CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-343

Administrative Documents

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-343 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 23-MAR-2001 Action Date: 23-JAN-2002

HFD -580 Trade and generic names/dosage form: Eligard™ (leuprolide acetate for injectable suspension)

Applicant: Atrix Laboratories, Inc. Therapeutic Class: GnRH Agonist

Indication(s) previously approved: palliative treatment of advanced prostate cancer

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} 1-23-02

Jeanine Best, MSN, RN
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Memo to the file

January 23, 2002

Reference: NDA 21-343 label final review

Product: Eligard

The final label submitted by the sponsor on January 16, 2002 is acceptable from the Pharmacology/Toxicology prospective.

/S/

Krishan L. Raheja

Reviewing Pharmacologist

NDA 21-343
Eligard™ (leuprolide acetate for injectable suspension)
ATRIX Laboratories, Inc.

There was no DSI Memo for GLP Inspections for this application.

12/3/01

NDA 21-343
Eligard™ (leuprolide acetate for injectable suspension)
ATRIX Laboratories, Inc.

Statistical Review of Carci Studies is NA for this application.

/S/ 12/15/03

NDA 21-343
Eligard™ (leuprolide acetate for injectable suspension)
ATRIX Laboratories, Inc.

CAC/ECAC Report is NA for this application.

NDA 21-343

Medical Team Leader's Wrap-Up Memo: New NDA

Date submitted: March 21, 2001
Date received: March 22, 2001
Memo completed: January 23, 2002

Sponsor: Atrix Laboratories; Fort Collins, CO
Drug product: ELIGARD™
Dose: 7.5 mg
Route: subcutaneous injection
Indication: palliative treatment of advanced prostate cancer

Executive summary:
The purpose of this memo is to inform the Division Director that all pending issues for NDA 21-343 have been resolved.

Of most importance, the Office of Compliance has completed its inspections of the Atrix manufacturing sites and has rendered a finalized "acceptable" opinion in EES. This allows Office of New Drug Chemistry to also render a final opinion of "acceptable".

The final proposed label was found acceptable to the sponsor and to the Division.

Therefore, in my judgement, an "approval" letter for NDA 21-343 should be issued to the sponsor today.

/S/ 1-23-02

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Arch NDA 21-343
cc: HFD-580/Div File
HFD-580/DShames/ABatra

NDA 21-343

Supervisory Medical Officer's Memorandum

Date submitted: March 21, 2001
Date received: March 22, 2001
Memo draft completed: January 16, 2002

Drug product (tradename): ELIGARD™
Drug product (non-proprietary): leuprolide acetate for injection
Dose: 7.5 mg monthly
Route: subcutaneous injection
Indication: palliative treatment of advanced prostate cancer

Sponsor: Atrix Laboratories, Fort Collins, CO
Related INDs: IND [redacted]

I. Executive summary:
The purpose of this medical team leader's memo is to provide a regulatory recommendation for NDA 21-343. I recommend that ELIGARD should be approved for the indication of palliative treatment of advanced prostate cancer *pending notification that manufacturing site inspections are completed and found to be acceptable from a chemistry perspective.*

Labeling negotiations are complete and the final draft label is considered acceptable.

II. Clinical and regulatory background:
ELIGARD is a novel subcutaneous formulation of leuprolide intended for palliative treatment of men with advanced, hormonally-sensitive prostate cancer. 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 "castrate". The Division uses this surrogate marker to determine efficacy in these types of products.

Given the extensive clinical experience with leuprolide in the treatment of prostate cancer, the Division has recommended that clinical drug development programs for this type of product (for this indication) consist of a single Phase 3 trial of approximately 100 to 150 patients supported by a small pharmacokinetics study. Atrix conducted their clinical development program in accord with this guidance from the Division.

The clinical results submitted included data from a single, multicenter, open-label, Phase 3 study in 120 men with advanced prostate cancer (treated for 6 months), and a single, open-label, Phase 1 pharmacokinetic study in 8 surgically castrated males.

III. Clinical results in brief:

1. Efficacy

Study AGL9904 enrolled 120 patients. The results from this trial demonstrated that after receiving six doses of ELIGARD™ 7.5 mg (given every 28 days), 112 of 119 (94%) patients achieved testosterone suppression of ≤50 ng/dL by Study Day 28 (1 patient withdrew on Day 14). By Study Day 42, all 118 patients remaining in the study had achieved this measure.

All patients who achieved castrate testosterone suppression (≤50 ng/dL) remained suppressed throughout the duration of the study. There were no castrate suppression "breakthroughs" (defined as a testosterone concentration of >50 ng/dL) after achieving suppression. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days.

