13 September 1999

NDA 21-088

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: **Ms Jeanine Best, Project Manager**
Division of Reproductive and Urologic Drug Products

Subject: **NDA 21-088, DUROS™ Leuprolide Implant 65 mg; Requested desk copies for volumes 1.1, 1.99, and 1.100**

Dear Ms Best:

Enclosed please find one copy of volumes 1.1, 1.99 (ISE), and 1.100 (ISS) of NDA 21-088; DUROS™ Leuprolide Implant 65 mg that you requested via voicemail on Friday, 10 September 1999.

Please feel free to contact me if you have any questions regarding this transfer; I can be reached at 650-237-2513 or via facsimile at 650-237-2581. In the event that you are unable to contact me, please contact Ms Susan Rinne, Vice President, Regulatory Affairs at 650-237-2523. We share the same facsimile number.

Sincerely,

Thomas J. Tarlow
Director, Regulatory Affairs
AIDS and Oncology Therapeutics

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

ORIGINAL
ORIG AMENDMENT

09 September 1999

NDA Number 21-088
Volume 7.1

Lisa Rarick, MD, Director
Food and Drug Administration
Division of Reproductive and Urologic
Drug Products (HFD-580)
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857

Via Federal Express

Subject: Amendment to Pending New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant

Dear Dr Rarick:

Reference is made to ALZA Corporation's New Drug Application 21-088 dated April 30, 1999 for DUROS® Leuprolide Implant. Pursuant to 21 CFR 314.60 (a), ALZA is submitting an amendment to pending NDA 21-088.

Provided herewith is updated and revised Chemistry, Manufacturing, and Controls information, and a Field Copy Certification. Change details are provided in the Amendment Overview.

Please feel free to contact me with any questions or comments at (650) 962-4282. In the event you are unable to reach me, please contact Elizabeth Clark, Director, Regulatory Affairs at (650) 564-2519. The regulatory facsimile number is (650) 564-2581.

Sincerely,

Janne Wissel
Senior Vice President
ALZA Corporation

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Enclosures: Archival (1)
Chemistry (1)
Desk (1) for Janine Best, Project Manager

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

ORIGINAL

NEW CORRESP

NC

August 30, 1999

NDA Number 21-088

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: Additional Desk Copy of Volume 1.1 for Clinical Site Inspector

Dear Dr. Rarick:

Reference is made to pending New Drug Application, 21-088, for the DUROS® Leuprolide Implant submitted on April 30, 1999. Please find enclosed an additional desk copy of Volume 1.1 for Dr. Turner in clinical inspections for the clinical site inspections.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me if you have any questions regarding this submission at 650-962-4282 or via facsimile at 650-237-2581. In the event that you are unable to contact me, please contact either Ms. Susan Rinne, Vice President, Regulatory Affairs at 650-237-2523 or Mr. Tom Tarlow, Director, Regulatory Affairs at 650-237-2513. We share the same facsimile number.

Sincerely,

Susan Rinne for

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

9/2/99
CSO INITIALS DATE

(Enclosures)
Copies: Desk (1) for: Dr. Turner
Clinical Inspections

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

August 19, 1999

NDA Number 21-088
Volume 6.1

Via Federal Express

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Subject: Amendment to Pending New Drug Application 21-088 for DUROS® Leuprolide Implant: Patent Information

Dear Dr. Rarick:

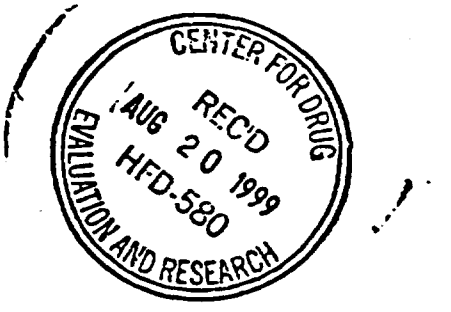
In accordance with 21 CFR 314.60, ALZA Corporation (ALZA) is hereby submitting an amendment to our pending New Drug Application (NDA), 21-088, for DUROS® Leuprolide Implant which was submitted on April 30, 1999. This amendment contains updated patent information.

In accordance with 21 CFR 314.50 (k) (3), ALZA hereby certifies that the field copy is a true copy of the technical section contained in the archival and review copies of the application.

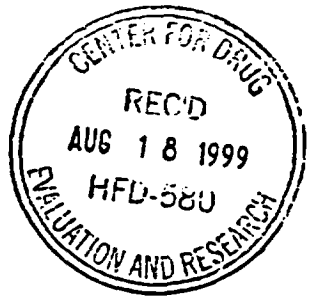
We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me if you have any questions regarding this submission at 650-962-4282 or via facsimile at 650-237-2581. In the event that you are unable to contact me, please contact either Ms. Susan Rinne, Vice President, Regulatory Affairs at 650-237-2523 or Mr. Tom Tarlow, Director, Regulatory Affairs at 650-237-2513. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations



ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com



13 August 1999

NDA Number 21-088
Volume 5.1

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857

Via Fed Exp

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: **Amendment to Pending New Drug Application 21-088 for DUROS® Leuprolide Implant**

Response to June 25th, 1999 Microbiology Information Request for New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant

Dear Dr Rarick:

Reference is made to ALZA Corporation's New Drug Application 21-088 for DUROS® Leuprolide Implant dated on April 30, 1999 and subsequent microbiology questions received in a letter dated June 25, 1999, from Terri Rumble. A detailed response to the microbiology questions is provided in this submission. The FDA questions are in bolded printed and the ALZA response immediately follows the question.

Please feel free to contact me with any questions or comments at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to reach me, please contact Mr. Tom Tarlow, Director, Regulatory Affairs at (650) 564-2513. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

Enclosures: Archival (1)
Review (2) for: chemistry, microbiology
Desk (1) for: Jennifer Mercier, Project Manager

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

ORIGINAL

NEW CORRESP

NC

NDA 8.6.99 Withd

August 2, 1999

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD 580)
Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Lisa Rarick, Director

Subject: General Correspondence: Authorization to Reference ALZA New Drug Application for DUROS® Leuprolide Implant (NDA # 21-088)

NDA Vol. 4.1

Dear Dr. Rarick,

Attached is an NDA cross-reference letter for ALZA's NDA for DUROS® Leuprolide Implant, currently under review in the Division. The letter, which was sent to Dr. McCormick of the Division of Anesthetics, Critical Care and Addiction Drug Products, authorizes FDA to reference specified information contained

If you have any questions regarding this authorization letter, please contact me at (650)237-2520 or via facsimile at (650)237-2581.

Sincerely,

Kimberley Gaumer
Associate Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
CSO INITIALS DATE

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.962.4000 http://www.alza.com

July 19, 1999

NDA Number 21-088
Volume 3.1

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Attention: Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products

Subject: Amendment to Pending New Drug Application 21-088 for DUROS® Leuprolide Implant:

Response to June 24th, 1999 Request for Information and June 25th, 1999 Information Request Letter

Dear Dr. Rarick:

In accordance with 21 CFR 314.60 (a), ALZA Corporation (ALZA) is hereby submitting an amendment to our pending New Drug Application (NDA), 21-088, for DUROS® Leuprolide Implant which was submitted on April 30, 1999.

