CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number _____

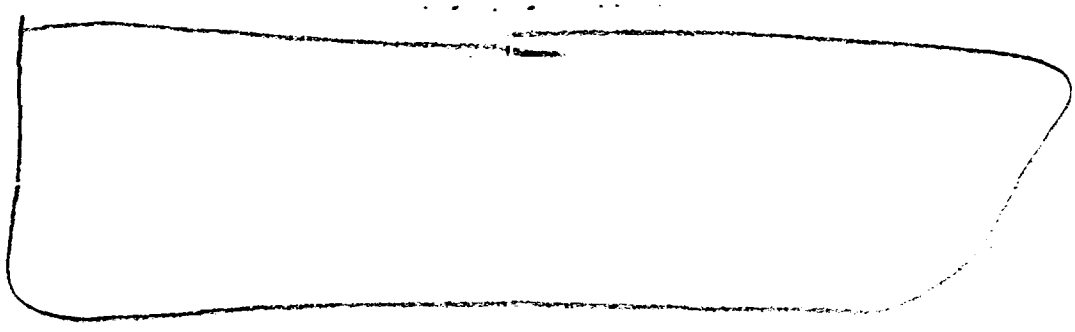
ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

ALZA Corporation response to the Chemistry Phase IV Commitment Request

ALZA Corporation commits to the following:

1.
cl

2
cl



ALZA Corporation response to the Biopharmaceutics Phase 4 Commitment Request

The Biopharmaceutics Phase 4 Commitment Request is as follows:

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 ≥ [redacted] of the leuprolide acetate content in Viadur™ implant.

ALZA Corporation Response:

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.

9 December 1999

NDA Number 21-088
Volume 11.1

Via Federal Express

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

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 including a newly issued patent and a correction to the expiration dates of both the patent submitted on August 18, 1999 in Amendment 6.1 and the patent submitted on April 30, 1999 in the original NDA.

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 650-564-4282 or via facsimile at 650-564-2581. In the event that you are unable to contact me, please contact either Ms. Susan Rinne, Vice President, Regulatory Affairs at 650-564-2523 or Mr. Tom Tarlow, Director, Regulatory Affairs at 650-564-2513. We share the same facsimile number.

Sincerely,

Susan Rinne for

Janne Wissel
Senior Vice President
Operations

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

NDA No. 21-088 Amendment: DUROS® Leuprolide Implant

SECTION 13. PATENT DECLARATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of DUROS™ Leuprolide Implant. This product is the subject of NDA application number 21-088 for which approval is being sought.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
5,728,396	Formulation and Method of Use	January 30, 2017	ALZA Corporation
5,932,547	Formulation	June 13, 2017	ALZA Corporation
5,985,305	Formulation	January 30, 2017	ALZA Corporation

ALZA Corporation

Peter D. Staple
Senior Vice President and General Counsel
Dated: 12/8/99

SECTION 1. INDEX

F. Patent Declaration

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of DUROS™ (leuprolide acetate) Implant System. This product is the subject of this application for which approval is being sought.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
5,728,396	Formulation and Method of Use	02/02/2016	ALZA Corporation

ALZA Corporation

Peter D. Staple
Vice President and General Counsel
Dated: March 5, 1999

EXCLUSIVITY SUMMARY FOR **NDA # 21-088 SUPPL # 000**

MAR 03 2000

Trade Name: **Viadur™** Generic Name: **leuprolide acetate implant**

Applicant Name: **Alza Corporation HFD # 580**

Approval Date If Known: **March 3, 2000**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data. answer "no.")

YES /X/ NO /___/

Required review of clinical data to support safety and efficacy of the Drug Delivery Device; not the Drug Product

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /X/

If yes, NDA #

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#	19-010.	**Drug Name**	Lupron Injection
	19-732		Lupron Depot Injection
	19-943		Lupron Depot Injection
	20-011		Lupron Depot 3.75 mg
	20-263		LupronDepot Pediatric Kit
	20-517		Lupron Depot-4 Month 30 mg
	20-708		Lupron depot 3 Month 11.25 mg

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /X/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

C-96-011
C-97-010

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /X/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

C-96-011
C-97-010

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # 52,635 YES /X/ ! NO /___/ Explain: _____
!

Investigation #2 !
!

IND # 52,635 YES /X/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!

YES /___/ Explain _____ ! NO /___/ Explain _____
!

_____ ! _____
!

_____ ! _____
!
!

Investigation #2 !
!

YES /___/ Explain _____ ! NO /___/ Explain _____
!

_____ ! _____
!

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

/S/

Signature Date
Title: Regulatory Project Manager

/S/

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21088	**Trade Name:**	DUROS/VIADUR(LEUPROLIDE ACETATE IMPLANT
Supplement Number:		**Generic Name:**	LEUPROLIDE ACETATE IMPLANT/LEUPROLIDE IM
Supplement Type:		**Dosage Form:**	DDS
Regulatory Action:	AP	**Proposed Indication:**	Palliative treatment of advanced prostate cancer

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Indication is for an adult male disease. There is no pediatric indication or plans for one with this drug product.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JEANINE BEST

/S/

Signature

3/3/00

Date

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

REQUEST FOR PEDIATRIC WAIVER

30 April 1999

Lisa D. Rarick, M.D.
Division of Reproductive and Urologic Drug Products
HFD-170
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-088
Viadur™ (leuprolide acetate implant)
Full Waiver Request for Pediatric Labeling

Dear Dr. Rarick,

ALZA Corporation requests a full waiver from the pediatric labeling use information required under 21 CFR §314.55 for Viadur™ (leuprolide acetate implant). The rationale for this request is that the drug product was studied in the palliative treatment of advanced prostate cancer. For this indication, ALZA references Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, 63 Fed. Reg. 66631, 66648 (1998) (to be codified in 21 CFR Parts 201, 312, 314, and 601).

Prostate cancer is not a pediatric disease. The drug does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of patients. Furthermore, the use of a leuprolide acetate implant in a pediatric male patient can result in the delay of the onset of puberty, representing an unsafe use of the drug in pediatric patients.

Thus, under the regulations concerning the necessity for pediatric labeling, ALZA Corporation requests a full waiver from these requirements for Viadur™ (leuprolide acetate implant) in the palliative treatment of advanced prostate cancer.

If you should have any questions or require additional information, please contact me by telephone at (650) 237-2523 or by facsimile at (650) 237-2851.

Sincerely,

Susan Rinne
Vice President, Regulatory Affairs

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

SECTION 16. DEBARMENT STATEMENT

ALZA hereby certifies that it did not, and will not, use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

JWissel 4/25/99

Janne Wissel Date
Senior Vice President
Operations

FEB 25 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: 02/25/00

LLP 2/25/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products, HFD-580

Subject: Review of financial disclosure documents for NDA 21-088

To: the file (NDA 21-088)

I have reviewed the financial disclosure information submitted by ALZA Corporation.in support of their NDA for Viadur (leuprolide acetate implant), NDA 21-088.

