

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020517/S002

TRADE NAME: Lupron Depot, 4 Month, 30 mg

GENERIC NAME: Leuprolide acetate

SPONSOR: TAP Holdings, Inc.

APPROVAL DATE: 05/30/97



NDA 20-517/S-002

Food and Drug Administration
Rockville MD 20857

MAY 30 1997

TAP Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
2355 Waukegan Road
Deerfield, IL 60015-1595

Dear Dr. Dabholkar:

Please refer to your new drug application dated May 30, 1996, received May 31, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot (leuprolide acetate), 4-month, 30 mg.

We also refer to your submissions dated July 12 and September 30, 1996; January 9, March 20, April 7, May 8, 9, 27, 29 and 30, 1997.

The User Fee goal date for this application is May 31, 1997.

This new drug application provides for a 4-month dosage form to be used for the palliative treatment of advanced prostatic cancer.

We have completed the review of this application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on May 30, 1996 (carton and container labels) and May 30, 1997 (physician and patient package inserts). Accordingly, the application is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

NDA 20-517/S-002

Page 2

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,



Lisa D. Rarick, M.D.

Director

Division of Reproductive and Urologic Drug
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-517/S-002 Trade (generic) names Lupron Depot (leuprolide acetate)

Check any of the following that apply and explain, as necessary, on the next page:

1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.
2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(r) for A&WC studies in children.
- a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.
- b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)
3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).
- a. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing.
- (2) Protocols have been submitted and approved.
- (3) Protocols have been submitted and are under review.
- (4) If no protocol has been submitted, on the next page explain the status of discussions.
- b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

NDA 20-517/S-002

Lupron Depot® (leuprolide acetate for depot suspension)
4-month, 30 mg

Advertising Material

No advertising material has been submitted.

NDA 20-517/S-002
Lupron Depot® (leuprolide acetate for depot suspension)
4-month, 30 mg

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-517/S-002

Lupron Depot® (leuprolide acetate for depot suspension)

4-month, 30 mg

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-517/S-002
Lupron Depot® (leuprolide acetate for depot suspension)
4-month, 30 mg

DSI Audit of Clinical Studies

No clinical audits were necessary as determined in the filing meeting held June 25, 1996.

NDA 20-517/S-002

Lupron Depot® (leuprolide acetate for depot suspension)
4-month, 30 mg

Division Director's Memo

This application will be signed off at the Division level. No memo is necessary.

MAY 30 1997

Group Leader Memorandum

NDA: 20-517/S-002

Drug and indication: Lupron Depot® (leuprolide acetate for depot suspension) 4-month, 30 mg for the palliative treatment of advanced prostatic cancer.

Dose: one injection of 30 mg every 16 weeks

Applicant: Tap Holdings, Inc.

Submission dated: May 30, 1996

Date of MO review: May 9, 1997

Date of Memorandum: May 29, 1997

In this application, the sponsor requests approval for a four month depot formulation of the approved drug leuprolide acetate. The primary source of evidence supporting the safety and efficacy of this product is the results of a single, multi-center, uncontrolled open-label study conducted in 49 men with advanced prostate cancer. Based on this study's results and comparisons to historical data, it appears that the safety and efficacy of this formulation are similar to that of other leuprolide depot formulations approved for palliative treatment of advanced prostate cancer. I concur with the recommendation of the primary reviewers that this application is approvable.

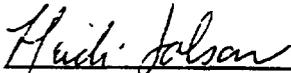
Two recommendations for phase IV studies were made by the Biopharmaceutics and Clinical reviewers, respectively. In the Biopharmaceutics review, a phase IV study was suggested to assess multi-dose leuprolide pharmacokinetics in the target population. However, following subsequent internal discussion of this issue, it was agreed that this requirement could be waived because accumulation of leuprolide following multiple administration is unlikely to be clinically significant and because the pharmacodynamic effect of multiple-dosing has been evaluated in the target population. In the Clinical review, Dr. Golden discusses the clinically important issue of acute testosterone "flare" reactions upon treatment initiation and recommends a study to evaluate the efficacy of concomitant anti-androgen administration in preventing these reactions. However, because this clinical question involves multiple sponsors, the Division will not require this study as a phase IV commitment from this sponsor at this time. The Division should have further internal discussion to determine how best to encourage development of anti-androgens for this indication.

The majority of substantive labeling issues have been adequately addressed by the sponsor at the time of this memorandum. Two labeling issues merit comment.

First, it should be noted that the Indications and Usage section has been revised to omit the statement,

This statement was omitted because: 1) it is vague and subject to interpretation; -2) it is outdated since estrogen is no longer the standard of care and GnRH agonists are widely used; 3) the choice of surgical or medical palliative treatment should be an individualized decision made by the patient and their health care provider and should be based on the respective (and quite different) risks and benefits of each treatment; and 4) practice recommendations that take into account factors such as cost and compliance should be made by the appropriate professional societies and not by FDA. For consistency, labels for other leuprolide and goserelin formulations should be similarly revised.

Second, because leuprolide is used for urologic and gynecologic indications at considerably different doses, the header of all leuprolide labels should contain a prominent statement regarding whether the drug is intended for men or for women. A request for this revision will be made post-approval.



Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-517/S-002
HFD-580/LRarick/LGolden/HJolson

c:\h\20517-2.gl

MAY 30 1997

MEDICAL OFFICER'S ADDENDUM to REVIEW OF NDA SUPPLEMENT (S-002)

NDA #	20-517 (S-002)	Submission Date (via e-mail):	5/27/97
Sponsor:	TAP Holdings Inc.	Receipt Date:	5/27/97
		User Fee Goal Date:	5/31/97
		Date Review Completed:	5/28/97

This pending NDA supplement for Leuprolide acetate for depot suspension (Lupron Depot 4 Month 30 mg) was previously reviewed (refer to MOR dated 5/9/97). The sponsor now submits revised draft labeling (via e-mail only; hard copy not yet received) in response to DRUDP's labeling comments conveyed to the sponsor by letter dated 5/23/97.

REVIEWER'S COMMENTS on REVISED DRAFT LABELING

Recommended revisions are briefly described below. Refer to handwritten comments on attached draft labeling for details of suggested revisions.

Description

Text should be added to this section to clearly indicate that this formulation is for use by men only. This revision may be made by post-approval supplement and should also be implemented, as appropriate
depending on approved indications) for all other affected Lupron formulations.

Clinical Pharmacology

Refer to handwritten comments for suggested clarifications to paragraph 2 of Clinical Studies subsection.

Indications and Usage

The previously deleted second sentence,

, should be restored to this section of the labeling.

This recommendation is based on the following:

- (1) All other approved Lupron labeling for prostate cancer contains the above statement, as does currently approved labeling for Zoladex (goserelin acetate implant) for prostate cancer, based on previous Advisory Committee recommendation (per today's discussion with Dr. Jean Fourcroy, Medical Officer, DRUDP).
- (2) The sponsor has not requested the removal of the above statement and has not submitted any scientific or clinical justification for its removal. In addition, this reviewer is not aware of any scientific or clinical documentation that would justify its removal on an efficacy or safety basis.

(3) Recent medical literature (Porter AT et al: Recommendations of the First Michigan Conference on Prostate Cancer. Urology 1996; 48:519-534) concludes that the primary therapy for symptomatic metastatic prostate cancer is "androgen deprivation therapy," with bilateral orchiectomy (surgical castration) and GnRH agonist therapy (medical castration) considered alternate treatment choices. Since severe "flare" reactions (observed in 15% of patients in the pivotal clinical trial for Lupron Depot-4 Month 30 mg) during the first 2-4 weeks of GnRH agonist therapy may be life-threatening and do not occur after bilateral orchiectomy, this reviewer concurs with the designation of orchiectomy as the "gold standard" treatment modality for this disease. The restored 2-sentence indication statement (which implies that GnRH analog therapy is second-line treatment) is consistent with this observation.

(4) Proposed expansion of the labeled indication from _____ treatment
(by deleting the second sentence above) should be supported by either:

- (A) Documentation of an adequate scientific rationale for such change, based on clinical safety/efficacy data, or
- (B) Recommendation of a specially constituted Advisory Committee with special expertise in urologic oncology.

Warnings

For consistency with currently approved Zoladex (goserelin acetate implant 3.6 mg, Zeneca Pharmaceuticals) labeling, the last sentence should be revised to read:

Precautions

The sponsor should be asked to provide clarification of the actual clinical observation period for orchiectomized patients in the Clinical Pharmacology study (i.e., 16 or 20 weeks), and to correct the text accordingly, as indicated.

Information for Patients

See attached consult report from Louis Morris, DDMAC, for numerous comments on the proposed PPI, all of which should be conveyed to the sponsor.

In addition, this reviewer has the following comments regarding page 7 of the PPI:

(1) The last sentence above the section should be revised to read:

(2) The section entitled should be deleted for consistency with the physician labeling.

Adverse Reactions

This section has been greatly improved and is now acceptable as proposed.

Dosage and Administration

The following clarification is still needed:

CONCLUSION

The revised draft labeling is significantly improved from previous versions but still needs a few substantive modifications, as described above.

RECOMMENDED REGULATORY ACTION

The suggested labeling changes detailed above and handwritten into the draft document should be conveyed to the sponsor, including those from DDMAC.


Linda J. Golden, M.D.
Medical Officer, HFD-580, DRUDP

Attachments: Lupron Depot 4 Month 30 mg Draft Labeling Revision dated 5/27/97

cc: Original NDA Arch
HFD-580
HFD-580/LRarick/HJolson/ADunson
HFD-580/LGolden (+ attachment)/JFourcroy (+ attachment)

MAY 19 1997

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT (S-002)

NDA # 20-517 (S-002)
Sponsor: TAP Holdings Inc.