Please find enclosed the disk of pharmacokinetics data in ASCII format as requested by the biopharmaceutics reviewer and a response to the chemist's question both relayed by phone to ALZA on June 24th, 1999. This submission also contains additional analyses requested by the statistical reviewer in a communication dated June 25th, 1999. A response to the questions posed by the microbiology reviewer in the same communication will follow at a later date. A more detailed description of the documents contained in this amendment is provided in the Amendment Overview section of this submission.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me if you have any questions regarding this submission at 650-962-4282 or via facsimile at 650-237-2581. In the event that you are unable to contact me, please contact either Ms. Susan Rinne, Vice President, Regulatory

Affairs at 650-237-2523 or Mr. Tom Tarlow, Director, Regulatory Affairs at 650-237-2513. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)
Copies: Archival (1) complete including data disk
Review (4) for: chemistry, statistics, field chemistry (no disk)
biopharmaceutics including data disk
Desk (1) for: Jennifer Mercier, Project Manager

ORIGINAL

ORIG AMENDMENT

BL

11 June 1999

NDA Number 21-088
Volume 2.1

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Document and Records Section
12420 Parklawn Dr.
Rockville, MD 20852

Via Fed Exp

Subject: **Amendment to Pending New Drug Application (NDA) 21-088 for DUROS™ Leuprolide Implant**

Dear Dr Rarick:

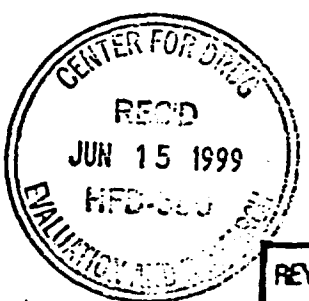
Reference is made to ALZA Corporation's New Drug Application 21-088 for DUROS™ Leuprolide Implant dated April 30, 1999. Pursuant to 21 CFR 314.60 (a), ALZA is submitting an amendment to pending NDA 21-088.

Provided herewith is updated Establishment information, revised Chemistry, Manufacturing, and Controls information, and a Field Copy Certification. Change details are provided in the Amendment Overview.

Please feel free to contact me with any questions or comments at (650) 237-2513. In the event you are unable to reach me, please contact Elizabeth Clark , Director, Technical Regulatory Affairs at (650) 237-2519. The regulatory facsimile number is (650) 237-2581.

Sincerely,

Tom Tarlow
Director, Regulatory Affairs
ALZA Corporation



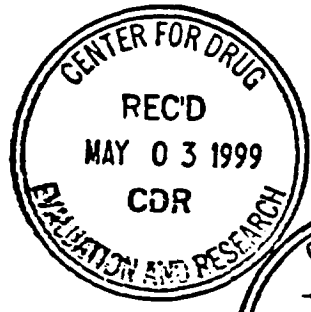
REVIEWS COMPLETED

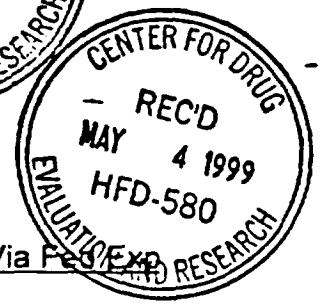
CSO ACTION:
☐ LETTER ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1010 JOAQUIN ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210
PHONE 650.962.4000
http://www.alza.com

ORIGINAL





30 April 1999

NDA Number 21-088
Volumes 1.1 – 1.108

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Food and Drug Administration
Document and Records Section
12420 Parklawn Dr.
Rockville, MD 20852

Via FedEx

Subject: **Submission of Original New Drug Application (NDA) 21-088 for DUROS™ Leuprolide Implant**

Dear Dr Rarick:

In accordance with Section 505 (b) of the Federal Food, Drug and Cosmetic Act, and with the provisions of 21 CFR 314.50, ALZA Corporation (ALZA) hereby submits, in 108 volumes (archival copy), an NDA for DUROS™ Leuprolide Implant, a single treatment, 12-month duration formulation of leuprolide acetate.

The efficacy and safety of the Implant were evaluated in two adequate and well-controlled clinical studies, C-96-011 and C-97-010, in a total of 131 patients. Twelve months data for study C97-010 are submitted in this application by prior agreement with the Division. The active substance, leuprolide acetate, is the subject of approved applications for daily and longer term formulations in the US and in Europe. We request exclusivity under 21 CFR 314.108 since ALZA conducted significant new clinical investigations that are essential to approve this application.

This NDA was developed in consultation with the Division of Metabolic and Endocrine Drug Products and the Division of Reproductive and Urologic Drug Products. Agency minutes from ALZA/FDA face-to-face meetings on 5 October 1995, 7 August 1997, 27 May 1998 and teleconference meetings on 3 December 1997, 23 September 1998, 26 January 1999, and 22 February 1999 are provided

ALZA CORPORATION 950 PAGE MILL ROAD P.O. BOX 10950 PALO ALTO CA 94303-0802 PHONE 650.494.5000 http://www.alza.com

in Volume 1.1 of this application.

ALZA appreciates the Division of Reproductive and Urologic Drug Products guidance in developing this new product. We believe that the information contained in this application clearly supports the efficacy and safety of DUROS™ Leuprolide Implant for use in the palliative treatment of advanced prostate cancer.

We look forward to our continued interactions as the review of this NDA proceeds. Please feel free to contact me with any questions or comments at (650) 962-4282, or via facsimile at (650) 237-2581. In the event you are unable to reach me, please contact Mr. Tom Tarlow, Director, Regulatory Affairs for AIDS and Oncology Therapeutics at (650) 237-2513. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations
ALZA Corporation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
ALZA Corporation	April 30, 1999
TELEPHONE NO. *(Include Area Code)* (650) 962-4282	FACSIMILE (FAX) Number *(Include Area Code)* (650) 237-2581

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-088

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
DUROS™ Leuprolide Implant	Viadur™ (leuprolide acetate implant)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*: see attachment

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
implant	65 mg leuprolide	subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
ative treatment of advanced prostate cancer

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☑ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☑ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☑ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION Original NDA

PROPOSED MARKETING STATUS (check one) ☑ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 108

THIS APPLICATION IS ☑ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see attachment

s References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see attachment

This application contains the following items: *(Check all that apply)*	
✓	1. Index
	2. Labeling (check one) ☑ Draft Labeling ☐ Final Printed Labeling
✓	3. Summary (21 CFR 314.50 (c))
✓	4. Chemistry section
✓	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
✓	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
✓	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
✓	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
✓	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
✓	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
✓	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
✓	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
✓	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
✓	16. Debarment certification (FD&C Act 306 (k)(1))
✓	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
✓	19. OTHER (Specify) Pediatric waiver and financial disclosure

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Janne Wissel, Senior Vice President, Operations	April 30, 1999

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802	(650) 962-4282

FDA Form 356h attachment

CODE NAME (*if any*)

Throughout the application, the dosage form may be referred to by one of the following names:

DUROS™ Leuprolide Implant

DUROS™ (leuprolide) Implant System

DUROS™ Leuprolide Implant System 65 mg

DUROS™ (leuprolide) Implant

Human Implantable Therapeutic System (HITS) Leuprolide

HITS Leuprolide Implant

ALZA internal code names CPC-2 or TDC-13 may be utilized as well. Sometimes the preceding names have a different combination of upper case and lowercase letters and appear without the registered trademark.

The tradename for the product is Viadur™ (leuprolide acetate implant).

FDA Form 356h Attachment

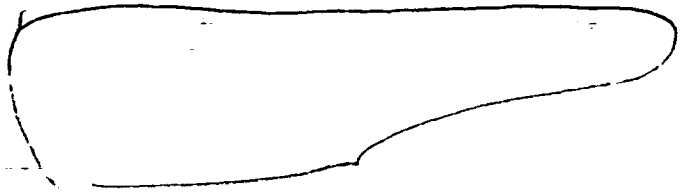
ESTABLISHMENT INFORMATION

The manufacture of DUROS™ Leuprolide Implant is performed at ALZA Corporation at the campuses headquartered at the following facilities:

ALZA Corporation	ALZA Corporation	ALZA Corporation
950 Page Mill Road	1010 Joaquin Road	700 Eubanks Drive
Palo Alto, CA 94304	Mtn. View, CA 94043	Vacaville, CA 95688
Contact: Brian Strehlke	Contact: Brian Strehlke	Contact: Bruce Daubenspeck
650.962.2302	650.962.2303	707.453.6440

ALZA Corporation performs the manufacturing, testing, packaging and labeling of the finished product DUROS™ Leuprolide Implant including the control of components, intermediates, finished product and the testing of stability samples.