Two studies were conducted to support the safety and efficacy of Viadur for the palliative treatment of prostate cancer. The study numbers and their respective outcomes with regard to financial disclosure obligations are summarized below:

Study No.	**Disposition regarding Financial Disclosure**
C-96-011	Ongoing as of February 2, 1999; appropriate documentation provided
C-97-010	Ongoing as of February 2, 1999; appropriate documentation provided

Conclusion:

The Form FDA 3454 and its supporting list of investigators are adequate to ensure that the sponsor is in compliance with 21 CFR 54.

cc:
Orig NDA 21-088
HFD-580/JBest

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Bruce C. Cozadd	Chief Financial Officer
FIRM/ORGANIZATION: ALZA Corporation	
SIGNATURE	DATE: 4/22/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

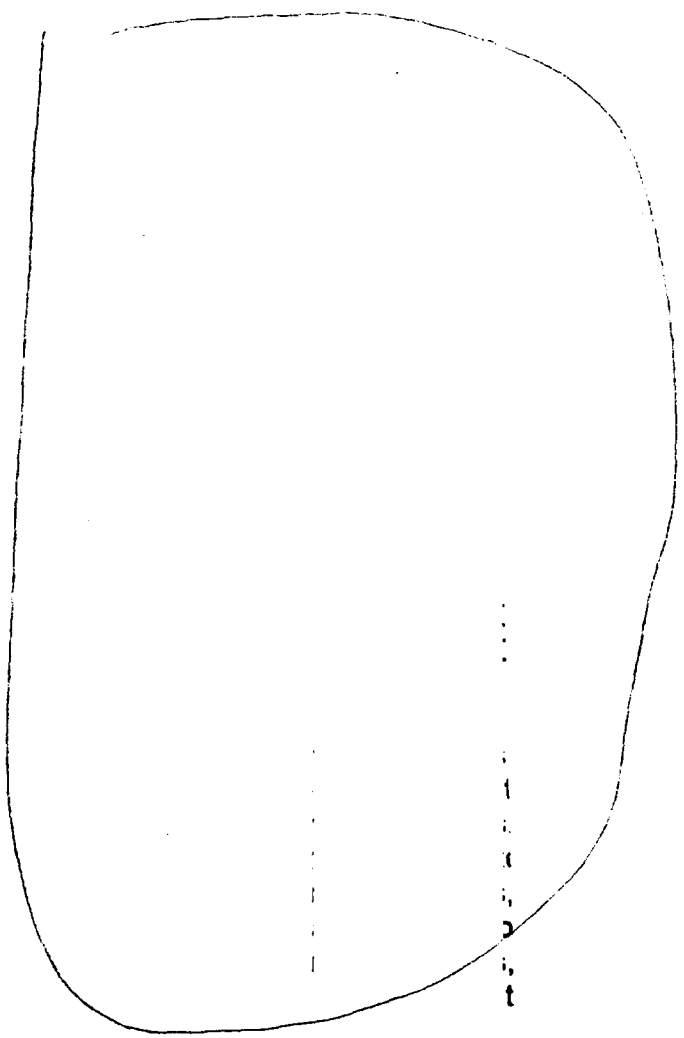
FORM FDA 3454 (3/99)

Form FDA 3454
Certification: Financial Interests and Arrangements of Clinical Investigators

The following is a list of clinical investigators who participated in the clinical studies in support of this application.

Study Number C-96-011: Feasibility, Functionality and Dose Ranging of Duros™ Leuprolide Implantable Therapeutic System in Patients with Advanced Prostate Cancer

Investigator Name	Name of Facility/Location
Andriole, G, MD	
Bardot, S, MD	
Beach, J, PAC	
Bernhard, P, MD	
Bihrle, W, MD	
Block, NL, MD	
Cama, C, MD	
Cook, DO, MD	
Currie, DP, MD	
Curtic, G, MD	
Fowler, J, MD	
Friedman, RM, MD	
Fuselier, HA, MD	
Gasparich, JP, MD	
Gottesman, J, MD	
Griffin, A, MD	
Hart, III, OJ, MD	
Hart, Jr, OJ, MD	
Howell, F, MD	



Cjrc2/km/4-21-99

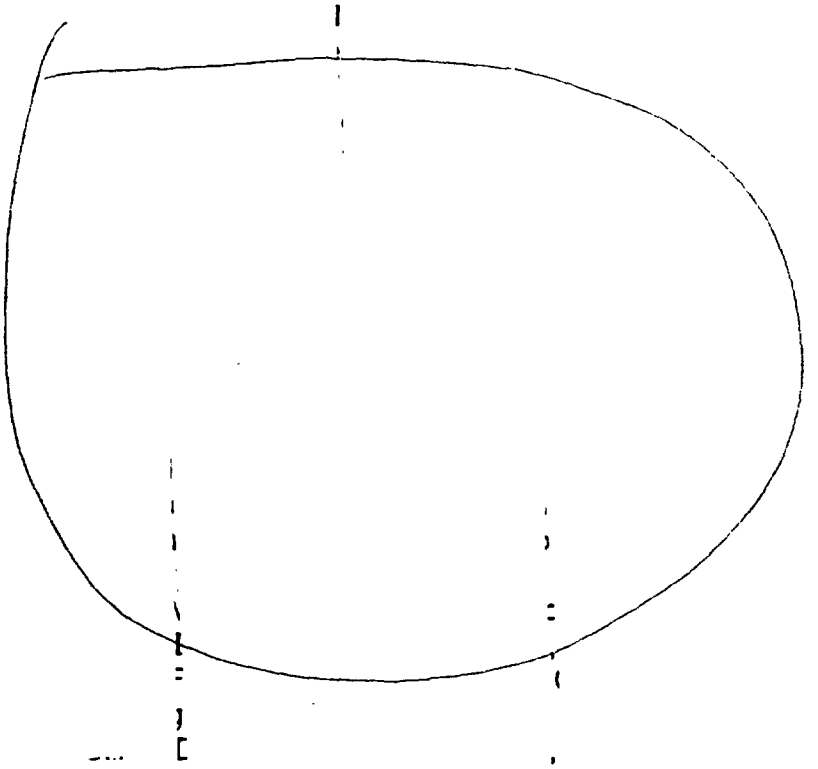
)RATION–CONFIDENTIAL

Libertino, JA, MD
Lilly, JD, MD
Malone, MJ, MD
Nieh, PT, MD
Prats, Jr, LJ, MD
Reddy, P, MD
Reid, CF, MD

Rivera-Ramirez, I, MD
Roth, RA, MD
Shown, T, MD

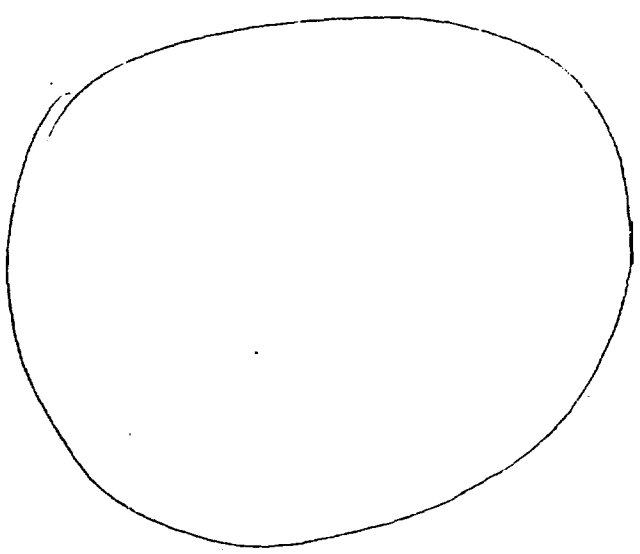
Smith, III, JJ, MD
Soloway, M, MD
Stubbs, AJ, MD

