

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-488

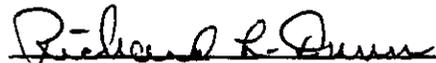
Administrative Documents

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA: 21-488	Efficacy Supplement Type SE-	Supplement Number N/A
Drug: Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg		Applicant: Atrix Laboratories, Inc.
RPM: Archana Reddy, M.P.H.		HFD- 580 Phone # 7-7514
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 21-379, Eligard™ 22.5 mg
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3s
• Other (e.g., orphan, OTC)		N/A
❖ User Fee Goal Dates		
		2/16/03
❖ 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
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ 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
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

2.5. Patent Information

The undersigned declares that the patents listed below in Table 4 cover the formulation, composition and/or method of use of ELIGARD™ 30 mg. This product is the subject of this application for which approval is being sought:


Richard L. Dunn, PhD
Senior Vice President, Drug Delivery

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
5,733,950	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

EXCLUSIVITY SUMMARY for NDA # 21-488 SUPPL # _____

Trade Name Eligard™ 30.0 mg

Generic Name leuprolide acetate for injectable suspension

Applicant Name Atrix Laboratories, Inc.

HFD- 580

Approval Date February 13, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES / X / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type (SE1, SE2, etc.)? _____

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 // NO /___/

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

3 years

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

YES /___/ NO //

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO //

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO //

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 /___/ NO /___/

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

NDA # _____
NDA # _____
NDA # _____

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.)

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 9. 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 / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 /_X_/ 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 9:**

- (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 /_X_/

- (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, Study # AGL 0001

Investigation #2, Study # _____

Investigation #3, Study # _____

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 /_X_/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 21-488 Study # AGL 0001
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # AGL 0001

Investigation # , Study #

Investigation # , Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES / X / ! NO / / Explain:

!
!
!
!

Investigation #2 !
!
IND # YES / / ! NO / / Explain:

!
!
!
!

Investigation #3 !
!
IND # YES / / ! NO / / Explain:

!
!
!
!

(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: _____

Archana Reddy, M.P.H. /S/ 02/12/03
 Signature of Preparer Date
 Title: Regulatory Project Manager

Daniel Shames, M.D. /S/ 02/13/03
 Signature of Office or Division Director Date

cc:
 Archival NDA 21-379

HFD-580/Division File
HFD- 580/Reddy
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-488

Supplement Type (e.g. SE5):

Supplement Number:

Stamp Date: April 13, 2002

Action Date: February 16, 2003

HFD Trade and generic names/dosage form: Eligard 30.0 mg

(leuprolide acetate for injectable suspension)

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

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: _____

NDA 21-488
Page 2

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}

Archana Reddy, M.P.H.

Regulatory Project Manager

cc: NDA 21-488

HFD-960/ Terrie Crescenzi

(revised 1-18-02)

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

2.6. Claimed Exclusivity 314.50 (j)

ELIGARD™ 30 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™ 30 mg is dependent on the ATRIGEL® Delivery System which differs from the delivery systems utilized in currently approved leuprolide acetate products. The new clinical investigation reported in this application (AGL0001) is essential to the approval of ELIGARD™ 30 mg and was conducted by Atrix Laboratories, Inc (Atrix). Atrix was named as the sponsor on the Form FDA-1571 submitted to IND [] for this study. No other clinical studies have been performed using 30 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™ 30 mg.

2.7. Financial Certification or Disclosure Statement (Part 54)

APPEARS THIS WAY
ON ORIGINAL

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

Atrix is requesting a full waiver from the pediatric use labeling information required under CFR §314.55 for ELIGARD™ 30 mg in the palliative treatment of prostate cancer. Atrix certifies that ELIGARD™ 30 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 30 mg.

2.10. Agency's Correspondence Dated April 11, 2000, September 22, 2000 and November 30, 2000

APPEARS THIS WAY
ON ORIGINAL

NDA 21-488

Supervisory Medical Officer's Memorandum

Date submitted: April 13, 2002
Date received: April 18, 2002
Memo draft completed: January 22, 2003
Memo final completed: February 12, 2003

Drug product (tradename): ELIGARD™ 30mg
Drug product (non-proprietary): leuprolide acetate for injection
Dose: 30mg every 4 months
Route: subcutaneous injection
Indication: palliative treatment of advanced prostate cancer
Sponsor: Atrix Laboratories, Fort Collins, CO
Related INDs/NDA: IND # [redacted] and:
IND# [redacted] and NDA 21-343 (1-month formulation)
IND# [redacted] and NDA 21-379 (3-month formulation)

1. Executive summary:

The purpose of this medical team leader's memo is to provide a regulatory recommendation for NDA 21-488. I recommend that ELIGARD 30 mg should receive a approval action for the indication of palliative treatment of advanced prostate cancer. The drug is safe and effective for this indication and all issues are resolved.

2. Clinical and regulatory background:

ELIGARD 30 mg is the third drug product in this sponsor's "leuprolide product line". ELIGARD 7.5 mg, a novel subcutaneous formulation of leuprolide intended for palliative treatment of men with advanced, hormonally-sensitive prostate cancer, was approved under Atrix' NDA 21-343 in January, 2002. ELIGARD 22.5 mg (every 3-month) was approved in May 2002 under NDA 21-379. IND # [redacted]

The 1-month product was launched in the United States in May 2002 and the 3-month product was launched in September 2002. The 4-month month formulation would allow prescribers the option of using ELIGARD in a manner similar to TAP's Lupron Depot®; specifically, patients would be started on the 1-month formulation and would continue treatment with either the 3 or 4-month formulation. Therefore, this product would be the second 4-month formulation available for this indication. Obviously, the advantage of a longer duration depot is patient convenience.

It should be noted that Lupron Depot® is an intramuscular injection and Zoladex® is a subcutaneous "implant". Atrix contends that ELIGARD may be an improvement upon these formulations since it is a subcutaneous suspension able to be delivered with a fine-gauge, fairly short needle. The three-month and four-month ELIGARD formulations are qualitatively similar in the ratio of lactide to glycolide subunits for the polymer, the ratio of polymer to leuprolide, and the polymer molecular weights. The only difference is the total mass of the injection, being 375 mg in the 3-month formulation and 500 mg in the 4-month.

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, the Division recommends that clinical drug development programs for this type of product (for this indication) may consist of a single Phase 3 trial. This trial usually consists of approximately 100 patients and is usually supported by a small pharmacokinetics study or by a pharmacokinetic "sub-study" within the body of the larger protocol.

Atrix conducted their clinical development program for ELIGARD 3-month in accordance with such guidance from DRUDP. In that regard, Phase 3 protocol AGL 0001 was submitted and reviewed in the very first submission to IND dated March 17, 2000. On October 31, 2000 (Serial 004), the sponsor requested permission to reduce the number of evaluable patients from approximately 100 to "70-80". The Division conveyed its agreement to this request on November 30, 2000. On March 13, 2002, the sponsor met with representatives of the Division by teleconference for a "Pre-NDA meeting". Of note, the only discussions held at this Pre-NDA meeting were those related to chemistry, manufacturing and controls requirements (see minutes).

The clinical results submitted herein include data from:

1. A single, multicenter, open-label, Phase 3 study (AGL 0001) in 90 men with prostate cancer treated for 8 months (two dosage administrations),
2. A pharmacokinetic "sub-study" conducted in 24 patients within AGL 0001, and
3. Study reports previously submitted in support of ELIGARD 7.5 mg and 22.5 mg.

3. Clinical results in brief:

3.1. Efficacy

Study AGL0001 enrolled 90 patients. The protocol called for the administration of two doses of 30mg to each patient, separated by an interval of 4 months.

First dosing period

One patient (#0401) withdrew from the trial on Day 14. He reported suicidal ideation and was hospitalized for psychiatric observation. Of note, his serum testosterone at baseline was 495 ng/mL. It rose to a maximum of 939 ng/mL on Day 3 after dosing and was last recorded as 248 ng/mL on Day 14 at the time of his withdrawal.

Of the remaining 89 patients, 85 (95.5%) achieved castrate suppression by Day 28. For purposes of determining efficacy, the definition of "achieving castrate suppression" *required at least two consecutive* serum concentrations ≤ 50 ng/mL, approximately 1 week apart. The initiation of castrate suppression was defined as that day upon which the first of these two consecutive samples was drawn. The four patients in whom the initiation of castrate suppression was not achieved by Day 28 are shown in detail in Table 1:

Table 1. Total testosterone concentrations in those patients who did not achieve castrate suppression by Day 28 (n=4).

	#0201	#0802	#1604	#2601
Baseline	460	776	631	365
Day 0 - Hr 2	-	650	839	481
Day 0 - Hr 4	410	593	801	603
Day 0 - Hr 8	415	666	757	565
Day 1	430	865	928	611
Day 2	510	916	948	773
Day 3	482	743	959	649
Day 7	314	724	815	528
Day 14	59	235	343	251
Day 21	46	74	122	-
Day 28	62	58	75	-
Day 35	64	35	39	-
Day 42	50	32	28	9.9
Day 49	28	17	34	14
Day 56	28	23	31	8
Day 63	26	21	28	-
Day 70	19	15	23	8.9
Day 77	16	11	26	3.6
Day 84	8.9	18	25	8.8
Day 91	9.4	20	21	6
Day 98	20	11	47	7.3
Day 105	24	15	49	<3
Day 112	66	13	36	9.2
Day 112 - Hr 2	-	22	58	11
Day 112 - Hr 4	91	13	48	11
Day 112 - Hr 8	143	21	69	9.8
Day 113	147	28	94	15
Day 115	111	33	110	9.8
Day 119	41	27	79	7
Day 126	20	16	59	6.9
Day 133	3.4	20	55	8.8
Day 140	4.4	22	39	17
Day 147	10	4.6	31	5.4
Day 154	-	8.9	19	9.1
Day 161	-	12	26	8.9
Day 168	7.7	8	38	7.5
Day 182	4.4	4.7	21	7.7
Day 196	11	6.9	33	3.1
Day 210	14	11	32	9
Day 224	13	10	53	14

As noted in Table 1, Patient #2601 missed blood draws on Days 21, 28 and 35. Therefore, it is not possible to assume that castrate suppression was initiated in this patient on or before Day 28. If he is excluded from the analysis, then the number of remaining patients for determining efficacy would be 88, and the number (proportion) of patients achieving castrate suppression by Day 28 would be 85 (96.6%).

Of the three patients who did not achieve castrate suppression by Day 28, Patients #0802 and #1604 achieved this endpoint on Day 35 (the very next blood draw), and Patient #0201 achieved this endpoint on Day 42. Therefore, of 88 evaluable patients on Day 35, 87 patients (98.9%) had achieved castrate suppression. Of 89 evaluable patients on Day 42, all 89 (100%) had achieved castrate suppression.