The following contract lab may be used for the testing of intermediates, finished product or stability samples.



NDA 21-088

MAR 0 1 2000

ADVICE LETTER

ALZA Corporation
Attention: Janne Wissel
Senior Vice President, Operations
1900 Charleston Road
P. O. Box 7210
Mountain View, CA 94039-7210

Dear Ms. Wissel:

Please refer to your April 30, 1999 new drug application for Viadur™ (leuprolide acetate implant).

We have reviewed the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following recommendations:

For future changes regarding Viadur™ drug formulation, implant components, manufacturing process, and/or manufacturing site, either an *in vitro* bioequivalence study or acceptable *in vitro/in vivo* correlation (IVIVC) should be used to support the approval of the changes. The following IVIVC assessments have been submitted:

- both *in vitro* release and estimated *in vivo* (humans) input rate data for leuprolide acetate for 7 days
- both *in vitro* and *in vivo* (humans) cumulative amount of leuprolide acetate released for 12 months
- both *in vitro* and *in vivo* (rats) cumulative amount of leuprolide acetate released for 3, 6, 9, and 12 months

None of the submitted data address the *in vitro/in vivo* relationship between 7 days and 12 months in humans. Therefore, to support future changes listed above in Viadur™, the Office of Clinical Pharmacology and Biophamaceutics (OCPB), recommends that additional *in vivo* cumulative amount of leuprolide acetate released data for Viadur™ be collected in humans at 1, 2, and 3 months to better substantiate the IVIVC. This would be in lieu of conducting a classical *in vivo* bioequivalence study for one full year of Viadur™ administration. Ideally, the clinically tested batch/lot and the new-marketed batch/lot should be compared both *in vitro* and *in vivo* in this study.

If you have any questions, call Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Susan Allen, M.D., M.P.H.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-088

INFORMATION REQUEST LETTER

ALZA Corporation
Attention: Janne Wissel
Senior Vice President, Operations
1900 Charleston Road
P. O. Box 7210
Mountain View, CA 94039-7210

JAN 28 2000

Dear Ms. Wissel:

Please refer to your April 30, 1999 new drug application for Viadur™ (leuprolide acetate implant).

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. [redacted] as

2. [redacted]

3. [redacted]

4. [redacted]

If you have any questions, call Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 21-088

JUN 25 1999

Alza Corporation
Attention: Janne Wissel
Senior Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your pending April 30, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Viadur® (leuprolide acetate) Implant.

We are reviewing the Statistical and Microbiology sections of your submission and have the following comments and information requests:

Statistical

Please submit subgroup analyses of the efficacy variables for race (both clinical studies) and baseline strata (for study C-96-011, only).

Microbiology

1. [redacted] This is a very high organism concentration in the challenge solution. This concentration may lead to organism clumping as well as "organism caking" on the filter face leading to better retention. This is also in contrast to the recirculation time of 24 hours. It is suggested that a more dilute challenge be delivered to the filters over a period that more closely resembles the "worst case" production time.

2. The dry heat depyrogenation descriptions should include methods used to inoculate endotoxin onto and recover endotoxin from test articles. Assay methods should also be described and include positive and negative control results.

3. The stopper and elastomeric closure washing validation should also include the methods used to inoculate endotoxin onto and recover endotoxin from the test articles. Assay methods should also be described and include positive and negative control results.

4. Regarding the environmental monitoring descriptions provided:

   a. The descriptions of the environmental monitoring protocols are too brief. The media and incubation conditions used for sampling should be specified. The description included with the bioburden limits indicates that these are for "routine environmental monitoring." Further, the table indicates that Class 100 areas are sampled weekly. Weekly sampling for a filling area

seems infrequent. Please clarify whether monitoring is performed during product filling. If so, clarify what and how many samples are taken during the filling process. If not, please provide a rationale for not sampling.

b. Please verify whether a selective media is used for yeast and mold sampling. The media and incubation conditions used for yeast and mold sampling should be specified. The limits for yeast and mold are not directly addressed and should be specified.

5. Regarding the media fill validation descriptions and data provided:

a. The number of units filled during the qualifying fills is relatively small. Therefore, the criteria for considering a media fill passing (or conversely, failing) should be specified.

b. In the case of a failed media fill, the disposition of product filled immediately prior to and between the fill and when results are available should be specified. Additionally, please provide the steps to be taken to requalify the line after a failed fill.

c. The media fill data reported indicate that approximately 15.6% of the units filled on December 22, 1998 were rejected. This number is more than three times greater than the next greatest percentage. An explanation for the high percentage of rejects during this fill should be provided.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 2/4/99

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-088

Alza Corporation
Attention: Janne Wissel
Senior Vice President, Operation
950 Page Mill Road
P.O. Box 10950
Pala Alto, CA 94303-0802

MAY - 6 1999

Dear Ms. Wissel:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: DUROS Leuprolide Implant (leuprolide acetate) Implant

Therapeutic Classification: Standard (S)

Date of Application: April 30, 1999

Date of Receipt: May 3, 1999

Our Reference Number: 21-088

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 2, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 3, 2000 and the secondary user fee goal date will be May 3, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in

accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Teleconference Meeting Minutes

Date: March 1, 2000 **Time:** 3:15-3:30 pm **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: ALZA Corporation

Type of Meeting: Chemistry Phase IV Commitment Request, Information Request

Meeting Chair: Dr. Susan Allen

External Lead: Michelle Landolfi

Meeting Recorder: Jeanine Best

FDA Participants:
Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Dan Shames, M.D., Team Leader, DRUDP(HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Terri Rumble, B.S.N, Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

ALZA Corporation Participants:
Michelle Landolfi, Manager, Regulatory Affairs
Darlene O'Banion, Senior Associate, Regulatory Affairs
Janne Wissel, Senior Vice President, Operations
Tom Dunn, Senior Engineer, Implant Research and Development
Darl Moreland, Manager Quality Assurance
Mary Prevo, Vice President, R&D Quality
Gail Stewart, Senior Manager, Quality Assurance
Robin Miller, Manager, Supplier Assessment

Meeting Objective: To request a Phase IV Commitment for production quality; to seek information on use of recalled DMSO material from [redacted]. Use of recalled DMSO in launch batches may affect the approvability of this NDA.

Background:
- Defects noted in some of the implants used in the clinical trials, (information provided in February 10, 2000 submission)

- [redacted]

Discussion:

- [redacted]
- Division Requests the following Phase IV Commitment to ensure product quality:

  In order to ensure that all the production batches of implant have uniform quality without any defect, the following Phase IV commitment should be fulfilled.

  1. Investigate the cause of the defects found in the clinical batches during the clinical trials, and submit the results together with corrective actions and validation data.

  2. Investigate the current sampling procedures for the release to see if the current sampling plan ensures statistically significant representation of each production batch, and, if not, propose a new sampling plan with a rationale.

