sponsor has submitted 5 studies that include one pivotal phase 3 clinical study of Eligard 45 mg and four study reports for previously approved Eligard products, as supporting information. The analyses on subpopulation groups, population PK/PD and bioequivalence issues have been deduced from the pivotal Phase 3 study results and are not submitted as separate studies. The effect of hepatic and renal impairment on the PK of Eligard 45 mg has not been evaluated. 				
	"X" if yes	Comments		
Application fileable ?	X	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Sandhya Apparaju, 03/23/04			
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-731
Compound: Leuprolide Acetate
Sponsor: Atrix

Date: 04/06/04
Reviewer: Sandhya Apparaju, Ph.D

Background: ELIGARD® 45 mg (also referred to as LA-2580 45 mg) is an injectable polymer-based, extended release formulation of leuprolide acetate, a potent LH-RH agonist. It is designed to deliver a nominal dose of 45 mg leuprolide acetate over a six month period after subcutaneous (SC) injection. As administered, it is a biodegradable polymeric formulation consisting of the polymer 85:15 poly(DL-lactide-co-glycolide) (PLG), the solvent *N*-methyl-2-pyrrolidone (NMP) and the active drug substance leuprolide acetate. The proposed indication is the palliative treatment of advanced prostate cancer, which is achieved through continuous suppression of gonadal testosterone synthesis.

Phase 3 Clinical Study: Atrix has conducted a pivotal phase 3 study to evaluate the safety and efficacy of Eligard 45 mg in prostate cancer patients (n = 109). The pharmacokinetics of the formulation was assessed in a subset of patients (n=27) who received two injections of Eligard 45 mg at 6 month intervals.

Applicant conclusions: Administration of Eligard 45 mg resulted in a multi-phasic profile of serum leuprolide concentrations. 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 _____ During the plateau phase the average rate of drug delivery from the depot was estimated to be _____. There was no evidence of accumulation after repeated dosing with ELIGARD® 45 mg in the pivotal phase 3 study. Serum leuprolide concentrations and AUCs following the second dose were similar to those observed after the first dose.

Pharmacodynamics: 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).

Formulations: The clinical trial formulation is reported to be identical to the to-be-marketed formulation.

Supporting data: Data from clinical pharmacokinetic studies of ELIGARD® 30 mg, ELIGARD® 22.5 mg, and ELIGARD® 7.5 mg formulations are summarized in the submission. Because of the compositional and therapeutic similarities of these four ELIGARD® formulations, clinical data from the previous formulations (ELIGARD® 30 mg (four-month), ELIGARD® 22.5 mg (three-month) and ELIGARD® 7.5 mg (one month)) is expected to support ELIGARD® 45 mg.

Proposed label: Preliminary review of the proposed label indicates that the subsections pertaining to human pharmacokinetics have been appropriately organized and appear to be based on the information derived from the Phase 3 clinical study and existing literature on the human pharmacokinetics of leuprolide acetate.

Manufacturing site considerations:

Eligard® 45 mg final product is comprised of two syringes, A and B.

SYRINGE A: Consists of ATRIGEL polymeric delivery system comprised of poly(DL-lactide – co-glycolide) (PLG) and N-methyl 2-Pyrrolidone (NMP). ATRIX LABORATORIES, INC. is proposed to be the primary site of manufacturing for Syringe A.

SYRINGE B: Consists of the active ingredient, leuprolide acetate. The manufacturing process for this syringe primarily involves filling of drug solution in water for injection (WFI) into syringes, [redacted] ATRIX laboratories, Inc., is proposed to be the primary manufacturing site for syringe B, while [redacted] (contract facility) is proposed to be the alternate manufacturing site.

The FINISHED drug product (Syringe A plus Syringe B) is packaged at ATRIX laboratories Inc. **Clinical trials** with ELIGARD 45 mg employed finished drug products from Lots 1522 and 1582. These finished products consisted of drug-containing syringes (syringe B) manufactured entirely in the alternate site, [redacted]. No clinical trials were conducted employing drug-containing syringes manufactured in the proposed primary site, Atrix laboratories, Inc.