Sundaram, CP, MD
Tapley, R, RRA
Vereb, M, MD
Wajsman, Z, MD
Wissman, WD, MD
Zinman, LN, MD



Study Number C-97-010: Safety and Efficacy of DUROS™ Leuprolide Implantable Therapeutic system in Pateients with Prostate Cancer

Investigator Name	Name of Facility/Location
Aldridge, C, RN	
Andriole, G, MD	
Antoci, JP, MD	
Antosek, R, DO	
Aronson, W, MD	
Bardot, S, MD	
Barmantz, M, MD	
Beach, J, PAC	
Berman, B, MD	
Block, NL, MD	



Cpc:/km/4-21-99

Boxer, R, MD
Cama, C, MD

Christ, MH, MD

Christine, B
Civitelli, KK, RN
Clements, N, MD
Cook, DO, MD

Cuesta, I, PA

Currie, DP, MD

Curtis, G, MD

Daniel, WA, MD
Deeths, J, MD
DeGuenther, MS, MD
Dennis, RL, MD
Dritz, SB, MD
Dunshee, C, MD
Feldman, R, MD
Fitch, W, MD
Flanagan, MJ, MD
Fowler, J, MD

Friedman, RM, MD

Fuselier, HA, MD
Gasparich, JP, MD
Gittelman, M, MD

Gleason, D, MD
Gordon, PM, MD
Gottesman, J, MD
Gottesman, W, CRC
Griffin, A, MD

Hammontree, LN, MD
Harris, R
Hart III, OJ, MD

Hart Jr., OJ, MD

Hicks, T, MD
Hirsch, R, MD
Hoffberger, R, DO

Howell, F, MD

Kantor, SD, MD
Killion, D, MD
Klimberg, IW, MD

Konigsberg, HA, MD
Koukol, SC, MD
Kraus, PA, MD
Kroeger, RM, MD
Leitner, WA, MD
Lilly, JD, MD
Locke, DR, MD

Longo, G, MD
MacDonald, J, MD
Mardis, HK, MD
Marks, L, MD
McEwan, SP, PA
Modling Jr., D, MD
Moody, TE, MD
Morgan Jr., C, MD
Morton, J, MD
Perez, N, PA

Pines, J, MD

Prats, LJ, MD
Reid, CF, MD

Reilly, R, MD
Rettig, M, MD
Rivera-Ramierez, I, MD

Cpc2/km/4-21-99

Rothenberg, L, PhD,
ARNP, CCM
Russell, RT, MD
Samowitz, H, MD

Sandock, DS, MD

Sanfelippo, CJ, MD
Schmidt, L, DO
Sethney, T, MD
Sharifi, R, MD

Shown, T, MD

Soloway, M, MD

Stubbs, AJ, MD

Suffecool, S, MD
Sundaram, CP, MD
Sweetser, PM, MD

Tapley, R, RRA

Tully Jr., A, MD
Tully, S, MD
Vick, S, MD
Wajsman, Z, MD

Weinstein, M, DO

Weissman, WD, MD
Wiatrak, M, MD

Winton, L, MD

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 19, 2000

TO: J. Best, Regulatory Project Manager
N. Marks, M.D. Clinical Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: David Lepay M.D., Ph.D
Division Director, HFD-45
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.,
Senior Regulatory Review Officer
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-088

APPLICANT: Alza Pharmaceutical Corporationt

DRUG: Viadur (leuprolide implant)

THERAPEUTIC CLASSIFICATION:

INDICATION: Palliation of advanced prostate cancer.

REVIEW DIVISION GOAL DATE: February 18, 2000
ACTION GOAL DATE (PDUFA Date): March 3, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this NDA submission is for the palliation of advanced prostate cancer.

b. There were no limitations on the inspection.

c. The inspection of this site was unremarkable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, the violations observed at one site was minor in scope and would not affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed

/S/

Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

/S/

David Lepay, M.D., Ph.D.
Division Director
Division of Scientific Investigations

FD-580

Jackson E. Fowler, Jr., M.D.
[redacted]

Food and Drug Administration
Rockville MD 20857

FEB - 2 2000

Dear Dr. Fowler:

On November 4 and 5, 1999, Mr. James W. Blakely, representing the Food and Drug Administration (FDA), inspected your conduct as the investigator of record of your clinical study (C-97-010) of the investigational drug DUROS® (leuprolide implant), that you conducted for ALZA Corporation. This inspection is part of the Agency's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Mr. Blakely presented his inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of: (a) the inspection report; (b) the documents copied during the inspection; (c) your oral responses to the inspectional observations; and (d) your letter of November 18, 1999, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular, we note deviations from the study protocol in that subject # 0911 was prescribed ketoconazole, a medication prohibited by the protocol. Subject #0913 experienced a surgical error (reimplantation of an original device requiring an additional surgical procedure to replace it with a new implant), and this adverse event was not included in the Case Report Form as required by the protocol.

Please ensure that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Mr. Blakely during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-088
HFD-580/Best
HFD-5180/Marks
HFD-45/Reading File
HFD-46/Chron File
HFD-46/CIB file # 09924
HFD-46/Blay
HFD-46/Huff
HFR-SE450/Goldstein
HFR-SE450/Asente
HFR-SE4570/Blakely

CFN:
Field Classification:
Headquarters Classification: VAI
_____1)NAI
_____2)VAI (no response required)
_____3)VAI-R (30 day response requested)
__x__4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
__x_deviation from protocol
____inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other ( )

O:/blay/fowler.rab
r/d: drafted/rab/1.28.00
final:nlp:1/31/2000

Note to Review Division:

The field investigator inspected the study-related records for 7 of the 13 subjects enrolled in protocol # C-97-010 at Dr. Fowler's site. The data appear acceptable for use in support of drug claims.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 31 2000

James E. Gottesman. M.D.

[redacted]

Dear Dr. Gottesman:

Between October 26 and November 2, 1999, Ms. Kerri Butler representing the Food and Drug Administration (FDA), inspected your conduct of two clinical studies (Protocols #C-96-011 and #C-97-010) of the investigational drug Duros™ Leuprolide Implantable Therapeutic System, that you conducted for ALZA Corporation. From our evaluation of the inspection report and the documents submitted with that report, we conclude that you conducted your study in compliance with applicable Federal regulations and good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

We appreciate the cooperation shown Ms. Butler during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy, HFD-45
Center for Drug Evaluation and Research
7520 Standish Place, Room 103
Rockville, Maryland 20855

DEPARTMENT OF HEALTH & HUMAN SERVICES

Best

580

Food and Drug Administration
Rockville MD 20857

Robert A. Feldman, M.D.

[redacted]

JAN 18 1999

Dear Dr. Feldman:

The purpose of this letter is to inform you of our conclusions concerning your conduct of the clinical study (protocol #10) of Duros that you conducted for the Alza Corporation.