The second dose was supposed to be delivered to all patients on Day 112. However, prior to Day 112, an additional 4 patients dropped out of the study. Therefore, a total of 85 patients received a second injection of study drug. During the first dosing period, there was only one serum T "breakthrough" concentration reported in one patient (serum T of 66 ng/mL in Patient #0201 on Day 112 prior to second injection). A breakthrough T is defined as a serum T >50 ng/mL in a patient who had already achieved castrate suppression. As previously noted, Patient #0201 is already considered a treatment failure, as he did not reach the castration threshold by Day 28. In the 4 withdrawn patients, no breakthroughs reported and all were castrate at the time of their last blood draw.

Therefore, on Day 112, immediately prior to the second injection, of 84 remaining "per-protocol" patients (excluding Patient #2601), 81 patients (96.4%) were still successful responders. And, of 85 evaluable patients (including Patient #2601), 81 (95.3%) had both achieved castrate suppression and had maintained it up to and including Day 112.

Second dosing period

The final assessment day was set as Day 224. During the second dosing period, an additional 3 patients dropped out of the study. Each of these patients was also castrate at the time of their withdraw and none had a "breakthrough". All told, the total number of patients who dropped out of the study prior to the Day 224 final assessment was 8. Thus, there were 82 patients evaluable on Day 224, and of that total, this reviewer considers 81 patients (representing all available patients minus Patient #2601) as "per-protocol" for purposes of determining efficacy.

Of all 89 patients who suppressed to castrate levels, ALL remained suppressed while on study EXCEPT for three patients (#0201, #1002, and #1604). Patients #0201 and #1604 are described in detail in table #1 above. Both of these patients failed as a consequence of both NOT achieving castrate suppression by Day 28 AND having at least one breakthrough serum T concentration.

Patient #0201 had a breakthrough value of 66 ng/mL on Day 112 immediately *prior* to his second injection. After this injection, his serum T values rose to maximum of 147 ng/mL on Day 113. Castrate suppression was re-achieved on Day 119 and maintained thereafter.

Patient #1604 had non-castrate values on Day 112 at Hours 2 and 8 *after* his second injection. After this, his serum T values rose to maximum of 110 ng/mL on Day 115. Castrate suppression was re-achieved on Day 140 and maintained until the very final draw (Day 225), when the T concentration was 55 ng/mL.

Finally, Patient #1002 had a single serum T value above 50 ng/mL. On Day 113, one day after his second injection, a T concentration of 53 ng/mL was reported in this patient. Serum T concentration on Day 115 and all those blood drawn thereafter were below castrate threshold.

Overall efficacy results:

Therefore, this reviewer believes that there are 81 total patients with sufficient data for assessment of efficacy (the reviewer's per-protocol population – or all evaluable patients on Day 224 minus Patient #2601). Of these, three failed as a consequence of not achieving castrate suppression by Day 28. While three patients had "breakthrough", two of these had already failed as a consequence of not achieving castrate suppression by Day 28 Patients #0201 and #1604). Therefore, only one additional patient should be added to the "failure" group (Patient #1002). Therefore, of 81 "per-protocol" patients, I believe that 77 patients (95.1%) should be considered successful responders.

If Patient #2601 is included in the analysis, and he is considered a failure as a consequence of not achieving castrate suppression by Day 28, then the overall success rate would be somewhat lower: in 82 evaluable patients there were 77 successful responders, or 93.9%.

Withdrawn patients

The total number of patients who actually withdrew from the trial was 8. These patients are described in detail below and in Table 2:

1. Patient #0401 discontinued on Day 14 after being admitted to the hospital with suicidal ideation. He chose not to return to study.
2. Patient #1802 discontinued on Day 98. He chose to withdraw because study procedures interfered with his vacation plans.
3. Patient #1710 discontinued on Day 105. He chose to withdraw because of hot flushes, fatigue and because study procedures interfered with vacation plans.
4. Patient #2304 discontinued on Day 112. He chose to withdraw as a consequence of "poor health" after undergoing heart valve replacement surgery.
5. Patient #1909 discontinued on day 112. He was withdrawn by the investigator due to adverse event (hot flushes, night sweats and loss of libido).
6. Patient #1606 discontinued on Day 154. He chose to withdraw "in order to return to his family" after being diagnosed with liver metastases.
7. Patient #1602 discontinued on Day 168. He chose to withdraw after moving from the area.
8. Patient #1004 discontinued on Day 182. He was "lost to follow-up".

APPEARS THIS WAY
ON ORIGINAL

Table 2. Total testosterone concentrations in all patient withdrawals (n=8).

	#0401	#1802	#1710	#2304	#1909	#1606	#1602	#1004
Baseline	495	515	166	224	411	396	187	545
Day 0 - Hr 2	720	723	153	220	582	454	212	690
Day 0 - Hr 4	452	673	153	239	645	425	195	856
Day 0 - Hr 8	707	513	157	290	694	432	254	754
Day 1	832	715	186	277	855	392	209	903
Day 2	829	883	187	349	1009	345	206	841
Day 3	939	869	189	305	898	433	221	1011
Day 7	578	593	158	235	292	300	168	571
Day 14	248	169	36	101	42	143	73	232
Day 21		46	10	23	23	56	27	58
Day 28		20	7.4	3.6	23	20	18	25
Day 35		18	-	4.6	16	21	10	8.3
Day 42		12	10	<3	15	4.9	13	8.1
Day 49		13	11	3.8	12	9.1	19	14
Day 56		12	9.3	7	12	5.9	<3	6.6
Day 63		18	7.9	<3	21	5.4	9.8	7.7
Day 70		<3	5	<3	6	10	12	13
Day 77		8.4	5.1	3.2	18	10	5.1	3.5
Day 84		5.8	13	3	8.1	5	3.6	3.1
Day 91		9.2	7.6	-	8.1	5	6.6	3.1
Day 98		4.3	9.1	6	5.2	21	7.5	<3
Day 105			20		7.4	11	10	<3
Day 112						5.9	13	6.3
Day 112 - Hr 2						<3	6.6	5.4
Day 112 - Hr 4						15	6.3	<3
Day 112 - Hr 8						9.4	6.2	4
Day 113						<3	7.5	6.5
Day 115						12	5.7	5.3
Day 119						5.8	<3	<3
Day 126						<3	<3	-
Day 133						5.2	26	<3
Day 140							14	-
Day 147							7	6.8
Day 154							7.7	<3
Day 161							8.6	7
Day 168							6.4	<3
Day 182								4.2
Day 196								
Day 210								
Day 224								

Reviewer's comment: Therefore, none of the premature discontinuations were related to failure of the formulation to induce or maintain medical castration.

The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days.

Acute-on-chronic responses

The sponsor states in the study report that no acute-on-chronic responses were observed in any patient following any of the post-baseline injections. However, the protocol actually defined "acute on chronic responses" as "an increase in serum testosterone above the castrate level of 50 ng/dL occurring within one week of the second injection of LA-2575 30mg." Such blood values were noted in three patients: Patient #0201, #1604 (see Table 1 above) and Patient #1002. In the case of Patient #0201, it is notable that there was a breakthrough serum T level concentration of 66 ng/mL on Day 112 immediately prior to the second injection. Therefore, by the strictest criteria, Patient #0201 was not below castrate threshold at the time of the second injection, therefore it is unclear whether the additional increase in T after the second injection should be considered a true "acute-on-chronic" response. However, Patient #1604 was castrate at the time of the second injection and still had an increase in serum T above the 50 ng/mL threshold after the second injection. His maximum serum T reached 110 ng/mL on Day 115. In the opinion of this reviewer, this must be considered an "acute-on-chronic response". Finally, Patient #1002 had a serum T concentration of 53 ng/mL on Day 113. While, this is only minimally above the castrate threshold, it is, in the strictest sense "an increase in serum testosterone above the castrate level of 50 ng/dL occurring within one week of the second injection of LA-2575 30mg."

Reviewer's comments:

1. Patient #0201 had a serum T concentration of 66 ng/ml on the last draw of the first dosing period and Patient #1604 had a serum T concentration of 55 ng/mL on the last draw of the second dosing period. I have considered whether this reflects potential failure of the product at the end of the dosing cycle and I am more convinced by the weight of evidence of successful results than I am concerned by these two fairly minor breakthroughs.
2. Clearly, Patients #1002, #0201 and #1604 had serum T concentrations >50 ng/mL within one week of second dosing. By strict per-protocol definition, these should all be considered acute-on-chronic responses. In fact, serum T reached maximum concentrations of 147 ng/mL (Day 113) and 110 ng/mL (Day 115) in Patients #0201 and #1604, respectively. I have considered whether these results represent a significant clinical concern. First, I believe that these results should be treated as breakthrough serum T values for purposes of the efficacy analysis. Despite inclusion of these negative results, the overall success rate for the product is still acceptable. Second, there is no evidence from the pharmacokinetic subgroup that leuprolide accumulates after the second dose, nor are leuprolide levels statistically different between the second dose and the first. It is interesting to note, however, that the maximum leuprolide concentration after the second dose was "slightly higher" than after the first, as per OCPB. In addition, the mean maximum LH level rose a bit after the second injection. Third, I do not consider the maximum attained T levels in these two patients to be very high. Fourth, the increases in T were not reflected in clinical symptomatology in these two patients, nor would such be expected given the actual concentrations and durations of exposure to those concentrations. Finally, acute-on-chronic responses of this degree are not unknown for other marketed leuprolide products. Therefore, I conclude that these results should not preclude approval and do not raise major safety concerns. However, in some way, these results should be made clear in the label.

3.2. 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, for this novel 4-month leuprolide preparation, such known drug-class adverse events as hot flashes (74%), fatigue/lethargy/weakness (21%), urinary frequency (10%), testicular atrophy/pain (4.4%), diminished libido (2.2%), and impotence (1.1%) were reported. The incidences and severity of these events were generally in line with that expected for the class. There were no deaths reported. There was one serious adverse event judged as possibly related to study medication reported. This 81 year old man required hospitalization for depression with suicidal ideation three weeks after his first injection of ELIGARD 30mg. Of note, the patient was on an anti-depressant medication at the time of screening.

Additionally, since ELIGARD 30mg is a novel subcutaneous preparation, the sponsor conducted extensive injection site assessments.

Of 175 injections administered, 41(23%) were associated with localized reaction. All but one of these were graded as mild in intensity, with only one moderate reaction (described as "moderate pain for a duration of two minutes). The majority of these were also not reported as clinical adverse events.