The finished drug product for ELIGARD 45 mg is an extended release (ER) formulation that is formed when contents from syringe A and syringe B, are mixed prior to injection. However, the leuprolide acetate contained in syringe B is a [redacted] leuprolide acetate in WFI (immediate release, IR) and therefore variations in the manufacturing site for this syringe may not have an impact on the extended release characteristics of the final product. [redacted]

[redacted] These possibilities were discussed with [redacted] and Dr. De (chemistry reviewer) and it was agreed upon that *in vitro* release comparisons should be requested for the final constituted products that employ drug syringes (B) from the two different sites.

Comments to the sponsor: The sponsor should provide *in vitro* release comparison data for the final drug product obtained after mixing contents of syringe A, with syringe B obtained from the two proposed sites of manufacture (Atrix Laboratores Inc., and [redacted]).

[redacted] We recommend that the f2 test be used to compare dissolution profiles and confirm similarity.

Other issues addressed in this submission:

1. Bioavailability/Bioequivalence information: The sponsor states that leuprolide acetate drug substance for the manufacture of Eligard 45 mg will be obtained from two different manufacturers [redacted]. The drug product used for the first dose and second dose of the clinical study were chosen to represent these two batches. Results of the clinical study demonstrate identical pharmacokinetic measures following the first and second doses. The sponsor states that the AUCs with both the batches of the formulation were very close to the expected AUC following intravenous administration, suggesting good bioavailability from the depot product.
2. In vitro dissolution testing: The *in vitro* release profiles of each lot of ELIGARD® 45 mg (Lots 1522 and 1582) used in the clinical pharmacokinetic studies were determined at various times during the dosing period. The test method utilizes accelerated release testing designed

to produce close to ___ , release within a _____ testing period. Mean in vitro release of ~ 90 % was observed during the testing of the 6-month release.

3. Analytical methods for leuprolide (LC-MS/MS) and testosterone (RIA) are reported along with their validation reports. The analysis for leuprolide was specific. RIA employed for testosterone analysis had a cross reactivity potential of _____
However, the sponsor claims that due to the solvent extraction and chromatography processes carried out on the samples prior to the RIA of testosterone, the specificity of the method is supposedly increased beyond the low level of interference indicated by the cross-reactions.
4. Special populations: Race (no impact of ethnicity on PK or PD was observed), Geriatrics (majority (71 %) of patients were elderly males; mean age 74 years)
Women and pediatrics need not be addressed due to the proposed indication _____ (cancer) which is a disease of adult male patients.
5. Drug-Drug interactions: No drug-drug interaction studies were conducted for Eligard 45 mg. Pharmacokinetic drug-drug interactions are unlikely to be observed with ELIGARD® 45 mg because leuprolide is primarily degraded by peptidase(s), and is less than — bound in the plasma.
6. Population PK/PD analysis: PK subset included patients of varied races, age, disease state, body weight etc. Inter-individual variability in the PK of leuprolide was observed, but did not appear to influence the efficacy of the formulation. No correlation was seen between body weight and systemic drug exposure.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-731 is fileable.

Sandhya Kiran Apparaju, Ph.D., Primary Reviewer _____ 04/06/04 _____

Ameeta Parekh, Ph.D., Team Leader _____ 04/06/04 _____

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

/s/

Sandhya Apparaju
4/7/04 02:53:33 PM
BIOPHARMACEUTICS

Ameeta Parekh
4/12/04 04:09:53 PM
BIOPHARMACEUTICS

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-731

**ADMINISTRATIVE / CORRESPONDANCE
DOCUMENTS**

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

RE 37,950

b. Issue Date of Patent

12/21/2002

c. Expiration Date of Patent

10/03/2008

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents:

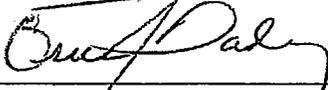
or this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, VP, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

(970) 482-9735

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

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1. GENERAL

a. United States Patent Number

B14,938,763

b. Issue Date of Patent

07/03/1990

c. Expiration Date of Patent

10/03/2008

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

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Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 1, 5, 14-18 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) To identify the composition of the product.

