

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

**APPLICATION NUMBER
21-379**

PHARMACOLOGY REVIEW(S)

Clinical formulation: Clinical formulation is similar to Atrix LA-2500 (one month formulation) as described under NDA 21-343 dated 3-22-2001 except that

1. the amount of leuprolide acetate is 3 times greater i.e., 22.5 mg/unit compared to 7.5 mg/unit in the one month formulation and
2. the ratio of DL-lactide-co-glycolide is 75:25 compared to 50:50 in the one month formulation

The quantitative composition of one month (LA-2500) and 3-month (LA-2550) formulation is shown in table below:

Component	LA-2500 (1- month formulation)		LA-2550 (3-month formulation)	
	% w/w	Dose delivered Mg/unit	% w/w	Dose delivered Mg/unit
Leuprolide acetate	—	7.5	—	22.5
Poly(DL-lactide-co-glycolide)	(50:50)	82.5	(75:25)	158.6
N-methyl-2-pyrrolidone	—	160.0	—	193.9
Total delivered amount		250 mg		375 mg

Thus the components of one-month and three-month formulations are similar except for the composition differences for the poly(DL-lactide-co-glycolide) polymer.

Route of administration: Subcutaneous

Proposed use: 22.5 mg leuprolide acetate formulation (LA-2550) is an injectable extended-release subcutaneous formulation intended for one injection every 3 months for the palliative treatment of advanced prostate cancer.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-379

Review number: 1

Serial number/date/type of submission: 000/9-26-2001/original application

Information to sponsor: Yes () No (*)

Sponsor and/or agent: ATRIX Laboratories, Fort Collins, CO

Manufacturer for drug substance: _____

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.

Division name: Reproductive and Urologic Drug Products

HFD #: 580

Review completion date: 4-3-2002

Drug:

Trade name: _____ (LA-2550 22.5 mg)

Generic name (list alphabetically): Leuprolide acetate for injectable suspension

Code name:

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

CAS registry number: 74381-53-6

Mole file number:

Molecular formula/molecular weight: C₅₉H₈₄N₁₆O₁₂. C₂H₄O₂/1269.48 Daltons

Structure:

See attached review dated 12-17-2001 for the original NDA 21-343 submission dated 3-22-2001

Excipient:

Generic name: 1-methyl-2-pyrrolidone

Synonyms/codes: N-methylpyrrolidone

NMP

N-methylpyrrol

H-20417

Case registry No.: 872-50-4

Molecular weight: 99.13

Structure

See attached review for NDA 21-343

Relevant INDs/NDAs/DMFs: INDs _____

NDA 21-343; DMF _____

Drug class: GnRH agonist

Indication: For the treatment of advanced prostate cancer

OVERALL SUMMARY AND EVALUATION:

For the following items see attached copy of the NDA 21-343 review for LA-2500 (Leuprogel 7.5 mg, once monthly injection) for the same indication as the proposed 3-month formulation submitted under present NDA 21-379.

Introduction:

Safety evaluation:

Safety issues relevant to clinical use:

Other clinically relevant issues:

Conclusions:

Communication review:

Labeling review:

RECOMMENDATIONS: Based on the review and recommended approval of NDA 21-343 for Leuprogel one-month formulation for the palliative treatment of advanced prostate cancer, Pharmacology recommends approval of NDA 21-379 for a 3-month extended release formulation having same components and intended for the same indication.

Internal comments: none

External recommendations (to sponsor): none

Draft letter content for sponsor (if not same as above):

NDA issues: none

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc: list:

Original NDA 21-379

HFD-580

HFD-580/A.Jordan/A.Batra/K.Raheja/J.Best

N21379.000/12-03-2001

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary): none

Studies reviewed within this submission: none

Studies not reviewed within this submission: All those previously reviewed under NDA 21-343 for Leuprogel one month formulation for the palliative treatment of advanced prostate cancer and intended to support the present 3-month formulation under NDA 21-379.

Introduction and drug history: see review for NDA 21-343.

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PHARMACOLOGY:

See review dated 12-17-2001 for the original NDA 21-343 submission dated 3-22-2001.

SAFETY PHARMACOLOGY:

See review for NDA 21-343

PHARMACOKINETICS/TOXICOKINETICS:

See review for NDA 21-343

TOXICOLOGY:

See review for NDA 21-343

Histopathology Inventory for NDA #

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				
Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				

Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed

*, organ weight obtained

GENETIC TOXICOLOGY:

See review for NDA 21-343

CARCINOGENICITY:

See review for NDA 21-343

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

See review for NDA 210343

SPECIAL TOXICOLOGY STUDIES:

See review for NDA 21-343

ADDENDUM TO REVIEW:

(if necessary)

APPENDIX/ATTACHMENTS:

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/s/

Krishan L. Raheja
4/29/02 04:20:36 PM
PHARMACOLOGIST

Alexander W. Jordan
4/30/02 10:15:09 AM
PHARMACOLOGIST

Memo to the file

Date: 11-16-2001

From: Krishan L. Raheja

To: Jeanine Best

Subject: Filing meeting for NDA 21-379 dated 9-25-2001 on 11-15-2001

Based on the data submitted for review, NDA 21-279 is fileable from P/T prospective.

Krishan

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/s/

Krishan L. Raheja
11/16/01 01:38:43 PM
PHARMACOLOGIST

NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

CAC/ECAC Report

This NDA was not the subject of a CAC/ECAC report.

OK 7/01/02

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