The following injection site reactions were reported commonly as adverse events:

1. Burning (34.4% of all patients, 16% of all injections)
2. Stinging (5.6% of all patients, 4% of all injections)
3. Pain (4.4% of patients, 2.3% of all injections)
4. Erythema (2.2% of patients, 1.1% of all injections)

The majority of reports of burning and stinging were very short in duration (e.g. minutes). Only three patients reported duration of burning beyond 5 minutes (two patients for 20 minutes and one for 30 minutes). The longest duration of "stinging" was 3 minutes. Of the four reports of pain, the only "moderate" pain reaction lasted for 2 minutes. In the other three cases, mild pain was reported for 5 days in one patient and two weeks in two patients. Localized erythema resolved in 6 days for both patients reporting it. All of the reported events resolved spontaneously without sequelae.

No patient reported itching.

4. Relevant issues from other disciplines

4.1. Chemistry

The draft chemistry review provided to me Dr. De on February 7, 2003 stated:

"From chemistry, manufacturing and controls point of view, this NDA may be approved, pending acceptable recommendation from the Office of Compliance."

Such a recommendation was received from Compliance on February 10,2003.

The major review issues were told to me at the time of the filing meeting and at three separate NDA review status meetings. To my knowledge, the major review issues during the review were:

1. The Los Angeles district inspector noted substantial compliance issues at the _____ site. This is one of three facilities that is being requested by Atrix for manufacture of _____ Atrix withdrew the _____ site on February 7, 2003. Based on this action, the Office of Compliance conveyed their final recommendation of "acceptable" on February 10, 2003.
2. The submitted stability data supports an expiry of 18 months, not _____ as the sponsor has requested.

Reviewer's comment:

The withdrawal of _____ is acceptable because the clinical trial material incorporated drug substance from _____ and not _____. Further, there is adequate information for all other chemistry requirements using drug product with _____ leuprolide.

Of note, the final preparation of drug product for all the ELIGARD products requires a mixing of two syringes prior to patient injection. Syringe A contains the Atrigel Delivery System. For the 30mg drug product, this delivery system consists of 560mg of a sterile polymeric delivery system (— % 75:25 lactide-co-glycolide [PLG] and — % N-methyl-2-pyrrolidone [NMP]). Syringe B will contain 35.8mg 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 30mg.

All FDA-proposed modifications to the container and carton labeling that were recommended for the ELIGARD 7.5mg and ELIGARD 22.5mg labeling have been incorporated into the new labeling for ELIGARD 30mg. Therefore, no additional container/carton labeling changes were required.

The microbiology consultant recommended approval and no microbiology deficiencies were identified (see Dr. Languille's review dated December 12, 2002 and signed off on December 18, 2002).

4.2. Clinical Pharmacology and BioPharmaceutics

A final review was provided to me by Dr. Al-Habet. OCPB found the submission "acceptable". Minor labeling comments were recommended and these were conveyed to sponsor and accepted. An OCPB regulatory review briefing was held and there were no major review issues noted in the briefing or in the written review.

In his review, Dr. Al-Habet made several comments and I have highlighted some of these here:

1. The pharmacokinetics and pharmacodynamics of leuprolide after each of two dose administrations were evaluated in a subset of 24 patients in AGL 0001. The procedures for these assessments were acceptable. He noted rapid absorption with peak leuprolide levels at 2-3 hours after dosing (the "burst phase") and subsequent decline to a relatively constant "plateau phase" by the first week.

2. The pharmacokinetic substudy used drug product from two lots, and both of these were considered identical to the to-be-marketed formulation.
3. The testosterone and leuprolide assays used were validated.
4. Eighty-five patients received two consecutive doses. Overall leuprolide exposure did not differ between dose 1 and dose 2, although C_{max} was modestly (but not statistically) higher after dose 2 (191.7 ng/mL) than after dose 1 (149.6 ng/mL).
5. In the "burst phase"-only, leuprolide AUC was statistically greater after dose 2 than after dose 1.
6. In the "plateau phase", leuprolide AUC was statistically lower after dose 2 than after dose 1.
7. Since the pK differences were so small between the two doses, this to Dr. Al-Habet that there was no drug accumulation with repeat dosing.
8. Looking at data from all three Eligard NDAs, Dr. Al-Habet noted a dose-proportional increase in the C_{max} during the burst phase after the first dose. In the plateau phase, the C_{max} across formulations appeared similar. Overall AUC appeared to increase with dose, but dose-proportionality was not established.
9. Population pK revealed a trend towards lower leuprolide exposure in patients of larger weights.
10. There was a "transient but slight" increase in LH after the second injection reaching a maximum of 0.4 mIU/mL by 4 hours.
11. There were two different lots used in AGL 0001 (Lot No. 1276 and No. 1317). Dr. Al-Habet noted that "these represent the same formulation of the to-be-marketed product."
12. The in-vitro dissolution method T448 was "shown to be highly discriminating for relatively small changes in the delivery system parameters of PLG molecular weight and NMP content."

4.3. Pharmacology/toxicology

Pharmacology recommended approval of ELIGARD 30mg for the palliative treatment of advanced prostate cancer based upon the

"the composition and therapeutic similarities of Eligard 30mg with that of the approved Eligard 7.5 mg formulation."

Dr. Raheja noted that the components of the 4-month formulation and the 3-month formulation are qualitatively similar to those of the 1-month formulation.

Three small non-clinical studies using the new formulation were submitted for review. These included measures of efficacy for the 30mg formulation in both rats and dogs. This confirmed therapeutic efficacy in both these species for at least 4 months. Further, injections site assessments in pig were conducted. These revealed only slight erythema at injection sites in one of two animals studied.

In previous reviews, Dr. Raheja had noted that there was a long regulatory and clinical usage history for leuprolide as well as an acceptable review of the literature and the relevant DMF and toxicity studies for the excipient, N-methyl-2-pyrrolidone (NMP).

Along with PLG, NMP serves to prolong delivery of leuprolide via the Atrigel Delivery System. 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. In this formulation, the total dose of NMP delivered in each ELIGARD 30mg injection will be 258.5mg, or approximately 8mg per day. Previously, Dr. Raheja had stated that the dose delivered with the

7.5mg formulation was approximately 5 mg/day, that the daily dose with the 22.5mg formulation was not different from that delivered in the 7.5mg formulation, and that 5mg/day was considered very low when compared to doses used safely in toxicology and toxicokinetic studies.

4.4. Biometrics

Biometrics conducted a very brief review of the efficacy results for AGL0001 at the time of filing this application. While the biometrics reviewer comments that the study results are completely descriptive, this is acknowledged to be consistent with current FDA guidance for conducting these sorts of trials.

4.5. ODS/DMETS

ODS consultation was obtained for purposes of tradename and container/carton safety review. There was no objection to the use of the proprietary name "ELIGARD 30mg".

ODS did however, make certain potential safety risk comments.

1. They states that there is some potential risk of "ELIGARD 30mg" being misinterpreted to mean that this product should be given every 30 days. ODS believes that the container/carton labeling is appropriate to reduce this risk.
2. They stated that since there is also some potential risk of mix-up between this product and the other two ELIGARD products. They recommend making the usual dosage statement "30 mg subcutaneously every 4 months" more prominent by placing it on the front panel of the carton and on the outer drug product pouch. I am of the opinion, that the statement is sufficiently prominent at this time and the carton/container labeling is acceptable.

It should be noted that the previous ELIGARD 22.5mg product launches have demonstrated substantial effort by sponsor to differentiate the dosage strengths. Further, we will confer with ODS/DSRCS during the post-marketing period when adverse events and periodic safety reports are submitted.

ODS also recommended that we refer to their previous ELIGARD carton/container comments since they have no new comments as this time. We did consider these in review of the current application.

4.6. DSI

Division of Scientific Investigations recommended against routine inspection of clinical sites for this NDA for the following reasons:

1. Prior inspections of both previous ELIGARD applications.
2. This product is not an NME.
3. Leuprolide is a well-know drug.
4. This application may be seen as a change in dosage strength only.
5. Previous inspections had also revealed no deficiencies.

Given the current regulatory policy guidelines of DSI in reference to "needed" versus "not needed" routine inspections, this Division agreed with DSI that routine inspections were not needed. Therefore, none were conducted.

4.7. DDMAC

DDMAC labeling review was conducted for the previously submitted Atrix NDA 21-343 (ELIGARD 7.5 mg). Since the label for ELIGARD 30mg mirrors the previous ELIGARD 7.5 mg label, a DDMAC review pre-approval was not considered necessary. All previous DDMAC comments were considered during labeling negotiations for this NDA.

5. Other relevant issues

5.1. Financial Disclosure

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

5.2. Pediatrics

ELIGARD 30mg will be indicated for the palliative treatment of advanced prostate cancer. A waiver for conducting pediatric studies is considered appropriate.

5.3. Phase 4 commitments

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

VI. Medical team leader's summary statement

Since all chemistry deficiencies have been successfully resolved, this reviewer recommends an approval action for ELIGARD 30mg. Labeling negotiations have been successfully concluded. ELIGARD is considered safe and effective for the palliative treatment of advanced prostate cancer. It offers another option for patient with advanced prostate cancer.

Mark S. Hirsch M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Arch NDA 21-488
cc: HFD-580/Div File
HFD-580/DShames/HHandelsman/AReddy

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/s/

Mark S. Hirsch
2/11/03 09:31:40 AM
MEDICAL OFFICER

Daniel A. Shames
2/11/03 06:34:41 PM
MEDICAL OFFICER

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

/S/

Signature, Meeting Chair
See appended electronic signature page
Mark Hirsch, M.D.

Cc:

HFD-580/Division Files

HFD-580/Reddy/Hirsch/Lin/De/Shames

Created by: Archana Reddy

Concurrence:

Finalized:

Filename: C:\Data\My Documents\NDAs\nda21488\207chemtcon.doc

Teleconference Minutes

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/s/

Archana Reddy
2/11/03 02:30:12 PM
CSO

Mark S. Hirsch
2/11/03 05:41:39 PM
MEDICAL OFFICER
I concur

MEMORANDUM OF TELECON

DATE: February 7, 2003

APPLICATION NUMBER: NDA 21-488

Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg

BETWEEN:

Name: Johanna Matz, Regulatory Affairs Project Leader

Phone: 970-482-5868

Representing: Atrix Laboratories

AND

Name: Archana Reddy, M.P.H., Regulatory Project Manager

Mark Hirsch, M.D., Medical Team Leader

Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: To discuss remaining labeling issues for NDA 21-488.