5. No Relevant Patents

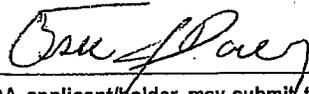
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

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Date Signed

12/07/2004

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, Vice President, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

(970) 482-9735

E-Mail Address (if available)

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,278,201

b. Issue Date of Patent

01/11/1994

c. Expiration Date of Patent

01/11/2011

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

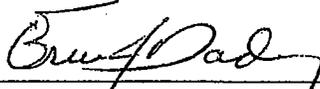
6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, Vice President, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

(970) 482-9735

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,324,519

b. Issue Date of Patent

06/28/1994

c. Expiration Date of Patent

10/20/2011

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) | Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
3,14,22-26

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Use as antineoplastic agent.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

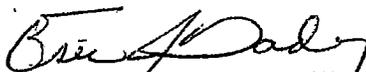
6. Declaration Certification

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Date Signed



12/07/2004

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, VP, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

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Telephone Number

(970) 482-5868

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Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,599,552

b. Issue Date of Patent
02/04/1997

c. Expiration Date of Patent
02/04/2014

d. Name of Patent Owner
Atrix Laboratories, Inc.

Address (of Patent Owner)
2579 Midpoint Drive

City/State
Fort Collins, CO

ZIP Code
80525

FAX Number (if available)
(970) 482-9735

Telephone Number
(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 3, 13, 21-26 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Use as an anti-neoplastic agent

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, Vice President, Drug Delivery

Address

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**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,739,176

b. Issue Date of Patent

04/14/1998

c. Expiration Date of Patent

10/09/2008

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. **Name of agent or representative** who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
1-8,16	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Use as antineoplastic agent.	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

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Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,395,293

b. Issue Date of Patent

05/28/2002

c. Expiration Date of Patent

09/28/2013

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	<input type="checkbox"/> Yes	<input type="checkbox"/> No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2 Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	
	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	<input type="checkbox"/> Yes
---	------------------------------

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, VP, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

(970) 482-9735

E-Mail Address (if available)

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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Department of Health and Human Services
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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,565,874

b. Issue Date of Patent

05/03/2003

c. Expiration Date of Patent

10/28/2018

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 26-32	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
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4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) Use to treat prostate cancer.
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5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

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6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/07/2004

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, Vice President, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

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*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-731

NAME OF APPLICANT / NDA HOLDER
Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S) Leuprolide Acetate	STRENGTH(S) 45 mg
--	----------------------

DOSAGE FORM
Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

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For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 6,566,144	b. Issue Date of Patent 05/20/2003	c. Expiration Date of Patent 03/27/2020
---	---------------------------------------	--

d. Name of Patent Owner Atrix Laboratories, Inc.	Address (of Patent Owner) 2579 Midpoint Drive	
	City/State Fort Collins, CO	
	ZIP Code 80525	FAX Number (if available) (970) 482-9735
	Telephone Number (970) 482-5868	E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

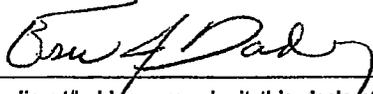
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Date Signed



12/07/2004

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Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, Vice President, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

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Telephone Number

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Department of Health and Human Services
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ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

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1. GENERAL

a. United States Patent Number

6,610,252

b. Issue Date of Patent

08/26/2003

c. Expiration Date of Patent

03/27/2020

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

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2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

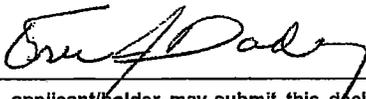
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)



Date Signed

12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, VP, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

Telephone Number

(970) 482-5868

FAX Number (if available)

(970) 482-9735

E-Mail Address (if available)

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Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER
21-731

NAME OF APPLICANT / NDA HOLDER
Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
6,626,870

b. Issue Date of Patent
09/30/2003

c. Expiration Date of Patent
03/27/2020

d. Name of Patent Owner
Atrix Laboratories, Inc.