Between November 1 and November 10, 1999, Ms. Patricia Murphy, representing the Food and Drug Administration (FDA), inspected the study identified above. This inspection is part of the FDA's Bioresearch Monitoring Program. This program includes inspections to determine the validity of clinical drug studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of the human subjects who participated in those studies have been protected.

At the close of the inspection, Ms. Murphy presented her inspectional observations (i.e., Form FDA 483) and discussed these observations with you. From our evaluation of: (a) the inspection report; (b) copies of study records obtained during the inspection; and (c) your oral responses during the inspection to the inspectional observations, we conclude that you did not adhere to all pertinent Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. In particular, we note that you failed to prepare and maintain adequate and accurate records of all observations and other data pertinent to your study for each subject in your clinical drug study as required by Federal regulations [21 CFR 312.62(b)]. Changes were made to source data that could not be verified.

We note your response to the observations and your assurance that corrective actions will be taken to prevent similar problems in your current and future studies.

We appreciate the cooperation shown Ms. Murphy during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, MD 20855

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: August 4, 1999

To: Gurston Turner, Ph.D. (HFD-344)

LLP 8/4/99

From: Lana L. Pauls, M.P.H., Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Request for Clinical Inspections for NDA 21-088

In support of the above mentioned NDA for Viadur™ DUROS (leuprolide acetate) implant, the sponsor, ALZA Corporation, submitted the results of the following pivotal protocols for the indications identified below:

Indication	Pivotal Protocol #	Investigator's Name/Address
Palliative treatment of advanced prostate cancer	C-96-011 C-97-010	J. Fowler, M.D.
	C-96-011 C-97-010	J. Gottesman, M.D.
	C-97-010	R. Feldman, M.D.

We have discussed this application with Gurston Turner and, as a result, identified the above protocols/sites for inspection.

We request that the inspections be performed and the Inspection Summary Results be provided by December 20, 1999. We intend to make a regulatory decision on this application by February 28, 2000.

Should you require any additional information please contact Jennifer Mercier, Project Manager, at 301-827-4260.

Distribution: NDA 21-088
HFD-580/Division File
HFD-580/Mercier/Rumble/Pauls
HFD-344/CIB Reviewer

Division Director Memorandum
New Drug Application

MAR 0 3 2000

NDA#:	21-088
Sponsor:	Alza Corporation
Drug:	DUROS™ Leuprolide implant
Trade Name:	Viadur™
Indication:	Palliative treatment of advanced prostate cancer
Dose:	120 mcg/day administered via continuous subcutaneous infusion over 12 months
Date of submission:	4/30/99
Date of memorandum:	3/3/00

Background

A subcutaneous formulation of leuprolide acetate (Lupron™), a GnRH agonist, was initially approved for the palliative treatment of advanced prostatic cancer in 1985. Since that time, one-month, three-month and four-month depot formulations of Lupron™ have been approved by the FDA for this indication. These sustained release formulations were administered via deep intramuscular injections at 30, 90 or 120 day intervals.

Viadur™ consists of a 4mm X 45 mm titanium cylinder containing 72 mg of leuprolide acetate. The product is designed to be implanted under local anesthesia in the subcutaneous space on the medial aspect of the inner arm. Once implanted, the device delivers 120 mcg of drug product per day. Per the sponsor, continuous delivery of drug product via the implant may result in increased compliance with dosing and offer an opportunity for early removal of the device if medically indicated or upon patient request.

As described in the primary and secondary clinical reviews, the safety and effectiveness of Viadur™ for palliative treatment of advanced prostate cancer was established in two phase 3 trials as reported in the current application. Effectiveness was measured as the percent of patients who attained and maintained serum levels of testosterone in the castrate range (i.e., serum testosterone levels < 50 ng/dl) with no escape of serum testosterone levels above 50 ng/dl

during the 12-month treatment period. Based upon this definition, the intent-to-treat success rate for Viadur™ was 97%.

Results contained in the application supported the safety of Viadur™ for the proposed indication. Adverse events noted during the conduct of the two phase 3 studies were typical of those seen in trials of GnRH agonists previously approved for the palliative treatment of advanced prostate cancer. Safety concerns unique to this product are related to insertion, removal and reinsertion of the device. As described in the clinical reviews, a 2% extrusion rate was noted during the phase 3 studies in patients who had a single implant. Difficulty in device removal was noted in 2 other patients. As noted by the sponsor, these extrusions and difficulties with implant removal could have been related to incorrect device insertion.

If deemed clinically appropriate, following 12 months of treatment and removal of the initial implant, reinsertion of a replacement implant into the previous insertion site is recommended by the sponsor. Although the mean duration of a reinsertion procedure was approximately 6 minutes, 3 such procedures were noted to be "somewhat difficult". If difficulties are encountered placing subsequent implants in the previous insertion site, replacement implants can be inserted in the contralateral arm. Modifications in the insertion instructions for the device were made to address this issue, and this section of the label was deemed acceptable.

Two final review issues, one a biopharmaceutics issue and the other a chemistry issue, resulted in phase 4 commitments from the sponsor. The first issue was related to the *in vitro* cumulative leuprolide acetate release rate method and specifications for the product. Although the release rate method and specifications submitted with the NDA accounted for the release of approximately 10 mg of leuprolide acetate from the implant, a phase 4 commitment to develop an accelerated *in vitro* release rate procedure accounting for release of significantly more than 10 mg of drug product was agreed to by the sponsor. The second issue related to an implant production defect in the installation of the device's diffusion moderator. This defect was noted in four units of a single production batch of the product that was used in the clinical trials. In order to ensure uniform quality of all production batches, the sponsor agreed to a phase 4 commitment to investigate the cause of any defects in alignment and seating of the diffusion moderator in all product batches used in the clinical trials.

Recommendations:

I agree with the conclusions of the primary and secondary discipline reviews that Viadur™ is safe and effective for the palliative treatment of advanced prostate cancer and recommend that this application be approved.

/S/ 3/3/00

Susan S. Allen, MD, MPH
Acting Director, HFD-580

Cc: NDA 21-088
HFD-580/Allen/Shames/Marks
HFD-103/Houn/Raczkowski

FEB 17 2000

Group Leader Memorandum

NDA:	**21-088**
Drug substance:	**leuprolide acetate**
Drug Product:	**DUROS™ Leuprolide implant**
Trade name:	**Viadur™**
Dose:	**120 mcg/day administered by continuous subcutaneous infusion over 12 months**
Indication:	**Palliative treatment of ~~advanced~~ prostate cancer**
Sponsor:	**Alza Corporation Mountain View, CA**
Date received:	**4/30/99**
Date of review:	**2/15/99**

General Background: The reduction of a patient's serum testosterone to castrate levels has been recognized as an effective method of palliation for men with advanced prostate cancer since the late 1940's. The original method used to achieve castration was surgical orchiectomy. Because of the need for an operative procedure and the reluctance of many patients to consent to this procedure in particular, other methods of "medical castration" were developed.