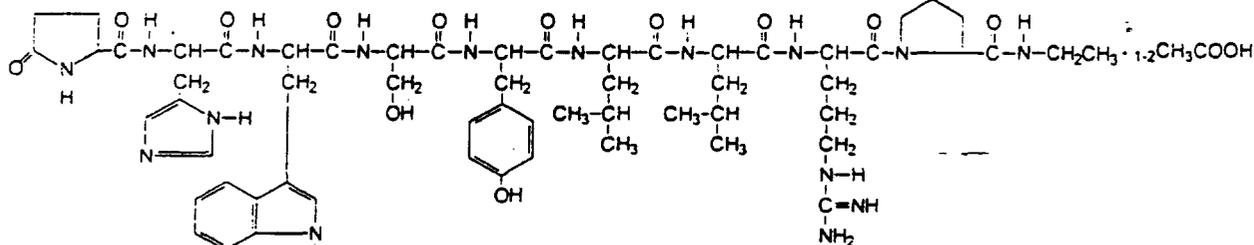
Original Submission Date: 5/30/96
Filing Date: 7/30/96
Date Assigned to M.O.: 8/29/96
User Fee Goal Date: 5/31/97
Date Review Completed: 5/97/97

1.0 General InformationName of drug

Generic name: Leuprolide acetate for depot suspension

Proposed trade name: Lupron Depot - 4 Month 30 mg

Chemical name: Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt).

Pharmacologic Category

Synthetic nonapeptide agonist analog of the naturally occurring gonadotropin releasing-hormone (GnRH or LH-RH)

Proposed Indication

Palliative treatment of advanced prostate cancer.

Dosage Form and Route of Administration

Depot suspension for intramuscular (IM) injection @ dose of 30 mg every 16 weeks (every 112 days).

The 30-mg depot formulation package consists of a single-dose vial containing lyophilized microspheres of leuprolide (30 mg) incorporated into a biodegradable lactic acid polymer and a 2-ml ampule of diluent; this dosage is based on 7.5 mg per month (dose for monthly depot) over 4 months.

NDA Drug Classification

3S

Related IND's and NDA's

Leuprolide acetate Injection (Lupron, TAP): NDA #19-010
Leuprolide acetate Depot (Lupron Depot, TAP):
IND NDAs #19-732, 19-943, 20-011, 20-263, 20-708

Related Drugs

Goserelin acetate (Zoladex, Zeneca): NDA #19-726
Nafarelin acetate (Synarel, Searle): NDA #19-886
Histrelin acetate (Supprelin, Roberts Labs): NDA #19-836

Related Reviews

Chemistry Review dated 4/25/97
Pharmacology Review dated 6/14/96
Clinical Pharmacology and Biopharmaceutics Review dated 2/20/97

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3.0 Material Reviewed

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Volume 8.7	Section V. Clinical/Statistical Section: Table of Contents, List of Investigators/IND's, Study Report of Open-label Clinical Trial M93-013	
Volume 8.8	Section V. Clinical/Statistical Section: Individual Patient Data	
Volume 8.9	Integrated Summary of Safety, Integrated Summary of Benefits and Risks, Post-Marketing Studies, 21 CFR 314.50(d)(5)(ix), (x) & (xi)	
Volumes 8.10-8.11	Case Report Form Tabulations for Study M93-013	—
Volume 8.12	Case Report Forms for Discontinuations due to Adverse Events, Deaths or Disease Progression for Study M93-013	
Volumes 9.1-9.4	Amendment #2: 4 Month Safety Update Report, 9/30/96	
Volumes 11.1-11.2	Amendment #3: Additional Requested Case Report Forms, 1/9/97	
Volume T53049	Amendment #5: Initial Response to FDA letter dated February 21, 1997, 3/20/97	
Volume T57618	Amendment #6: Further Response to FDA letter dated February 21, 1997, 4/7/97	

4.0 Chemistry/Manufacturing Controls

Please refer to the Chemistry Review.

Sponsor states (pg. 2 of application cover letter), "the microsphere [TAP-144-MC(3M)] powder used for Lupron Depot-4 Month 30 mg product is the same as that used for our approved product Lupron Depot-3 Month 22.5 mg, with the exception of the additional weight of the powder packaged in a vial." The additional drug quantity is intended "to provide adequate leuprolide blood levels over 16 weeks." Sponsor notes that the clinical and pharmacokinetics studies submitted to support this supplemental application were conducted using the Lupron Depot-4 Month 30 mg product proposed for marketing.

The depot formulation package contains a single-dose vial containing lyophilized powder and an ampule of diluent. It may be stored at room temperature until administered.

5.0 Animal Pharmacology/Toxicology

Please refer to the Pharmacology Review.

a. Pharmacodynamics

(1) Primary pharmacologic classification and mechanism of action:

Leuprolide acetate is a synthetic gonadotropin releasing hormone (GnRH) agonist analog which possesses greater potency than the natural hormone. When given continuously in therapeutic doses, it acts as a potent inhibitor of gonadotropin secretion. Chronic administration to animals and humans results in an initial stimulation, then prolonged suppression of ovarian and testicular steroidogenesis which is reversible upon discontinuation of drug treatment. In rats, leuprolide acetate administration results in growth inhibition of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and MBBA-induced mammary tumors in female rats) and atrophy of the reproductive organs.

(2) Other Actions: None known.

(3) Results of human studies (per 12/21/95 MOR of NDA #20-517 for Lupron Depot-3 Month 22.5 mg and its currently approved labeling):

Leuprolide acetate administration to humans results initially in increased circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), with correspondingly increased levels of the gonadal steroids, testosterone (T) and dihydrotestosterone (DHT) in males, and estrone (E₁) and estradiol (E₂) in pre-menopausal females. Ongoing continuous administration then results in decreased levels of LH and FSH, with corresponding reductions in sex steroid levels (T in males, and estrogens in pre-menopausal females) to the castrate range within two to four weeks after treatment initiation. In prostate cancer patients, castrate levels of testosterone have been demonstrated with continuous administration for periods of up to five years.

Leuprolide acetate is not active when given orally.

b. Pharmacokinetics (per 12/21/95 MOR of NDA #20-517 and currently approved labeling)

(1) Blood level data in humans:

Absorption: Following a single IM injection of the 3-month formulation (Lupron Depot 22.5 mg) in patients, the mean peak plasma leuprolide concentration was 48.9 ng/ml at 4 hours, which declined to 0.67 ng/ml at 12 weeks. The onset of steady-state levels was observed during the third week after dosing, when leuprolide appeared to be released at a constant rate with steady plasma concentrations through the 12-week dosing interval.

Although the assay employed in the study could not distinguish intact leuprolide from an inactive major metabolite, leuprolide levels remained detectable at all measurement points in all patients. The release pattern of an initial burst followed by rapid decline to a steady-state level was similar to that seen with the monthly formulation.

Distribution: In healthy male volunteers, the mean steady-state volume of distribution was 27 L and the mean systemic clearance was 7.6 L/hr following a 1 mg intravenous (IV) bolus dose of leuprolide. The terminal elimination half-life was approximately 3 hours based on a 2-compartment model. In vitro binding to human plasma proteins ranged from %.

Metabolism: In 5 prostate cancer patients, the major metabolite (Metabolite-I, a pentapeptide) reached maximum plasma concentrations 2 to 6 hours after dosing at approximately % of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately % of mean leuprolide concentrations. [Rats and dogs metabolize administered ¹⁴C-labeled leuprolide to smaller inactive peptides, the pentapeptide M-I, tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV), all of which may be further catabolized.]

(2) **Excretion:** Following administration of Lupron Depot 3.75 mg to 3 patients, less than % of the dose was recovered as parent and M-I metabolite in the urine.

(3) **Special Populations:** The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

c. **Toxicology:** Refer to Pharmacology Review.

6.0 Clinical Background

6.1 Relevant human experience

a. Previous similar human studies (Refer to section 6.2 below for information regarding approved GnRH analog drugs other than leuprolide acetate):

Clinical studies of leuprolide acetate treatment of metastatic prostate cancer patients (by daily subcutaneous and monthly IM depot injections) have shown that serum testosterone (T) is effectively suppressed after two to four weeks of treatment to a range similar to that observed in surgically castrate patients. This "medical castration" appears to be mediated by desensitization of the pituitary to stimulation by native GnRH with resulting suppression of gonadotropin release. Gonadal testosterone production is secondarily suppressed, with corresponding reduction of circulating T to castrate levels. The resulting androgen deprivation may cause both primary and metastatic androgen-dependent tumor proliferation to slow, stabilize, or regress, with possible reduction in pain related to metastatic skeletal lesions. In TAP-sponsored clinical studies of advanced prostate cancer, the sponsor has reported favorable objective responses in 72% to 86% of Lupron-treated patients, with most improving/stabilizing on Eastern Cooperative Oncology Group (ECOG) performance status.

The extended release depot formulation containing 22.5 mg of leuprolide (for administration at 12 week intervals) was studied in two pivotal safety and efficacy trials (#M91-583 and #M91-653), conducted to support marketing approval of NDA #20-517. The primary pivotal safety/efficacy trial (M91-583) studied 60 patients with Stage D2 (metastatic) prostate cancer. The objective of the secondary trial (M91-653) was to demonstrate therapeutic equivalence of the clinical formulation (of pilot plant manufacture) studied in M91-583 to the formulation proposed for marketing. Study M91-653 enrolled 33 patients with Stage D2 prostate cancer. Both studies were open-label, uncontrolled, multicenter trials (18 centers, of which two participated in both trials) of nearly identical design, in which the 22.5 mg depot formulation was administered as an IM injection every 12 weeks (84 days). The primary efficacy endpoint was serum T level suppression and maintenance, from baseline to castrate levels (defined as 50 ng/dl or less), as assessed by weekly blood sampling for 24 weeks. Study M91-583 included an expanded blood sampling schedule for a subgroup of patients, with serum LH and T₂ levels determined at half-weekly intervals during the last 2 weeks of the first two dosing periods and immediately following the week 12 depot injection. Clinical response to treatment and general safety parameters were assessed every 12 weeks. After the initial 24-week phase, patients were continued indefinitely on the study, with serum T level monitoring every 12 weeks, until clinical benefit was no longer evident. NDA approval was based primarily on the first 24 weeks data.