Address (of Patent Owner)
2579 Midpoint Drive

City/State
Fort Collins, CO

ZIP Code
80525

FAX Number (if available)
(970) 482-9735

Telephone Number
(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

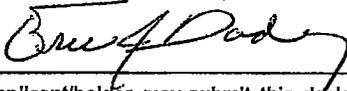
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)



Date Signed

12/07/2004

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Eric Dadey, VP, Drug Delivery

Address

Atrix Laboratories, Inc.
2579 Midpoint Drive

City/State

Fort Collins, CO

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80525

Telephone Number

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Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**
*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21-731

NAME OF APPLICANT / NDA HOLDER

Atrix Laboratories, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ELIGARD® 45 mg (leuprolide acetate for injectable suspension)

ACTIVE INGREDIENT(S)

Leuprolide Acetate

STRENGTH(S)

45 mg

DOSAGE FORM

Subcutaneous Injectable

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6,773,714

b. Issue Date of Patent

08/10/2004

c. Expiration Date of Patent

10/28/2018

d. Name of Patent Owner

Atrix Laboratories, Inc.

Address (of Patent Owner)

2579 Midpoint Drive

City/State

Fort Collins, CO

ZIP Code

80525

FAX Number (if available)

(970) 482-9735

Telephone Number

(970) 482-5868

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Claim Number (as listed in the patent) 26-32 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
Use to treat prostate cancer

5. No Relevant Patents

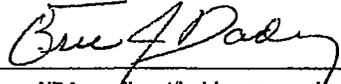
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed 12/07/2004
---	-------------------------------



NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Eric Dadey, Vice President, Drug Delivery	
Address Atrix Laboratories, Inc. 2579 Midpoint Drive	City/State Fort Collins, CO
ZIP Code 80525	Telephone Number (970) 482-5868
FAX Number (if available) (970) 482-9735	E-Mail Address (if available)

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Rockville, MD 20857

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2.5 Patent Information

The undersigned declares that the patents listed below in Table 2 cover the formulation, composition and/or method of use of ELIGARD® 45 mg. This product is the subject of this application for which approval is being sought:

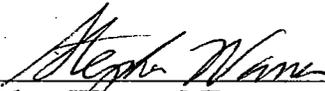

 Stephen Warren, MD
 Chief Scientific Officer

Table 2 List of ELIGARD® 45 mg Patents		
Patent Number	Description	Expiration
B1 4,938,763	Methods for forming an implant in-situ in the body using a syringeable liquid biodegradable polymer system.	10-03-2008
5,278,201	Compositions for forming a solid biodegradable implant in-situ in the body using a liquid polymer system.	1-11-2011
5,324,519	Compositions and methods for forming a solid or gelatinous microporous implant in-situ in the body using a liquid thermoplastic or thermosetting biodegradable polymer system.	10-20-2011
5,599,552	Compositions and methods for forming a solid microporous implant in-situ in the body using a liquid thermoplastic or thermosetting biodegradable polymer system.	2-04-2014
RE 37,950	Compositions and methods for forming a solid biodegradable implant in-situ in the body using a flowable thermoplastic polymer system.	10-03-2008
5,739,176	Compositions and methods for forming a solid biodegradable implant in-situ in the body using a liquid thermoplastic biodegradable polymer system.	10-03-2008
6,395,293	In-situ implants formed from a biodegradable polymer, a biocompatible solvent, and a biologically active agent.	9-28-2013

6,565,874	Compositions and methods for forming a solid biodegradable implant in-situ in the body using a flowable thermoplastic biodegradable polymer system and leuprolide acetate.	10-28-2018
6,566,144	Methods for lyophilizing a pharmaceutical solution in delivery containers with a cover plate to prevent escape of the lyophilizate.	3-27-2020
6,610,252	A system for lyophilization of pharmaceuticals that prevents escape of the lyophilizate from the delivery containers.	3-27-2020
6,626,870	A syringe assembly that maintains sterility of a medication in a syringe, and a process for lyophilizing a medication in the syringe assembly.	3-27-2020

