CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-343

Chemistry Review(s)

CHEMISTRY REVIEW

NDA 21-343

ELIGARD™
(Leuprolide acetate for Injectable suspension)

ATRIX LABORATORIES INC.

SWAPAN K. DE

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-343

2. REVIEW # 2

3. REVIEW DATE: 23-JAN-2002

4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
See Chemistry Review#1	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-MAR-2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Atrix Laboratories, Inc.
Address:	2579 Midpoint Drive Fort Collins, CO 80525-4417
Representative:	Elyse Wolff
Telephone:	(970) 482-5868

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Eligard™
b) Non-Proprietary Name (USAN): Leuprolide acetate for Injectable suspension
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

11. DOSAGE FORM: Injectable suspension

12. STRENGTH/POTENCY: 7.5 mg leuprolide acetate

13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:
_____SPOTS product – Form Completed
___x___Not a SPOTS product
_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
See Chemistry Review #1

17. RELATED/SUPPORTING DOCUMENTS:
See Chemistry Review #1

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	**Acceptable**	**1/23/02**	**J.D. Ambrogio (HFD-324), O.C.**
Pharm/Tox	Adequate	12/17/01	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	12/12/01	Myong-Jin Kim, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Deficient Adequate	07/03/01 12/12/01	Nora Roselle, Pharm.D.
EA	Categorical exclusion granted	1/16/02	
Microbiology	Deficient Adequate	11/19/01 1/02/02	Bryan S. Riley, Ph.D.

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

The Chemistry Review for NDA 21-343

The Executive Summary

I. Recommendations

A. From chemistry, manufacturing, and controls point of view, this NDA may be **approved** based on the provided information and acceptable recommendation from the Office of Compliance, with regard to cGMP inspections (dated 23 January, 2002).

II. Summary of Chemistry Assessments

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

Dosage form: Injectable suspension
Strength: 7.5 mg Leuprolide acetate
Route of Administration: Subcutaneous

Description:
The drug product, ELIGARD™ is a new polymeric matrix formulation and consists of a two syringe mixing system, a 20 gauge half-inch needle, and a silica or silica gel desiccant pouch to control moisture. One syringe (Syringe A) contains the ATRIGEL Delivery System. This delivery system consists of of a sterile, polymeric delivery system solution of % 50:50 Poly(DL lactide-co-glycolide) (PLGH) and % N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains . of 1 leuprolide acetate. These two syringe assemblies are manufactured at separate locations. The ATRIGEL® Delivery System(50:50 PLGH and NMP; Syringe A) is compounded, filled into syringes, and pouched at Atrix Laboratories Inc. in Fort Collins, CO. This subassembly is then . An aqueous solution of leuprolide acetate is in syringes (Syringe B), and pouched at the .
The final assembly occurs at Atrix Laboratories Inc., in Ft. Collins, CO and consists of a large foil pouch containing two pouched sterile assemblies with the sterile needle and the desiccant. The quality is controlled by tests of both parts of the drug product, Syringe A and Syringe B. Syringe A tests include color, appearance, polymer identification (by NMR), polymer molecular weight, water content, sterility (USP <71>) and endotoxin (USP <85>). Syringe B tests include color, appearance, identification related substances , sterility(USP <71>) and endotoxin (USP <85>). Furthermore, the reconstituted product is released by regulatory specifications and is controlled by tests that include color, appearance, polydispersity, leuprolide acetate content and drug release.

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

The plunger tip is and the plunger rod is (Syringe A). The secondary packaging is a foil laminate pouch after syringe placement. The Syringe B is constructed of a , with the syringe tip cap and the plunger tip composed of A second plunger tip behind the primary plunger tip is incorporated to ensure a clear zone for the primary tip to travel during product mixing. A is installed to assist with injection. The assembled unit is then packaged in a foil laminate pouch and Both foil laminate pouches are then placed together in a larger foil laminate pouch with a sterile 20-gauge half-inch needle and a desicant pouch and heat-sealed to enclose all the components. The required DMF's (DMF , DMF and DMF for the packaging components are found adequate. From Microbiologist's point of view, container/closure integrity is deemed satisfactory.