DISCUSSION:

Labeling Comments:

- On Page 1, the sponsor agreed to replace the word SALT; however they indicated that this was not required for their 1 month or 3 month label for Eligard.
- On Page 4, the sponsor agreed to remove the word advanced from the line reading 90 patients with advanced prostate cancer (since Jewitt Type A and B patients are not considered advanced).
- On Page 10 below the Table, the sponsor agreed to remove the from the patient.
- The sponsor agreed to remove the and 1/90 from the line under Table 1 on Page 10.
- The sponsor agreed to add the word depression after insomnia under Table 1 on Page 10.
- The rest of the label is acceptable.

Chemistry

_____ -Status of Withhold recommendation from the District

- The sponsor faxed the letter from the LA District Office to DRUDP as requested and DRUDP determined that the District did not overturn the "withhold" recommendation for _____
The sponsor indicated that they would discuss internally whether they would withdraw _____ by Tuesday, February 11, 2003.
- DRUDP will not convey the letter sent by Atrix regarding the status of _____ to the Office of Compliance.

Action Item:

- The sponsor should provide the revised label by Monday, February 10, 2003 and convey their decision about _____ by Tuesday to DRUDP.

/S/

Signature: Meeting Chair
See appended electronic signature page
Mark Hirsch, M.D.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Cc:

HFD-580/Division Files

HFD-580/Reddy/Hirsch/Lin/De/Shames

Created by: Archana Reddy, 2.10.03

Concurrence: mh/2.10.03

Finalized: ar/2.10.03

Filename: C:\Data\My Documents\NDAs\nda21488\207labeltcon.doc

Teleconference Minutes

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/s/

Archana Reddy
2/11/03 02:26:11 PM
CSO

Mark S. Hirsch
2/11/03 05:38:26 PM
MEDICAL OFFICER
I concur.

NDA 21-488

Memo to File: Teleconference with sponsor

Date of tcon: February 6, 2003

Meeting Chair: Mark S. Hirsch, MD, Medical Team Leader, DRUDP

Meeting Type: NDA guidance teleconference

FDA Attendees

Mark Hirsch MD, Medical Team Leader, HFD-580
Scott Monroe MD, Medical Team Leader, HFD-580

Sponsor Attendees

Johanna Matz, Regulatory Project Leader, Atrix

Discussion

Sponsor was informed of significant compliance issues at _____ These issues have led to "withhold" recommendation for that site by Los Angeles FDA district office. Final FDA Compliance recommendation still pending.

Sponsor offered the following options:

1. Wait for the final Compliance recommendation.
2. Wait until Tuesday and have another teleconference with DRUDP.
3. Withdraw _____ site of drug substance manufacture.

Sponsor inquired whether withdrawal of _____ would have an impact on product expiry, on stability data, or any other chemistry review status. Dr. Hirsch was unable to answer that question and sponsor was instructed to contact Dr. De directly.

Sponsor concluded by stating that they would consider their options and that they appreciated the call. Sponsor also stated that they would be submitting a revised PI and PPI tonight.

MS

Mark S. Hirsch MD
Medical Team Leader, Urology, HFD-580

Arch NDA 21-488

Cc: HFD-580/Div File

HFD-580/DShames/SMonroe/MHirsch/DLin/SDe/AReddy

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/s/

Mark S. Hirsch
2/11/03 05:56:07 PM
MEDICAL OFFICER
I concur.

Teleconference Meeting Minutes

Date: March 13, 2002 **Time:** 12:30-1:00 PM **Location:** Parklawn; 17B-45

IND **Drug:** LA-2575 30 mg (leuprolide acetate for injectable suspension)

Indication: the palliative treatment of advanced prostate cancer

Sponsor: Atrix Laboratories, Inc.

Type of Meeting: CMC Pre-NDA

Meeting Chair: Dr. David Lin

External Lead: Ms. Johanna Matz

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:

David Lin, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Jeanine Best, MSN, RN, Senior Regulatory Associate, DRUDP (HFD-580)

External Participants:

Atrix

Cody Yarborough, Manager, Process Development

Suzanne Braman, Stability Coordinator

Chris Barrett, Senior Packaging Engineer

Larry Tamura, Director, Regulatory Affairs

Johanna Matz, Regulatory Affairs Project Leader

Meeting Objective: To provide Chemistry comments and guidance to the sponsor in response to the Pre-NDA Meeting Package, dated February 11, 2002.

Background: LA-2575 30 mg (Eligard™ 30 mg) is a 4-month formulation of leuprolide acetate for injectable suspension for the palliative treatment of advanced prostate cancer. Eligard™ 7.5 mg (1-month) was approved on January 23, 2002, and Eligard™ 22.5 mg (3-month) is currently under review with a PDUFA date of July 26, 2002.

Discussion:

Question #1 with regard to stability requirements to support three active substance suppliers

- the proposed submission of primary stability data from three drug substance suppliers is not a filing issue as long as complete information is presented in the NDA or cross-reference is provided to a DMF, the information will be reviewed with concentration on equivalence among the suppliers; the impurity profiles are qualified and similar for drug substances obtained from _____ if the impurity profile is higher for _____ then those impurities will have to be qualified
- submit as much stability data as possible, for the three drug substance suppliers; based on the submitted stability data, different re-test periods might be granted for the three suppliers

Question # 2 with regard to stability requirements to change the secondary packaging

- stability data on the packaging configuration must be provided on one lot of the 30 mg product along with stability data submitted from the 22.5 mg product as supportive data; this data can be submitted as an amendment prior to 90 days before the end of the review clock (this data would be considered a major amendment and the Division can either extend the review clock or base the action on previously submitted data and defer review of late submitted data to another review clock); the 22.5 mg product must be approved before the stability data can be used as supportive data for the 30 mg product; the other alternative is to submit the 30 mg product with the current pouch packaging for approval and then submit a post-approval supplement for the revised packaging
- detailed information must be provided for the packaging material in the NDA submission; information may be cross-referenced to a DMF
- sterility assurance must be provided, the sponsor needs to ensure that adequate testing is done to demonstrate that the new packaging ensures the sterility of the product

Question # 3 with regard to supportive clinical study reports

- the Clinical team is not at this meeting because no clinical data was submitted in the meeting package for review; any previously submitted data can be cross-referenced; for ease of review, desk copies are requested for the individual reviewers

Other:

- sponsor clarified that if test methods conform to USP methods, details of the test method do not have to be provided; sponsor is conforming to USP General Chapters test methods and will not be submitting details of these methods in the 30 mg NDA; the Division responded that if the details of the test methods that do not conform are recorded, it is easier for the lab to repeat the test as reported in the Methods Validation Package, and therefore, beneficial to the sponsor
- the Division again informed the sponsor that no Methods Validation Package had been received for the approved 7.5 mg product (NDA 21-343); the sponsor will be submitting the MV package and a list of the reagents shortly
- the Division requested that the sponsor amend the CMC section of the 22.5 mg NDA (NDA 21-379, that is currently under review with a PDUFA date of July 26, 2002), with information that addressed the deficiencies noted during the review of the approved 7.5 mg NDA (NDA 21-343) and are applicable to NDA 21-379; the sponsor will be submitting this information, along with updated stability data before the 7-month of the review cycle
- the sponsor reported that the NDA for the 30 mg product will be submitted in mid-April, 2002.

Decisions Made:

- stability data to support three drug substance suppliers will be a review issue, not a filing issue
- stability data for the new packaging configuration must be submitted for one lot of the 30 mg product along with one lot of the 22.5 mg product as supportive data

Action Items:

- meeting minutes to the sponsor within 30 days

|S|

Minutes Preparer

|S|

Concurrence, Chair

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

IND:
Meeting Minutes
Page 4

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Lin/De

drafted: JAB/March 13, 2002
concurrence: De, 03.13.02/Lin, 03.20.02
final: JAB/March 21, 2002
MEETING MINUTES

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/s/

Jeanine Best
3/21/02 02:51:36 PM
CSO

David T. Lin
3/22/02 02:26:54 PM
CHEMIST
I concur.

MEMORANDUM OF TELECON

DATE: November 30, 2000

APPLICATION NUMBER: IND [redacted]

BETWEEN:

Name: Elyse Wolfe, MT, Regulatory Affairs Project Leader
Phone: (970) 482-5868
Representing: Atrix Laboratories, Inc.

AND

Name: Jeanine Best, M.S.N., R.N.
Division Of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Amendment to Protocol AGL0001, Serial #004, Dated October 31, 2000, for LA-2575 30 mg, 4-month product for the palliative treatment of advanced prostate cancer

The Division concurs with reducing the number of patients to 70-80 from the proposed 100 patients to be studied under Protocol AGL0001.

151

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

cc:

Archival IND [redacted]
HFD-580/Division Files
HFD-580/Hirsch

Drafted by: JAB/November 30, 2000
Final: December 1, 2000
Filename:

TELECON

/s/

Jeanine Best

12/1/00 12:45:30 PM

CSO

Meeting Minutes

Date: January 14, 2003 **Time:** 11:05 – 11:40 AM **Location:** Parklawn; 17B-43

NDA: 21-488 **Drug:** Eligard™ 30.0 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Atrix Laboratories, Inc.

Type of Meeting: 10-Month Status Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:

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

Harry Handelsman, M.D., Medical Officer, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

David Lin, Ph.D., Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Sayed Al-Habet, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

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

Meeting Objective: 10-Month Status Meeting

Background:

Eligard™ 30.0 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30.0 mg of leuprolide acetate at a controlled rate over a four-month period. Eligard™ 30.0 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one open-label, multicenter study (AGL0001), in which 90 patients with prostate cancer were treated with at least a single injection of Eligard™ 30 mg (a total of 82 patients completed the study and 81 had testosterone concentrations of ≤ 50 ng/dL).

Discussion:

Clinical

- draft review is complete; needs a lot of revision
- total of 90 patients started the study but only 82 patients completed the study; all drop-outs were castrate at the time of discontinuation except single patient who withdrew on Day 14
- four failures in total; 3 patients failed by Day 28 and one additional patient had a breakthrough
- drug can be approved; no safety concerns
- failures accounted for; 95 % success rate
- all issues discussed at last status meeting have been resolved
- labeling reviews should be complete by next Friday
- secondary review will be complete within one week

Clinical Pharmacology

- draft review is complete and with the Clinical Pharmacology Team Leader for review
- OCPB Briefing will be held next week
- individual efficacy and PK data have been looked at; PK data looks very clean
- no concern with acute on-chronic events
- Cmax for leuprolide looks slightly higher after second dose compared first

Chemistry

- draft review will be completed by next week
- IR letter sent to the sponsor last week; awaiting response
- drug substance review is complete and acceptable
- stability data has been reviewed and acceptable for an expiry of 18 months not —
- overall recommendation for the establishment is pending from the Office of Compliance
- District recommendation for the . — is pending
- dissolution data and new method are acceptable; New method proposed; less of an expiry period

Pharmacology/Toxicology

- sponsor is referencing data from NDA 21-379; review entered into DFS

Statistics

- memo entered into DFS (only descriptive statistics)

Microbiology

- review done and entered in DFS; recommend approval

Decision Reached:

- The PM will forward the action package to the Medical Team Leader by January 23, 2003 and to the Division Director by February 9, 2003.

