CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-088

CHEMISTRY REVIEW(S)

Summary of Chemistry Review of NDA 21-088

MAR 0 2000

A. Drug Substance:

The drug substance, leuprolide acetate, is a synthetic nonapeptide analog of GnRH with leucine replaced for glycine in the 6th position of the natural peptide, and is known to have a greater potency than the natural form. It has been used for other drug products as an agonist for alleviating the symptom of prostate cancer or endometriosis. [redacted] manufactures the drug substance and the facility is deemed in compliance to cGMP.

The structural analysis of the leuprolide acetate was carried out with mass spectrometry, amino acid analysis, amino acid sequencing, NMR, elemental analysis, and FT-IR spectroscopy. Based on the provided data, it is deemed that the structure of the leuprolide acetate is identical to the previously approved one.

The quality of the leuprolide is adequately controlled by tests such as identification, appearance, assay, microbial content, bacterial endotoxins, peptide content, acetic acid content, water content, trifluoroacetate, specific optical rotation, residual acetonitrile, amino acid analysis, and impurities. The proposed specifications for these tests are considered to be adequate.

B. Drug Product:

The implant, Viadur, is a novel drug delivery device which is a titanium cylinder containing 72mg (equivalent to 65mg of leuprolide) of leuprolide acetate in 104mg of DMSO in one compartment and osmotic engine (sodium chloride crystals) in the other compartment separated by an elastomeric piston. The drug compartment side has a diffusion moderator through which the drug solution is released at a rate of 120μg/day for one year as the membrane at the other end of the implant allows permeation of water thereby hydrating the osmotic engine and pushing the piston.

The safety of this implant device was cleared by CDRH.

This implant is manufactured, packaged, tested, and released by Alza Corp. as well as [redacted] These facilities are in compliance to cGMP.

The functionality and quality of the implant is controlled by tests and specifications such as identification, assay, degradation products/impurities, sterility, bacterial endotoxins, drug release rates, and packaging integrity. Although there were some observations of defective implant during the clinical trial, with sponsor's Phase IV commitment to address this issue, the proposed tests and specifications are deemed satisfactory.

The implant is packaged into a glass vial with a rubber stopper and aluminum seal, and these packaging components are properly controlled to protect the product during the shelf life. It is co-packaged with an implanter (trocar) and an accessory kit, which contains sixteen necessary items for a brief surgical procedure.

The implanter was also reviewed and cleared by the CDRH.

Since the implant is to be in patient for **12 months at 37°C**, stability of leuprolide in DMSO under that condition is **critical**. The sponsor addressed this issue by conducting stability studies under **37°C for up to 24 months**, and demonstrated that the peptide in DMSO is very stable under that condition.

Based on all available stability data of the implant, **24-month of expiry date** at room temperature is granted.

The tradename, **Viadur**, was accepted by **Labeling and Nomenclature Committee** and no objection was made by OPDRA. The labeling as well as other labels are considered to be satisfactory.

C. Conclusion and Recommendation:

From chemistry point of view, this NDA can be approved.

/S/ - 3/2/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

MAR 02 2000

Addendum to Chemistry Review #3

- **Final Status of EER:** **Satisfactory**

The pending EER issue for the chemistry, manufacturing and controls for the NDA 21-088 (Viadur™) is now resolved and it is acceptable (see Appendix 1.1 for EER summary report).

- **Response to March 1, 2000 comments on Dimethyl Sulfoxide:** **Satisfactory**

The firm was notified about a recall letter on three batches of DMSO (USP990817, USP990614 and USP990727), which DMF holder send to the agency on February 29, 2000. Through a t-con and by fax the sponsor certified that the above mentioned recalled DMSO lots were not and will not be used to produce any batches of product for commercial distribution (see Appendix 1.2 for letter from the sponsor).