  3. The above information should be submitted as a CBE supplement before the validation batches are launched.

Decisions Made:

- Sponsor to submit documentation stating they have not used the recalled DMSO Lots in their product launch batches
- Sponsor agrees to Phase IV commitments to ensure quality of the implant production batches

Action Items:

- J. Best to fax sponsor the Phase IV Commitment Request this afternoon
- Sponsor to fax by COB today (followed by Federal Express hard copy):

  [redacted]

  2. Phase IV Commitments ensuring that all production batches of the implant have uniform quality without defect

/S/
Minutes Preparer

/S/
Concurrence, Chair
3/3/00

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Allen/Mann/Shaems/Rheem/De/Rumble
drafted: JAB/March 1, 2000/N21088ChemTcon030100.doc
final:JAB/March 3, 2000
concurrence:Mann,03.02.00/Shames,03.02.00/Allen,03.02.00/Rumble,03.02.00/De,03.02.00/Rhee,03.02.00
MEETING MINUTES

Teleconference Memo

Date: February 25, 2000 **Time:** 12:30-12:40 pm **Location:** Parklawn; 17B-45

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: ALZA Corporation

Type of Meeting: Clarification of Phase 4 Commitment

FDA Attendees:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameeta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

ALZA Corporation Attendees:
Michelle Landolfi, Regulatory Affairs
Steve Sherman, Director, Regulatory Affairs
Darlene O'Banion, Senior Associate, Regulatory Affairs
Janne Wissel, Senior Vice President, Operations
Gayatri Sathyan, Research Scientist, Clinical Pharmacology
Tom Dunn, Senior Engineer, Implant Research and Development

Meeting Objective: To clarify details of Phase 4 Commitment presented to the sponsor on 2/24/00.

Discussion:
Division:
Request for Phase 4 Commitment submitted to sponsor on 2/24/00:

The proposed Viadur™ *in vitro* cumulative leuprolide acetate release rate method and specifications are acceptable on an interim basis.

Since the proposed *in vitro* release rate method and specifications only account for the release of about 10 mg of leuprolide acetate in Viadur™ implant (total + 65 mg) up to 42 days, an accelerated *in vitro* release rate procedure is recommended as a Phase 4 commitment to investigate and account for of the leuprolide acetate content in Viadur™ implant.

ALZA Corporation:
Phase 4 Proposal from 2/24/00:

"ALZA Corporation commits to developing an accelerated in vitro release rate method that accounts for release of greater than 10 mg of leuprolide in a time period similar to that in the current specification. ALZA will collect data from 25 commercial lots in order to show consistency in the method. The data and results will then be submitted for Agency review."

- Sponsor needs to develop an accelerated *in vitro* release rate method that accounts for release of greater than 10 mg of leuprolide in a time period similar to that in the current specification, cannot commit to this time because work to date shows that may not be achievable

Decisions Made:

- Division and sponsor came to agreement on the Phase 4 commitment proposal with the addition of the word "significantly"

  "ALZA Corporation commits to developing an accelerated in vitro release rate method that accounts for release of **significantly** greater than 10 mg of leuprolide in a time period similar to that in the current specification. ALZA will collect data from 25 commercial lots in order to show consistency in the method. The data and results will then be submitted for Agency review."

Action Items:

- Sponsor to fax Phase 4 commitment proposal (followed by Federal Express hard copy) with text identical to agreed upon wording under above **Decisions Made** by COB today

Memo Preparer

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Rhee/Parekh
final:JAB/February 25, 2000/N21088BIOPHARMtcon022500.doc
Meeting Minutes Memo

Meeting Minutes

Date: February 23, 2000 **Time:** 1:15-2:00 pm **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate implant)

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status/Labeling

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Jeanine Best

FDA Attendees:
Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Daniel Shames, M.D., Team Leader, DRUDP (HFD-580)
Jeanine Best, M.S.N, R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To finalize labeling comments for sponsor

Background: Viadur™ is leuprolide acetate in a 12-month titanium implant device that delivers a steady daily dose of the drug product. Dose finding studies revealed that one implant was as effective as two in attaining and maintaining serum testosterone to castration concentrations, and there was no testosterone flair at 12-month reinsertion.

Discussion:
The sponsor has submitted label revisions based on Division edits.

Pharmacology/Toxicology:
- Reviews complete
- No further labeling comments; P/T section acceptable

Clinical/Biometrics:
- Reviews complete
- Revise the following statement regarding PSA concentrations in the **CLINICAL STUDIES** section from:

  "From weeks 12 through 52, the mean reduction from baseline remained between 86.4% and 90.4%."

  to:

  "At six months, PSA concentrations decreased from baseline by at least 90% in 74.2% of the 97 evaluable patients."

the sponsor's statement is less informative for clinicians and needs to include other statistical parameters to be fully understood; the Division statement gives accurate information with regard to Viadur™ study patients; the Division would prefer no reference to PSA levels in this label, but will negotiate wording since reference to PSA levels appears in other leuprolide acetate labels

- Add the following statement to the **INSERTION AND REMOVAL PROCEDURES** insert after the statement "The new Viadur™ implant may be placed through the same incision site.":
  "If difficulty is encountered placing subsequent implants in the previous insertion site, consider insertion of the new implant in the contralateral arm"

Chemistry:
- Review is being completed; awaiting recent facility inspection reports
- No further labeling comments; Chemistry section acceptable

Biopharmaceutics:
- Review is being completed
- Phase 4 commitment will be requested from sponsor with regard to dissolution testing
- Add the following statement to the **PHARMACOKINETICS** section, **Metabolism** subhead:
  "A pentapeptide (M-I) is the major leuprolide metabolite upon administration with different leuprolide-acetate formulations."

[redacted]

Action Items:
- J. Best to relay labeling comments to the sponsor today; will schedule T-con with sponsor if necessary for labeling negotiations
- J. Best to relay Biopharm Phase 4 commitment to sponsor by tomorrow; will schedule T-con between Biopharm group and sponsor if necessary for negotiations
- NDA Action to be taken by COB March 3, 2000.

/S/
Minutes Preparer

/S/
Concurrence, Chair
2/25/00

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Allen/Shames
drafted: JAB/February 24, 2000/N210888LABmtg022300.doc
final:JAB/February 24, 2000
concurrence: Allen,02.24.00/Shames,02.24.00

MEETING MINUTES

Teleconference Meeting Minutes

Date: February 18, 2000 **Time:** 1:35-1:55 pm **Location:** Parklawn; 17B-45

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Moo-Jhong Rhee

External Lead: Michelle Landolfi

Meeting Recorder: Jeanine Best

FDA Attendees:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Alza Corporation Attendees:
Micheile Landolfi, Regulatory Affairs
Steve Sherman, Regulatory Affairs
Elizabeth Clark, Regulatory Affairs
Teresa Loftus, New Product Planning

Meeting Objective: To recommend labeling information for the Viadur™ vial, implanter, and brand box; to confirm whether the three California Alza Manufacturing sites were inspected

Discussion:
- For Viadur vial add the statement "dissolved in 104 mg dimethyl sulfoxide" to the label
- Division feels that the NDC number should be put on each component; the vial, implanter and the kit, not just the brand box, and that each component should have a unique NDC number
- Sponsor reports that the FDA regulations do not support the use of separate NDC numbers when the kit is not going to be sold as separate components
- For the Brand Box, expand the contents descriptions for the implanter and the kit; can borrow descriptions from the package insert
- Sponsor reports that all three of their California manufacturing sites were inspected January 25, 2000 to January 31, 2000; all three sites were issued a 482 from the San Fransisco District Office

Decisions Made:
Sponsor agrees to place NDC number on each component; but further internal discussion will be done to decide if a separate number is to be assigned to each component

Action Items:
- Sponsor to fax inspection reports recommending approval of the drug product
- Sponsor to submit proposal for placing NDC number on each component of the brand box
- Sponsor to expand the contents section of the packaging for the implanter and the kit

/S/

Minutes Preparer

/S/

Concurrence, Chair

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Rhee/De
drafted: JAB/February 18, 2000/N210888Chemtcon021800.doc
final:JAB/February 22, 2000
concurrence:Rhee,02.18.00
MEETING MINUTES