Meeting Minutes
NDA 21-488
Page 3 of 4

Action Item:

1. The PM will submit FDA revised labeling to the sponsor once all changes have been incorporated into the label.

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes
NDA 21-488
Page 4 of 4

Cc:
HFD-580/Division Files
HFD-580/Reddy/Hirsch/Handelsman/De/Lin/Parekh/Al-Habets/Raheja/Welch

Created by: Archana Reddy
Concurrence: kr/2.06.03, dtl/2.06.03, mh/2.04.03, sd/2.05.03
Finalized: 2.07.03
Filename: C:\Data\My Documents\NDAs\n21488\10mthmm.doc

Meeting Minutes

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/s/

Mark S. Hirsch
2/7/03 04:31:36 PM
I concur.

Meeting Minutes

Date: November 14, 2002 **Time:** 11:05 – 11:45 AM **Location:** Parklawn; 17B-43

NDA: 21-488 **Drug:** Eligard™ 30.0 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Atrix Laboratories, Inc.

Type of Meeting: 8-Month Status Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:

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

Harry Handelsman, M.D., Medical Officer, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II
(DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Sayed Al-Habet, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics
Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

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

Meeting Objective: 8-Month Status Meeting

Background:

Eligard™ 30.0 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30.0 mg of leuprolide acetate at a controlled rate over a four-month period. Eligard™ 30.0 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one open-label, multicenter study (AGL0001), in which 90 patients with prostate cancer were treated with at least a single injection of Eligard™ 30 mg (a total of 82 patients completed the study and 81 had testosterone concentrations of ≤ 50 ng/dL).

Discussion:

Clinical

- 1/3rd of the review is complete
- no approvability issues; clinical likely to recommend approval
- N of 90 patients; 85 patients got at least two doses; all patients received at least one dose
- Medical Officer will assess drop outs; 3 patients demonstrated breakthrough; but it is not clear how breakthrough was defined; Medical Officer will determine an overall success rate
- 95 % success rate shown

Clinical Pharmacology

- NDA review is almost complete; no changes in the 2 lots (7.5 mg /22.5 mg doses included; the three formulations will be "linked"
- review expected to be complete by early January/end of December
- PK study with 24 patients; the 7.5 mg and the 22.5 mg formulations will be "linked" in the review to provide additional support
- reviewer has confirmed that the clinical formulation is the same as the to-be-marketed formulation
- PK of lueprolide and testosterone will be the focus of the review and how many failures out of the 24 patients studied in the PK study

Chemistry

- 1/3rd of the review is complete
- 4 major DMFs submitted
 - 2 are adequate
 - 1 addresses the new drug substance supplier , _____
- no major issues; drug product review is half-way complete
- stability data submitted in mid November for 4 drug product batches; the data has not been reviewed
- clinical trial lots include drug substance from two suppliers and found to be equivalent
- information request letter will be sent to the sponsor in December or early January
- new dissolution method used for the drug product; the data has not been reviewed yet; critical issue will be the composition of the solvent

Pharmacology/Toxicology

- sponsor is referencing data from NDA 21-379; review entered into DFS

Statistics

- memo entered into DFS (only descriptive statistics)

• **Microbiology**

chemistry reviewer will confirm that microbiology review has been signed off in DFS

Other Issues:

- DMETS has found the tradename to be acceptable; carton/container mockups to be requested from sponsor and the sent to DMETS
- DSI – Inspections not needed (me-too drug product)
- Four month safety update has been submitted by the sponsor.
- Financial disclosure is acceptable.

Action Item:

- The PM will request the mock-ups of the carton/vial labeling.

Decision Reached:

- The PM will forward the action package to the Medical Team Leader by January 23, 2003 and to the Division Director by February 9, 2003.

APPEARS THIS WAY
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Meeting Minutes
NDA 21-488
Page 4 of 4

Cc:
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Created by: Archana Reddy
Concurrence: kr/2.06.03, sah/2.06.03, dtl/2.06.03, sd/2.05.03, mh/2.04.03
Finalized: ar/2.07.03
Filename: C:\Data\My Documents\NDAs\n21488\8mthmm.doc

Meeting Minutes

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/s/

Mark S. Hirsch
2/7/03 04:29:16 PM

Meeting Minutes

Date: October 22, 2002 **Time:** 11:00 – 11:30 AM **Location:** Parklawn; 17B-43

NDA 21-488 Drug: Eligard™ 30.0 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Atrix Laboratories, Inc.

Type of Meeting: 7-Month Status Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:

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

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Sayed Al-Habet, Ph.D., Office of Clinical Pharmacology and Biopharmaceutics Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

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

Meeting Objective: 7-Month Status Meeting

Background:

Eligard™ 30.0 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30.0 mg of leuprolide acetate at a controlled rate over a four-month period. Eligard™ 30.0 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one open-label, multicenter study (AGL0001), in which 90 patients with prostate cancer were treated with at least a single injection of Eligard™ 30 mg (a total of 82 patients completed the study and 81 had testosterone concentrations of ≤ 50 ng/dL).

Discussion:

Clinical

- review has not started

- clinical review to be reassigned to Dr. Handelsman due to workload considerations
- relatively small number of patients (N = 90)
- 10 % dropout initially; it is unclear why
- 3 patients failed at the end of the first injection; remains a review issue
- it was decided that no clinical sites would be inspected by DSI since this is a me-too drug product

Clinical Pharmacology

- NDA review is underway
- review expected to be complete by early January/end of December
- PK study with 24 patients; the 7.5 mg and the 22.5 mg formulations contain additional data
- reviewer will confirm that the clinical formulation is the same as the to-be-marketed formulation

Chemistry

- drug substance reviewed to confirm that there were no changes or updates
- review will be complete by the end of January
- facilities inspections – 6/8 are acceptable (7 U.S. sites and one foreign site)
- updated stability data (6 to 9 months) is reviewed

Pharmacology/Toxicology

- sponsor is referencing data from NDA 21-379; review entered into DFS

Statistics

- memo entered into DFS; reviewer not present

- **Microbiology**
review pending

Decision Reached:

- The PM will forward the action package to the Medical Team Leader by January 23, 2003 and to the Division Director by February 9, 2003.

Meeting Minutes
NDA 21-488
Page 3 of 3

Cc:

HFD-580/Division Files

HFD-580/Reddy/Hirsch/Handelsman/De/Lin/Parekh/Al-Habets/Raheja/Welch

Created by: Archana Reddy

Concurrence: kr/2.06.03, sah/2.06.03, dtl/2.06.03, mh, 2.04.03, sd/2.05.03

Finalized: ar/2.07.03

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Meeting Minutes

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/s/

Mark S. Hirsch
2/7/03 04:26:48 PM

Meeting Minutes

Date: May 31, 2002 **Time:** 3:00 – 3:30 PM **Location:** Parklawn; 17B-43

NDA 21-488 Drug: Eligard™ 30.0 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Atrix Laboratories, Inc.

Type of Meeting: Filing Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Archana Reddy, M.P.H.

FDA Attendees:

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

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Zili Li, M.D., Medical Officer, DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

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

Sayed Al-Habet, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP
(HFD-580)

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

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

Meeting Objective: 45-Day Filing Meeting

Background:

Eligard™ 30.0 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30.0 mg of leuprolide acetate at a controlled rate over a four-month period. Eligard™ 30.0 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one open-label, multicenter study (AGL0001), in which 90 patients with prostate cancer were treated with at least a single injection of Eligard™ 30 mg (a total of 82 patients completed the study and 81 had testosterone concentrations of ≤ 50 ng/dL).

Discussion:

Clinical

- NDA is fileable
- erythema was reported in 2.2 % of patients following 1.1 % of injections; these events were all reported as mild and generally resolved within a few days post-injection
- no patients discontinued therapy due to an injection site adverse event.
- no deaths were reported; 19 serious adverse events were reported by a total of eight patients during the treatment phase of the study
- 8 patients withdrew from the study and one treatment related serious adverse event was reported
- preliminary review shows that the sponsor has an acceptable pivotal study and the submission is organized adequately
- site for Inspection
 - Dineen was inspected in NDA 21-379 and found to be acceptable
 - Dr. Batra will select two sites for inspection

Clinical Pharmacology

- NDA is fileable
- sponsor is referencing the previous NDA 21-379 for Eligard 7.5 mg formulation
- 24 subjects were studied in a PK/PD study
- clinical formulation is the same as the to-be-marketed formulation
- issue of dissolution needs to be resolved
- adequate information is available to assess acute-or-chronic phenomenon

Chemistry

- NDA is fileable
- stability data – sponsor seeks — month expiry; they currently have — months of stability data from four batches
- NDA is well-organized and all DMFs are listed
- all Establishments and facilities inspections have been submitted (total of 8 sites to be inspected)
- new dissolution method provided; limited data provided for 3 months
- dissolution and stability will be considered a review issue
- new supplier of drug substance leuprolide — this drug product has the same ratio of polymer to leuprolide as Eligard 22.5 mg (NDA 21-273)

Pharmacology/Toxicology

- NDA is fileable
- sponsor is referencing data from NDA 21-379 except one small study in pigs

Statistics

- NDA is fileable
- statistical reviewer will enter a memo into DFS

Decisions Reached:

- NDA is fileable.
- The PM will forward the action package to the Medical Team Leader by January 23, 2003 and to the Division Director by February 9, 2003.

Action Items:

- The PM will forward the consult for clinical inspections to DSL, if it is decided they are needed.
- The PM will forward a consult for tradename review to DMETS.
- The PM will consult the submission to Microbiology for review.
- The Medical Officer will complete the Financial Disclosure Review for this NDA.

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes
NDA 21-488
Page 4 of 4

Cc:
HFD-580/Division Files
HFD-580/Reddy/Hirsch/Handelsman/De/Lin/Parekh/Al-Habets/Raheja/Welch

Created by: Archana Reddy
Concurrence: sah/2.06.03, mk/2.04.03, sd/2.05.03, dtl/2.06.03, kr/2.06.03
Finalized: ar/2.07.03
Filename: C:\Data\My Documents\NDAs\n21488\filingsmm.doc

Meeting Minutes

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/s/

Mark S. Hirsch
2/7/03 04:23:38 PM
I concur.

Memo to the file

Date: 6-11-2002

Subject: NDA 21-488 filing meeting

NDA 21-488 – ALIGARD 30 mg indicated for the palliative treatment of advanced prostate cancer is filable from the P/T prospective.