- **Response to March 1, 2000 Phase IV Commitment Request:** **Satisfactory**

The sponsor submitted an amendment on February 9, 2000, which resulted from the investigation into a patient with rising Prostate Specific Antigen (PSA) and elevated testosterone level during an open-label safety extension study for the drug. It has been found that the diffusion moderator of the removed implant was not seated properly in the titanium reservoir. The sponsor explained the incidence as a possible cause for manufacturing process of the clinical supplies. ALZA took necessary action, which includes the notification to all the clinical investigators of the event, and request them to notify their respective IRB. Additionally, ALZA is requesting the clinical investigators to notify their patients of the event and ask the patient for more frequent blood sampling for analysis of leuprolide and testosterone.

Because of this incidence following Phase IV commitments was requested through a t-con on March 1, 2000.

1.

2.

3.

Response: The sponsor agreed to the Phase IV commitment as the agency suggested (see Appendix 1.3 for letter from the sponsor).

Conclusion: The issues on CMC information are now resolved and this NDA may be approved.

3/2/00
Swapan K. De, Ph.D.
Review Chemist

3/2/00
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader

DEPARTMENT OF HEALTH AND HUMAN SERVICES MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue

CONSULTATION REVIEW

Date: October 12, 1999

To: CDER/Division of Reproductive and Urologic Drug Products (HFD-580)

Thru: Branch Chief,
Patricia Cricenti
Division Director,
Timothy A. Ulatowski

From: Scientific Reviewer/HFZ-480

Document No: NDA 21-088
Company Name: ALZA Corporation
Device: DUROS™ Leuprolide Implant

Indications for Use:
The controlled delivery of leuprolide acetate over a one-year period for the palliative treatment of advanced prostate cancer.

This is a review of a nonbiodegradable, osmotically driven miniaturized implant device designed to deliver leuprolide acetate over a one-year period at a controlled rate of approximately 0.12ml/day. The implant measures 4mm by 45mm and contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide) dissolved in 104mg dimethyl sulfoxide. The device is inserted subcutaneously in the inner aspect of the upper arm using a trocar-like implanter made of plastic and stainless steel. A surgical procedures kit is separately available and recommended for use by the sponsor.

Currently, leuprolide acetate can be administered by daily injections or periodic depot injections at intervals of 1, 3, and 4 months. The efficacy of Leuprolide in the palliative treatment of advanced prostate cancer has been established. The sponsor cited clinical studies in which patients received 20mg of leuprolide acetate daily for two years to support the safety of the device should the full contents of the drug be accidentally administered to the patient. The intent of the Leuprolide implant is to provide consistent, continuous therapy over one year as an alternative to periodic depot injections.

The device is a metal cylinder that is both a drug container and structural component that houses the mechanical elements of the device. The sponsor described the device as an extension of their osmotic drug delivery technology that includes the ALZMET® osmotic pump and the Veterinary Implantable Therapeutic System. The device components and materials of constructions are

The device is intended as a long-term (>30 days) implant. The cylinder, the diffusion moderator, and the rate-

controlling membranes are direct tissue and tissue fluids contact surfaces. The recommended biocompatibility testing for materials intended for long-term implants include Irritation, Sensitization, Cytotoxicity, Acute systemic toxicity, Hemocompatibility, Pyrogenicity, Implantation, Mutagenic, Subchronic toxicity, Chronic toxicity, and Carcinogenecity. The biocompatibility and suitability of these materials were established through testing and the reviews of appropriate literature. Titanium and titanium alloys are materials commonly used in the manufacture of implantable devices, and are used as a negative control implant material. Specifications and physical properties for Ti-6Al-4V have been established and are described in ASTM Standard F 136-96. The diffusion moderator is made of thermoplastic, high-density, polyethylene (HDPE). HDPE is a commonly used material for implantable devices, and is also used as a negative control article in biological reactivity testing. Material testing included subchronic and chronic toxicology, carcinogenicity, 90-day implantation, biological reactivity, cytotoxicity, and genotoxicity.

