CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
21-379

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-379

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 21-379

2. REVIEW # 1

3. REVIEW DATE: 03-JULY-2002(revised)

4. REVIEWER: Swapan K. De

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-SEP-2001
Amendment #003	19-MAR-2002
Amendment #004	25-APR-2002
Amendment #007	26-JUN-2002
Amendment #009	03-JULY-2002
Amendment #010	10-JULY-2002
Amendment #011	12-JULY-2002
Amendment #012	17-JULY-2002
Amendment #013	17-JULY-2002

7. NAME & ADDRESS OF APPLICANT:

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ELIGARD™ 22.5 mg
b) Non-Proprietary Name (USAN): Leuprolide acetate for Injectable suspension
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

11. DOSAGE FORM: Injectable suspension

13. ROUTE OF ADMINISTRATION: Subcutaneous

12. STRENGTH/POTENCY: 22.5 mg leuprolide acetate

14. Rx/OTC DISPENSED: _x_Rx ___OTC

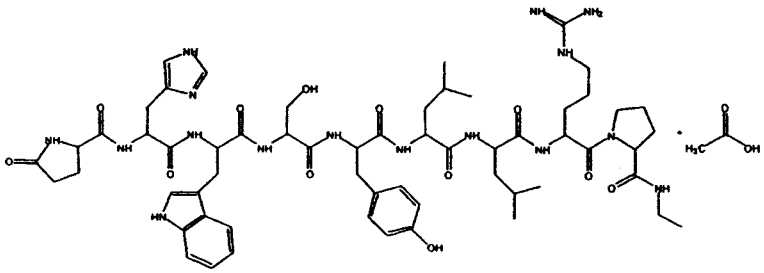
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

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

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

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:



Chemistry Review Data Sheet

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
[redacted]	II	[redacted]	Yes	3	Adequate	01/17/2000	Reviewed by S.K.De
[redacted]	II	[redacted]	Yes	1	Adequate	11/29/01	Reviewed by S.K.De
[redacted]	II	[redacted]	Yes	3	Adequate	06/10/02	Reviewed by S.K.De
[redacted]	II	[redacted]	Yes	1	Adequate	1/03/02	Reviewed by S.K.De
[redacted]	III	[redacted]	Yes	3	Adequate	12/06/01	Reviewed by S.K.De
[redacted]	III	[redacted]	Yes	3	Adequate	2/17/98	Reviewed by E.G.Pappas

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF

Chemistry Review Data Sheet

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 [redacted]

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-APR-2002	Office of Compliance
Pharm/Tox	Adequate	30-APR-2002	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	19- JUL-2002	Myong-Jin Kim, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	05-JUN-2002	Hye-Joo Kim, Pharmacist.
EA	Categorical exclusion granted	03-JUL-2002	Swapan K. De, Ph.D.
Microbiology	Deficient Adequate	10-MAY-2002 22-JUL-2002	Stephen Langille, 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:

Executive Summary Section

The Chemistry Review for NDA 21-379

The Executive Summary

I. Recommendations

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

II. Summary of Chemistry Assessments

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

Dosage form: Injectable suspension
Strength: 22.5 mg Leuprolide acetate
Route of Administration: Subcutaneous

Description:
The drug product, ELIGARD™ is a 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 — g of a sterile, polymeric delivery system solution of —% 75:25 Poly(DL lactide-co-glycolide) (PLG) and —% N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains — mg —%) of — lyophilized leuprolide acetate. These two syringe assemblies are manufactured at separate locations. The ATRIGEL® Delivery System(75:25 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 — (through — filters) and lyophilized 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 — 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 — mL — syringes —

Executive Summary Section

... The plunger tip is [redacted] and the plunger rod is [redacted] (Syringe A). [redacted] The Syringe B is constructed of [redacted], with the syringe tip cap and the plunger tip composed of [redacted] 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 [redacted] is installed to assist with injection. The assembled unit is then packaged in [redacted] and [redacted] Both [redacted] pouches are then placed together in a larger [redacted] pouch with a sterile 20-gauge half-inch needle and a desiccant pouch and [redacted] to enclose all the components. The required DMF's (DMF [redacted]) 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, an18-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 the primary as well as the secondary packaging.