Teleconference Meeting Minutes

FEB 10 2000

Date: February 8, 2000 **Time:** 3:00-3:10 **Location:** Parklawn; 17B-45

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Guidance

Meeting Chair: Dr. Moo-Jhong Rhee

External Lead: Dr. Cynthia Stevenson

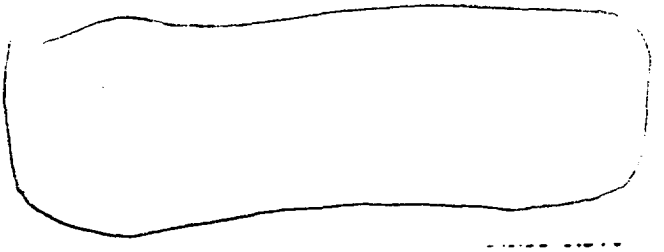
Meeting Recorder: Jeanine Best

FDA Attendees:
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Alza Corporation Attendees:
Cynthia Stevenson, Ph. D. Chemist
Doris Boesch, Stability Manager
Darlene O'Banion, Senior Regulatory Associate
Elizabeth Clark, Regulatory Affairs, Director
Michelle Landolfi, Regulatory Affairs

Meeting Objective: To discuss Question #1 from the Chemistry Information Request Letter sent on January 28, 2000:

1. Please tighten the specifications of the individual and total impurities/degradation products as recommended below:



Discussion:

- [redacted]
-
-
-
-

Decisions made:

- There will be no problem with the review clock if sponsor responds to the IR issues in a timely manner

Action Items:

- Division Chemists to review batch data of the above two impurity/degradation products and determine if sponsor proposal is acceptable
- J. Best to inform Sponsor of Chemist decision by end of business week

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Rhee/De
drafted: JAB/February 8, 2000/N210888Chemtcon020800.doc
final:JAB/February 9, 2000
concurrence: De,02.09.00/Rhee,02.09.00
MEETING MINUTES

FEB 10 2000

Meeting Minutes

Date: February 2, 2000 **Time:** 11:00 am-11:45 am **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status/Labeling

Meeting Chair: Dr. Dan Shames

Meeting Recorder: Jeanine Best

FDA Attendees:
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D, Pharmakokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP, (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss label revisions sent by the sponsor.

Background: Viadur™ is leuprolide acetate in a 12-month titanium implant device that delivers a steady daily dose of the drug product. Dose finding studies revealed that one implant was as effective as two in attaining and maintaining serum testosterone to castration concentrations, and there was no testosterone flair at 12-month reinsertion.

Discussion:
The sponsor has submitted label revisions based on initial Division edits.

Clinical/Biometrics:

- Sponsor prefers to keep a statement in the label regarding their use of PSA monitoring as a secondary endpoint; the Division prefers that there be no reference to PSA as a secondary endpoint, but will consider allowing statement to remain per sponsor preference

Chemistry:

- The sponsor has deleted the composition amounts of the osmotic tablets found in the Duros® device; Division agrees that this release information should be provided in case there is damage to the device while in use.

Biopharmaceutics:

- Add release rate of drug product
- Again, delete figure B, this information is redundant
- Delete statements regarding the major metabolite (M-1) because this data is from the Lupron® 4-month label, not sponsor's product; add statement that no information on metabolism is available for this product
- J. Lau reports that only IV/IVC review is left to complete

Decisions made:
None

Action Items:
- All reviewers to continue with label edits on the unmarked copy ("Final") of the label located on the "N" Drive
- J. Best to follow-up with reviewers in one week on the status of label edits, so that a revised copy can be sent to the sponsor

/S/
Minutes Preparer

/S/
Concurrence, Chair

**APPEARS THIS WAY
ON ORIGINAL**

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Shames/Marks/Parekh/De/Lau/Rumble
drafted: JAB/February 2, 2000/N210888Statlabelmtg020200.doc
final:JAB/February 10,2000
concurrence: Lau,02.02.00/Shames,02.02.00/Rumble,02.02.00/Mann,02.03.00
MEETING MINUTES

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Date: January 18, 2000 **Time:** 9:30 am-10:30 am **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status/Labeling

Meeting Chair: Dr. Dan Shames

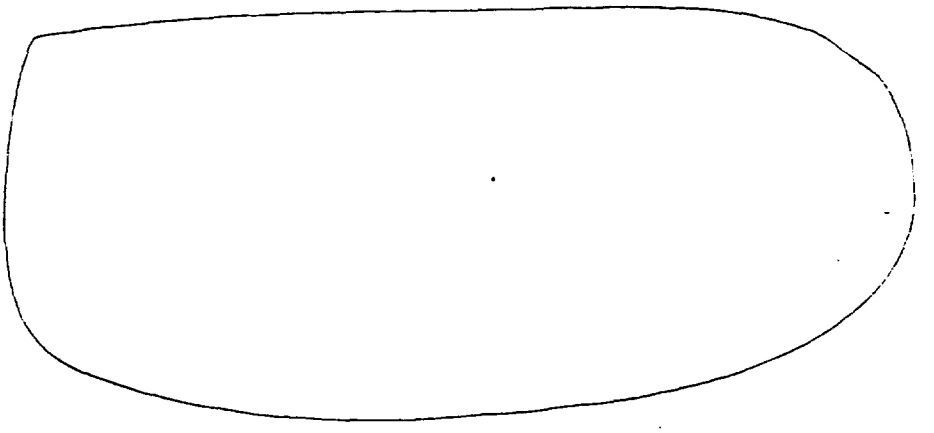
Meeting Recorder: Jeanine Best

FDA Attendees:
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D, Pharmakokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP, (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Denise Toyer, Pharm.D., Safety Evaluator, Office of Post Drug Marketing Drug Risk Assessment (OPDRA, HFD 440)
Celia Delawter, Policy Analyst, Executive Office of the Secretary (EOS, HFD-006)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To continue labeling discussions in order to provide the sponsor with initial comments.

Background: Viadur™ is leuprolide acetate in a 12-month titanium implant device that delivers a steady daily dose of the drug product. Dose finding studies revealed that one implant was as effective as two in attaining and maintaining serum testosterone to castration concentrations, and there was no testosterone flair at 12-month reinsertion.

Discussion:
All reviewers with the exception of J. Lau, have had the opportunity to review all label edits on the "N" Drive. Certain draft label revisions were discussed among disciplines.



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- the
-

Decisions made:

- The edits to this label are initial comments only and may be changed as reviews progress

Action Items:

- All reviewers (except J.Lau), and team leaders to give J. Best label comments and concurrence by 1/19/00 at 12 noon
- J. Best to forward copy of initial Division label revisions to sponsor COB 1/19/00

/S/

Minutes Preparer

/S/

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Shames/Marks/Parekh/ /Raheja/Meaker/Lau/Rumble
HFD-440/Toyer
HFD-006/Delawter
drafted: JAB/January 18 2000/N210888Statlabmtg011900.doc
final:JAB/January 27, 2000
concurrence: Shames,01.19.00/Meaker,01.19.00/Lau01.19.00/Raheja,01.19.00
MEETING MINUTES

Meeting Minutes

Date: January 5, 2000 **Time:** 11:00 am-12:00 pm **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status/Labeling

Meeting Chair: Dr. Dan Shames

Meeting Recorder: Jeanine Best

FDA Attendees:
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinica' Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss technical aspects of electronic labeling editing and revisions

Background: Viadur™ is leuprolide acetate in a 12 month titanium implant device that delivers a stable daily dose of the drug product. Dose finding studies revealed that one implant was as effective as two in attaining and maintaining serum testosterone castration levels, and there was no testosterone flair at 12-month reinsertion.