The rate-controlling membrane is made of [redacted] r. Material testing included cytotoxicity, hemolysis, systemic injection, intracutaneous injection, intramuscular implantation, microsomal assay, 90-implantation, biological reactivity, and genotoxicity. In addition, the sponsor stated that all polymers used in the manufacture of the device were evaluated for safety per the USP XXIII Class VI biological reactivity tests, the Elution cytotoxicity assays, and the MTT assay.

The device uses an "osmotic engine" to push the piston forward to eject the drug through the diffusion moderator into the surrounding subcutaneous tissue. The osmotic engine consists of two salt tablets, designed to absorb water and volumetrically expand. The water, from the fluids in the tissue in which the device is implanted, enters the osmotic engine by permeation across the rate-controlling membrane. The permeation rate is a function of the materials mix that comprises the membrane, specifically the ratio of polyethylene glycol to polytetramethylene glycol.

Performance evaluation of the device included bench testing (release rate assays per sponsor's Analytical Method 1.451f (reverse phase HPLC), dose accuracy and drug release per the USP XXIII General Chapter 724 Drug Release "Extended-release Article - Drug Release Standard, Acceptance Table 4"), animal implant studies (rat, dog, and swine) and clinical trials (single and repeated dose pharmacokinetics).

The device is radioopaque, not affected by MRI, and can be visualized by X-ray, which has no effects on its performance. The device function after implant is determined by monitoring serum levels of testosterone, as well as prostate-specific antigen (PSA).

III. Conclusion:

This review of the ALZA Corporation's DUROS™ Leuprolide Implant did not raise any engineering or performance-related concerns with the Implant as a drug delivery device. The Implant does not raise any new issues in terms of intended uses and technological characteristics, nor does it raise any new questions of safety and effectiveness in its ability to deliver leuprolide acetate over a one-year period at a controlled rate. The device was not evaluated as a drug container/closure.

If you have any questions, please call me at [redacted]

/S/

Von Nakayama

FEB 25 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-088 **DATE REVIEWED: 02-24-2000**

REVIEW #: 3 **REVIEWER: Swapan K. De**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	04-30-99	04-30-99	05-06-99
Correspondence	02-21-00 (fax)		02-23-00

NAME & ADDRESS OF APPLICANT: ALZA Corporation.
950 Page Mill Road
P.O.Box 10950
Palo Alto, California 94304-1090

DRUG PRODUCT NAME

Proprietary:	Viadur™
Established:	Leuprolide acetate implant
Code Name/#:	DUROS™ Leuprolide Implant, Human implantable Therapeutic System (HITS) Leuprolide, HITS Leuprolide Implant, ALZA internal code names CPC-2 or TDC-13
Chem.Type/Ther.Class:	3 S

PHARMACOL. CATEGORY/INDICATION: Palliative treatment of advanced prostate cancer

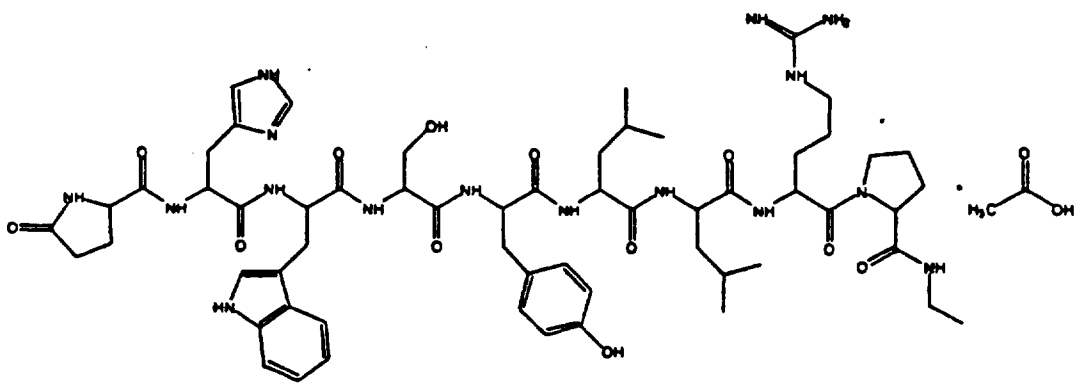
DOSAGE FORM: Implant
STRENGTHS: 65 mg leuprolide
ROUTE OF ADMINISTRATION: Subcutaneous
Rx/OTC: _x_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _x_ No
(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