During FDA review of NDA #20-517, a discrepancy was noted in the reported serum T levels of treated patients. Despite T level determination by the same laboratory () that had assayed serum T concentrations for all prior TAP-sponsored Lupron trials in advanced-stage prostate cancer patients (i.e., Lupron administered by daily SC injection and by monthly 7.5 mg IM depot injection), on-treatment T values reported for studies M91-583 and M91-653 were consistently higher (while still in or near the castrate range) than those reported from the prior TAP-sponsored Lupron trials. This prompted an investigation of the discrepant findings, including re-examination of historical and contemporaneous T values of patients still active in the previous studies, and re-assay/validation of numerous samples by two separate methods¹ by both

) routinely uses either of two purification procedures to prepare serum samples for T level quantitation by () methodology. The appropriate purification procedure is determined by the range of T values expected in the samples to be assayed. Thus, a () procedure is sufficient to quantify T levels in the normal adult male range of approximately 300 ng/dl or higher. A () purification procedure () in which extraction from the serum sample is followed by () is utilized to enhance assay sensitivity and precision for T level determinations near the castrate range (approximately () ng/dl or less). The respective lower limits of testosterone detection for () are 10 ng/dl after () purification by the () versus 3 ng/dl after () purification by the ()

The investigation concluded that the higher-than-expected T levels resulted from inadvertent use of a _____ method _____ for the range of T levels expected in the M91-583 and M91-653 clinical samples, due to a communication error between TAP Pharmaceuticals Inc. and _____. Since T levels near the castrate range are expected with leuprolide administration, use of the more sensitive _____ is indicated to improve the accuracy of T level measurements in Lupron-treated prostate cancer patients. To confirm this explanation, all but 4% of the M91-653 clinical samples were re-assayed using the _____ for purification and the re-assayed T results were found to be consistent with prior Lupron study data.

The reanalysis of studies M91-583 and M91-653, using _____ derived data, showed that serum T was suppressed to castrate levels within 30 days in 87 of 92 (95%) patients and within an additional two weeks in three patients. In two patients, however, T levels did not suppress for 15 and 28 weeks, respectively. Once achieved, suppression was maintained in all except two patients: one with transient minimal T elevations; the other with serum T above the castrate range during the first 12-hour period after a subsequent injection (suggesting re-stimulation of gonadotropin secretion following a 12-week period of desensitization, referred to by the sponsor as an "acute-on-chronic" response). During the initial 24 weeks of treatment, the sponsor reported an 85% rate of "no progression" and normalization of PSA values (_____ ng/ml or less) in 63% of the patients.

- b. Literature references that are especially appropriate: None submitted.

6.2 Important information from related IND's and NDA's

Lupron Injection (leuprolide acetate 1 mg/0.2 ml for subcutaneous injection) was first approved in 1985 at the dosage of 1.0 mg SC daily for the palliative treatment of advanced prostate cancer. Lupron Depot (leuprolide acetate for depot suspension) – developed to provide prolonged continuous-leuprolide release – was first approved in 1989 as a 7.5 mg 28-day IM depot formulation, based on clinical study #M85-097, which demonstrated suppressed gonadal function in 53 evaluable treated patients with stage D2 prostatic carcinoma. In 1995, based on clinical studies #M91-583 and #M91-653 (see section 6.1, above), the 22.5 mg 3-month depot formulation was approved for IM dosing at 84-day intervals for palliative treatment of advanced prostate cancer.

The following formulations of Lupron have received FDA approval to date for the indications listed:

Product	NDA #	Approval Date	Labeled Indication
Lupron [®] Injection 1 mg/0.2 ml	✓19-010	4/9/85	Advanced Prostate Cancer
Lupron Depot 7.5 mg/vial	✓19-732	1/26/89	Palliative Treatment of Advanced Prostate Cancer
Lupron Depot 3.75 mg/vial	✓20-011	10/22/90	Management of Endometriosis
Lupron Depot-PED 7.5, 11.25, and 15 mg/vial	✓20-263	4/16/93 1/21/94	Treatment of Central Precocious Puberty
Lupron Depot 3.75 mg/vial	✓19-943	3/30/95	Treatment of Anemia Secondary to Uterine Fibroids
Lupron Depot-3 Month 22.5 mg/vial	✓20-517	12/22/95	Palliative Treatment of Advanced Prostate Cancer
Lupron Depot-3 Month 11.25 mg/vial	✓20-708	3/7/97	Management of Endometriosis Pre-op Treatment of Anemia Secondary to Uterine Fibroids

The approval of NDA #20-517 specified a Phase IV commitment requiring the sponsor to conduct a postmarketing study to further characterize the possible agonist effect of leuprolide following re-injections and to compare the response associated with the 1-month (28-day) and 3-month (84-day) depot formulations. On 9/13/96, the sponsor submitted a new protocol for study #M96-458 ("Phase IV Study Evaluating the Agonistic Stimulation of Serum Testosterone Following Re-injection with Lupron Depot-3 Month 22.5 mg and Lupron Depot 7.5 mg and Assessment of the PK/PD Relationship for Lupron Depot-3 Month 22.5 mg") to satisfy this commitment. Sponsor stated that the multicenter, randomized, open-label study (M96-458) would be conducted in 60 advanced stage prostate cancer patients – 30 receiving 4 monthly doses of the 7.5 mg formulation and 30 receiving 4 quarterly doses of the 3-month formulation – and would be initiated 3 to 4 weeks thereafter.

A second approved GnRH analog drug for palliative treatment of advanced prostate cancer is Goserelin acetate (Zoladex, NDA #19-726, sponsored by Zeneca). Zoladex was first approved in 1989 as a 3.6 mg 28-day subcutaneous (SC) implant, based on clinical evidence that the drug reduced mean serum T levels to the castrate range between treatment weeks 4 and 12, and that mean serum T levels remained suppressed at weeks 4, 8, and 12. In 1996, a 3-month (84-day) 10.8 mg depot formulation was also approved for treatment of advanced prostate cancer. In addition, the 3.6 mg depot formulation received approval in 1993 for monthly (28-day) treatment of endometriosis in premenopausal women.

GnRH analog drugs approved for indications other than prostate cancer include:

- (1) Nafarelin acetate (Synarel Metered Nasal Spray, sponsored by Syntex, marketed by Searle):
NDA #19-886 approved 1990 for treatment of endometriosis, and
NDA # 20-109 approved 1992 for treatment of precocious puberty.
- (2) Histrelin acetate (Supprelin, sponsored by RWJohnson/PRI, marketed by Roberts Labs):
NDA #19-836 approved 1991 for treatment of precocious puberty.

Native gonadotropin releasing hormone (GnRH) is also approved in two formulations:

- (1) Gonadorelin hydrochloride (Factrel Injection, marketed by Wyeth Ayerst)
NDA #18-123 approved 1982 for diagnostic use.
- (2) Gonadorelin acetate (Lutrepulse Kit, marketed by Ferring Labs):
NDA #19-687 approved 1989 for diagnostic use.

6.3 Foreign experience

On March 20, 1997, the sponsor stated that the Lupron Depot-4 Month 30 mg formulation had never been marketed nor studied in clinical research in any country other than the U.S.

6.4 Human pharmacology, pharmacokinetics, pharmacodynamics

Refer to Biopharmaceutics Review, which notes the following significant issues/recommendations:

- 1) The multiple dose pharmacokinetics (PK) of Lupron Depot-4 Month 30 mg have not been assessed in the target population for drug treatment;
- 2) The pharmacodynamic (PD) effect of Lupron Depot-4 Month 30 mg (suppression and maintenance of serum T levels within the castrate range) appears similar to that shown for the approved Lupron Injection, Lupron Depot 7.5 mg, and Lupron Depot-3 Month 22.5 mg formulations;
- 3) As observed with the previously approved Lupron Depot formulations, no PK/PD correlation could be established for the Lupron Depot-4 Month 30 mg formulation.
- 4) The above issues may be addressed by a post-approval requirement for a Phase IV multiple dose PK/PD study in the target population, including assessment of both leuprolide and testosterone levels after at least 3 administrations of the 4-month depot formulation.

The application references NDA's #19-010 (Lupron Injection 1 mg/0.2 ml) and #19-732 (Lupron Depot 7.5 mg/vial) for background information on the clinical pharmacology of leuprolide acetate.

The application includes the report of Study M93-012, a multicenter, open-label, clinical pharmacokinetics study, conducted in 24 orchiectomized prostate cancer patients at 5 investigational sites to evaluate plasma leuprolide levels following a single IM injection of the Lupron Depot-4 Month

30 mg formulation. PK findings from this study were reviewed by Dr. K. Gary Barnette, Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation II, Office of Clinical Pharmacology and Biopharmaceutics. For safety information pertinent to this study, refer to section 8.1.2, below.