EXCLUSIVITY SUMMARY

NDA # 21-731 SUPPL # 000
Trade Name **Eligard® 45mg**
Generic Name **leuprolide acetate for injectable suspension**
Applicant Name **Atrix Laboratories, Inc.**
HFD # 580
Approval Date **December 17, 2004**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / **X** / NO / /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / **X** / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / **X** / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / **X** /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES / / NO / **X** /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / **X** / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	21-343	Eligard® 7.5mg
NDA#	21-379	Eligard® 22.5mg
NDA#	21-488	Eligard® 30mg

NDA#	19-010	Lupron® Injection
NDA#	19-732	Lupron® Depot 7.5mg
NDA#	19-943 & 20-011	Lupron® Depot 3.75mg
NDA#	20-517	Lupron® Depot 22.5mg & 30mg
NDA#	20-708	Lupron® Depot 11.25mg
NDA#	21-088	Viadur®

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
 NDA# _____
 NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical

investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / **X** /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 **AGL0205**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / **X** /

If you have answered "yes" for one or more investigations,

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!		!
YES /___/ Explain _____	!	NO /___/ Explain _____	!
_____	!	_____	!
_____	!	_____	!
Investigation #2	!		!
YES /___/ Explain _____	!	NO /___/ Explain _____	!
_____	!	_____	!
_____	!	_____	!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / **X** /

If yes, explain: _____

Signature
John Kim, R.Ph., J.D.
Regulatory Health Project Manager

Date

Signature
Daniel Shames, M.D.

Date

Division Director

cc:

Archival NDA

HFD-580/Division File

HFD-580/John Kim, RPM

HFD-093/Mary Ann Holovac

HFD-104/PEDS/T. Crescenzi

Form OGD-011347 Revised 05/10/2004

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/s/

Daniel A. Shames
12/14/04 10:34:26 AM

2.6 Claimed Exclusivity [21 CFR §314.50 (j)]

ELIGARD® 45 mg is a unique and novel drug product for sustained release of leuprolide acetate intended as a palliative treatment for prostate cancer.

Although leuprolide acetate is a well characterized drug, the safety and efficacy of ELIGARD® 45 mg is dependent on the ATRIGEL® Delivery System, which differs from the microsphere delivery systems utilized in currently approved leuprolide acetate products.

The new clinical investigation (AGL0205) reported in this application is essential to the approval of ELIGARD® 45 mg and was conducted by Atrix Laboratories, Inc (Atrix).

Atrix was named as the sponsor on the Form FDA 1571 submitted to IND 64,779 for this study. No other clinical studies have been performed using 45 mg of leuprolide acetate in the ATRIGEL® Delivery System.

Therefore, pursuant to FDCA §505(c)(3)(D)(iii) and 21 CFR §314.108(b)(4), Atrix is claiming marketing exclusivity for three years following the approval date of the ELIGARD® 45 mg.

2.8 Debarment Certification

Atrix hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

2.9 Pediatric Labeling Waiver [21 CFR §314.55]

Atrix is requesting a full waiver from the pediatric use labeling information required under CFR §314.55 for ELIGARD® 45 mg in the palliative treatment of prostate cancer.

Atrix certifies that ELIGARD® 45 mg does not represent a meaningful therapeutic benefit over existing treatment for pediatric patients and is not likely to be used in a substantial number of pediatric patients since prostate cancer is not a pediatric disease. Moreover, the established pharmacology of leuprolide acetate indicates that the drug product would be neither effective and might not be safe in all pediatric age groups at the proposed dose of 45 mg.

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-731 Supplement Type (e.g. SE5): N/A Supplement Number: 000

Stamp Date: February 18, 2004 Action Date: December 17, 2004

HFD 580 Trade and generic names/dosage form: Eligard® (leuprolide acetate) 45mg for injectable suspension

Applicant: Atrix Laboratories, Inc. Therapeutic Class: 3S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Palliative treatment of advanced prostate cancer

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

John Kim, R.Ph., J.D.
Regulatory Project Manager

cc: NDA 21-731
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Daniel A. Shames
12/14/04 10:31:13 AM

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO

If yes, explain: The Sponsor holds unexpired exclusivity on lower dosage formulations.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
 If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

If no, explain:

- If an electronic NDA, does it follow the Guidance? YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- If in Common Technical Document format, does it follow the guidance? YES NO