**Krishan L. Raheja
P/T reviewer**

N21488.filing/6-11-02

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/s/

Krishan L. Raheja
6/11/02 01:10:01 PM
PHARMACOLOGIST

NDA 21-488

Filing meeting : 30 mg-Atrix Labs Inc.

CLINICAL REVIEWER: ASHOK BATRA

DRUG:

LA-2550 30mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 30mg of leuprolide acetate at a controlled rate over a 4-month therapeutic period.

Dose: It is designed to deliver 30 mg of leuprolide acetate at a controlled rate over a three-month therapeutic period.

Delivery: LA-2550 30mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration.

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 co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains leuprolide acetate and the constituted product is designed to deliver 30 mg of leuprolide acetate at the time of subcutaneous injection.

INDICATIONS

One Every 4 Month 30mg is indicated for the palliative treatment of advanced prostate cancer

Proposed label

Preliminary review of label shows its organized appropriately for the claim sought. The subsections also appropriately organized.

EFFICACY: In a pivotal, open label, multicenter study (AGL0001), 90 patients with prostate cancer were treated with at least a single injection of ELIGARD™ 30 mg. Of these, 85 patients received a total of two injections given once every four months. At Baseline, 2 patients had Jewett stage A disease, 38 had stage B disease, 16 had stage C disease and 34 patients had stage D disease. This study evaluated the achievement and maintenance of serum testosterone suppression over eight months of therapy. A total of 82 patients completed the study.

The mean testosterone concentration increased from 385.5 ng/dL at Baseline to 610.0 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 17.2 ng/dL on Day 28. At the conclusion of the study (Month 8), mean testosterone concentration was 12.4 ng/dL.

Serum testosterone was suppressed to below the castrate threshold (< 50 ng/dL) by Day 28 in 85 of 89 (96%) patients remaining in the study. *All 89 (100%) of patients remaining in the study attained the castrate threshold by Day 42.* Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, **three patients (3%) demonstrated breakthrough (concentration above 50 ng/dL) during the study.** These patients again reached castrate suppression following the second injection of study drug with one patient showing repeat breakthrough. Of 82 evaluable patients in the study at Month 8, 81 had testosterone concentrations of < 50 ng/dL.

SAFETY:

1. Local adverse events

175 injections of ELIGARD™ 30 mg were administered. Transient burning/stinging was reported at the injection site following 35 (20%) injections, with all (100%) of these events reported as mild. Pain was reported following 2.3% of study injections (3.3% of patients) and was generally reported as brief in duration and mild in intensity. Erythema was reported following 1.1% of injections (2.2% of patients). These events were all reported as mild and generally resolved within a few days post-injection. No patient discontinued therapy due to an injection site adverse event.

2. Systemic AE

Table : Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥ 2% of Patients (n = 90) Treated with ELIGARD™ 30 mg for up to Eight Months in Study AGL0001

Body System	Adverse Event	Number	Percent
Vascular	Hot flashes*	66	73.3%
General Disorders	Fatigue	12	13.3%
Reproductive	Testicular atrophy*	4	4.4%
	Gynecomastia*	2	2.2%
	Testicular pain	2	2.2%
Skin	Clamminess*	4	4.4%
	Night sweats*	3	3.3%
	Alopecia	2	2.2%
Renal/Urinary	Nocturia	2	2.2%
	Urinary frequency	2	2.2%
Nervous system	Dizziness	4	4.4%
Psychiatric	Decreased libido*	3	3.3%
Musculoskeletal	Myalgia	2	2.2%
Gastrointestinal	Nausea	2	2.2%

3. Serious AE's

- No Deaths were reported.
- There were 19 SAE's reported by a total of eight patients during the treatment phase of the study. One treatment-related SAE was reported (#0401, hospitalized for severe depression with suicidal ideation).
- 8 patients withdrew from the study

Summary: (FILABLE)

Preliminary review showed that the sponsors have an acceptable pivotal study The submission is organized adequately to lend itself to a timely review process

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/s/

Ashok Batra
7/2/02 08:49:37 AM
MEDICAL OFFICER

Mark S. Hirsch
7/3/02 04:35:53 PM
MEDICAL OFFICER

MEMORANDUM

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

Date: June 24, 2002

From: Ashok Batra, MD
Medical Reviewer
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-488

I have reviewed the financial disclosure information submitted by Atrix Laboratories in support of their NDA 21-488 for Eligard™ 30 mg (leuprolide acetate for injectable suspension).

One pivotal study was conducted to assess the safety and efficacy of Eligard™ 30 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 AGL0001/ "A Eight -Month. Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics, and Endocrine Efficacy of Two Doses of LA-2575 30 mg in Patients with Advanced Prostate Cancer"	Study Start: January 29, 2001 Study Complete: November 5, 2001	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- FDA Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
- Clinical Study Report

Study AGL0001

There were 118 principal and subinvestigators (investigators) at 26 sites in this trial, enrolling 90 patients. Eight sites had subinvestigators (18 total) that left the employment of the site during the conduct of the study. These subinvestigators provided financial disclosure information at the study start; none had any disclosable information at the study start. Complete financial disclosure information was received for the remaining principal and subinvestigators; 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
7/2/02 08:46:10 AM
MEDICAL OFFICER

Mark S. Hirsch
7/3/02 04:33:16 PM
MEDICAL OFFICER

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

General Information About the Submission				
	Information		Information	
NDA Number	21-488	Brand Name	ELIGARD 30MG	
OCPB Division I	HFD-870	Generic Name	Leuprolide acetate	
Medical Division	HFD-580	Drug Class	Hormone	
OCPB Reviewer	Sayed Al Habet, Ph.D.	Indication(s)	Advance Prostate Cancer	
OCPB Team Leader	Amesta Parakh, Ph.D.	Dosage Form	Sterile injection	
		Dosing Regimen	Once every 3 months	
Date of Submission	April 13, 2002	Route of Administration	Subcutaneous	
Estimated Due Date of OCPB Review	January 15, 2003	Sponsor	Atrix Laboratories	
PDUFA Due Date	February 13, 2003	Priority Classification	3S	
Division Due Date	February 1, 2002			
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:	X	1		
multiple dose:	X	1		
<i>Patients-</i>				
single dose:	X	1		
multiple dose:	X	1		
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:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	Yes	1		
Data sparse:	Yes	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				

Food-drug interaction studies:			
Dissolution:	X	1	
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		5	
Fileability and QBR comments			
	"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		There is extensive clinical experience with this drug. In addition, the division has recently approved a similar formulation for a one-month SC injection from the same sponsor (NDA# 21-343). Most of the PK data are crossed reference to NDA #21-343 and will be reviewed when applicable. The application can be filed.	
Primary reviewer Signature and Date		Sayed Al-Habet, Ph.D.	
Secondary reviewer Signature and Date		Ameeta Parekh, Ph.D.	

CC: NDA 21-289, HFD-850 (p. Lee), HFD-580 (Reddy), HFD-870 (Al-Habet, Parekh, Malinowski, Hunt), CDR (biopharm file)

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

/s/

Sayed Al-Habet
6/11/02 01:57:14 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/9/02 10:51:40 AM
BIOPHARMACEUTICS
I concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-488
Stamp Date: 04/16/02
Drug Name: LA-2575 30 mg

Applicant: ATRIX LABORATORIES INC.

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: 05/30/02

Team Leader: David Lin, Ph. D.

Date: 05/30/02

cc:
Original NDA 21-488
HFD-580/Division File
HFD-580/Chem/De/Lin
HFD-580/PM/AReddy
HFD-580/DivDir/DShames

SUMMARY

DRUG SUBSTANCE

Chemical Type/Therapeutic class: 3/GnRH agonist

Description:

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.

Synthesis & Characterization:

DRUG PRODUCT:

Dosage form: Injectable **Strength:** 30 mg Leuprolide acetate **Route of Administration:** Subcutaneous
Description:

Drug product, LA2575 30 mg, is a new polymeric matrix formulation of leuprolide acetate intended for subcutaneous (SC) dosing once every four months. The drug product consists of two syringe mixing system, a 20 gauge 5/8-inch needle, and a silica or silica gel desiccant pouch. One syringe contains 35.8 mg of leuprolide acetate. The other syringe contains the ATRIGEL Delivery System. The delivery system consists of 0.56 g of a sterile, polymeric delivery system solution of 75:25 Poly(DL lactide-co-glycolide) (PLG) and 2% of N-methyl-2-pyrrolidone (NMP). Prior to administration of the drug product the two syringes are coupled and the formulation are mixed by passing the formulation from syringe to syringe until a homogeneous solution is achieved. Following mixing, the syringes are decoupled and sterile needle is affixed to the male syringe for patient injection. The total deliverable injection weight is 500 mg including 30 mg of leuprolide acetate. The drug product is manufactured under sterile conditions and the application contains a sterility assurance section, which has been sent for microbiology review.

Leuprolide is presently marketed (in various formulations) under the trademarks Lupron, Lupron Depot and Lupron Dept-PED™ by TAP pharmaceuticals, Inc., Eligard™ by Atrix Laboratories Inc.

NDA Number: 21-488
Applicant: Atrix Laboratories, Inc.
Drug Name: LA2575, 30 mg

Have all DMF References been Identified: yes

DMF Number	Holder	Description	LOA Included	Status	
		Type II	Yes	Reviewed Adequate	
		Type II	Yes	Reviewed Adequate	
		Type II	Yes	Review in progress	
		Type II	Yes	Review in progress	
		Type II	Yes	Reviewed	
		Type III	Yes	Review in progress	
			Yes	Review in progress	
		L	Type III	Yes	Review in progress
			Type III	Yes	Review in progress
			Type III	Yes	Review in progress
			Type III	Yes	Review in progress

Manufacturer:

Manufacturing stage	Address	Status of EER to OC
/		Submitted on 5/30/02
		Submitted on 5/30/02
	/	Submitted on 5/30/02
Drug Product- Manufacturer	Atrix Laboratories, Inc. 701 Centre Avenue Ft. Collins, CO 80525	Submitted on 5/30/02
/	/	Submitted on 5/30/02
		Submitted on 5/30/02
/		Submitted on 5/30/02
		Submitted on 5/30/02

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
6/12/02 08:26:55 AM
CHEMIST

David T. Lin
6/17/02 12:22:27 PM
CHEMIST
I concur.

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

Advisory Committee Meeting

This new drug application was not the subject of an advisory committee meeting.

ak 2/11/03

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

Federal Register Notice

This new drug application was not the subject of a Federal Register Notice.