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

Leuprolide acetate is manufactured and supplied by [redacted] On the contrary, [redacted]

The major differences in the impurity profile between [redacted] drug substance batches are:

- [redacted]
- [redacted]

Toxicology and clinical studies qualifies the above impurities [redacted] 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 [redacted] and [redacted]

The tests performed on the starting materials ([redacted]) has been provided in the respective DMF from [redacted] (DMF [redacted] DMF [redacted]), and are adequate.

Stability of leuprolide acetate is established with five batches [redacted] four batches [redacted] The proposed retest period of the drug substance of [redacted] months and [redacted] months for

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

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

Three month Eligard 22.5 mg is supplied as two prefilled sterile syringes and a sterile needle. The product should come to room temperature before use. Prior to administration of the drug product the two syringes are coupled and the contents of the two syringes are mixed by passing the contents from syringe to syringe. It should be mixed for approximately 45 seconds to achieve a uniform suspension. When thoroughly mixed, the suspension will appear as a light tan to tan color. Following mixing, the contents are transferred into syringe B and the syringes are decoupled. A sterile needle is then affixed to the syringe B for patient injection. The total deliverable injection weight is 375 mg including 22.5 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 three months.
The drug product has an 18-month expiry date, when stored at 2-8°C.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided adequate data to demonstrate product quality. Therefore, from a CMC point of view, the data support approval of the NDA.
The original submission of this NDA had many deficiencies and through a teleconference on 12-Feb-2002, the sponsor was asked to submit an amendment with updated information and to address the applicable deficiencies sent to them for a previously approved similar product (Eligard 7.5 mg, NDA21-343). The sponsor's submission of amendment #003 (19-Mar-2002) includes updated information applicable with ELIGARD 7.5 mg, which include acceptance criteria for the drug product as well as revision of package insert. Amendment #004 (25-APR-2002) includes the updated information on stability. However, since the formulation of ELIGARD™ 22.5 mg is not identical to ELIGARD™ 7.5 mg, a list of deficiencies were communicated to the sponsor on 7-June-2002 (see chemist's review notes for details). The sponsor agreed to most of the recommended changes and submitted amendment #007 (26-JUNE-2002). In a response(amendment #009, dated July 3, 2002) to the July 1, 2002 teleconference the sponsor provided information, adjusted acceptance criteria of PLG and proposed alternative acceptance criterion for the dissolution method of the drug product. Both PLG molecular weight and in vitro release acceptance criteria were further discussed on July 11, 2002 and on July 12, 2002 (amendment #012), the sponsor agreed to use the PLG polymer molecular weight acceptance criterion [redacted], recommended by the agency in the June 7, 2002 information request letter. Amendment #012 (17-July-2002) contains additional information on photostability, residual solvent information and updated specifications. The sponsor's submission of amendment #010 and amendment #013 are the response on the recommended changes for the package insert, carton, pouch and syringe labels.
Some of the major issues and their resolution are described below.

- **Additional Drug Product Specifications/Tests:** 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.
- **Change in Acceptance Criterion of NMP :** The acceptance criterion of NMP is changed from [redacted] % to [redacted] %.
- **Residual solvent:** [redacted] is used during the manufacture of the excipient PLG and there was no residual solvent test. It is now added to the specifications and acceptance criterion of PLG.
- **Change in Acceptance Criterion of polymer PLG molecular weight:** The acceptance criterion of PLG molecular weight is changed from [redacted] to [redacted] based on the clinical and primary stability batches.
- **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 July 1, 2002. Final resolution was achieved through a t-con and amendment (#011) on July 12, 2002 and the sponsor agreed to narrow the acceptance for the extended release [redacted] hour sampling timepoint from [redacted] % as recommended by the agency on July 1, 2002.