6.5 Other relevant background information

According to recent statistics published by the American Cancer Society (Parker SL et al, 1996), prostate cancer is the most common malignancy in US men with an estimated 1996 incidence of 317,100 new cases/year, accounting for 41% of all new invasive malignancies in American men. Its course is unpredictable, ranging from an asymptomatic, indolent condition to a virulent malignancy with rapid progression to bone metastases and death (Garnick MB, 1993). Its 1996 mortality is estimated at 41,400 American men/year, which accounts for 14% of male cancer deaths, making it the second leading cause of cancer mortality (after lung cancer) in American men. American males face a 1 in 5 overall lifetime probability of developing invasive prostate cancer, with markedly rising risk associated with increasing age, especially after age 50. In addition, African Americans are disproportionately affected by prostate cancer incidence and mortality, with an incidence of 264 per 100,000 African American men compared with 194 per 100,000 Caucasian men (Michigan Cancer Statistics, 1995). For the year 1992, prostate cancer mortality comprised 9.4% of all cancer deaths (5485 deaths due to prostate cancer) among African Americans and 6.3% of all cancer deaths (28,430 deaths due to prostate cancer) among Caucasians. By comparison, the proportion of 1992 cancer mortality due to female breast cancer was 8.3% of cancer deaths among both Caucasian and African American women (37,797 and 4779 deaths due to breast cancer, respectively). The most important known risk factors for prostate cancer are age, race, and family history in a first degree relative (father, brother or cousin). Current guidelines for prostate cancer screening (Porter AT et al, 1996) suggest a Digital Rectal Exam (DRE) and Prostate Specific Antigen (PSA) starting at age 40 for high risk men (i.e., men of any race with a family history of prostate cancer in a first degree relative, and all African American men) and at age 50 for all other men with a life expectancy of more than 10 years.

Since metastatic prostate cancer remains incurable, the primary goals of treatment are to improve the quality of remaining life and to increase the time to progression and perhaps survival. With androgen deprivation treatment, 70% of men with metastatic disease will experience a symptomatic and often a clinical regression, but most will relapse within 18 to 24 months. In view of this short life expectancy, the most clinically significant endpoint of treatment is quality of life, especially regarding issues of immediate and long-term impotence, urinary symptoms including incontinence, degraded bowel function, pain, altered social function, and treatment-associated risks. Unfortunately, standardized, validated and well-accepted measurement instruments for these quality of life issues are still being developed.

Despite the availability since 1985 of GnRH agonist treatment (Lupron Injection 1 mg/0.2 ml) for "medical castration," and the availability since 1988 of combination leuprolide/flutamide treatment for "total androgen blockade," orchiectomy has remained the gold standard for prostate cancer treatment. "Total androgen blockade" remains controversial because of lingering questions regarding the role of adrenal androgens in the disease process and the uncertain advantage of concomitant antiandrogen

treatment. To address these questions, a systematic international meta-analysis was recently undertaken of the available evidence, using individual patient data from 5,710 patients enrolled in 22 of the 25 known randomized trials with a "maximum androgen blockade" treatment arm (i.e., castration plus an antiandrogen: flutamide, cyproterone acetate, or nilutamide) versus surgical or medical castration alone. Crude mortality rates over a median follow-up period of 40 months, during which 3283/5710 or 57% of the patients died, were 58% for castration alone and 56% for "MAB." Life-table estimates of the corresponding 5-year survival rates were 22.8% and 26.2%, respectively, indicating a non-significant survival difference of 3.5% (95% CI 0-7%) in favor of "MAB." Since no obvious sources of bias could account for the results, the authors concluded that the available evidence from randomized trials did not demonstrate that "MAB" results in longer survival than conventional castration. (Prostate Cancer Trialists' Collaborative Group, 1995). A possible explanation for these negative findings may relate to the late effect of prolonged androgen deprivation (which causes prostate adenocarcinoma cells to become apoptotic) to facilitate the inevitable emergence of more undifferentiated, androgen-independent tumor cells. (Middleman MN et al, 1996).

Castrate serum levels of testosterone have traditionally been defined as less than 50 ng/dl based on measurement in prostate cancer patients post-orchietomy. However, this standard of surgical castration was established, prior to the availability of highly sensitive technology, using methods of lower sensitivity and specificity, including urinary ketosteroid excretion assays (which cross react with various adrenal androgens). With current assay methods, castrate levels of testosterone are usually considerably less than 50 ng/dl, as demonstrated by recent data from trials of Lupron and Zoladex for prostate cancer. Clinical data from the pivotal trials supporting these approvals demonstrated surgical castration levels generally less than 30 ng/dl and both surgical and medical castration levels frequently as low as 15 ng/dl (Sharifi R et al, 1990). Variations in testosterone assay procedures may still confound the clinical interpretation of levels near the 50 ng/dl range, however (see section 6.1, above).

6.6 Directions for Use

Refer to section 11.0, below, for reviewer's comments regarding the Dosage and Administration section of the proposed labeling.

7.0 Description of Clinical Data Sources

This NDA supplement contains the reports of two clinical trials:

Study #M93-013: "Safety and Efficacy Study of a Four-Month Depot Formulation of Leuprolide in Patients with Stage D2 Prostatic Adenocarcinoma," an uncontrolled pivotal safety/efficacy trial in 49 target population patients;

Study #M93-102: "Pharmacokinetics of a Four-Month Depot Formulation of Leuprolide in Prostate Cancer Patients," an uncontrolled human pharmacokinetics study designed to measure plasma leuprolide levels for 20 weeks following a single IM injection of the Lupron Depot-4-Month 30 mg formulation in 24 orchietomized prostate cancer patients.

8.0 Clinical Studies

8.1 Indication

For the palliative treatment of advanced prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

8.1.1 Reviewer's Trial #1: Sponsor's Protocol #M93-013 (Protocol date April 1993; Amendment #1 incorporated January 1994)

8.1.1.1 Objective/Rationale

Objective of the study:

To demonstrate the effectiveness – defined as sustained suppression of serum testosterone levels to the castrate range during the first 32 weeks of treatment – and safety of the 30-mg formulation injected once every 16 weeks in advanced stage prostate cancer patients.

Rationale for the study:

Since approximately 80% of prostate cancer patients have androgen-dependent disease, suppression of serum testosterone to castrate levels may favorably modify the course of disease progression. Clinical studies using both the daily SC injection (Lupron Injection 1 mg/0.2 ml) and the depot IM formulations (Lupron Depot 7.5 mg/vial and Lupron Depot-3 Month 22.5 mg/vial) have demonstrated effective T suppression to castrate levels with maintenance during long-term treatment and potential remission or stabilization of disease, reduced pain, increased daily activity (performance status), and improved quality of life. The 30-mg depot formulation, with its 16-week dosing interval, is intended to increase patient acceptance of the dosing schedule.

8.1.1.2 Design

A Phase III, open-label, uncontrolled, multicenter clinical trial conducted at 17 investigational sites (refer to section 8.1.1.4.1, below).

8.1.1.3 Protocol

8.1.1.3.1 Population

a. Demography

40 male patients with Stage D2 (metastatic) prostatic adenocarcinoma were to be recruited by the principal investigators

b. Inclusion criteria:

- (1) Stage D2 prostate adenocarcinoma, histologically confirmed, i.e., bone metastases, lymph node metastases above the aortic bifurcation, or metastases to other sites such as liver or lung;
- (2) Two or more clinically measurable or evaluable lesions, including the prostate (if present), skeletal or visceral metastases and/or lymph node metastases above the aortic bifurcation;
- (3) Prestudy serum T concentration at least ng/dl;
- (4) ECOG performance status 0, 1, or 2, per the ECOG Performance Scale:
 - 0 = fully active
 - 1 = ambulatory/able to carry out light or sedentary work
 - 2 = ambulatory/capable of self-care/
up and about more than % of waking hours
- (5) Recovered from effects of any major surgery;
- (6) Signed voluntary informed consent.

c. Exclusion criteria:

- (1) Absence of an intact hypothalamic-pituitary-gonadal axis (e.g., prior orchiectomy, hypophysectomy, or adrenalectomy);
- (2) Antineoplastic medication within 4 weeks prior to the initial depot injection or during the study (e.g., estrogen, antiestrogen, progestogen, antiandrogen, other steroid treatment, chemotherapy); [Amendment #1 -- incorporated January 1994 -- permitted antiandrogen treatment during the study after week 32]
- (3) Prior GnRH analog treatment;
- (4) Current radiation therapy (including implants) to a site of primary, recurrent, or metastatic disease;
- (5) Life expectancy less than 12 months;
- (6) Underlying disease that would place the patient in additional jeopardy by participating in the study.

8.1.1.3.2 Procedures

a. Specific formulations used in study:

"Abbott-43818": Leuprolide acetate for depot suspension (Lupron Depot-4 Month):
Lyophilized microspheres of leuprolide (30 mg) incorporated into a biodegradable polylactic acid polymer (mg) with mannitol (mg);
Lot # 79-423-S2 used in clinical trial.

Diluent: 2 ml ampule of solution containing carboxymethylcellulose sodium (mg),
mannitol (mg), polysorbate 80 (mg) and water for injection, USP;
Lot #79-424-S2 used in clinical trial.

Just prior to injection, the preparation was reconstituted by withdrawing 1.5 ml of the diluent from the ampule and injecting it into the vial containing the lyophilized powder. After shaking, the resulting suspension was withdrawn into a syringe and injected IM (usually gluteal) using a 22-gauge needle. Injection sites were to be rotated and the previous injection site examined at the time of the next injection.

b. Type of experimental controls:

Determinations of serum T levels (primary efficacy endpoint) by a central laboratory
Per discussion with Dr. Jean Fourcroy, Urology Medical
Officer, HFD-580, and primary reviewer of GnRH analogs for use in prostate cancer, these procedures are considered appropriate and adequate as the primary surrogate endpoint for the palliative treatment of advanced stage prostate cancer.

c. Dosage schedule, duration of use, and route of administration:

Lupron Depot 30 mg by IM injection was to be administered every 16 weeks, or once every 112 days. Based on previous clinical data, this regimen seems appropriate.

d. Desirable concomitant medications: None specified.