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

Chemical names: 1. 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

CAS number: 74381-53-6

Structural Formula:



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

Molecular Formula: $C_{59}H_{84}N_{16}O_{12}$, free base
$C_{59}H_{84}N_{16}O_{12}$. $(C_2H_4O_2)$

Relative molecular mass: 1209.4, Leuprolide free base
1269.4 Leuprolide Monoacetate

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
	Type II Drug Substance		Reviewed Adequate	01/17/00	N/A
	Type II Inactive ingredient (DMSO)		Reviewed Adequate	02/03/00	N/A
	Material Master file Silicone Fluid, !		N/A		N/A
	Type III Packaging materials Pellets, HDPE		Reviewed Adequate	1/20/00	N/A
	Material Master File For Pellets, Thermoplastic Elastomer		N/A		N/A

	Type III Packaging materials Vial, Type 1 Glass 15 ml		KG-33 and N-51A Reviewed by D.N. Klein Adequate	10/8/99	N/A
	Type I Packaging materials Seal, Full Tear, 20 mm		N/A		N/A
	Type III Packaging materials Stopper, mm		Reviewed Adequate	5/25/99 by S.K.De	N/A
	Indication: Palliative treatment of advanced prostate cancer		N/A		N/A

RELATED DOCUMENTS (if applicable): None

REMARKS/COMMENTS:

The February 21, 2000 correspondence contains satisfactory response for deficiencies concerning the packaging components.

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable pending acceptable cGMP status of the drug product manufacturing and packaging facilities.

/S/ 2/24/00

Swapan K. De, Ph.D.
Review Chemist

cc:
Org. NDA 21-088
HFD-580/Division File
HFD-580/SDe
HFD-580/JBest
HFD-580/MRhee
HFD-820/JGibbs/Koepke (NMEs only)
R/D Init by: Moo-Jhong Rhee, Ph. D. MJRhee 2/24/00

filename: NDA21088.3

Summary of Chemistry Review

Drug Substance:

Description & Characterization: Satisfactory. See Chem. Rev. #2.

Manufacturers: Satisfactory. See Chem. Rev. #2.

Synthesis: Satisfactory. See Chem. Rev. #2.

Process Controls: Satisfactory. See Chem. Rev. #2.

Reference Standard: Satisfactory. See Chem. Rev. #2.

Specifications/Methods: Satisfactory. See Chem. Rev. #2.

Container: Satisfactory. See Chem. Rev. #2.

Stability: Satisfactory. See Chem. Rev. #2.

Drug Product:

1/2. Components/Composition: Satisfactory. See Chem. Rev. #1.

Specifications/Methods for Drug Product Components: Satisfactory. See Chem. Rev. #1.

Manufacturer: Satisfactory. See Chem. Rev. #1.

Methods of Manufacturing: Satisfactory. See Chem. Rev. #1.

Regulatory Specifications/Methods: Satisfactory. See Chem. Rev. #2.

Device Evaluation: Satisfactory. See Chem. Rev. #2.

Trade name: Satisfactory. See Chem. Rev. #2.

Container/Closure System: Satisfactory. See Chem. Rev. #2.

Microbiology: Satisfactory. See Chem. Rev. #1.

Stability: Satisfactory. See Chem. Rev. #1.

Investigational Formulations: Satisfactory. See Chem. Rev. #1.

Environmental Assessment: Satisfactory. See Chem. Rev. #1.

Methods Validation: Satisfactory. See Chem. Rev. #1.

Labeling: Satisfactory. See Chem. Rev. #3.