III. Administrative

A. Reviewer's Signature

/S/

B. Endorsement Block

/S/

HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.
HFD-580/A. Reddy

C. CC Block

HFD-580/Division File/NDA 21-379
HFD-580/S. K. De, Ph.D.
HFD-580/D. T. Lin, Ph.D.
HFD-580/A. Reddy

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

/s/

Swapan De
7/22/02 03:37:33 PM
CHEMIST

David T. Lin
7/22/02 03:52:05 PM
CHEMIST
I concur.

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commercial

information

NDA 21-379
Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

Statistical Dissolution/Stability Review

CMR 7/01/02

No review required.

JUN 1 1 2002

DMF REVIEW COVER FORM

DMF: — DMF Type: II
Title: 75/25 Poly(D,L-lactide-co-glycolide)

1. CHEM REVIEW # 1

2. REVIEW DATE: 04/30/02

3. **ITEM REVIEWED**

A. IDENTIFICATION

USAN : None
Ingredient Dictionary name: Poly(D-L-lactide-co-glycolide)
Trade name: None
Manufacturer's code: None
Chemical name: Poly(D-L-lactide-co-glycolide)
CAS number: 96880-31-8

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	08-Nov-2001	Vol. 1.1
Amendment	10-May-2002	Vol.1.1
Amendment	24-May-2002	Vol.1.1
Amendment	05-June-2002	Vol.1.1

4. PREVIOUS DOCUMENTS: N/A

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

NAME:
ADDRESS:

CONTACT PERSON'S NAME: —
ADDRESS: Same as above

TELEPHONE NUMBER: —

6. **DMF REFERENCED FOR:**

NDA: NDA 21-379
PRIMARY DMF (as needed) N/A
APPLICANT NAME: Atrix Laboratories, Inc.
LOA DATE: 08-01-00
DRUG PRODUCT NAME: Leuprolide Acetate for injectable suspension
DOSAGE FORM: Subcutaneous injection CODE: 706

STRENGTH: 22.5 mg leuprolide
ROUTE OF ADMINISTRATION: Subcutaneous CODE: 003

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF: Not reviewed**
DATE OF LAST UPDATE OF DMF: 05/10/02
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAS BEEN PROVIDED: 08/01/01

9. **CONSULTS:** None

10. **COMMENTS:** The original submission of the DMF was found deficient since it had no information regarding the specifications, manufacturing batch records and certificate of analysis for the specific polymer [75/25 poly(DL-lactide-co-glycolode)] used for the manufacture of the drug product. The information mentioned above was received on 13-May-2002 following a telephone conversation with Mr. [redacted] on 30-April-2002. Following review of the sent materials and the original DMF, the sponsor was asked through a T-con on 13-May-2002, to submit more information on test methods [redacted] and [redacted]), and justification for not including residual solvents test for the polymer. The information was received on 28- May-2002 and 5-June-2002 and were deemed satisfactory (see chemist's review notes).

11. **CONCLUSION:**

The DMF holder provided significant information to support NDA#21-379. However, since the drug product, formulation used only PLG copolymer (75:25), this chemistry review is adequate only for *75/25 poly(DL-lactide-co-glycolide).*

/S/

Swapan K. De, Ph.D.
Review Chemist, HFD-580

/S/

David T. Lin, Ph.D.
Chemistry Team Leader

cc:
Original DMF [redacted] (2 copies)
HFD-580/NDA21-379/Division File
HFD-580/SDe, Review Chemist
HFD-580/DTLin, Chemistry Team Leader
HFD-580/Reddy, CSO

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NDA 21-379
Eligard™ 22.5 mg (lueprolide acetate for injectable suspension)

ENVIRONMENTAL ASSESSMENT

A categorical waiver was granted.