CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-731

CHEMISTRY REVIEW(S)

NDA 21-731

ELIGARD™, 45 mg
(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 21-731

2. REVIEW # 1

3. REVIEW DATE: 20-NOV-2004 (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	18-FEB-2004
Amendment #001 (response to IR letter dated April28, 2004	20-MAY-2004
Amendment #002 (labeling amendment)	11-AUG-2004
Amendment #003 (updated stability data)	17-SEPT-2004
Amendment #004 (updated specifications)	23-NOV-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Atrix Laboratories, Inc.
Address:	2579 Midpoint Drive Fort Collins, CO 80525-4417
Representative:	Cheri L. Jones
Telephone:	(970) 212-4901

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ELIGARD™ 45 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

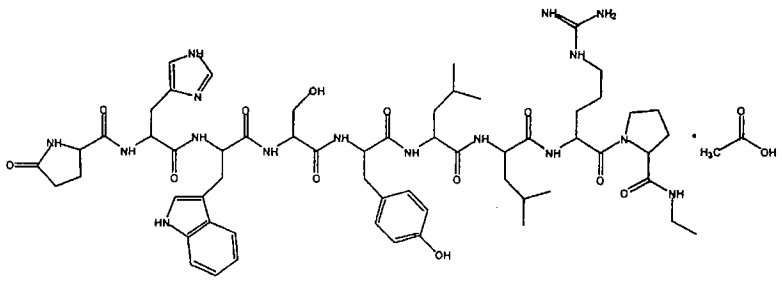
12. STRENGTH/POTENCY: 45 mg leuprolide acetate

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____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

Chemistry Review Data Sheet

Molecular formula: $C_{59}H_{84}N_{16}O_{12} \bullet C_2H_4O_2$
Relative molecular mass: 1269.48 Daltons (Leuprolide acetate)
CAS Registry number: 74381-53-6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
1	II	[redacted]	Drug substance (Leuprolide acetate)	3	Adequate	01/17/2000	Reviewed by S.K.De
	II		Drug substance (Leuprolide acetate)	3	Adequate	11/29/01	Reviewed by S.K.De
	II		Polymer (85/15 Poly(D,L-lactide-co-glycolide)		Adequate	12/08/04	Reviewed by S.K.De
	II		N-methyl-2-Pyrolidone (excipient)	3	Adequate	1/03/02	Reviewed by S.K.De
	III		[redacted]	3	Adequate	12/12/01	Reviewed by S.K.De
	III			3	Adequate	1/22/04	Reviewed By G.W. Holbert

Chemistry Review Data Sheet

	III	3	Adequate	7/14/00	Reviewed By Young-de Lu
	III	3	Adequate	2/17/98	Reviewed by E.G.Pappas
	III		Adequate	9/21/04	Reviewed by Swapan K. De
	III		Adequate	9/23/04	Reviewed by Swapan K. De

[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 64-779, NDA 21-343, NDA 21-379 and NDA 21-488

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	29-NOV-2004	Office of Compliance
Pharm/Tox	Adequate	17-MAY-2004	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	06-DEC-2004	Sandhya Apparaju, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	5-OCT-2004	Denise Toyer, Drug safety reviewer
EA	Categorical exclusion granted	14-JAN-2004	Swapan K. De, Ph.D.
Microbiology	Adequate	24-NOV-2004	Bryan Reily, 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 21-731

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: 45 mg Leuprolide acetate
Route of Administration: Subcutaneous

Description:
The drug product, ELIGARD™, 45 mg is a polymeric matrix formulation of leuprolide acetate intended for controlled delivery of the drug product over a six-month period for the palliative treatment of prostate cancer. The drug product consists of a two syringe mixing system, a 19 gauge 5/8-inch needle, and a silicone desiccant pouch to control moisture uptake. One syringe (Syringe A) contains the ATRIGEL® Delivery System. This delivery system consists of — of a sterile, polymeric delivery system solution of — 85:15 Poly(DL lactide-co-glycolide) (PLG) an — N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains — filled, lyophilized leuprolide acetate.
The ATRIGEL® Delivery System (85:15 PLG 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 [ ] lyophilized in syringes (Syringe B) and packaged at Atrix Laboratories Inc. in Fort Collins, CO [ ] The final assembly occurs at Atrix Laboratories Inc., in Ft. Collins, CO and either consists [ ]
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, polydispersity, water content, NMP content, sterility (USP <71>) and endotoxin (USP <85>). Syringe B tests include color, appearance, identification (IR and HPLC), related substances (HPLC), 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, 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 [redacted] syringes [redacted]

[redacted] The required DMF's (DMF [redacted] DMF [redacted] DMF [redacted] and 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, an24-month expiry date is granted. The tradename, ELIGARD™, 45 mg has been accepted by DMETS, 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.

[redacted]

The sponsor has provided data to show the comparability of the drug substances among the two suppliers and they are deemed satisfactory. Toxicology and clinical studies qualifies the above impurities 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.

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

Six month ELIGARD™, 45 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 45 mg of leuprolide acetate. Once mixed the drug product should be administered within 1 hour.
The drug product is administered subcutaneously and provides continuous release of leuprolide for six months.
The drug product has an 24-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 sponsor submitted the original submission of this NDA following their other approved products (ELIGARD™, 7.5 mg, ELIGARD™, 22.5 mg and ELIGARD™, 30 mg) and thus, had minor deficiencies. These deficiencies were sent to the sponsor on April 28, 2004. The sponsor's submission of amendment #001 (20-May-2004) includes the response to the deficiencies and was found adequate. Amendment #003 (17-Sept-2004) includes the updated information on stability (to provide more stability data) and revised specifications. Amendment #004 dated 23 Nov, 2004 includes response on PLG polymer specification and extended release specification based on the recommendation forwarded through t-con dated Nov 9-2004 and Nov 12-2004. Some of the major issues and their resolution for this NDA include submission of information for the justification of drug product overage, adjustment of PLG molecular weight and extended release acceptance criteria based on qualification and batch record. Thus, considering the provided information, this NDA is deemed satisfactory regarding CMC and may be approved.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-580/S. K. De, Ph.D.
HFD-580/M.J. Rhee, Ph.D.
HFD-580/J. Kim

C. CC Block

HFD-580/Division File/NDA 21-488
HFD-580/S. K. De, Ph.D.
HFD-580/M.J. Rhee, Ph.D.
HFD-580/ J. Kim

69 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 141

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
12/9/04 10:51:24 AM
CHEMIST

Moo-Jhong Rhee
12/9/04 01:30:07 PM
CHEMIST
I concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-731 **Applicant: ATRIX LABORATORIES INC.**
Stamp Date: 18-FEB-2004
Drug Name: ELIGARD, 45 mg

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: 26-MAR-2004

Team Leader: Moo-Jhong Rhee, Ph. D. Date: 26-MAR-2004

cc:
Original NDA 21-731
HFD-580/Division File
HFD-580/Chem/De/Rhee
HFD-580/PM/Kimj
HFD-580/DivDir/DShames