8.1.1.3.3 Endpoints

Efficacy

a. Primary:

Serum testosterone (T) and LH levels were determined at baseline and on post-treatment days 4 and 7, at the end of weeks 2 through 20, 22, 24, 26, 28, 30, 32, and every 16 weeks thereafter, and at 4-hours, 8-hours, and 12-hours following the week-16 depot injection (to assess whether a stimulatory effect, due to incomplete pituitary down-regulation, was present; see section 8.1.1.4.2, pg 26 below) in all subjects. In a subgroup of patients

(selected by their voluntary participation in an "expanded blood collection schedule"), LH and T levels were also determined at weeks 14.5, 15.5, 16.5, 30.5, 31.5, and 32.5. Blood samples were sent to _____ on a weekly basis until all patients completed the first 32 weeks of the study.

On-treatment levels of 50 ng/dl or less were considered clinically successful, with individual patients classified as "responders" or "nonresponders" according to whether their serum T level reached 50 ng/ml or less ("castrate") for two consecutive tests within the first 8 weeks after the first depot injection. "Responders" were further classified as persistent responders or "escapes" from successful treatment based on whether their serum T levels exceeded 50 ng/ml on 2 consecutive tests ("escape") after having achieved castrate levels on 2 consecutive tests. "Nonresponders" and patients with "escape" from T suppression were continued on study at the discretion of the investigator.

b. Secondary:

(1) Clinical/Tumor Evaluation, by physical examination and tumor lesion evaluation, consisting of digital rectal examination (DRE), bone scan, and other imaging procedures, if necessary, to determine "objective tumor response":

"Complete response" defined as total disappearance of tumor masses and/or osteoblastic/osteolytic lesions, normalization of all pretreatment laboratory abnormalities (i.e., acid phosphatase elevation, liver function abnormalities) and/or hepatomegaly, and without significant cancer-related weight loss (> 10%), symptom worsening, or performance status deterioration;

"Partial response" defined as reduction (> 50%) in cross-sectional area of at least one tumor mass or in liver size/function (30% or greater improvement), with associated non-progression or normalization of all other tumor indicators;

"Objectively stable" defined as no new lesions or significant increase (> 25%) in cross-sectional area of measurable lesions or of hepatomegaly (> 30%); non-progression or improvement in osteoblastic/osteolytic lesions, acid phosphatase, liver function; and without significant cancer-related deterioration in weight (> 10%), symptoms, or performance status;

"Progression" defined as any significant cancer-related deterioration in weight, symptoms, performance status, appearance of new areas of malignant disease, or increase in any previously measurable lesion by > 25% cross-sectional area.

(2) Serum levels of prostate-specific antigen (PSA) (assayed by _____ prostatic acid phosphatase (PAP), and alkaline phosphatase (both assayed at _____

(3) ECOG Performance status assessment.

Safety

a. Clinical studies:

History and physical examinations, adverse event/concomitant medication reporting at baseline and weeks 16 and 32;

b. Laboratory studies:

Routine clinical chemistries, hematology, urinalysis at baseline and weeks 16 and 32;

c. Indications for removing a patient from the study:

Serum T exceeds 50 ng/dl on two consecutive measurements, i.e., "nonresponse" or "escape" as defined above (see Primary Efficacy Endpoint). Dropouts not replaced.

8.1.1.3.4 Statistical analysis plan

Study results were to be summarized at the conclusion of 32 weeks of treatment or withdrawal of all enrolled subjects. All data were summarized using the Statistical Analysis System (SAS Institute, Inc., Version 6.09), with significance defined for any test as a p-value 0.050 or less (rounded to 3 digits), based on two-tailed tests. For all variables, baseline was defined as the final value obtained before the start of study drug administration. On-treatment data were grouped into time intervals (categorized visits) according to the midpoints between scheduled visits or collection times for each variable. If multiple values were obtained for a hormone variable during an interval, the maximum value was used in analysis; for non-hormone data, the value closest to the scheduled collection time was used.

For pivotal efficacy and safety analyses, the analyzed data were selected using cut-off conventions for the number of days after the second (or last for dropouts) injection. The duration of treatment for any injection was defined to be 112 days, and all analyzed data for any laboratory variable were obtained no later than $112 + 15 = 127$ days after the second injection. For clinical response variables, data obtained up to $112 + 43 = 155$ days after the second injection were used in analysis.

Summary statistics were calculated for the baseline characteristics of age, race, height, weight, and baseline disease status (time since prostate cancer diagnosis, prior treatments, DRE results, and performance status). The primary efficacy analysis focused on suppression of serum T levels during the first 32 weeks of treatment, and estimated the proportion of patients who achieved "T suppression" (defined as 50 ng/dl or less for 2 consecutive tests within 8 weeks after the first depot injection) and the proportion of suppressed patients who experienced "escapes" from T suppression (defined as T levels greater than 50 ng/dl for 2 consecutive tests after achieving suppressed T levels). One-sided exact 95% confidence bounds were calculated on these estimates using the binomial distribution. Median duration was not estimated, since suppression continued beyond 32 weeks in most patients. Summary statistics were also

provided for T and LH values at each categorized visit with and without respect to the time of the second injection; at 4-hours, 8-hours, and 12-hours following the week 16 injection; and for the subgroup participating in the "expanded blood collection schedule" during weeks 14, 14.5, 15, 15.5, and 16. Linear trends were tested across time by repeated measures analysis of variance. Paired t-tests were used to analyze mean changes from baseline in T and LH at weeks 16 and 16.5, at weeks 32 and 32.5, and at times 0, 4-hours, 8-hours, and 12-hours post-dose after the second injection, to evaluate responses (see section 8.1.1.4.2, pg 26 below).

Secondary efficacy analyses included summarization at weeks 16, 32, and "final visit" of the proportions of patients with graded outcomes on objective tumor response, and changes from baseline in prostatic DRE findings, PSA, PAP, and performance status.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

During the recruitment period (October 1993 through April 1994), 17 investigational sites enrolled a total of 49 men, of whom 45 completed the first 32 weeks of the study and were considered evaluable for the primary efficacy analysis. Sponsor states, "the enrollment goal of 40 was exceeded because 9 patients were enrolled within 4 days after the 40th patient had been dosed" (Vol. 8.9, p 011). Although the long term phase of the study is ongoing, the last patient completed the initial 32 weeks of treatment in December 1994, and, per prior FDA/sponsor agreement, the efficacy data from only the first 32 weeks of treatment were to be considered pivotal. While all treated patients were analyzed for safety, only the evaluable population was initially analyzed for efficacy. In response to a request for intent-to-treat (ITT) analyses as the basis for all labeling claims (FDA letter to sponsor dated 2/21/97), ITT analyses for all efficacy outcomes were submitted as Amendment #5. At the end of the initial 32-week treatment period, 43 patients continued into the long-term treatment period.

The participating investigators are listed below and on the next page.

Investigator	Institution	Location	# Pts Enrolled
Austenfeld	Univ. of Kansas Medical Center	Kansas City, KS	2
Childs	Brookwood Urology	Birmingham, AL	2
Ercole	St. Paul-Ramsey Medical Center	St. Paul, MN	1
Fowler	Univ. of Mississippi Med Center	Jackson, MS	1
Kandzari	West Virginia University	Morgantown, WV	1
Knoll	Ctr. for Urologic Treatment & Research	Nashville, TN	5
Kramolowsky	The Virginia Urology Center	Richmond, VA	8

Investigator	Institution	Location	# Pts Enrolled
Krasnow	VA Medical Center	Washington, DC	1
Lynch	Georgetown University Hospital	Washington, DC	2
Ning	Western Urological Associates, PC	Denver, CO	2
Patterson	University of Tennessee	Memphis, TN	3
Ross	Hattiesburg Clinic	Hattiesburg, MS	1
Sanfilippo	Urology Associates	Birmingham, AL	4
Sharifi	University of Illinois/VA Med. Center	Chicago, IL	8
Smith	Vanderbilt University	Nashville, TN	4
Tuttle	Clinic for Urologic Wellness	Lexington, KY	1
Zinner	Doctor's Urology Group	Torrance, CA	3

DEMOGRAPHICS:

For evaluable patients, the mean age was 70 years (range . . . years), mean height 69 inches (range . . . inches), and mean weight 172 pounds (range . . . lbs). The racial distribution was 51% Caucasian, 47% Black, and 2% Hispanic. Demographics were essentially unchanged for the ITT population, with 49% Caucasian (n=24), 49% Black (n=24), and 2% Hispanic (n=1) men enrolled.

Prostate cancer diagnosis occurred at a mean of approximately 7 months (0.6 years) prior to enrollment, with 31/45 (69%) of the evaluable patients having been diagnosed within 3 months, and 43/45 (96%) within 3 years of study entry. One month or more prior to entry, 16/45 (36%) of the patients had received prostate cancer treatment, which included radiation therapy (RT) alone (4 patients), prostatic resection (TURP) alone (5 patients), radical prostatectomy alone (1 patient), ketoconazole alone (1 patient), or combinations of these treatments (5 patients). Despite prior treatment, all 16 previously treated patients had qualifying baseline serum T levels.

DROPOUTS

Patients who completed at least 225 study days and received at least 3 injections were considered to have completed the study. At or prior to week 32, 6 patients terminated from the study. During the long-term treatment phase, 17 additional patients terminated from the study for a total of 23 patients who dropped out by the data cutoff date for the safety update (9/7/96). Pertinent details regarding these patients are noted below.