Discussion:
- Alza Corporation has furnished electronic labeling for edits and revisions which is located on the "N" drive
- Each reviewer can edit and revise the same copy of the label that should:
    1. Allow other reviewers to see edits prior to meetings
    2. Encourage dialogue between reviewers prior to meetings
    3. Enable labeling revision to be performed in a more time efficient manner
    4. Have one clean electronic copy to forward to the sponsor

Decisions made:

- Editing and revision of the label will be done electronically on the same copy of the label:
- Deletions to be done with a double strike through
- Additions to be italicized
- All deletions and additions to be bolded
- Add reviewer initials to changes so others can see who performed the editing
- J.Best will copy label changes onto diskette daily to use a s backup in case label edits are accidentally deleted

Action Items:

- All reviewers to complete initial label revisions by COB 1/7/00
- All team leaders and reviewers to concur on label by placing initials at end of label, complete by COB 1/13/00
- J.Best to forward copy of Division Label revisions to sponsor By 1/14/00

/S/ mSW.Rn
Minutes Preparer

/S/
Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Shames/Marks/Parekh/Des/Raheja/Meaker/Rumble
drafted: JAB/January 6, 2000/N210888Statlabmtg010500.doc
concurrence: Shames,01.07.00
final:JAB/January 14, 2000
MEETING MINUTES

Meeting Minutes

Date: December 17, 1999 **Time:** 11:00 am-12:00 pm **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status/Labeling

Meeting Chair: Dr. Dan Shames

Meeting Recorder: Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Shames, M.D., Team Leader, DRUDP (HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Swapan De, Ph.D., Chemist, Division Of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D, Pharmakokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Kate Meaker, M.S., Statistician, Division Of Biometrics II (DBII) @ DRUDP (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To begin labeling discussions for this NDA; Division Goal date of February 18, 2000.

Background: Viadur™ is leuprolide acetate in a 12 month titanium implant device that delivers a stable daily dose of the drug product. Dose finding studies revealed that one implant was as effective as two in attaining and maintaining serum testosterone castration levels, and there was no testosterone flair at 12-month reinsertion.

Discussion:
Chemistry:
- Preliminary electronic label revisions are completed for chemistry section and were shared with other disciplines
- The Chemistry sections need to be expanded and more descriptive in nature with regard to the drug product

Pharmacology:
- Preliminary electronic label revisions are completed for Pharmacology sections; and were shared with other Disciplines

- Carcinogenic Study Data doses should be expressed in terms of body surface area

Biopharm:

-
-
-
-
-

Clinical/Stats:

-
-
-
-
-

Decisions made:

- Editing and revision of the label will be done electronically

Unresolved decisions:

-
-

Action Items:

- J.Best to request controlled release rate data from the sponsor
- Reviewers to provide electronic label revisions to J. Best by January 3, 2000
- J. Best will convey labeling comments to sponsor during or after the week of January 2, 2000

/S/ JRW

Minutes Preparer

/S/

Concurrence, Chair

cc:
Original NDA 21-088
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Mann/Shames/Marks/Benson/De/Raheja/Lau/Meaker/Rumblet

drafted: JAB/December 20, 1999
concurrence:
Rumble,12.20.99/Shames,12.20.99/Meaker,12.20.99/Mann,12.20.99/Benson,12.21.99/Lau,12.21.99
final: JAB/December 29,1999

MEETING MINUTES

Internal Meeting Minutes

Date: October 15, 1999 **Time:** 11:30-11:50 am **Location:** Parklawn, 17-B43

NDA 21-088 **Drug:** Viadur™ (leuprolide acetate) implant

Indication: Palliative treatment of advanced prostate cancer

Sponsor: Alza Corporation

Type of Meeting: Status Meeting

Meeting Chair: Dan Shames, M.D.

Meeting Recorder: Jeanine Best

FDA Attendees:
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP, (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Johnny Lau, R.Ph., Ph.D, Pharmakokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP, (HFD-580)
Jeanine Best, MSN, RN, Regulatory Project Manager, DRUDP, (HFD-580)

Meeting Objective:
To discuss the feasibility of draft review completion by December 15, 1999 to accelerate the action goal date to December 31, 1999, due to increased Division workload in 1st quarter 2000.

Discussion:
Review staff was polled for feasibility and comments:

- **Clinical:** Review will be completed in mid-December; appears approvable, with questions regarding the timing of blood chemistry and hematology testing to be clarified.
- **Chemistry:** Review may not be complete in December; depends upon the timing of Dr. De's return to work; concerns regarding stability of peptide in the body for one year; the effect of possible degradation product(s) is unclear and whether; does the device causes irritation or interferes with absorption in the body
- **Biopharm:** Unsure at this time if December date is feasible for review completion; will be able to determine review completion in a few weeks
- **P/T:** Feasible for review completion in December
- **Stats:** Not present
- **Microbiology:** Not present
- **CDRH Device consults:** Requested consult completion by December 18, 1999

Decisions made:
None at this time.

Unresolved decisions:
Action completion date.

Action Items:
Jeanine to reschedule 1st labeling/status meeting for mid-November.

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
Original IND
HFD-580/DivFile
HFD-580/Shames/Marks/Rheem/Lau

drafted: JAB/October 15.1999
concurrence: Shames, 10.18.1999/Marks, 10.19.1999/Rumble/10.20.1999
final: JAB/10.22.1999/N21088stmtg10.99.doc

MEETING MINUTES

Meeting Minutes

Date: June 16, 1999 **Time:** 10:30-11:00 AM **Location:** Parklawn; 17B-43

NDA 21-088 **Drug:** Viadur™(leuprolide acetate) **Indication:** palliative treatment of advanced prostate cancer

Sponsor: ALZA Corporation

Type of Meeting: Filing Meeting

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:
Lisa Rarick, M.D. – Director, Division of Reproductive and Urologic Drug Products; (DRUDP; HFD-580)
Daniel Shames, M.D. – Team Leader, DRUDP (HFD-580)
Norman Marks, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. – Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Swapan De, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
Kate Meaker, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Meeting Objective: To ascertain the fileability of this application.

Decisions made:
Clinical
- this application is fileable

Chemistry
- this application is fileable

Statistics
- this application is fileable

Biopharmaceutics
- this application is fileable

Unresolved decisions: None

Action Items:

- check status of the electronic submission
- Pharmacokinetics data in electronic diskette (ASCII format) should be provided
- No bioanalytical report was submitted for serum PSA measurement, the sponsor should provide bioanalytical report for serum PSA determination

/S/

Minutes Preparer

/S/

Concurrence, Chair

APPEARS THIS WAY
ON ORIGINAL

cc:
Original IND
HFD-580/DivFile
HFD-580/Rumble/Mercier
HFD-580/Rarick/Mann/Shames/Marks6.21.99/Raheja/Jordan/Rhee6.21.99/De6.22.99/Parekh6.21.99/
Lau6.21.99/Kammerman/Meaker6.21.99

drafted: June 16, 1999/Mercier
concurrence: Marks6.21.99/Raheja/Jordan/Rhee6.21.99/De6.22.99/Parekh6.21.99/
Lau6.21.99/Meaker6.21.99
final: June 25, 1999

MEETING MINUTES

NDA 21 088 DUROS leuprolide acetate implant - VIADUR
[65 mg of GnRH analog dissolved in dimethylsulfoxide; titanium alloy reservoir]

15 June, 1999

45 day filing meeting – filing date July 2, 1999

Clinical

- The clinical section is organized, indexed, paginated, and legible so that substantive review can begin

- Pre-IND mtg in oct. 95 and pre-phase II mtg in sept 97; division supported the drug development plan submitted as adequate for safety/efficacy review if no 'surprises'

  Dose ranging done in **study C96-011 [phase II/III]**

  9 centers, 51 evaluable patients; pts stage D1/D2 or failures of RRP or XRT; two doses [1 implant=27; 2 implants=24; 20-25% black; last pt completed wk 52 end of june 1998 [so 2nd yr safety extension data completed end of june 1999]; wk 52-60 data from 2nd implant submitted with NDA; wk 61-104 data to be reported separately?]