There was no evidence of acute rises in the serum testosterone upon repeated dosing (the so-called "acute-on-chronic" phenomenon).

The sponsor analyzed the results of AGL9904 using a serum total T concentration cut-point for "castration" of 20 ng/dL (rather than 50 ng/dL) and found that virtually all patients were below this level at Month 6. While the data from this NDA confirms this finding, it is not clear that 20 ng/dL represents an improvement over 50 ng/dL. Nor is clear whether similar results would be obtained for the currently approved products if such post-hoc data analysis was conducted. Therefore, this claim was not allowed and was removed from the labeling.

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 one month. This initial rise can occasionally cause a "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, this potential 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.

In this specific NDA, such known drug-related adverse events as hot flashes, dizziness/giddiness, malaise/fatigue, testicular discomfort/atrophy, diminished libido, and impotence were reported. The incidences and severity of these events were generally in line with that expected for the class.

Additionally, since ELIGARD is a novel subcutaneous preparation, the sponsor conducted extensive injection site assessments. Local pain, itching, swelling, erythema, induration, and rarely ulceration were reported. 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.

IV. Relevant issues from other disciplines

1. Chemistry

At the time of writing this memo, the manufacturing site inspections had yet not been conducted. They are scheduled for January 17th and 18th. The Division awaits the results of these inspections. In order to proceed with an action, the Division must receive the results of these critical inspections.

The relevant chemistry sections of the label have been reviewed by Chemistry and have been found acceptable. The carton labeling is acceptable.

In this section, it is appropriate to note that the drug product will be supplied in two separate syringes. Syringe A will contain the Atrigel Delivery System. This delivery system consists of grams of a sterile polymer (% 50:50 lactide-co-glycolide [PLGH] and % N-methyl-2-pyrrolidone [NMP]). Syringe B will contain milligrams of 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 7.5 milligrams.

The major chemistry review issue centered on the *in vitro release test*. The sponsor's release test method was revised during stability testing of the primary batches. Thus there was little experience with the method. The results from the primary batches were not consistent with the results from the clinical batches. It is my understanding that the clinical batches met the dissolution specification while the primary batches did not. The sponsor initially addressed this inconsistency this by widening the test acceptance criteria. This was not acceptable to the Division. Eventually, the sponsor agreed to tightened in vitro dissolution test specifications and these were acceptable to the Division.

The microbiology review recommended approval.

2. Clinical Pharmacology

OCPB found the submission acceptable. Minor labeling comments were conveyed to the sponsor and were appropriately enacted. There were no major review issues noted in the written review and none were brought up at the time of the OCPB Briefing.

3. Pharmacology/toxicology

Pharmacology recommended approval of ELIGARD based upon the long regulatory and clinical usage history for leuprolide and an acceptable review of the literature and the relevant DMF and toxicity studies for the excipient, N-methyl-2-pyrrolidone (NMP).

Along with PLGH, NMP serves to prolong delivery of leuprolide via the Atrigel Delivery System for a duration of approximately one-month. NMP is approved as an excipient in the drug Atridox, which is used for the treatment of periodontal disease. In that formulation, NMP is delivered as a single dose of 450 mg. The reviewer comments that the daily dose of NMP from ELIGARD will amount to 5.3 milligrams, an amount considered very low compared to doses used safely in toxicology and toxicokinetic studies.

4. Biometrics

A brief review of the efficacy data-set for AGL9904 was conducted for this open-label trial by Biometrics. This review confirmed the sponsor's presentation of the study results. While the reviewer comments that the study results are completely descriptive, this is acknowledged and is consistent with guidance for conducting these sorts of trials.

5. OPDRA

OPDRA consultation was obtained for purposes of tradename and container/carton safety review. After initially rejecting the proposed tradename [redacted] OPDRA eventually accepted the tradename "ELIGARD".

All carton and container labeling recommendations were considered appropriate and were enacted by sponsor.

6. DSI

Data on twenty-seven (27) patients from two sites from Pivotal Study AGL9904 was considered acceptable and useful in support of this NDA.

7. DDMAC

At the Division's request, DDMAC conducted a proposed label review. Extensive comments were provided to the Division. Labeling negotiations proved successful in enacting all relevant and clinically important comments.

V. Other relevant issues

1. Financial Disclosure

There was no disclosure of financial interests that could bias the outcome of the trials.

2. Pediatrics

ELIGARD 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

Pending acceptable inspection of the manufacturing sites, ELIGARD is considered safe and effective for the palliative treatment of advanced prostate cancer and should be approved for marketing. It offers an option for patient care in these unfortunate patients.

/S/ 1-23-02

Mark S. Hirsch M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Arch NDA 21-343
cc: HFD-580/Div File
HFD-580/DShames/ABatra/JBest