During the First 32 Treatment Weeks:

<u>Pt #</u>	<u>Age/Sex/Race</u>	<u>#Days in Study</u>	<u>#Injections Rec'd</u>	<u>Reason for Dropout</u>
70M	Black	113	2	Progressive Disease/Sxs: Increased lymphadenopathy @ week 16 CT scan;
79M	Caucasian	111	1	Death due to prostate cancer
60M	Caucasian	225	2	Pt request: Refused week 32 injection; Prefers monthly inj/local MD f/u
80M	Black	195	2	Death due to prostate cancer
68M	Black	153	2	Adverse Event: Increased back pain, Weight loss
70M	Black	183	2	Progressive disease/Symptoms

In summary, the primary reasons for premature termination during the first 32 weeks of treatment were:

<u>REASON for Dropout</u>	<u>Number of Patients</u>
Death from Prostate Cancer	2
Worsening of Disease	2
Adverse Event	1
Patient Request	1
Total	6

During the Long Term Treatment Phase:

<u>Pt #</u>	<u>Age/Sex/Race</u>	<u># Days in Study</u>	<u>Reason for Termination</u>
81M	Caucasian	898	Death due to respiratory failure
77M	Caucasian	648	Death due to prostate cancer
72M	Caucasian	730	Death due to prostate cancer
77M	Caucasian	621	Death due to prostate cancer
60M	Black	416	Death due to prostate cancer
65N	Oriental	450	Adverse Event: Fever, Thrombocytopenia; Death due to prostate cancer

During the Long Term Treatment Phase (continued from previous page):

<u>Pt #</u>	<u>Age/Sex/Race</u>	<u># Days in Study</u>	<u>Reason for Termination</u>
75M	Black	417	Death due to acute MI
62M	Caucasian	692	Worsening of Disease/Symptoms: Lymph node mets obstructing iliac vessels causing thrombosis s/p orchiectomy
66M	Black	446	Adverse Event: Abnormal liver function tests
71M	Caucasian	437	Death due to prostate cancer
61M	Caucasian	253	Worsening of Disease/Symptoms: Elevated PSA, Right scapular pain, RT, possible chemo/flutamide Rx
63M	Caucasian	712	Patient Request: Prefers to follow PSA alone
64M	Caucasian	449	Worsening of Disease/Symptoms: Bone marrow involvement requiring chemotherapy
68M	Caucasian	654	Death due to unknown cause
56M	Caucasian	605	Noncompliance with visit schedule
76M	Black	673	Adverse Event: Cerebrovascular accident
68M	Black	400	Death due to prostate cancer

In summary, the primary reasons for premature termination during the long term treatment phase (i.e., by the data cutoff date for the safety update) were:

REASON for Dropout	Number of Patients
Death from Prostate Cancer	6
Worsening of Disease	3
Death from other cause	3
Adverse Event	3
Patient Request	1
Non-Compliance with visit schedule	1
Total	17

PROTOCOL VIOLATORS:

During the first 32 weeks of the study, all data from 4 patients were excluded from the efficacy analyses because of protocol violation. A fifth patient (Pt see below) had his efficacy data excluded for week 32 only because the injection was delayed by more than 14 days.

Patients Excluded from Efficacy Analysis during the First 32 Weeks:

<u>Pt #</u>	<u>Age/Sex/Race</u>	<u># Days in Study</u>	<u># Injections Received</u>	<u>Reason for Exclusion from Efficacy Analysis</u>
68M	Black	153	2	No qualifying baseline T result T result (T = 131 ng/dl)
70M	Black	113	2	No qualifying baseline T result T result (T = 133 ng/dl)
58M	Black	756	7	Insuff evidence of metastatic lesions
71M	Caucasian	740	7	Insuff evidence of metastatic lesions

In summary, the primary reasons for exclusion of efficacy data during the first 32 weeks of treatment were the following protocol violations:

<u>REASON for Exclusion</u>	<u>Number of Patients</u>
Insufficient Evidence of Metastatic Lesions	2
No Qualifying Baseline Testosterone Result	2
Total	4

During the long term treatment phase, specific efficacy data were excluded in additional patients for the reasons indicated below.

Patients Excluded from Efficacy Analysis during the Long Term Phase:

<u>Pt #</u>	<u>Rx Days (Weeks) Excluded</u>	<u>Specific Data Excluded</u>	<u>Reason for Exclusion</u>
	246 (35) and 477 (68)	T, LH, PSA, PAP; DRE @ day 246 only	Procedures within 28 days after late injection
	801 (114)	T, LH, PSA, PAP	Procedures within 28 days after late injection

**Patients Excluded from Efficacy Analysis during the Long Term Phase
(continued from previous page):**

<u>Pt #</u>	<u>Rx Days (Weeks) Excluded</u>	<u>Specific Data Excluded</u>	<u>Reason for Exclusion</u>
	469 (67) and 722 (103)	T, LH, PSA, PAP	Procedures within 28 days after late injection
338 (48)		T, LH, PSA, PAP	Antineoplastic Rx (5-FU) for prostate ca
607 (87)		T, LH, PSA, PAP	Procedures within 28 days after late injection
605 (86)		T, LH, PSA, PAP	Procedures within 28 days after late injection

REVIEWER'S COMMENT: Although this analytic methodology ("evaluable" analysis) may be accepted for secondary efficacy analyses, all primary efficacy analyses should be based on the intent-to-treat population (i.e., using all available data). As noted above (section 8.1.1.4.1, pg 17) in response to a written request, (FDA letter to sponsor dated 2/21/97), the sponsor submitted ITT analyses for all efficacy endpoints (Amendment #5 to this application; see section 8.1.1.4.2, below, for results of these analyses).

CONCURRENT MEDICATIONS:

Concurrent medications were used by 47/49 patients (96%) during the first 32 weeks of treatment, and by all patients (100%) during the long term treatment phase. The most common categories of concomitant medications are listed below (adapted from Sponsor's Statistical Table 11 and Appendix B.10, NDA vol. 9.1):

Drug Class	Patients = 49	
	n	(percent)
Total Patients with Any Usage	49	(100%)
Analgesics/Antipyretics/ Anti-inflammatory agents	37	(76%)
Opiate agonists	26	(53%)
Antitussives	22	(45%)
Anti-Gout agents	21	(43%)
Anticoagulants	19	(39%)
Oral Minerals/Electrolytes	16	(33%)
Anxiolytics/Sedatives/Hypnotics	14	(29%)
Histamine H-1 Receptor Antagonists	13	(27%)
Antacids/Adsorbents	12	(25%)
Diuretics	12	(25%)
Hormones and Synthetic Substitutes	12	(25%)

Drug Class (continued from previous page)	Patients = 49	
	n	(percent)
Adrenal Corticosteroids	11	(22%)
Histamine H-2 Receptor Antagonists	11	(22%)
Sympathomimetic agents	11	(22%)
Urinary anti-infectives	11	(22%)
Antibiotics	10	(21%)
Antiemetics	10	(21%)
Saline Laxatives	10	(21%)

Protocol Amendment #1 (effective January 1994) permitted antiandrogen treatment to be added to the regimen after the first 32 weeks of study drug treatment at the discretion of the investigator. During the long term phase of the study, the following 11 patients received flutamide. All efficacy data obtained in these patients after the initiation of flutamide treatment were identified as such by the sponsor.

<u>Pt #</u>	<u>Time Flutamide Treatment Initiated</u>
	Week 49
	Week 81
	Week 40
	Week 100
	Week 59
	Week 81
	Week 35
	Week 79
	Week 80
	Week 80
	Week 85

COMPLIANCE WITH DRUG REGIMEN:

Although the study required a 112-day dosing interval, the number of days between injections ranged from _____ days (median 112 days). In 5 patients, the week 16 or 32 injection was delayed by 3 or more days (median 3.5 days, range _____ days). In these patients, the T levels just prior to delayed dosing were all within the castrate range (including any values excluded from the efficacy analysis), as were the T levels next measured (if performed).

<u>Pt #</u>	<u>Age/Sex</u>	<u>Day of First Injection</u>	<u>Day of 2nd Injection (# Days Delayed)</u>	<u>Day of 3rd Injection (# Days Delayed)</u>
	72M	1	113 (on time)	246 (21 days)
	62M	1	117 (4 days)	232 (3 days)
	72M	1	116 (3 days)	225 (on time)
	61M	1	117 (4 days)	225 (on time)
	59M	1	116 (3 days)	226 (on time)

8.1.1.4.2 Efficacy endpoint outcomes

PRIMARY EFFICACY OUTCOME: SERUM TESTOSTERONE LEVELS

Rounded to 3 significant figures, the mean baseline serum T levels were 411 ng/dl with a range of _____ ng/dl for all enrolled patients (Statistical Table 13, NDA vol. 9.1). Following the initial depot injection, evaluable T levels increased on day 4 to a mean of 660 ng/dl, then declined to 401, 104, and 28.9 ng/dl at weeks 1, 2, and 3, respectively, and remained within the castrate range (50 ng/dl or less) with mean levels below 15 ng/dl at all subsequent time points. Testosterone suppression (defined as T values of _____ ng/dl or less for 2 consecutive tests within 8 weeks after the first depot injection) was achieved by 39/45 or 87% of the evaluable patients (84% of the intent-to-treat population) by week 3, by 43/45 or 96% (94% by ITT) by week 4, and by all patients (including those whose data were excluded from efficacy analysis, per Appendix B.11, NDA vol. 9.2) by week 6, yielding a one-sided lower 95% confidence bound of 94% for the proportion of patients achieving suppression. The median time to onset of castrate levels for all patients during the initial 32 week treatment period was 22 days, with a range of 9 to 43 days.

Once achieved, suppression was maintained throughout the initial 32 week treatment period in all except two (Pts _____) of the 49 enrolled patients. In both cases, the T elevations ("escape" from testosterone suppression - defined as serum T levels above _____ ng/dl on 2 consecutive tests after levels of _____ ng/dl or lower had been achieved on 2 consecutive tests - or transient T elevation above the castrate range) occurred during the first week following the second depot injection and thus are more appropriately classified as "acute-on-chronic" responses (see pg. 26, below).