AK 2/11/03

Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	X (2.11.03)
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() 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)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ 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)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X (March 13, 2002)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Filing/Status Meeting Minutes
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical Review Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X (2/11/03)
❖ Clinical review(s) (indicate date for each review)	X (1/27/03)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	X (Refer to MO Review)
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X (Full Waiver Granted)
❖ Statistical review(s) (indicate date for each review)	X (Memo; 6/05/02)
❖ Biopharmaceutical review(s) (indicate date for each review)	X (2/04/03)
❖ 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)	X (2/13/03)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	X (2/13/03)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	X (12/18/03)
❖ Facilities inspection (provide EER report)	Date completed: 1/12/03 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X (6/11/02)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

3.2. Pharmacological Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits

3.2.1. Drug Product Information

Pharmacological Class: Luteinizing Hormone-Releasing Hormone Agonist Analog

Name of Drug Product: ELIGARD™ 30 mg

Active Ingredient: Leuprolide Acetate

3.2.2. Scientific Rationale

Leuprolide acetate is a potent LH-RH agonist used clinically for the palliative treatment of advanced prostate cancer. Sustained delivery of leuprolide disrupts pulsatile stimulation of the adenohypophysis, by hypothalamic LH-RH. The result is reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (≤ 50 ng/dL in serum). Extensive clinical experience with leuprolide acetate has demonstrated that it achieves prolonged testosterone suppression after daily administration of as little as 1 mg, or after administration in depot formulations at intervals of one month or longer.¹ Leuprolide has a wide safety margin, and has been administered for prolonged periods at doses of up to 20 mg/day.²

Atrix has developed the ELIGARD™ 30 mg drug product, a sustained release formulation of leuprolide acetate, for the palliative treatment of prostate cancer. Repeated treatment every four months with ELIGARD™ 30 mg provides sustained levels of active drug resulting in continuous suppression of gonadal testosterone synthesis.

ELIGARD™ 30 mg delivers a nominal dose of 30 mg leuprolide acetate over a four-month period using the ATRIGEL® Delivery System. As administered, it is a biodegradable polymeric formulation consisting of — % 75:25 Poly (DL-lactide-co-glycolide) (PLG) — % *N*-methyl-2-pyrrolidone (NMP) and —% leuprolide acetate (w/w).

A clinical study (AGL0001) was performed to characterize the pharmacokinetic and pharmacodynamic profile after ELIGARD™ 30 mg administration. Patients with advanced prostate cancer were given an

¹ Chrisp P and Sorkin EM. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic disorders. *Drugs & Aging* 1991; 1(6):487-509.

² Yamanaka H, Makino T, Yajima H et al. Efficacy of (D-Leu⁶) - des-Gly-NH₂¹⁰ - LH-RH ethylamide against prostatic cancer. *Prostate* 1985; 6:27-34.

injection of ELIGARD™ 30 mg once every four months for a total of two injections during the eight-month study.

Ninety-four percent (94%) of the phase 3 clinical patients reached castrate testosterone suppression levels (≤ 50 ng/dL) by Month 1 (Day 28) following the Baseline injection. Ninety-nine percent (99%) of patients attained suppression by Day 42, with the only exception being a patient withdrawn from the study following Day 14. Once testosterone suppression at or below serum concentrations of 50 ng/dL was achieved, three patients (3.3%) demonstrated breakthrough (concentration above 50 ng/dL) during the study. These patients again reached castrate suppression after receiving the second injection of study drug. Of the 82 evaluable patients in the study at Month 8, 99% had testosterone concentrations of ≤ 50 ng/dL. The pharmacokinetics evaluation in a subset of 24 patients demonstrated that treatment with ELIGARD™ 30 mg resulted in an initial burst phase characterized by high (> 100 ng/mL) serum leuprolide concentrations. Following the burst, the formulation maintained relatively constant mean serum leuprolide levels (0.1 - 1.0 ng/mL), while individual levels ranged from < 0.05 ng/mL to 5.8 ng/mL.

These clinical study results verify that injection of ELIGARD™ 30 mg every four months provides sustained serum leuprolide concentrations and results in testosterone suppression to below medical castrate levels in patients with advanced prostate cancer.

3.2.3. Intended Use

ELIGARD™ 30 mg is an injectable sustained-release subcutaneous (SC) formulation intended for injection every four months as palliative treatment for advanced prostate cancer.

3.2.4. Potential Clinical Benefit

Repeated therapy every four months with ELIGARD™ 30 mg provides constant serum levels of leuprolide resulting in continuous suppression of gonadal testosterone synthesis. Suppression of serum testosterone to below castrate levels (≤ 50 ng/dL) has been shown to improve survival rates and objective tumor responses in patients with advanced prostate cancer.

3.3. Foreign Marketing History

ELIGARD™ 30 mg has not been commercially marketed either domestically or internationally and no foreign clinical studies have been conducted using this product.

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/ocder/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 N021488
2. TELEPHONE NUMBER (Include Area Code) (970) 482-5868	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> 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: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME ELIGARD™ 30 mg (leuprolide acetate for injectable suspension)	6. USER FEE I.D. NUMBER 4295

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> 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.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

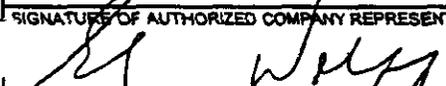
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See item 8, reverse side if answered YES)

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 Director, Technical Affairs	DATE April 13, 2002
--	--------------------------------------	------------------------

Reddy, Archana

From: Blay, Roy A
Sent: Thursday, August 08, 2002 3:54 PM
To: Reddy, Archana
Cc: U, Khin M
Subject: NDA 21-488, Eligard, Need for Inspections

I have spoken with Dr. Batra regarding this NDA, and he has stated that he has no clinical concerns with this application. In briefly reviewing the protocol, it appears that this drug is very similar to previously approved leuprolide products other than its matrix formulation and its SC route of administration.

Since Eligard is neither an NME nor is it being used for a new indication, it does not fit within our general parameters for consideration for inspection. In addition, all of the sites are of very low enrollment suggesting that any inspectional findings may be of little benefit. Of course, if Dr. Batra's review of the application has revealed clinical concerns, we can initiate the inspections and focus on those items of concern.

Given the above considerations, could you revisit the issue of whether inspections are actually needed? If you have any questions or would like to discuss this further, please don't hesitate to call me.

Thanks,

Roy

Reddy, Archana

From: Blay, Roy A
Sent: Wednesday, August 14, 2002 4:41 PM
To: Reddy, Archana
Subject: NDA 21-488, Eligard, Atrix Laboratories, No need for inspections

This e-mail is to confirm your voice mail of 13 Aug 02 in which you indicated that there would be no need to do DSI inspections for NDA 21-488. If my understanding is incorrect, please let me know as soon as possible.

Thank you for your help.

Roy

Redacted

6

pages of trade

secret and/or

confidential

commercial

information

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

Non-clinical Review Inspection Summary

Not required.

AR 2/11/03

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

DDMAC

This new drug application did not require a DDMAC consult prior to approval, since this is the third NDA for Eligard that is being approved. NDA 21-379 labeling was already reviewed by DDMAC and these comments were taken into consideration during labeling negotiations.

AR 2/11/03

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

Adverstising Information

Advertisting will be requested for this new drug application upon approval.

our 2/11/03

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Hye-Joo Kim, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Through: Alina Mahmud, RPh
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Archana Reddy
Project Manager
HFD-580

Date: January 15, 2003

Re: ODS Consult 02-0131-1; Eligard 30 mg (Leuprolide Acetate For Injection 30 mg); NDA 21-488

This memorandum is in response to a January 8, 2003 request from your Division for a re-review of the proprietary name, "Eligard 30 mg". "Eligard 30 mg" was found acceptable by the Division of Medication Errors and Technical Support (DMETS) on August 1, 2002 (ODS consult 02-0131).

Since the initial review, DMETS has not identified any safety concerns that would render the proposed name objectionable. Therefore, we have no objections to the use of this proprietary name.

The labels and labeling for Eligard 30 mg were not previously reviewed in our August 1, 2002 consult. Additionally, the labels and labeling were not provided with this final review. Therefore, DMETS requests the labels and labeling for Eligard 30 mg be forwarded to DMETS before the approval of this product for review and comment.

We consider this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Hye-Joo Kim
1/24/03 08:33:11 AM
PHARMACIST

Alina Mahmud
1/24/03 09:35:50 AM
PHARMACIST

Carol Holquist
1/24/03 09:51:57 AM
PHARMACIST

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 06/06/02

DUE DATE: 08/16/02

ODS CONSULT: 02-0131

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Archana Reddy
Project Manager
HFD-580

PRODUCT NAME:

Eligard 30 mg
(Leuprolide Acetate For Injection)
30 mg

NDA #: 21-488

MANUFACTURER: Atrix Laboratories, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support conducted a review of the proposed proprietary name "Eligard 30 mg" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS has no objection to the use of the proprietary name Eligard 30 mg.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

/s/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office Drug Safety
Phone: 301-827-3242 Fax: (301) 443-5161

/s/

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Building Room 15B-32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 1, 2002
NDA NUMBER: 21-488
NAME OF DRUG: Eligard 30 mg
(Leuprolide Acetate For Injection)
30 mg
NDA SPONSOR: _____

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the proprietary name *Eligard 30 mg* for their proposed product that delivers "30 mg of leuprolide acetate at a controlled rate over a four-month period." The labels and labeling for Eligard 30 mg were not supplied, but DMETS refers the sponsor to our comments for Eligard 7.5 mg and Eligard 22.5 mg (ODS consult 02-0042).

The sponsor, Atrix, currently markets "Eligard 7.5 mg". The sponsor also submitted an NDA for "Eligard 22.5 mg" (NDA 21-379). DMETS completed a Proprietary Name Review for "Eligard 22.5 mg," which is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period and had no objection to the use of the proprietary name, "Eligard 22.5 mg" (see ODS 02-0042).

PRODUCT INFORMATION

Eligard 30 mg, which is a polymeric matrix formulation of leuprolide acetate for subcutaneous injection, delivers 30 mg of leuprolide acetate at a controlled rate over a four-month period. Eligard 30 mg is indicated for the palliative treatment of advanced prostate cancer. The usual dose is 30 mg subcutaneously every four months. The proposed product is supplied in a kit that consists of a two-syringe mixing system and a 20-gauge half-inch needle. One syringe contains the ATRIGEL® Delivery System. The ATRIGEL® Delivery System is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable poly (DL-lactide-co-glycolide) (PLGH), polymer formulation dissolved in a biocompatible solvent, N-methyl-2-pyrrolidone (NMP). PLGH is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains 30 mg of leuprolide acetate. The contents of two separate syringes are mixed immediately before administration.

II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Eligard" has been utilized in the U.S. marketplace since January 2002. The Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name "Eligard."

