

**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.

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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

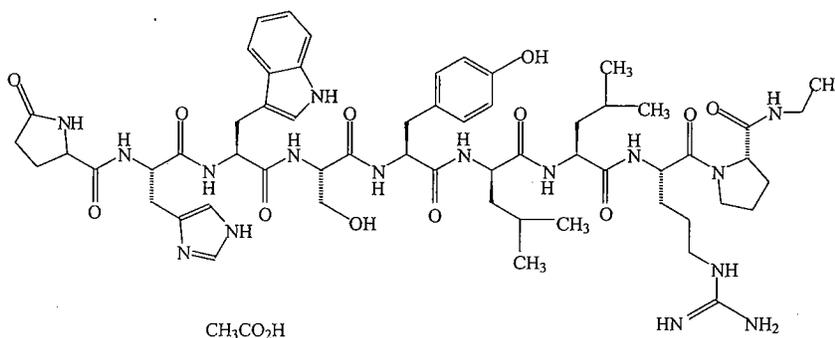
Code name: -

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.]

2.6.2 PHARMACOLOGY

Primary pharmacodynamics: Eligard 45 mg therapeutic effect is through suppression of serum testosterone to castrate levels.

Mechanism of action: Leuprolide acetate acts by preventing pulsatile hypothalamic stimulation of adenohypophysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (< 50 ng/dl in serum).

Drug activity related to proposed indication: suppression of serum testosterone to castrate levels

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not Submitted

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

The following P/K studies have been submitted for Eligard 45 mg formulation:

Studies reviewed within this submission: Six preclinical studies results are submitted in support of 6-month Atrigel formulation. All these studies were conducted by [redacted] [redacted] The findings of these studies are summarized below:

1. Evaluation of the efficacy of 180-day Atrigel formulations containing leuprolide acetate administered subcutaneously in rats. Protocol No. ATRS-404, [redacted] 129.372.

The objectives of this study were a) to evaluate the efficacy of 4 Atrigel formulations [redacted] in maintaining suppressed testosterone levels to [redacted] for a period of 6 months, b) to investigate the effect of monomer composition and drug load on the formulation efficacy, and c) to macroscopically observed test site reaction to the injected formulation. The formulations had the following composition:

Group 1:	75/25 PLG (IV 0.31)/	NMP w/	LA, mixed
Group 2:	75/25 PLG (IV 0.31)/	NMP w	LA, mixed
Group 3:	85/15 PLG (IV 0.27)/	NMP w/	LA, mixed
Group 4:	85/15 PLG (IV 0.27)/	NMP w/	LA, mixed

Each dose group had 5 male rats. The drug dosage was 4.95 mg (18 mg/kg/180 days) and injected SC in volumes of 82.5 ul and 41.25 ul for the [redacted] and [redacted] LA, respectively. Blood was collected at various time intervals until termination of the study on day 196.

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 ATRIGEL 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 ___

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/s/

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