Establishment Inspection: *Pending*. See Chem. Rev. #2.

FEB 14 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-088 **DATE REVIEWED:** 02-14-2000

REVIEW #: 2 **REVIEWER:** Swapan K. De

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	04-30-99	04-30-99	05-06-99
Correspondence	02-09-00	02-10-00	02-14-00

NAME & ADDRESS OF APPLICANT: ALZA Corporation.
950 Page Mill Road
P.O.Box 10950
Palo Alto, California 94304-1090

DRUG PRODUCT NAME

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Established:	Leuprolide acetate implant
Code Name/#:	DUROS™ Leuprolide Implant, Human implantable Therapeutic System (HITS) Leuprolide, HITS Leuprolide Implant, ALZA internal code names CPC-2 or TDC-13
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SPECIAL PRODUCTS:	__ Yes _x_ No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

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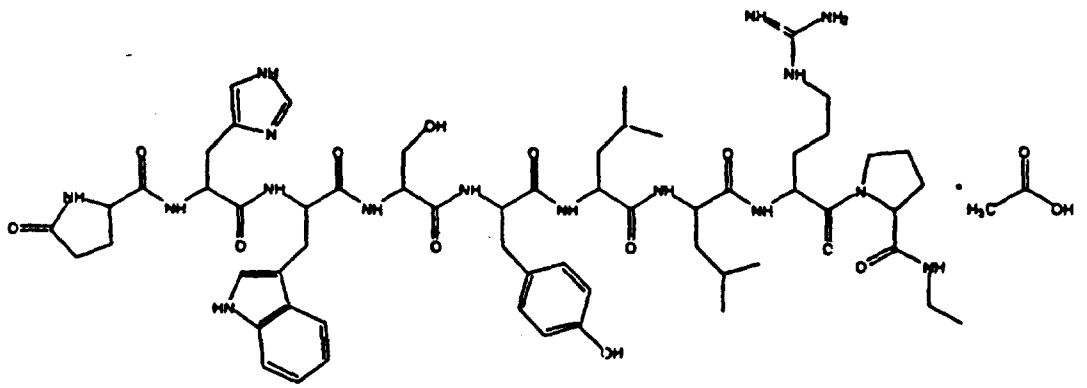
CAS number: 74381-53-6

Structural Formula:



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

Molecular Formula: $C_{59}H_{84}N_{16}O_{12}$, free base
$C_{59}H_{84}N_{16}O_{12}$. $(C_2H_4O_2)$

Relative molecular mass: 1209.4, Leuprolide free base
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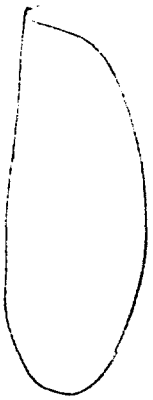
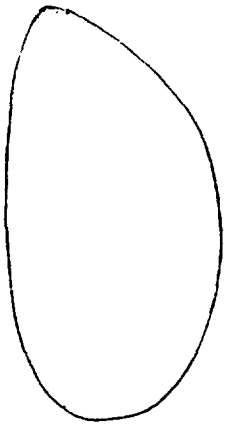
	Type II Inactive ingredient (DMSO)		Reviewed Adequate	02/03/00 by S.K.De	N/A
	Material Master file Silicone Fluid,		N/A		N/A
	Type III Packaging materials Pellets, HDPE		Reviewed Adequate	1/20/00 by S.K.De	N/A
	Material Master File For Pellets, Thermoplastic Elastomer		N/A		N/A

	Type III Packaging materials Vial, Type 1 Glass 15 ml		KG-33 and N-51A Reviewed by D.N. Klein Adequate	10/8/99	N/A
	Type I Packaging materials Seal, Full Tear, 20 mm		N/A		N/A
	Type III Packaging materials Stopper, mm		Reviewed Adequate	5/25/99 by S.K.De	N/A
	Indication: Palliative treatment of advanced prostate cancer		N/A		N/A