On August 2, 2002, we searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Eligard. The Meddra Preferred Term (PT), "Medication Error" and the drug name "Eligard%" were used to perform the search. The search resulted in one potential medication error report involving Eligard. The following is the summary of this medication error report:

(Date of Report 02/26/02):

The reporter wanted to express concerns over the recently released drug product names, _____ and Eligard (Leuprolide). Although the two products are very different and are for different indications, the reporter was concerned that both are newly released and may be unfamiliar to healthcare professionals.

B. SAFETY EVALUATOR RISK ASSESSMENT

Eligard was approved by the Agency on January 3, 2002. Since then, DMETS received only one potential medication error report involving name confusion between Eligard and _____. Therefore, there is insufficient evidence at this time to conclude that the proprietary name Eligard has significant potential for name confusion. However, since Eligard was recently approved, DMETS will continue to monitor post-marketing medication errors in association with the proprietary name Eligard.

Eligard 30 mg contains the same active ingredient, leuprolide acetate, as Eligard 7.5 mg and 22.5 mg. In addition, Eligard 30 mg uses the same ATRIGEL® Delivery System as Eligard 7.5 mg and 22.5 mg to deliver leuprolide acetate subcutaneously. Like Eligard 22.5 mg, the ATRIGEL® Delivery System for Eligard 30 mg consists of PLGH that is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. ATRIGEL® Delivery System for Eligard 7.5 mg, on the other hand, consists of PLGH that is a co-polymer with a 50:50 molar ratio of DL-lactide to glycolide containing carboxyl end groups. Eligard 7.5 mg is "designed to deliver 7.5 mg of leuprolide acetate at a controlled rate over a one month period" and Eligard 22.5 mg is "designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period." Eligard 30 mg has been "designed to deliver 30 mg of leuprolide acetate at a controlled rate over a four-month period. Consequently, the use of the proprietary name Eligard for this proposed product is appropriate.

Additionally, DMETS has no objection to the use of the modifier "30 mg" in conjunction with the proprietary name Eligard. In general, we discourage the use of numbers as a part of the proprietary name. However, numbers have been successfully used with certain products such as the oral contraceptive drug products (e.g., 1/35 and 1/50). Similarly, the numerical suffix "30 mg" will assist in distinguishing the proposed product from Eligard 7.5 mg and Eligard 22.5 mg and prevent potential selection errors among Eligard 7.5 mg, Eligard 22.5 mg, and Eligard 30 mg. We acknowledge that the numerical suffix "30" may be confused for "30 days", however, Eligard available in three strengths. Therefore, prescriptions for these products would require inclusion or clarification of the specific strength (Eligard 7.5 mg, Eligard 22.5 mg, and Eligard 30 mg) prior to

dispensing. It is unlikely that the numerical suffix would be confused for "30" syringes to be dispensed, because this would likely be for a quantity of 1 to 3, a common quantity for syringes that is long-acting. We acknowledge that there is a potential risk where "Eligard 30 mg" could be inappropriately dispensed instead of "Eligard 7.5 mg" or "Eligard 22.5 mg." Therefore, "Eligard 30 mg" may be prone to more frequent administrations than the recommended 4-month interval. Consequently, we recommend increasing the prominence of the usual dosage statement "30 mg subcutaneously every 4 months" by placing it on the front panel of the outer pouch and carton labeling. We also recommend careful monitoring and sufficient education regarding the difference among Eligard 7.5 mg, Eligard 22.5 mg, and Eligard 30 mg upon the launch of this product.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

The labels and labeling for Eligard 30 mg were not supplied, but DMETS refers the sponsor to our comments for Eligard 7.5 mg and Eligard 22.5 mg (ODS consult 02-0042).

IV. RECOMMENDATIONS:

DMETS has no objection to the use of the proprietary name, Eligard 30 mg.

DMETS decision is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)

Concur:

/S/

Alina R. Mahmud, RPh.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Hye-Joo Kim
8/14/02 01:48:35 PM
PHARMACIST

Alina Mahmud
8/14/02 02:56:28 PM
PHARMACIST

Jerry Phillips
8/14/02 03:01:23 PM
DIRECTOR

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type): 21-488, Eligard™ (leuprolide acetate for injectable suspension), 30.0 mg

Applicant: Atrix Laboratories, Inc.

Date of Application: April 13, 2002

Date of Receipt: April 16, 2002

Date of Filing Meeting: May 31, 2002

Filing Date: June 13, 2002

Indication(s) requested: Palliative treatment of advanced prostate cancer

Type of Application: Full NDA Supplement

(b)(1) (b)(2)

[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S P

Resubmission after a withdrawal or refuse to file N/A

Chemical Classification: (1,2,3 etc.) 3s

Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug 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 the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid Waived (e.g., small business, public health) N/A
Exempt (orphan, government)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee ID# 4295

Clinical data? YES NO Referenced to NDA#

Date clock started after UN N/A

User Fee Goal date: 2/16/03

Action Goal Date (optional) 2/14/03

- Does the submission contain an accurate comprehensive index? YES NO
- Form 356h included with authorized signature? YES NO
If foreign applicant, the U.S. Agent must countersign.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?
 YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
 YES NO NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
 YES NO NA

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

Clinical

• If a controlled substance, has a consult been sent to the Controlled Substance Staff?
 YES NO

Chemistry

• Did sponsor request categorical exclusion for environmental assessment? YES NO
 If no, did sponsor submit a complete environmental assessment? YES NO
 If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

• Establishment Evaluation Request (EER) package submitted? YES NO

• Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)?
 (Normally, FDA will refuse-to-file such applications.) YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
 If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
 If yes, the application must be refused for filing under 314.54(b)(2) YES NO

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation, whether another Division is involved, foreign marketing history, etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical:

Handelsman

Secondary Medical:

Hirsch

Statistical:

Welch

Pharmacology:

Raheja

Statistical Pharmacology:

N/A

Chemist:

De

Environmental Assessment (if needed):

Biopharmaceutical:

Al-Habet

Microbiology, sterility:

Langille

Microbiology, clinical (for antimicrobial products only):

DSI: since this is a me-too product; it was determined that DSI inspections are not required

Project Manager: Reddy

Other Consults: DMETS

Per reviewers, all parts in English, or English translation?

YES NO

CLINICAL -

File

Refuse to file

• Clinical site inspection needed:

YES

NO

MICROBIOLOGY CLINICAL -

File

Refuse to file

STATISTICAL -

File

Refuse to file

BIOPHARMACEUTICS -

File

Refuse to file

• Biopharm. inspection Needed:

YES

NO

PHARMACOLOGY -

File

Refuse to file

CHEMISTRY -

• Establishment(s) ready for inspection?

YES NO

File Refuse to file

REGULATORY CONCLUSIONS/DEFICIENCIES: NDA can be filed

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

_____ The application is unsuitable for filing. Explain why:

/S/

Regulatory Project Manager, HFD-

DMF REVIEW COVER FORM

DMF Number: DMF Type: II

TITLE: Leuprolide Acetate

1. CHEM REVIEW No.: 5

2. REVIEW DATE: 12/24/02

3. ITEM REVIEWED: Drug Substance

A. IDENTIFICATION

USAN: Leuprolide acetate

Ingredient Dictionary Name:

Trade name: NA

Manufacturer's code: 8050

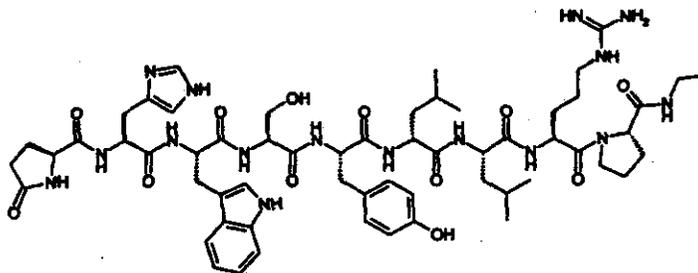
Chemical names: 1. L-Pyroglutamyl-L-Histidyl-L-Trptophyl-L-Seryl-L-Tyrosyl-D-Leucyl-L-Leucyl-L-Arginyl-L-Proline-N-ethylamide, acetate salt.

CAS registry number: 74381-53-6 (leuprolide acetate)

Molecular Formula (acetate): C₅₉H₈₄N₁₆O₁₂ (net); C₅₉H₈₄N₁₆O₁₂, C₂H₄O₂ (leuprolide acetate)

Relative molecular mass (acetate): 1209.5 (net) + 60.1 (acetate) = 1269.65 (leuprolide acetate)

Structural Formula:



B. LOCATION IN DMF

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Amendment	7 September, 2001	Vol. 3.1
Amendment	29 January, 2002	Vol. 3.1
Supplement	28 October, 2002	Vol. 3.1

4. PREVIOUS DOCUMENTS:

Original	21 August, 1998	Vol. 1.1, 1.2
Review#1	17 May, 1999	Vol. 1.1 (Deficient)
Deficiency response	11 June, 1999	Vol. 2.1(Deficient)
Amendment	24 August, 1999	Vol. 2.1, 2.2
Review#2	28 December, 1999	Vol. 2.1(Deficient)
Deficiency response	20 January, 2000	Vol. 3.1
Review#3	03 August, 2000	Vol. 3.1(Adequate)
Amendment	01 September, 2000	Vol. 3.1
Review#4	12 November, 2000	Vol. 3.1(Adequate)

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:

ADDRESS:

REPRESENTATIVE or U.S. AGENT (if applicable): N/A
CONTACT PERSON'S NAME, TITLE, DEPARTMENT

Address:

Telephone No.:

Fax:

6. DMF REFERENCED FOR:

~~NDA~~~~ANDA~~~~IND~~: NDA 21-488

PRIMARY DMF (as needed) N/A

APPLICANT NAME: Atrix Laboratories

LOA DATE: 04-10-2001

DRUG PRODUCT NAME: ELIGARD 30 mg (proposed)

DOSAGE FORM: Injection

CODE: 705

STRENGTH: 30 mg leuprolide acetate

ROUTE OF ADMINISTRATION: Subcutaneous

CODE: 005

7. SUPPORTING DOCUMENTS: None

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

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

Application Integrity Policy Information

This new drug application is not on the AIP list.

cur 2/11/03

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

User Fee Goal Date

This new drug application has a user fee goal date of 2/16/03.

arr 2/16/03

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

Special Programs

This new drug application does not qualify for consideration under one of the special programs (Orphan designation, Subpart H, rolling review etc.).

cur 2/11/03

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

Press Office/Public Communications

This new drug application was not the subject of a Press Office release.

cur 2/11/03

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

Post Marketing Commitments

This new drug application was not the subject any P4 commitments.

AMR 2/11/03

78 pages redacted from this section of
the approval package consisted of draft labeling