- Is it an electronic CTD? YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES 3 years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES NO
- List referenced IND numbers: **64,779**
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
 If no, did applicant submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Florian Zielinski (HFD-357)? YES
 NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE:

March 29, 2004

BACKGROUND:

Eligard[®] 45mg (Aatrix laboratories; NDA 21-731) is a six-month, controlled release polymeric depot injection of leuprolide acetate intended for the palliative treatment of advanced prostate cancer. Leuprolide acetate is a synthetic agonist of the gonadotropin releasing hormone. The Agency had previously approved the Eligard[®] 7.5 mg, 22.5 mg and 30 mg formulations for sustained release of leuprolide over one, three and four months, respectively for the same indication.

ATTENDEES:

Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580

Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)

John Kim, R.Ph., J.D. – Regulatory Project Manager, DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D. – Pharmacologist, DRUDP (HFD-580)

Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. – Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Sandhya Apparaju, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Batra
Secondary Medical:	Hirsch
Statistical:	Welch
Pharmacology:	Raheja
Statistical Pharmacology:	
Chemistry:	De
Environmental Assessment (if needed):	
Biopharmaceutical:	Apparaju
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Blay
Regulatory Project Management:	Kim
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed: YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY NA FILE _____ REFUSE TO FILE _____

STATISTICS FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

• Biopharm. inspection needed: YES NO

PHARMACOLOGY NA _____ FILE REFUSE TO FILE _____

• GLP inspection needed: YES NO

CHEMISTRY FILE REFUSE TO FILE _____

• Establishment(s) ready for inspection? YES NO

• Microbiology YES NO

ELECTRONIC SUBMISSION:

Any comments: Electronic copies of the proposed labeling, text of the Human Pharmacokinetics and Bioavailability Technical Section, Clinical/Statistical Technical Section, text of clinical studies, line listing of AGL0205 data, and SAS transport files were provided to the Central Document Room.

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- DDMAC, DMETS, and Microbiology (sterility) consults will be requested.
- CMC and Clinical Pharmacology issues will be conveyed to applicant by Day 74.

 John Kim, R.Ph., J.D.
 Regulatory Project Manager, HFD-580

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/s/

John C. Kim
12/8/04 02:46:39 PM
CSO

John C. Kim
12/8/04 02:49:47 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-731	Efficacy Supplement Type SE- N/A	Supplement Number 000
Drug: Eligard® (Leuprolide Acetate) 45mg		Applicant: Atrix Laboratories, Inc.
RPM: John Kim	HFD- 580	Phone # 301-827-3003
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input checked="" type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): N/A
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		
		17-Dec-04
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4671
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<ul style="list-style-type: none"> Exception for review (Center Director's memo) 	N/A
<ul style="list-style-type: none"> OC clearance for approval 	N/A
<ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. 	(X) Verified
<ul style="list-style-type: none"> ❖ Patent 	
<ul style="list-style-type: none"> Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	(X) Verified
<ul style="list-style-type: none"> Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) () Verified N/A
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	21 CFR 314.50(i)(1) () (ii) () (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	N/A
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p> <p>(Note: This can be determined by confirming whether the Division has</p>	<p>(X) N/A (no paragraph IV certification) () Verified</p> <p>() Yes () No</p> <p>() Yes () No</p> <p>() Yes () No</p>

received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
• Exclusivity summary	14-Dec-04
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	08-Dec-04

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	07-Dec-04 (received 08-Dec-04)
• Most recent applicant-proposed labeling	15-Sep-04 (received 17-Sep-04)
• Original applicant-proposed labeling	12-Feb-04 (received 18-Feb-04)
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	30-Sep-04 (DDMAC) 05-Oct-04 (DMETS)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	13-Feb-04
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	23-Nov-04 11-Aug-04
• Reviews	05-Oct-04 (DMETS)
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	28-Apr-04 01-Mar-04
❖ Memoranda and Telecons	09-Jun-04
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	09-Jul-02
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	10-Dec-04
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	06-Dec-04 27-Apr-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Clinical Review, § 9.10, page 38
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	14-Dec-04
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	06-Dec-04 12-Apr-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	09-Dec-04 22-Apr-04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	09-Dec-04 (Satisfactory) Chemistry Review, § IV, page 77
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	24-Oct-04
❖ Facilities inspection (provide EER report)	Date completed: 29-Nov-04 (X) Acceptable () Withhold recommendation
❖ Methods validation	(X) Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	17-May-04 29-Mar-04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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this page is the manifestation of the electronic signature.**