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

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

Leuprolide acetate is manufactured and supplied by

The major differences in the impurity profile drug substance batches are:

-
-

Toxicology and clinical studies qualifies the above impurities from and is deemed acceptable.

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

The tests performed on the starting materials (modified amino acids) has been provided in the respective DMF from and are adequate.

Stability of leuprolide acetate is established with five batches from . The proposed retest period of months and months for

when stored at 2-8°C, is acceptable. The product can also be stored at to qualify for a month retest period.

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

One month Eligard 7.5 mg is supplied as two prefilled sterile syringes and a sterile needle. The product is allowed to come to room temperature before use. 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. It should be mixed for approximately 45 seconds to achieve a uniform suspension. When thoroughly mixed, the suspension will appear as a light tan to tan color. Following mixing, the contents are transferred into syringe B and the syringes are decoupled. A sterile needle is then affixed to the syringe B for patient injection. The total deliverable injection weight is 250 mg including 7.5 mg of leuprolide acetate. Once mixed the drug product should be administered within 30 minutes.
The drug product is administered subcutaneously and provides continuous release of leuprolide for one month.
An month expiry date is granted for the drug product, when stored at 2-8°C.

C. Basis for Approvability or Not-Approval Recommendation

The original submission of this NDA had deficiencies in many areas (see chemist's review notes for details). However, through teleconferences (11/18/01, 12/18/01, 12/20/01, 1/2/02) and a discipline review letter dated November 16, 2001, the sponsor provided information, adjusted acceptance criteria and performed studies to demonstrate the quality of the drug product. The final outcome is deemed satisfactory. The pending recommendation from the Office of Compliance with regard to facility inspections was resolved on January 23, 2002 and the facilities overall recommendation is acceptable.

Some of the major issues and their resolution are described below.

- **Drug Product Impurities:** Specified impurities in the regulatory specifications were expanded based on the ICH Q3b guidance. Initially, the drug product had only one listed specified related impurity Based on literature and provided data additional related impurities were included in the regulatory specifications with acceptance criteria. Therefore, three other specified impurities) have been added.
- **Additional Drug Product Specifications/Tests:** Considering the deleterious effects of the polymer (PLGH) with increased water uptake, water content is now included in the regulatory specifications of the drug product. Polydispersity is unique for this product and shown to increase during stability. Thus, it was recommended that polydispersity to be tested during stability and it is now added to the regulatory specification.
- **Drug Product In vitro Release Test:** The sponsor revised the method during stability testing of the primary batches and thus, has limited experience with the new method. The data from the clinical batches did not match with the recent primary stability batches and therefore the sponsor proposed an acceptance criteria that was too wide (see Chemistry

Assesment Section, pg. 37 for details). The Division of Biopharmaceutics provided their opinion that "the issue of in vitro dissolution performed using organic solvents has no physiological relevance". Since the test is an important measure of the drug product quality, the acceptance criteria was tightened and conveyed to the sponsor in a teleconference on 12/20/01. Final resolution was achieved through amendment #020, submitted on 12/21/01.

III. Administrative

A. Reviewer's Signature

/S/

B. Endorsement Block

HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.
HFD-580/J. Best

C. CC Block

HFD-580/Division File/NDA 21-343
HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.
HFD-580/J. Best

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Chemistry Review Data Sheet

1. NDA 21-343

2. REVIEW # 1

3. REVIEW DATE: 16-JAN-2002

4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-MAR-2001
Amendment#2	04-JUL-2001
Amendment #5	31-JUL-2001
Amendment #8	23-OCT-2001
Amendment#14	16-NOV-2001
t-con	18-NOV-2001
Amendment#15	10-DEC-2001
Amendment #15	10-DEC-2001
Amendment #16	14-DEC-2001
t-con	18-DEC-2001
t-con	20-DEC-2001
Amendment#18	20-DEC-2001
Amendment#19	20-DEC-2001
Amendment#20	21-DEC-2001
t-con	02-JAN-2002
Amendment#22	08-JAN-2002