In the 70's and 80's medical castration was accomplished by the administration of estrogen, mainly diethylstilbestrol. Because of adverse events related to estrogens, more acceptable forms of medical castration were studied. In the early 1980's, the GnRH agonist, leuprolide was studied in a daily (1 mg) subcutaneous dose. This study was submitted by TAP Pharmaceuticals in NDA 19-010. Leuprolide (Lupron) became the first GnRH superagonist approved for the treatment of prostate cancer. GnRH agonists are presently the most widely used drugs for prostate cancer patients when medical castration is appropriate. Several GnRH agonists (leuprolide and goserelin) are currently available in the US in a variety of sustained-release, injectable formulations that allow drug release for up to 4 months.

GnRH is synthesized in the cells of the hypothalamic neurons and secreted in a pulsatile fashion into the hypothalamic-hypophyseal portal circulation. GnRH stimulates the gonadotroph cells to synthesize and release the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH bind to receptors in the ovary and testis and regulate gonadal function by promoting sex steroid production and gametogenesis. Hypothalamic release of GnRH and its action on the pituitary is controlled by biofeedback mechanisms based on the amount of sex steroid in circulation. Secretion of LH and FSH are episodic with secretory bursts that occur each hour and are mediated by the episodic release of GnRH. The pulsatile nature of GnRH release is critical for sustaining gonadotropin secretion. A continuous administration of GnRH or GnRH agonist evokes an initial increase in LH and FSH followed by prolonged suppression of gonadotropin secretion. This phenomenon may be explained by down-regulation of GnRH receptors on the pituitary gonadotroph cells.

Therefore, in men, the chronic administration of a GnRH agonist will ~~result~~ in an initial stimulation of gonadotropins and thus testosterone for several weeks. This is followed by a significant, sustained decrease in testosterone usually to castrate levels (50 ng/dl). The chronic administration of GnRH agonists induces gonadal stimulation during the first week of so of therapy causing an elevation of testosterone to 140-170% of basal levels (testosterone flare). By the end of the fourth week, testosterone levels should be below castrate levels and ideally remain there. In addition to the initial testosterone flare, there are two other forms of "failure" in this drug group. The first is "escape" of testosterone above castrate level after suppression has been achieved. The second is a stimulatory effect upon reinjection ("acute on chronic effect" or "secondary flare") which results in an increase in testosterone level. These failures to "attain or maintain" testosterone suppression can potentially ~~result in adverse clinical events such as~~ exacerbation of tumor pain, urinary obstruction and spinal cord compression. Serum testoster~~one levels~~ have evolved as a surrogate marker for the clinical ~~effectiveness of drugs~~ that are used to treat patients with prostate cancer by medical castration. ~~The~~ standard for approval of drugs in this class requires that castration is attained by week 4 (28 days) and maintained throughout the treatment period. ~~Any rise in serum~~ testosterone ~~above~~ 50 ng/ml is considered a "failure" of treatment. ~~Historical data reveal that drugs in~~ this class are successful (do not fail in any of the categories described above) about 95% of the time.

Viadur Background: Viadur™ is a 4mm x 45~~mm titanium cylinder~~ that weighs 1.1g. It is capped on one end by a polyurethane rate-controlling membrane and the other end by a polyurethane diffusion moderator. Viadur™ is essentially an osmotic pump similar to systems that have been used in veterinary medicine for 10 to 15 years. It contains 72 mg of leuprolide (equivalent to 65 mg of leuprolide free base) and delivers 120 mcg/day of drug substance.

The device is a sterile, nonbiodegradable, single-use device designed to deliver a continuous dose of leuprolide over a 12-month period. The device is implanted under local anesthesia in the subcutaneous space of the upper arm in the groove between the

biceps and triceps muscles. It is removed after 12 months and another device is implanted into the same space (if clinically appropriate) also under local anesthesia. After implantation, water is drawn into the reservoir through the rate-controlling membrane in response to the osmotic gradient between the osmotic tablets within the device and the fluid in the subcutaneous space. The water causes an osmotic engine to expand, exerting pressure on an elastomeric piston, which pushes the leuprolide through the diffusion moderator into the subcutaneous space.

Description of trials: Viadur™ was studied in two core trials, C-96-011 (N=51) and C-97-010 (N=80). Neither study incorporated an active or placebo control group. C-96-011 was a multicenter, open label, "dose ranging", two-armed study comparing one and two implants. After it was determined, by study C-96-011, that one implant was as effective as two in producing medical castration, C-97-010 was performed. C-97-010 was a multicenter, open-label, one-arm study using one implant. Both trials were conducted in two phases, a one-year treatment phase followed by a one-year safety extension. After the first year of treatment, implants were removed and replaced by new single implants in both studies.

In study C-96-011, after an interim analysis on day 112 of the treatment phase, all patients received a single implant during the 1-year safety phase. One implant was placed in all patients during study C-97-010 for both the one-year treatment and one-year safety extension phases. Subjects in both trials had advanced carcinoma of the prostate. However, patients in trial C-97-010 were allowed to have earlier stages of "advanced disease". Subjects in trial C-96-011 had stage D_1 or D_2 disease (with PSA≥ 6ng/ml) or were local failures whereas subjects in trial 97-010 could have stage A_2, B, C, D_1 and D_2 (with PSA≥6 ng/ml). Entry criteria were broadened for the second trial to improve enrollment. The less advanced patients included in this trial, are often treated with GnRH agonists by physicians expert in therapy of prostate cancer patients. The sponsor understands that the broadening of the patient population allowed in the trial will not broaden the indication in the drug label. A total of 131 patients participated in one or the other of these trials.

The effectiveness of Viadur™ for the palliative treatment of prostate cancer was measured by its "success" in attaining and maintaining serum levels of testosterone in the castrate range (< 50 ng/dl). This surrogate analysis has been accepted as an endpoint in this patient population. The results of those subjects from the 12 month treatment phase in C-96-011 that received one implant (27 of 53 subjects) and all the patients in C-97-010 (all received one implant, N=80) were pooled for the analysis regarding attaining and maintaining castrate levels of testosterone (N= 107). All patients who received a "reimplant" from either study were analyzed for "acute on chronic " effect (N=97). All available data submitted with the original NDA and 4-month safety update was used for the safety analysis (N=131).

Efficacy Results: To understand the efficacy analysis of this product, one must understand the disposition of the patients in the "treatment" and "safety" phases of the trials. **One hundred and seven** subjects received one implant from either of the trials during the treatment phase. Nine patients did not complete the 12-month treatment period. These 9 discontinuations were due to 5 deaths, 2 expelled implants and 2 adverse events. The deaths and 2 adverse events were not related to the treatment. Therefore, 98 patients who had a single implant placed, finished the 12-month treatment phase. Of these 98 patients, one failed to have testosterone suppressed to castrate levels by four weeks (suppressed at 28 weeks). Once testosterone was suppressed to castrate level, it remained there in all patients even in the patient that had delayed suppression.
The Sponsor's original protocol proposed that success be measured in terms the product's ability to produce castrate levels of testosterone by 6 weeks (rather than 4) and maintain castrate levels throughout the treatment period. The sponsor defined failure as two (rather than one) consecutive testosterone spikes above 50 ng/dl rather than one. Both their ITT and per protocol analyses were structured this way. Recently, The Division has suggested that success be defined by obtaining castrate levels of testosterone by four weeks and with no spikes above 50 ng/dl during the treatment period. However, because all subjects in this study except one became castrate by 4 weeks and there were no escapes above 50 ng/dl, an ITT and PP analysis using the recent more strict criteria could be performed.