Since T suppression continued beyond 16 weeks in most patients, median duration of long term efficacy was not estimated. However, the adequacy of the 4-month dosing interval was explored by measuring T levels at half-weekly intervals during the last weeks of the first and second dosing periods (weeks 14, 14.5, 15, 15.5, 16, and weeks 30, 30.5, 31, 31.5, 32, respectively) in a subgroup of 11 patients (Pt _____).

In this subgroup, no significant linear trend was observed over time in the means for either serum T (range _____ ng/dl during weeks 14 to 16; range _____ ng/dl during weeks 30 to 32) or LH (range _____ mIU/ml during weeks 14 to 16; range _____ mIU/ml during weeks 30 to 32) for either dosing interval.

During the long-term treatment phase of the study, two patients (Pts _____) experienced "escapes" from testosterone suppression on T level assessments just prior to the week 48 injection. Their cases are summarized below.

Patient

This 67-year-old Black man was diagnosed with adenocarcinoma of the prostate, Gleason grade 9 with capsular and periprostatic fat invasion, by needle biopsy 3 weeks prior to study enrollment. During prestudy evaluation, the prostate was enlarged (4.5 x 4.0 cm by DRE), extensive metastatic disease.

of skull, spine, ribs, sacrum, iliac bones, ischium, and trochanteric femurs was present on bone scan, and chest x-ray revealed a moderate left pleural effusion. Past medical history was significant for longstanding asthma and arthritis, with chronic medications of Primatene mist and acetaminophen PRN, and a history of ethanol abuse. Baseline serum T level of 258 ng/dl rose to 405 ng/dl 4 days after the initial Lupron Depot injection. T levels then dropped to 45, 26, and 6.1 ng/dl at post-dose weeks 1, 2, and 3, respectively, and remained at castrate levels (range ng/dl) through the week 32.5 evaluation. At week 16, the clinical tumor response was objectively stable, with performance status "1" (restricted strenuous activity but ambulatory and able to carry out light work or pursue a sedentary occupation). At week 32, the clinical tumor response was objectively stable, with performance status "0" (fully active without restriction). The sole reported adverse event was mild, intermittent hot flushes of onset prior to the second injection. At week 48 (treatment day 338, or 112 days after the week 32 injection), his T level was found to be 433 ng/dl (414 ng/ml on repeat determination) with LH 12.0 mIU/ml prior to the fourth Lupron Depot injection. Concomitant flutamide treatment was initiated 10 weeks thereafter with T levels subsequently ranging ng/dl from samples drawn on treatment days 366 (week 52), 50 (week 64), 534 (week 76), 646 (week 92), and 758 (week 108). As of 10/96, he continued in the study with concomitant flutamide and no further adverse events reported nearly 2.5 years after original diagnosis.

Patient

This 68-year-old Black man was diagnosed with moderately-differentiated adenocarcinoma of the prostate, Gleason grade 7, on transrectal prostate biopsy 2 weeks prior to study enrollment. During prestudy evaluation, the prostate was enlarged (40 grams by DRE) and bone scan revealed multiple asymmetric foci of abnormal uptake consistent with metastatic disease. Past medical history was significant for constipation without clear etiology, nailbed fungal infections, a small left testicle, and no chronic medications. Baseline serum T level of 337 ng/dl rose to 881 ng/dl 4 days after the initial Lupron Depot injection. T levels then dropped to 236, 64, and 48 ng/dl at post-dose weeks 1, 2, and 3, respectively, and remained at castrate levels (range ng/dl) through the 32nd week. At week 16, the clinical tumor response was inconclusive; by week 32, progressive disease was evident on bone scan with performance status "0" (fully active without restriction). Concomitant treatment with Colace was begun at week 32 for persistent constipation. At week 40 he was hospitalized for paralytic ileus, due to metastatic prostate cancer to the colon (per colon biopsy), and started on Percocet for pain. At week 48 (treatment day 338, or 112 days after the week 32 injection), paralytic ileus persisted and his T level was found to be 86 ng/dl prior to the fourth Lupron Depot injection. He died of prostate cancer less than 3 months thereafter, nearly 14 months after initial diagnosis.

SERUM LH LEVELS:

On initial post-injection day 4, a mean increase over baseline values was observed, followed by a decline to below pretreatment levels by week 1, and a further decline to the lower end of the normal range (3-10 mIU/ml) by week 3, where it remained through week 32. These results were essentially unchanged for the intent-to-treat population.

"ACUTE-ON-CHRONIC" RESPONSE:

Stimulation of the hypothalamic-pituitary-gonadal axis, with consequent increase in serum LH and T over pretreatment levels, characteristically occurs during the initial weeks of treatment with GnRH analogs and may be associated with transient exacerbations of symptoms. As described above, this pattern of an early "spike" in LH and T levels was observed on day 4 after the initial depot injection of the 30-mg formulation.

To explore whether this stimulatory pattern recurred after subsequent depot injections of the 30-mg formulation response: acute leuprolide-induced stimulation of gonadotropin secretion in the setting of chronic leuprolide-induced gonadotropin suppression, indicating persistent pituitary gonadotropin reserve and stimulating secondary testosterone secretion, with potential flare of disease activity), LH and T levels were determined at 4-hours, 8-hours, and 12-hours after the week-16 injection, and in a subgroup of patients also at 3-5 days after the depot injections at weeks 16 and 32 (i.e., at weeks 16.5 and 32.5, respectively). In comparing these values with the mean values obtained just prior to the week-16 and week-32 depot injections, no clinically significant differences were found. Although the mean rise in LH levels 3-5 days after the week-32 injection was statistically significant ($p=0.007$), the measured values rose from 4.7 (± 0.7 SD) mIU/ml to 5.2 (± 1.1 SD) mIU/ml, a change well within the normal range. The increases in mean LH following the week-16 injection were also statistically significant ($p < 0.001$ at 4-hours, $p < 0.01$ at 8-hours, $p < 0.05$ at 12-hours) while the specific values consistently remained within the normal range. Since the highest individual LH value on this day was 8.3 mIU/ml, a level notably below the original baseline mean of 13.5 mIU/ml, these statistically significant changes were not considered clinically significant.

The changes in mean T observed at 4-hours, 8-hours, and 12-hours after the week 16 depot injection were not statistically or clinically significant except in the two patients who experienced "escape" from prior pituitary suppression, with detectably increased testosterone secretion. Their cases are summarized on the following pages. When re-analyzed for the intent-to-treat population, these LH and T results were essentially unchanged.

Pt

This 75-year-old Black man was diagnosed with moderate to poorly-differentiated adenocarcinoma of the prostate during TURP for BPH 5.5 years prior to study enrollment. He received external beam irradiation to the prostate and pelvis 6 months thereafter. During prestudy evaluation, the prostate was enlarged (3 x 2.5 cm by DRE) and bone scan showed focal uptake in the left scapula and mid-thoracic spine suspicious for metastatic lesions. Past medical history was significant for acute myocardial infarction (MI) 8 years prior, bradycardia, hypercholesterolemia, eczema, bilateral hearing loss, degenerative arthritis, and lumbar laminectomy 18 years prior to enrollment. Chronic medications included Nitrodur and Ibuprofen only. Baseline serum T level of 562 ng/dl rose to 821 ng/dl 4 days after the initial Lupron Depot injection. T levels then fell to 428, 90, and 14 ng/dl at post-dose weeks 1, 2, and 3, respectively; rose to 66 and 73 ng/dl at weeks 4 and 5, respectively; then fell to castrate levels at week 6 (range ng/dl), where they remained through week 16. After the second Lupron Depot injection, T levels of 25, 50, 74, 87, and 55 ng/dl were reported, respectively, at post-injection times 4-hours, 8-hours, 12-hours, and study weeks 16.5 and 17. By week 18, the T level was again within the castrate range, where it remained through week 32, ranging ng/dl. The patient reported no associated symptoms, and his clinical tumor response was "objectively stable" with performance status "0" (fully active without restriction) at 16 and 32 weeks. Adverse events during the study included hot flushes after the first month and mild neutropenia (WBC 2900) around week 16. He participated in the long-term phase of the study and received the last study injection approximately 11 weeks before his death, due to acute MI, nearly 14 months after initial study entry.

Patient

This 59-year-old Black man was diagnosed with moderate- to poorly-differentiated adenocarcinoma of the prostate, Gleason grade 4 + 5 = 9, on prostate needle biopsy 10 weeks prior to study enrollment. During prestudy evaluation, the prostate was enlarged (4.5 x 4 cm by DRE) with a normal bone scan. MRI of the pelvis confirmed the enlarged prostate with possible infiltration into the central portion of the seminal vesicles and posterior bladder wall; a 1 cm right inguinal node and a small, < 1 cm para-aortic node were not considered evidence of lymph node metastasis. Past medical history was significant for diabetes mellitus with retinopathy, hypertension, peritoneal dialysis-dependent chronic renal failure, anemia, hypercholesterolemia, and GI bleeding due to Mallory-Weiss syndrome following protracted vomiting. Chronic medications included Procardia XL, hydralazine, cimetidine, simethicone, metaclopramide, and nephroivitamins. Baseline serum T level of 414 ng/dl rose to 742 ng/dl 4 days after the initial Lupron Depot injection. T levels then fell to 211, 86, 71, and 33 ng/dl at post-dose weeks 2, 3, 4, and 5, respectively, (week 1 sample missed), and remained at castrate levels (range ng/dl) through the 16th week. After the second Lupron Depot injection,

T levels remained at 22, 37, and 35 ng/dl, respectively, at post-injection times 4-hours, 8-hours, and 12-hours, but rose to 65 ng/dl at the week 17 determination (week 16.5 not assessed). By week 18, the T level was again — within the castrate range (26 ng/dl), where it remained through week 32, ranging 5.1 to 20 ng/dl. The patient reported no associated symptoms, and his clinical tumor response was “objectively stable” with performance status “0” (fully active without restriction) at 16 weeks. By week 32, the clinical tumor response was “partial response” with prostate size returning toward normal on DRE and MRI, stable bone scan (except focally increased uptake due to a healing rib fracture sustained in a motor vehicle accident), and performance status “0.” Reported adverse events included an episode of GI bleeding attributed to preexisting gastritis, intermittent hot flushes after the third month, injection site pain lasting one day following the week 16 dose, and elbow and rib pain due to MVA injuries sustained around week 24 of the study. After week 32, he participated in the long-term phase of the study, reporting additional adverse events of unilateral eye redness (mild) and esophagitis (treated with omeprazole). Three years after prostate cancer diagnosis, he remained an active study participant although his data were excluded from the sponsor’s evaluable efficacy analyses due to insufficient evidence of metastatic disease.