Amendment#23	11-JAN-2002
Amendment#24	16-JAN-2002
Amendment#25	17-JAN-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Atrix Laboratories, Inc.
Address:	2579 Midpoint Drive Fort Collins, CO 80525-4417
Representative:	Elyse Wolff
Telephone:	(970) 482-5868

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Eligard™
b) Non-Proprietary Name (USAN): Leuprolide acetate for Injectable suspension
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

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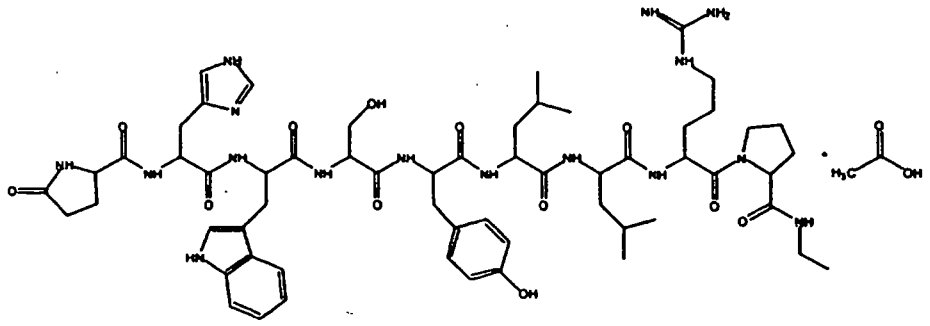
_____SPOTS product – Form Completed
___x___Not a SPOTS product
_____Not a SPOTS product

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

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

Chemical Structure:



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

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

Relative molecular mass: 1269.48 Daltons (Leuprolide Monoacetate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFER-ENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Yes	3	Reviewed by S.K.De Adequate	01/17/2000	N/A
	II		Yes	1	Reviewed by S.K.De Inadequate Adequate	8/25/01 11/29/01	8/27/01 N/A
	II		Yes	7	Reviewed by S.K.De Adequate	12/05/01	N/A

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	II	Yes	1	Reviewed by S.K.De Adequate	1/03/02	N/A
	III	Yes	7	Reviewed by S.K.De Adequate	12/06/01	N/A
	III	Yes	7	Reviewed by E.G.Pappas Adequate	2/17/98	N/A
	III	Yes	7	Reviewed by S.K.De Adequate	12/12/01	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: IND

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	1/16/02	Office of Compliance
Pharm/Tox	Adequate	12/17/01	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	12/12/01	Myong-Jin Kim, Ph.D.
LNC	N/A		

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Methods Validation	Will be initiated		N/A
OPDRA	Deficient Adequate	07/03/01 12/12/01	Nora Roselle, Pharm.D.
EA	Categorical exclusion granted	1/16/02	
Microbiology	Deficient Adequate	11/19/01 1/02/02	Bryan S. Riley, Ph.D.

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

APPEARS THIS WAY ON ORIGINAL

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ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **RSP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **RSP** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **18-JUN-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-OCT-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21343/000**
Stamp: **23-MAR-2001** Regulatory Due: **23-JAN-2002**
Applicant: **ATRIX**
2579 MIDPOINT DR
FORT COLLINS, CO 80525

Priority: **3S** Org Code: **580**
Action Goal: District Goal: **24-NOV-2001**
Brand Name: [redacted]**LEU(LEUPROLIDE ACETATE)7.5MG I**
Established Name:
Generic Name: **LEUPROLIDE ACETATE**
Dosage Form: **INJ (INJECTION)**
Strength: **7.5 MG**

FDA Contacts:
J. BEST (HFD-580) 301-827-4260 , Project Manager
S. DE , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation:

ACCEPTABLE on 23-JAN-2002 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: **1724031**
ATRIX LABORATORIES INC
701 CENTRE AVE
FORT COLLINS, CO 80525

DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **23-JAN-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-MAY-2001**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **11-MAY-2001**

Responsibilities:

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

There was no Statistical review of Dissolution/Stability for this application.

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

See Chemistry Review, Page 64 for the Environmental Assessment and acceptance of the categorical exclusion.

/S/

1/2002

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

Methods Validation is NA at this time.