Group Leader's per protocol analysis: Of the 107 patients who received one implant, 98 completed the 12 month treatment period and only one failed to suppress (by 4 weeks) or maintain suppression. Therefore the PP success rate is 99% (97/98).

Group Leader's ITT analysis: All patients that dropped out before 12 months maintained suppression until dropping out. This was even true of the patients who experienced extrusion of their implants. I would argue that the only true "failures" were the subjects who had extrusions (2) and the patient who did not suppress until 28 weeks. The testosterone data from the other "dropouts" could be imputed by last-observation–carried-forward since their withdrawals were not secondary to an adverse event caused by device failure. I therefore, calculated the ITT success rate as 97%(104/107). I would consider either of these rates (ITT or PP) high enough to demonstrate efficacy in this drug class.

An additional important efficacy analysis that is performed on this class of drugs is the rate of "acute on chronic" flare or the incidence of testosterone spike above 50 ng/dl when the drug is readministered. Examination of all patients that were reimplanted at 12 months (N=97) revealed that there was no case of "acute on chronic" flare.

Safety Results:
Adverse events during the two trials submitted with the NDA and in the four month safety update were typical for trials of GnRH agonists in the population of patients with prostate cancer. I will address potential safety issues that are unique to this system of delivering leuprolide. These are implantation, extrusion and reimplantation issues.

Viadur™ was partially extruded though the incision sites in three patients. In study C-96-011, two patients experienced extrusions. One was in a patient who had a single implant placed (after 65 days) and one in a patient in which one of two implants extruded (after 367 days). In study C-97-010, there was one patient with an extrusion (121 days). The sponsor blames incorrect implantation for the extrusions of the single implants and blames migration of one implant causing extrusion of the other in the doubly implanted patient.

The initial implant procedures lasted an average of 4 minutes (2-12 minutes) and were rated as "very easy" or "somewhat easy" by 99% of the patients. Implant removal was rated as "very easy" of "somewhat easy" in 86% of the patients but two patients required x-ray localization to find the implant. The duration of reinsertion procedure was 6 min (1-28 minutes). Two weeks after the initial and reimplantation, the application site was rated as "very good" by 96% of patients. After initial insertion, all patients rated the anesthesia "good" or better. At reinsertion, 90% of patients rated the ~~anesth~~esia as "good" or better.

It is clear from the above information that that there may be some technical problems with this device. However, I believe that the **INSERTION AND REMOVAL PROCEDURES** that accompany the device adequately addresses the procedural techniques. The reinsertion procedure may be more difficult but should be easily performed by providers with experience in minor surgical procedures.

Conclusion: I agree with the primary medical officer that Viadur™ is a safe and effective method of delivering leuprolide to patients with prostate cancer. It should be approved for the indication of palliative treatment of advanced prostate cancer.

/S/

Daniel A. Shames MD
Team Leader, Urologic Drugs
DRUDP, HFD-580
CDER/FDA

APPENDIX 1.1
EER SUMMARY REPORT

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21088/000
Stamp: 03-MAY-1999 Regulatory Due: 03-MAR-2000
Applicant: ALZA
950 PAGE MILL RD
PALO ALTO, CA 943030802

Priority: 3S Org Code: 580
Action Goal: District Goal: 03-JAN-2000
Brand Name: DUROS/VIADUR(LEUPROLIDE ACETATE IMPLANT
Established Name:
Generic Name: LEUPROLIDE ACETATE IMPLANT/LEUPROLIDE IM
Dosage Form: DDS (DRUG DELIVERY SYSTEM)
Strength: 65 MG

FDA Contacts: S. DE (HFD-580) 301-827-7516 , Review Chemist

Overall Recommendation:

ACCEPTABLE on 01-MAR-2000 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 2914228
ALZA CORP
950 PAGE MILL RD
PALO ALTO, CA 943030802

DMF No:
AADA No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-FEB-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 2938701
ALZA CORP
700 EUBANKS DR
VACAVILLE, CA 95688

DMF No:
AADA No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-FEB-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 2950681
ALZA CORP
1015 JOAQUIN ST
MOUNTAIN VIEW, CA 94043

DMF No:
AADA No:

Profile: NEC OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-MAR-2000
Decision: ACCEPTABLE

Responsibilities: FINISHED DOSAGE MANUFACTURER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JUL-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment:

INC

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **30-JUN-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

APPENDIX 1.2

Letter from the sponsor concerning the use of DMSO lots from

1 March 2000

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: **Susan Allen, MD, Acting Director**
Division of Reproductive and
Urologic Drug Products

Subject: **Response to:**
March 1, 2000 Chemistry Comments
concerning Dimethyl Sulfoxide

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA's) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. In response to the Agency's comment regarding the use of Dimethyl Sulfoxide Lot Nos. USP990614, USP990727 and USP990817 supplied by [redacted], ALZA hereby certifies that these recalled lots were not and will not be used to produce any batches of product for commercial distribution.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

APPENDIX 1.3
Letter from the sponsor concerning Phase IV Commitment

1 March 2000

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: **Susan Allen, MD, Acting Director**
Division of Reproductive
and Urologic Drug Products

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

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA's) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached ALZA's response to the March 1, 2000, Chemistry Phase IV Commitment Request.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 PHONE 650.564.5000
MOUNTAIN VIEW CA 94039-7210 http://www.alza.com

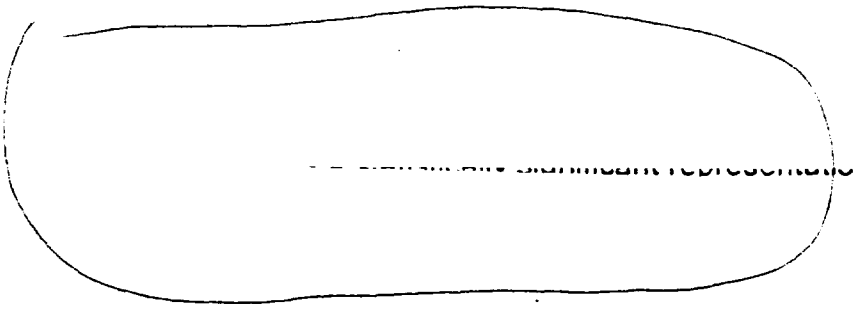
ALZA Corporation response to the Chemistry Phase IV Commitment Request

ALZA Corporation commits to the following:

1. cli

2. c
p

3. on
b



APPEARS THIS WAY
ON ORIGINAL

FEB 2 9 2000

Memo

To: NDA 21-088

From: Swapan K. De, Ph.D. 2/29/00

Through Moo-Jhong Rhee, Ph.D., Chemistry Team Leader 2/29/00

Date: 02/29/00

Re: Viadur™ Implanter

To clarify the safety of the Viadur™ implanter, I called Mr. Von Nakayama of the Center for Device and Radiological Health who reviewed the Viadur™ NDA for device section on February 29, 2000. He stated that the Viadur™ implanter is deemed safe to be used with Viadur™, and this is considered to be a dedicated device to Viadur™ (leuprolide acetate implant).