  Efficacy – 51 pts; one died of unrelated cause; one extruded implant at day 65; 49 pts were suppressed by wk 6 and remained suppressed for 12 mo treatment period [100%]; ITT success rate = 98%; expulsion rate = 2%; one implant supressed as well as two; dose proportional on PK; no acute on chronic flare on re-implant;

  Safety – 51 pts analyzed; 15 pts with serious AEs, none judged related to treatment; one death; 75% reported vasodilation, 66% reported some implant related reaction; 3 pts required oral antibiotics and local care for implant inflammation

- Two well controlled pivotal studies

  C97-010 study of efficacy/safety of one implant for 12 mo treatment period with 12 mo safety extension; 19 centers; 80 pts enrolled; open label; last pt completed 52 wk end of dec 1998; safety extension will be submitted at the four month safety update; 22% black pts; 21% were stage D, 76% stage B/C;

Efficacy – 91% completed study; 4/7 died of unrelated causes, 1/7 withdrew for progression, 1/7 discontinued for AEs unrelated to med, one implant was extruded on day 121; T suppression success rate = 98.6% [72/73 pts]; ITT success rate = 97.5%; 1.4% expulsion rate;

Safety – 70/73 continued on 2nd year of safety extension; 80 pts in safety analysis; fifteen serious AEs; one death; no serious AEs judged to be treatment related;

- Pivotal efficacy studies are designed to address claims made in proposed labeling
- Data sets are complete and available
- Line listings are in a reasonable format for review
- Case records for safety review have been submitted
- Safety data is in a reviewable format
- Draft labeling is submitted in reviewable format

Using much of the Lupron-4 mo labeling wording; *"indicated in the palliative treatment of advance prostate cancer";*

Study sites for inspection visits
- J. Fowler, M.D., (
- J. Gottesman, M.D.
- R. Feldman, M.D.,

From a clinical perspective, this NDA is fileable

DF

JUN 18 1998

MEETING MINUTES

Date: May 27, 1998 Time: 2:00 - 3:30 PM Location: C/R "B"

IND: 52,635 Drug Name: DUROS (leuprolide Implant) 65 mg

External Participant: ALZA External Participant Lead: Mr. Tom Tarlow

Type of Meeting: Pre-NDA

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Alvis Dunson

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Florence Houn, M.D., M.P.H. - Deputy Director, Office of Drug Evaluation II (ODE-II; HFD-102)
Daniel Shames, M.D. - Medical Officer, DRUDP (HFD-580)
Mark Hirsch, M.D. - Medical Officer, DRUDP (HFD-580)
Kate Meaker, M.S. - Mathematical Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Paul Stinavage, Ph.D. - Microbiologist, Office of New Drug Chemistry
Sam H. Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M. - Pharmacologist, DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

Samuel Saks, M.D. - Clinical Director
Roman Skowronski, M.D., Ph.D. - Associate Director, Clinical
David Kardatzke, Ph.D. - Research Scientist, Biostatistics
Gayatri Sathyan, Ph.D. - Manager, Clinical Pharmacology
Matthew Cukierski, Ph.D. - Associate Director, Toxicology
Kevin Brodbeck - Product Development Manager
Cynthia Stevenson, Ph.D. - Formulation Chemist
Ivan Chin - Director, Microbiology
Janne Wissel - Senior Vice President, Operations, Regulatory Affairs, and Quality Sciences
Tom Tarlow, Associate Director, Regulatory Affairs

Meeting Objectives:

To discuss the contents of a proposed NDA submission and to obtain Agency concurrence regarding specific proposals and questions from ALZA.

TELECONFERENCE MINUTES

Date: December 3, 1997 **Time:** 8:30 - 9:30 AM **Location:** Parklawn; Room 17B-43

IND: 52,635 **Drug Name:** DUROS (leuprolide Implant) 65 mg

External Participant: ALZA **External Participant Lead:** Mr. Tom Tarlow

Type of Meeting: End of Phase 2

Meeting Chair: Heidi Jolson, M.D., M.P.H.

Meeting Recorder: Alvis Dunson

FDA Attendees:

Heidi Jolson, M.D., M.P.H. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Shames, M.D. - Medical Officer, DRUDP (HFD-580)
Mark Hirsch, M.D. - Medical Officer, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Statistical Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Laurie Burke, R.Ph., M.P.H. - Senior Regulatory Research Officer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-40)
Mark Askine, R.Ph - Regulatory Review Officer, DDMAC (HFD-40)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

Roman Skowronski, M.D., Ph.D. - Associate Director, Clinical Research
YK Chiang, Ph.D. - Statistics
P. Peebles, Ph.D. - Pharmacology
K. Seither - Marketing
Tom Tarlow, Associate Director, Regulatory Affairs
J Wright, Ph.D. - Technical Consultant
J. Mackowiak, Ph.D. - Center for Outcomes Res.

Meeting Objectives:

To discuss the sponsor's Quality of Life (QOL) analysis plan and Phase 3 Protocol C-97-010.

Discussion Points:

- the analysis of Quality of Life (QOL) data does not meet the standard of evidence requirement when making a QOL claim

- hypothesis testing is required for QOL parameters
- a comparator arm is required when making claims to support QOL
- all labeling claims to support an indication should be made upfront

Unresolved Issues: None

Decisions Reached:

- the sponsor indicated no QOL claim was anticipated

/S/
Signature, minutes preparer

/S/
Concurrence, Chair

drafted: ADunson/2.4.98/i52635.3im

cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/2.4.98

Concurrences:
DShames, LPauls2.4.98/MHirsch, MAskine2.5.98/LKammerman2.11.98

DFF

MEETING MINUTES

Date: August 7, 1997 **Time:** 3:30-5:00 PM **Location:** Parklawn; Room 13B-45

IND: 52,635 **Drug Name:** DUROS™ (leuprolide implant), 65 mg

External Participant: ALZA

Type of Meeting: End-of-phase 2

Meeting Chair: Heidi Jolson, M.D., M.P.H. **External participant Lead:** Tom Tarlow

Meeting Recorder: Alvis Dunson

FDA Attendees:

Heidi Jolson, M.D., M.P.H.- Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Jean Fourcroy, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)
Mark Hirsh, M.D. - Medical Officer, DRUDP (HFD-580)
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC) @ DRUDP (HFD-580)
Kasturi Srinivasachar, Ph.D. - Chemist, DNDCII @ DRUDP (HFD-580)
Gary Barnette, Ph.D. - Pharmacokineticist, Division of Pharmaceutical Evaluation II (DPEII; HFD-870) @ DRUDP(HFD-580)
Laurie Burke, R.Ph., M.P.H. - Senior Regulatory Research Officer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-40)
Mark Askine, R.Ph - Regulatory Review Officer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-40)
John Markow, J.D. - Consumer Safety Officer, DRUDP (HFD-580)
Alvis Dunson, B.S. - Consumer Safety Officer, DRUDP (HFD-580)

External Constituents:

Roman Skowronski, M.D., Ph.D. - Associate Director, Clinical Research
Jerry Wright, Ph.D. - Senior Reasearch Fellow, DUROS Implant Unit
Matthew Cukierski, Ph.D. - Research Scientist, Nonclinical Science
Janne Wissel, Vice President, Regulatory and Quality Affairs
Tom Tarlow, Associate Director, Regulatory Affairs

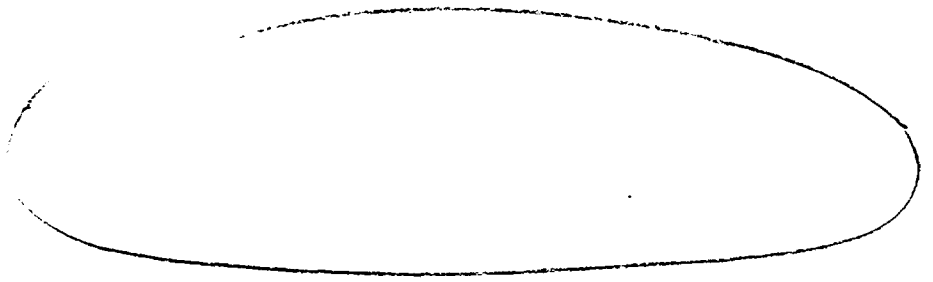
Meeting Objectives:

The sponsor would like concurrence regarding dose selection and study endpoints for the pivotal Phase 3 protocol and concurrence on the nonclinical safety studies.