/s/

John C. Kim
12/14/04 10:52:50 AM

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Atrix Laboratories, Inc.
2579 Midpoint Drive
Fort Collins, CO 80525-4417

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021731

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(970) 482-5868

3. PRODUCT NAME

ELIGARD® 45 mg (Leuprolide Acetate for Injectable Suspension)

6. USER FEE I.D. NUMBER

4671

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

DATE



Vice President, Regulatory Affairs

02/01/2004

Office of Drug Safety

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products, HFD-580

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise Toyer, Pharm.D.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

Date: September 29, 2004

Re: ODS Consult 04-0232;
Eligard, (Leuprolide Acetate for Injectable Suspension), 45 mg;
NDA 21-731

This memorandum is in response to an August 16, 2004 request from the Division of Reproductive and Urologic Drug Products for an evaluation of the proprietary name, Eligard. Additionally, container labels, carton and insert labeling were submitted for review and comment.

The Division of Medication Errors and Technical Support (DMETS) had previously evaluated the proprietary name, Eligard for the NDA 21-343, leuprolide acetate for injectable suspension, 7.5 mg, for potential confusion with other proprietary or established names. In consult #01-0150-1, dated December 7, 2001, DMETS did not have any objections to the use of the proprietary name, Eligard. The sponsor is currently marketing the proprietary name, Eligard, for three leuprolide acetate for injectable suspension products, NDA's 21-343, 21-379, and 21-488. DMETS only had the opportunity to review and comment on the initial black and white draft labeling for NDA 21-343, which was the first NDA approved for the Eligard product line. Since the approval of NDA 21-343, the sponsor has used the same format for the labels and labeling for NDA's 21-379 and 21-488.

DMETS searched the FDA Adverse Event Reporting System (AERS) database for any post-marketing safety reports of medication errors involving "Eligard". The MedDRA Preferred Term (PT) "Medication Error", the tradename, and verbatim for "Elig%" and "leupro%" were used to perform the searches. The search did not reveal any actual medication errors due to confusion between the Eligard proprietary name and other marketed proprietary or established names or medication errors related to the labels or labeling. However, one report was submitted to express concern with the potential for confusion between the proprietary names, Eligard and Elidel.

1 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

Scott Dallas
10/5/04 01:46:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/5/04 04:23:39 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 7, 2004

From: Ashok Batra MD
Medical Officer
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-731

I have reviewed the financial disclosure information submitted by Atrix Laboratories in support of their NDA 21-731 for LA-2580 45 mg (leuprolide acetate for injectable suspension). One pivotal study was conducted to assess the safety and efficacy of LA-2580 45 mg (leuprolide acetate for injectable suspension). This product is indicated for the palliative treatment of advanced prostate cancer. The study number and the results of the review of financial disclosure documents is summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study AGL 0205 : "A 12 Month, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Endocrine Efficacy of Two Doses of LA-2805 45 mg in Patients with Advanced Prostate Cancer"	Study Start: August 13, 2002 Study Complete: October 23, 2003	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

1. FDA Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
2. Clinical Study Report

Study AGL 0205

There were 22 investigators in this trial, enrolling 111 patients. Complete financial disclosure information was received for the investigators; none had any disclosable information.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

Ashok Batra
6/8/04 03:56:20 PM
MEDICAL OFFICER

Mark S. Hirsch
6/9/04 05:13:36 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-731

Atrix Laboratories, Inc.
Attention: Cheri Jones, MS, RAC
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Dear Ms. Jones:

Please refer to your February 13, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELIGARD[®] 45mg (leuprolide acetate for injectable suspension).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 16, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and requests for additional information:

- 1) Drug substance acceptance criterion:
 - According to the certificate of analysis data, the leuprolide content ranges from _____ Therefore, the acceptance criterion for leuprolide content should be changed to NLT _____
- 2) Drug product composition:
 - Provide justification for _____ overage of leuprolide acetate, as well as poly (DL-lactide-co-glycolide) and N-methyl-2 pyrrolidone. The justification can include actual data to show loss due to material holdup in the syringe and needle following mixing.