This was further confirmed by the sponsor through a recent correspondence (02/21/00), that they do not have plan to sell the implant and implanter separately.

Thus, the information of the Viadur™ implanter is deemed satisfactory.

1 March 2000

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: Susan Allen, MD, Acting Director
Division of Reproductive and
Urologic Drug Products

Subject: Response to:
March 1, 2000 Chemistry Comments
concerning Dimethyl Sulfoxide

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA's) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. In response to the Agency's comment regarding the use of Dimethyl Sulfoxide Lot Nos. USP990614, USP990727 and USP990817 supplied by Gaylord Chemical Corporation, ALZA hereby certifies that these recalled lots were not and will not be used to produce any batches of product for commercial distribution.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

EQUISTAR

Equistar Chemicals, LP
One Houston Center, Suite 1600
1221 McKinney Street
P.O. Box 2583
Houston, Texas 77252-2583
Phone: 713.652.7200

January 19, 2000

Dr. Swapan De
Food and Drug Administration

Fax: 301-594-0747

RE: Release Specifications of Petrothene® LS 6901-00

Dear Dr. De:

The following is in response to your request regarding Equistar Chemicals, LP LS 6901-00 High Density Polyethylene Resin.

Below are the release specifications of LS 6901-00. The test results are generated by the manufacturing site laboratory.

Laboratory Test	Acceptable Range
Melt Flow	8.00 – 13.00 g/10 min.
Density	0.951 – 0.955 g/cc
Irganox 1076 [CAS # 2082-79-3]	150 – 2500 ppm
Calcium Stearate [CAS # 1592-23-0]	200ppm Target
Color Index	70 min.
Contamination	None
Corrosion	Pass / Fail
Oxidation	1 - 5

If you need additional information regarding Equistar resins, please contact me at (713) 309-7531.

Sincerely,

Karen J. Wheatley

Karen J. Wheatley
Regulatory Associate

*Petrothene® is a registered trademark of Equistar Chemicals, LP
G:\Corporate HSE\2000 Reg Letters\kjw0088.doc

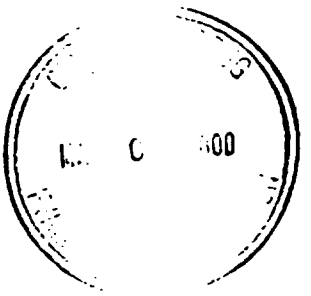
xxx TOTAL PAGE.01 xxx

1 March 2000

ORIGINAL

ORIG AMENDMENT

BC



NDA Number 21-088
Amendment 17.1

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: **Susan Allen, MD, Acting Director**
Division of Reproductive
and Urologic Drug Products

Subject: **Responses to:**
March 1, 2000 Chemistry comment concerning
Dimethyl Sulfoxide and
Phase IV Commitment Request

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA's) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached the original letters FAXed to the Agency on 1 March, 2000 regarding the March 1, 2000, Chemistry comment and Phase IV Commitment Request.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

28 February 2000

ORIG AMENDMENT

BZ

NDA Number 21-088
Volume 16.1

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: **Susan Allen, MD, Acting Director**
Division of Reproductive and Urologic Drug Products

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

Responses to:
February 18, 2000 Chemistry Comments
February 24, 2000 Labeling Comments and Biopharmaceutics Request

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA's) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find enclosed ALZA's responses to the Agency's chemistry, labeling and biopharmaceutic's requests communicated by facsimile and/or telephone on February 18 and 20, 2000. A more detailed description of the specific documents contained in this amendment is provided in the Amendment Overview section of the submission. CD-R discs of the revised physician insert and patient information leaflet are provided only in the Archival and desk copies of this submission.

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 submission. In addition, ALZA certifies that the enclosed CD-R discs have been scanned for viruses using McAfee VirusScan version 4.0.02 (Virus definitions 4.0.4066, last updated 2/23/00) and have been found to be virus free.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ALZA Corporation response to the Biopharmaceutics Phase 4 Commitment Request

The Biopharmaceutics Phase 4 Commitment Request is as follows:

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 Response:

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.

ORIGINAL

ORIG AMENDMENT

BL

16 February 2000

NDA Number 21-088
Volume 15.1

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: **Susan Allen, MD, Acting Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant :
Response to February 11, 2000 Labeling comments

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached ALZA's response to the Agency's comments dated 11 February, 2000 regarding the physician insert (Attachment 1). The revised physician insert (including insertion and removal instructions) with revisions indicated is included in Attachment 2 and the insert with revisions incorporated but not indicated is provided in Attachment 3. The Patient Instruction Leaflet with revisions indicated is included in Attachment 4 and with revisions incorporated but not indicated in provided in Attachment 5. Attachment 6 contains electronic versions of Attachments 2 through 5.

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. In addition, ALZA certifies that the enclosed CD-R discs have been scanned for viruses using McAfee VirusScan version 4.0.02 (Virus definitions 4.0.4064, last updated 2/9/00) and have been found to be virus free.

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

10 February 2000

NEW CORRESP

NDA Number 21-088

AIC

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: **Susan Allen, MD, Acting Director**
Division of Reproductive and Urologic Drug Products

Subject: **Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant :
General Correspondence

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached for your cross-reference the requested Investigational New Drug information amendment submitted to IT

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

09 February 2000

ORIG AMENDMENT

13C

NDA 21-088
Volume 14.1

Lisa D Rarick, MD, Director
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: Response to FDA Chemist's Questions Concerning Pending New Drug Application 21-088 for Viadur®

Dear Dr Rarick:

Enclosed please find a response to the questions from the FDA chemist transmitted to Janne Wissel via a faxed letter dated January 28, 2000. The questions are bolded and capitalized; the answer to each question is provided below the question (Attachment 1).

ALZA certifies that the field copy submitted to the San Francisco District is a true copy of the technical section contained in the archival and review copies of this response.

Please feel free to contact me by telephone at (650) 564-4282 or Darlene O'Banion at (650) 564-2535 if you have questions or comments. The regulatory facsimile number is (650) 564-2581.

Sincerely,

Janne Wissel
Senior Vice President, Operations

Copy: Patricia Ziobro, San Francisco District Office

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

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

ORIG AMENDMENT

7 February 2000

RM

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

Subject: **Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant
Mock-up of Product Presentation

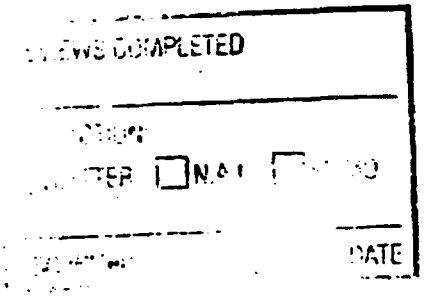
Dear Jeanine:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find enclosed a mock-up of the proposed product presentation for DUROS® Leuprolide Implant as requested by the Medical Reviewer (ALZA and the Agency's 2/7/00 phone conversation). Please note that the enclosed kit and implanter are not sterile and are for demonstration purposes only. The "skin protectant" was not available at the time the demonstration kits were prepared and there is a note indicating that inside the kit. Skin protectant will be provided in the final product presentation. The implant supplied is a non-sterile "dummy" implant for demonstration purposes only which has all constituents but does not contain drug formulation. The vial is a light amber color as a result of being irradiated. The commercial product will be supplied in a colorless vial.

Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

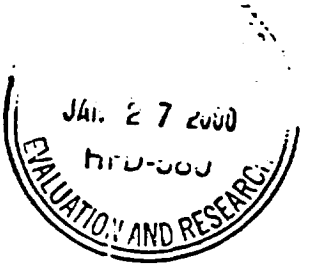
Janne Wissel
Senior Vice President
Operations



ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

26 January 2000

ORIGINAL



NDA Number 21-088
Volume 13.1

ORIG AMENDMENT

BL

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: **Susan Allen, MD, Acting Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant :
Response to January 19, 2000 Labeling comments
Hard copy of FAXed responses to 12/15/99 and 1/11/00
Information Requests

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached ALZA's response to the Agency's comments dated 19 January, 2000 regarding the physician insert (Attachment 1). The revised physician insert with revisions indicated is included in Attachment 2 and the insert with revisions incorporated but not indicated is provided in Attachment 3. Attachment 4 contains electronic versions of Attachments 2 and 3. For completeness, we have also attached hard copies of the responses to the12/15/99 (Attachment 5) and 1/11/00 (Attachment 6) Information Requests that were FAXed to the Agency on 12/23/99 and 1/11/00 respectively.

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. In addition, ALZA certifies that the enclosed discs have been scanned for viruses using McAfee VirusScan version 4.0.2 (Virus definitions 4.0.4061, last updated 1/19/00) and have been found to be virus free.

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible] ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

7 January 2000

ORIGINAL

NDA Number 21-088
Volume 12.1

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

ORIG AMENDMENT

BM

Attention: **Susan Allen, MD, Acting Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant
Response to January 3, 2000 Request for Information

Dear Dr Allen:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Please find attached (Attachment 1) our responses to the Medical Officer's questions.

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Ms. Susan Rinne, Vice President, Regulatory Affairs at (650) 564-2523. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

(Enclosures)
Copies: Archival (1)
Clinical(1)
Desk (1) - Jeanine Best, Project Manager

CENTER FOR DR...
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JAN 10 2000
HFD-580
EVALUATION AND RESE...

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIG AMENDMENT

ORIGINAL

BC

9 December 1999

NDA Number 21-088
Volume 11.1

Via Federal Express

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

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 including a newly issued patent and a correction to the expiration dates of both the patent submitted on August 18, 1999 in Amendment 6.1 and the patent submitted on April 30, 1999 in the original NDA.

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 650-564-4282 or via facsimile at 650-564-2581. In the event that you are unable to contact me, please contact either Ms. Susan Rinne, Vice President, Regulatory Affairs at 650-564-2523 or Mr. Tom Tarlow, Director, Regulatory Affairs at 650-564-2513. We share the same facsimile number.

Sincerely,

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

2 December 1999

NDA Number 21-088
Volume 10.1

ORIG AMENDMENT
BC

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088 for DUROS® Leuprolide Implant**
Revised Labeling: Physician Instruction Manual
Chemistry, Manufacturing and Controls Information

Dear Dr Rarick:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. As previously discussed, ALZA is submitting additional packaging information in this amendment. In addition, we are taking this opportunity to submit two revised methods to the Chemistry, Manufacturing and Controls section of the NDA. An Amendment Overview containing a summary of the information provided in this submission is attached. Please note revised, current establishment information is provided as an attachment to the FDA Form 356h.

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact 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

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

(Enclosures)
Copies: Archival (1)
Chemistry (1)
Field Copy (1) - SF district office
Desk (1) - Jeanine Best, Project Manager

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

ORIG AMENDMENT

BM

4 November 1999

NDA Number 21-088
Volume 9.1

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088 for DUROS® Leuprolide Implant – Additional Information for Medical Officer**

Dear Dr Rarick:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. ALZA is submitting in this amendment additional clinical trial information in tabular form (Study C-96-011, Attachments 1 and 3; Study C-97-010, Attachments 2 and 4) in response to the Medical Officer's request. An Amendment Overview containing a summary of the information provided in this submission is attached.

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

Sincerely,

Janne Wissel
Senior Vice President
Operations

ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

(Enclosures)
Copies: Archival (1)
Clinical (1)
Chemistry (1) - Cover letter, application form with attachment only
Field Copy (1) - Cover letter, application form with attachment only - SF district office
Desk (1) - Jeanine Best, Project Manager

ORIGINAL

NEW CORRESP

NC

18 October 1999

NDA Number 21-088 21-188

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

Subject: **Replacement floppy diskette of labeling for DUROS® Leuprolide Implant: Pending New Drug Application 21-088**

Dear Dr Rarick:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. Provided here please find a floppy diskette containing files of the proposed labeling for DUROS® Leuprolide Implant as a replacement for the one damaged during submission of our 4-month safety update. Also included is a hard copy of the README document found on the disk.

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Tom Tarlow, Director, Regulatory Affairs at (650) 564-2513. We share the same facsimile number.

Sincerely,

for

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

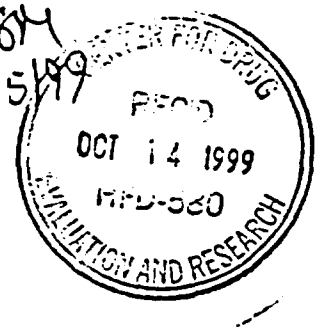
ALZA CORPORATION 1900 CHARLESTON ROAD P.O. BOX 7210 MOUNTAIN VIEW CA 94039-7210 PHONE 650.564.5000 http://www.alza.com

ORIGINAL

ORIG AMENDMENT

NDA 21-088: 4 Month Safety Update

noted
N564
10/15/99



13 October 1999

NDA Number 21-188
Volumes 8.1 to 8.9

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 D Rarick, MD, Director**
Division of Reproductive and Urologic Drug Products

Subject: **Amendment to Pending New Drug Application 21-088**
for DUROS® Leuprolide Implant – 4 Months Safety Update

Dear Dr Rarick:

Reference is made to ALZA Corporation's (ALZA) New Drug Application (NDA) 21-088 for DUROS® Leuprolide Implant submitted on 30 April 1999. In accordance with to 21 CFR 314.50 (d)(5)(vi)(b) and 314.60 (a), ALZA is submitting an amendment to pending NDA 21-088. An Amendment Overview containing a summary of the information provided in this submission is attached (Volume 8.1).

Please note the new three-digit prefix, 564, for all ALZA Regulatory Affairs telephone numbers as well as the new ALZA corporate address as of 1 October 1999:

ALZA Corporation
1900 Charleston Road
P O Box 7210
Mountain View, CA 94039-7210

We look forward to our continued interactions as the review of this NDA proceeds. Please contact me with any questions regarding this submission at (650) 564-4282, or via facsimile at (650) 564-2581. In the event you are unable to contact me, please contact Tom Tarlow, Director, Regulatory Affairs at (650) 564-2513. We share the same facsimile number.

Sincerely,

Thomas J. Tarlow for

Janne Wissel
Senior Vice President
Operations

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

APPEARS THIS WAY
ON ORIGINAL