RELATED DOCUMENTS (if applicable): None

CONSULT REVIEWS:

a. Microbiology: **Satisfactory**

The Microbiology team has reviewed the microbiology section of the NDA. The DUROS™ implant employs a combination of aseptic filling and terminal irradiation for sterility assurance. Paul Stinavage, Ph.D. of the Microbiology team, reviewed the microbiology section as a consult. An information request for some deficiencies was send to the sponsor on June 25, 1999. A satisfactory response was obtained on August 8, 1999 (see Micro Review #2, dated November 23, 1999).

b. Device Evaluation: **Satisfactory**

The Office of Device Evaluation has reviewed the nonbiodegradable, osmotically driven miniaturized implant device section of the NDA. Mr. Von Nakayama of the device evaluation has reviewed the complete implant system and concluded that ALZA Corporation's DUROS™ Leuprolide did not raise any engineering or performance-related concerns as a drug delivery device. It is also mentioned that the implant does not raise any new issues in terms of intended uses and technological characteristics as well as any new questions of safety and effectiveness in its ability to deliver leuprolide acetate over a one year period at a controlled rate. (see attached review dated October 12, 1999).

C. Establishment Evaluation: **Pending**

Compliance division has been consulted for EER. Overall recommendation is not placed in the EES system because inspection reports of the finished dosage manufacturer is overdue.

D. Trade Name: **Satisfactory**

OPDRA was consulted for the tradename. However, OPDRA send the materials back, saying that since the Labeling and Nomenclature Committee has accepted the name, they have no objection to accept the decision. The copy of the acceptance of the tradename from the Labeling and Nomenclature Committee is shown in the next page:

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1055a	HFD#	580	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	MOO-JHONG RHEE			VIADUR	leuprolide acetate implant

A. Look-alike/Sound-alike

	Potential for confusion:
VIAGRA	___ Low XXX Medium ___ High
VIACAPS	XXX Low ___ Medium ___ High
THEODUR	XX Low ___ Medium ___ High
IMDUR	XXX Low ___ Medium ___ High
	___ Low ___ Medium ___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE WITH CONCERNS ___ UNACCEPTABLE

F. Signature of Chair/Date: /S/

REMARKS/COMMENTS:

Viadur™ (leuprolide acetate implant) is a sterile, non-biodegradable, single use, system that is designed to deliver leuprolide continuously at a nominal rate of 120 µg/day over one year, for the palliative treatment of prostate cancer. The implant is designed to be implanted subcutaneously and after one year the implant is removed and may be replaced with a new one.

NDA 21-088 was reviewed for Chemistry, Manufacturing and Controls concerns and resulted in deficiency questions (see Chemistry review #1). The response of the applicant to these questions is reviewed in this submission.

CONCLUSIONS & RECOMMENDATIONS:

Responses to the deficiencies of the first chemistry review are still inadequate. Some changes in the labeling of the packaging components have been suggested. The EER is still pending.

/S/ 2/14/00

Swapan K. De, Ph.D.
Review Chemist

cc:
Org. NDA 21-088
HFD-580/Division File
HFD-580/SDe
HFD-580/JBest
HFD-580/MRhee
HFD-820/JGibbs/Koepke (NMEs only)
R/D Init by: Moo-Jhong Rhee, Ph. D. /S/ 00

filename: NDA21088.2

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1.3
Letter from the ALZA Corporation

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1055a	HFD#	580	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	MOO-JHONG RHEE			VIADUR	leuprolide acetate implant

A. Look-alike/Sound-alike

	Potential for confusion:		
VIAGRA	___ Low	XXX Medium	___ High
VIACAPS	XXX Low	___ Medium	___ High
THEODUR	XX Low	___ Medium	___ High
IMDUR	XXX Low	___ Medium	___ High
	___ Low	___ Medium	___ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

___ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE

___ UNACCEPTABLE

WITH CONCERNS

F. Signature of Chair/Date /S/ 3/98