3) Manufacturing of Syringe B:

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/s/

Margaret Kober
4/28/04 04:12:12 PM
Chief, Project Management Staff

Memo to the file

Date 3-29-04

NDA 21-731

Submission date: 2-13-04

Subject: 45 day Filling Meeting

Sponsor: Atrix

Drug name: Eligard 45 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment of advanced prostate cancer

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Supervisor: Lynnda Reid, Ph.D

The NDA 21-731 is filable from the P/T prospective.

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/s/

Krishan L. Raheja
3/29/04 02:16:18 PM
PHARMACOLOGIST

Lynnda Reid
3/29/04 02:27:55 PM
PHARMACOLOGIST



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-731

Atrix Laboratories, Inc.
Attention: Cheri Jones, MS, RAC
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Dear Ms. Jones:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ELIGARD[®] 45mg (leuprolide acetate for injectable suspension)

Review Priority Classification: Standard (S)

Date of Application: February 13, 2004

Date of Receipt: February 18, 2004

Our Reference Number: NDA 21-731

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 16, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 17, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Reproductive and Urologic Drug Products, HFD-580

Attention: Division Document Room, 8B-45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.

Chief, Project Management Staff

Division of Reproductive and Urologic Drug
Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

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/s/

Margaret Kober
3/1/04 09:50:57 AM
Chief. Project Management Staff

4 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Office of Drug Safety

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products, HFD-580

From: Scott Dallas, R.Ph.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Denise Toyer, Pharm.D.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

Date: September 29, 2004

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DMETS has determined the potential for name confusion between Eligard and Elidel does not warrant action at this time. DMETS will continue to monitor potential confusion between Eligard and Elidel.

In the review of the container label, carton and insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user errors.

A. General Comments:

1. DMETS considers the color used on the labels and labeling to be very similar to the color on the labels and labeling for Eligard 22.5 mg, NDA 21-379. Therefore, DMETS recommends the selection of a more contrasting color, in order to differentiate the labels and labeling of Eligard 45 mg from the labels and labeling of Eligard 7.5 mg, 22.5 mg and 30 mg.
2. DMETS recommends the graphic design presented in front of the proprietary name, Eligard should be relocated or removed on all labels and labeling. The graphic design can interfere with the readability of the proprietary name.

B. Syringe A and B Labels:

1. The following comments pertain to syringe A:
 - a. DMETS recommends that the proprietary name, "ATRIGEL Delivery System" is the most prominent information on the label, which actually reflects the contents of the syringe. The proprietary name and product strength, Eligard 45 mg is currently presented in a position of prominence on the label.
 - b. The label should state that this product is used to constitute Eligard 45 mg, leuprolide acetate for injectable suspension contained in Syringe B.
2. The following comments pertain to syringe B:

DMETS recommends increasing the prominence of the proprietary name and product strength, Eligard 45 mg.

C. Tray-Pouch and Outer Pouch Labeling:

1. Comments B.1.a. and b. also pertain to the labeling for Syringe A Tray-Pouch label.
2. DMETS recommends increasing the prominence of the route of administration statement, "For subcutaneous injection".

D. Carton Labeling

DMETS recommends including the route of administration, subcutaneous, in the "Recommended dose" statement.

In summary, DMETS has no objections to the use of the proprietary name, Eligard. DMETS recommends implementation of the label and labeling revisions outlined above for NDA 21-731, and suggests the sponsor consider these label and labeling revisions for NDA's 21-343, 21-379, and 21-488.

If you have any questions or need clarification, please contact the project manager, Sammie Beam at 301-827-2102.

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/s/

Scott Dallas
10/5/04 01:46:41 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/5/04 04:23:39 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, Director DMETS