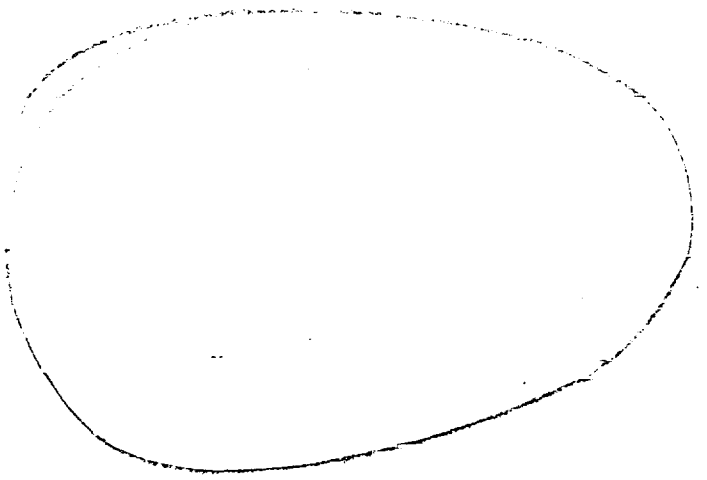
Discussion Points:

The sponsor proposed the following questions and requests for comments:

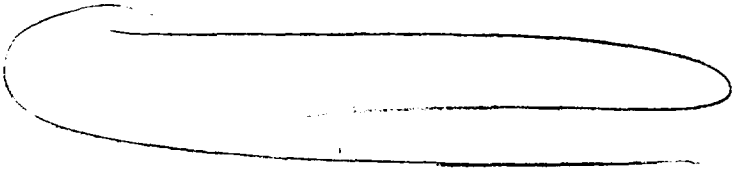
Dose Selection



Phase3/Pivotal Protocol



Implantation/explantation/reimplantation

A3. 

Clinical Database

Q4. The clinical database for efficacy and safety experience with the DUROS™ Leuprolide Implant 65 mg system that will be utilized for US registration will be comprised of all treated patients in the following protocols:

Study C-96-011; 51 patients treated (40 evaluable)

51 patients treated with either one or two implant systems for 12 months followed by explantation and reimplantation with one implant system for 2 months treatment. The clinical database at NDA submission will capture the initial 12 months treatment and two months additional treatment following reimplantation.

Protocol C-97-010; 75 patients enrolled (60 evaluable)

75 patients treated with one implant system for 12 months followed by explantation and reimplantation with one implant system for an additional 12 months. The clinical database for the NDA submission will capture the first 12 months treatment with one implant system. The safety update that is submitted during the original NDA review period will provide additional safety data with respect to reimplantation of single implant systems (see above).

Does the Division concur that the clinical program described above will support an NDA for twelve months palliative hormonal therapy in advanced prostate concer patients?

A4. The clinical program appears sufficient to support filing of an NDA. However, if unexpected safety or efficacy issues develop, additional clinical data may be required.

Nonclinical Registration Study

Q5. ALZA proposes BIO-95-B046-4094 (see IND 52,635, Section 8 and Attachment 5) as the chronic treatment registration safety study for the DUROS™ Leuprolide Implant product. BIO-95-B046-4904 is a 12 month canine study of implant system functionality and safety that included a two month reimplantation safety extension. BIO-95-B046-4904 monitored testosterone suppression as well as local tissue reaction visually and histopathologically at necropsy. Does the Division concur that BIO-95-B046-4904 fulfills the nonclinical registration requirement for the DUROS™ Leuprolide Implant 65 mg system?

A5. BIO-95-B046-4904 meets the nonclinical registration requirement for the DUROS™ Leuprolide Implant 65 mg system.

Device

Q6. What will be the format and content of Agency review for device-related issues for the DUROS™ Leuprolide Implant 65 mg product?

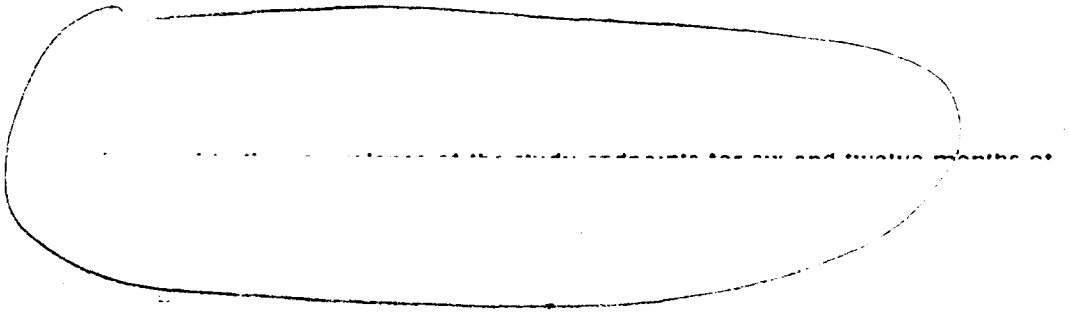
A6. Any device-related information should be submitted as a separate section in the NDA in DRUDP. A review copy will be forwarded the Center for Devices and Radiological Health (CDRH) for review and evaluation as a consultation to CDER. The sponsor was encouraged to have a teleconference with the CDRH reviewer to discuss their requirements for the submission.

Q7. Will the trocar that is used to assist system placement during implantation require device registration?

A7. NO; individual device registration is not required because the trocar is considered part of the delivery system and can only be used with the DUROS™ Leuprolide Implant 65 mg system.

Other

Q8



A8.

Decisions reached:

Biopharmaceutics

- sponsor should propose the blood sampling scheme to assess the acute stimulation of testosterone upon reimplantation of this product; data currently available for Study C-97-010 should be used to justify these sampling times

Other

- Quality of Life - sponsor should submit as part of the study protocol;
  - instrument description with documentation of development and validation procedures
  - complete set of analytical plans that includes plans for handling all multiplicity issues
  - proposed labeling or marketing claims
- sponsor would like a teleconference with CDRH to discuss device related issues

Unresolved Issues: None

Action Items:

Item:	Responsible Person:	Due Date:
submission of protocol C-97-010 to include proposed labeling and marketing claims	ALZA	?
submission of reimplantation data and a timeline on the availability of new explantation data	ALZA	?
submission of four month patient data	ALZA	?
set up a teleconference between ALZA and CDRH	Alvis Dunson	?
submission of alternative proposals for an accelerated development plan	ALZA	?

/S/
Signature, minutes preparer

/S/
Concurrence, Chair

drafted: ADunson/8.8.97/i52635im

cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/8.8.97

Concurrences:
HJolson, KSrinivasachar, MAskine, LBurke8.11.97/MHirsch8.12.97/LPauls8.13.97/
GBarnette8.15.97/JFourcroy8.25.97

NDA 21-088
Viadur™ (leuprolide acetate implant)
Alza Corporation

There was no Advisory Committee held for this drug product.

NDA 21-088
Viadur™ (leuprolide acetate implant)
Alza Corporation

There were no Federal Register Notices regarding this drug product.