SECONDARY EFFICACY OUTCOMES:

Objective Tumor Response:

The 45 patients evaluable for this endpoint were included in the sponsor’s initial analysis, with patients who prematurely terminated due to disease progression or death (due to prostate cancer) being assigned a rating of “progression” for the next (missing) evaluation. At week 16, 4/39 or 10% of the patients had a rating of “progression” (an unfavorable response) and 90% (86% by intent-to-treat analysis) had a “favorable response” defined as either stable disease or complete or partial response (i.e., “no progression”). At week 32, 9/44 or 20% of the patients had a rating of “progression” and 80% (77% by ITT analysis) had a “favorable response.” The overall “best response” achieved during treatment was “favorable” (i.e., no progression) in 41/45 or 91% of evaluable patients (43/49 or 88% of ITT patients).

Local Prostate Involvement (assessed by DRE):

All patients evaluated at week 16 or week 32 showed either no progression or improvement in prostate status (a “favorable” outcome). No patient showed 25% or greater worsening of local disease, including the 4 patients at week 16 and the 9 patients at week 32 whose objective tumor response rating was “progression.” These results were essentially unchanged for the intent-to-treat population.

Prostate-Specific Antigen (PSA) and Prostatic Acid Phosphatase (PAP):

PSA normalized to 3.9 ng/ml or less at weeks 16 and/or 32 in 23/42 or 55% of the patients with an elevated pre-treatment value and at least one measurement during treatment (25/47 or 53% by ITT analysis). By this reviewer's count, 15/48 or 31% of patients with elevated pre-treatment values achieved on-treatment PSA levels of 1 ng/ml or less (see Appendix E.10.E, NDA vol. 8.8, pp. 215-227).

Changes in PAP were generally similar to those for PSA, with PAP levels decreasing, but not typically to within the normal range, in 86% of ITT patients with elevated pre-treatment values.

Performance Status (ECOG):

"Favorable" ratings, defined as "without worsening", were experienced by 36/44 or 82% of the patients evaluated at week 16, by 36/42 or 86% of the patients evaluated at week 32, and by 38/44 or 86% of the patients evaluated at the "final visit." These results were essentially unchanged for the intent-to-treat population.

HISTORICAL COMPARISONS

In response to a request for ITT analyses as the basis for comparative labeling claims (FDA letter to sponsor dated 2/21/97), the sponsor submitted summaries of the ITT efficacy and safety results of three previous pivotal NDA studies compared with the ITT results of the current pivotal trial for Lupron Depot 4-Month, 30 mg (Amendment #6, 4/7/97):

<u>Formulation Studied</u>	<u>Pivotal Trial</u>	<u>Sample Size (n)</u>
Lupron Depot 7.5 mg	M85-097	56
Lupron Depot 3-Month 22.5 mg	M91-583 M91-653	61 33
Lupron Depot 4-Month 30 mg	M93-013	49

All submitted historical comparison data are from the initial 24 treatment weeks of studies M85-097 (6 dosing intervals) and M91-583/M91-653 (2 dosing intervals), corresponding to the treatment intervals submitted as pivotal clinical data for the respective NDA approvals. The patient population for all four clinical trials were Stage D2 prostate cancer patients with prestudy serum testosterone levels of 150 ng/dl or greater; efficacy endpoints for the trials were serum T and LH levels and clinical response to treatment as assessed by bone scan, digital rectal exam, and performance status. Based on these parallel ITT analyses, the following results were reported:

Serum Testosterone Levels showed characteristic increases over pre-treatment levels on day 4, followed by declines to the castrate range by week 3 in all studies, with median time to onset of castrate levels being 22 days in all 4 studies. Sponsor states that the 94% rate of T suppression within 30 days in study M93-013 is comparable to the rates previously reported for this time-frame with the 1-month (91%) and 3-month (92-97%) Lupron Depot formulations (see attached Table 1: Serum Testosterone, and Table 2: Summary of Testosterone Suppression, NDA Amendment #6, 4/7/97, pp. 5-6).

During the 24/32 week treatment periods, 3 patients experienced "escapes" from suppression (defined as 2 consecutive T values outside the castrate range) without reported symptomatology - 2 patients on the 3-month depot formulation and one patient on the 1-month depot formulation - for an overall "escape" incidence of 2-3% (see attached Table 3: Summary of "Escape" Incidence, NDA Amendment #6, pg. 6). Also, one patient on the 3-month formulation and one patient on the 4-month depot formulation experienced "acute-on-chronic" responses (defined as 2 consecutive T values outside the castrate range following a re-injection). These data do not include patients who experienced single T value increases and those who experienced "escapes" during the long term treatment phases of these ongoing studies, however (see attached Table 4: Mean (+/- std. dev) Hormone Levels Immediately Prior to Re-injection and 2-5 Days Post-Injection, and attached Table 5: Mean Hormone Levels Immediately Prior to Re-injection and 4, 8 and 12 Hours Post-Injection, NDA Amendment #6, pp. 8-9).

Generally good compliance with the required dosing intervals of 28, 84, or 112 days was reported in the 4 studies, with a total of 33/195 patients having doses delayed by 3 or more days (total of 37 delayed injections). In these 33 patients, only two delayed doses (2 and 3 weeks late dosing with the 1-month depot) resulted in documented "escapes" from T suppression (see attached Table 6: Summary of Injection Delays, NDA Amendment #6, pg. 6).

Serum LH response patterns were similar in all 4 studies, with an initial increase in the mean on day 4 over pre-treatment levels followed by a progressive decline to below pre-treatment levels by week 2 and to the lower normal range by week 3, where it remained through week 24/32. No historical comparative data were submitted for the statistically significant "acute-on-chronic" response demonstrated in study M93-013 following the week 32 injection (see attached Table 4, NDA Amendment #6, pg. 8).

Objective Tumor Response ratings showed similar proportions of patients with a "favorable" response (i.e., no progression) across the 4 studies, with a range of 6 "favorable" responses at week 12/16 and 77-84% "favorable" responses at week 16/32. The range for the proportion of patients having an "unfavorable" (progressive disease) rating across studies was 14-22% at week 12/16 and 16-23% at week 24/32. The range of patients receiving a "favorable" rating as their "best response" was 83% with the 1-month formulation, 83-87% with the 3-month formulation, and 88% with the 4-month formulation (see attached Table 7: Summary of "Best" Objective Response Rates, NDA Amendment #6, pg. 11).

Local Prostate Involvement (by DRE) was stable or improved in 95-100% of patients across the 4 studies during the 24/32 week treatment phases (see attached Table 8: Status of Prostatic Involvement at "Final Visit," NDA Amendment #6, pg. 11).

Prostate-Specific Antigen (PSA) levels were not determined for the 1-month formulation, but were determined for the 3-month and 4-month formulations. While both mean and median PSA levels declined from baseline to the "final visit" with both formulations, only the median PSA levels declined to within the normal range, which the sponsor attributes to several "outlier" values in each study (see attached Table 9: Changes in PSA, NDA Amendment #6, pg. 12). The proportion of patients with elevated pre-treatment PSA values whose PSA levels normalized on treatment ranged from % with the 4-month formulation to % with the 3-month formulation (see attached Table 10: Proportion of Patients with Normalized PSA, NDA Amendment #6, pg. 13).

Prostatic Acid Phosphatase (PAP) level changes were generally similar to those for PSA, with 67%, 52%-61%, and 51% of patients with elevated pre-treatment levels normalizing on treatment, respectively, with the 1-month, 3-month, and 4-month formulations (see attached Table 11: Proportion of Patients with Normalized PAP, NDA Amendment #6, pg. 14).

Performance Status ratings across the 4 studies were reportedly "favorable" (i.e., not worsened) in at least 74% of the patients by the "final visit" (i.e., end of the 24/32 week treatment phase) for all formulations studied (see attached Table 12: Changes in Performance Status at the "Final Visit," NDA Amendment #6, pg. 16).

Based on the above analyses, the sponsor concludes that each of the depot formulations was shown effective in suppressing serum testosterone to, and maintaining it at, castrate levels over the intended dosing intervals, and that the overall clinical response to treatment was favorable for all parameters and consistent for the three formulations.

8.1.1.4.3 Safety outcomes

Data from all patients who received leuprolide in study M93-013 were included in the safety analysis, which assessed changes in vital signs and clinical laboratory variables from baseline to each visit using paired t-tests. Also, the sponsor states that specific values of potential clinical significance were identified using criteria recommended by the FDA.

Treatment exposure in study M93-013 consisted of a total of 49 patients who received at least one dose of the 30 mg leuprolide depot formulation, 43 (88%) of whom completed the initial 32 weeks of treatment and continued on the long-term phase of the study. Of the 6 patients who prematurely terminated during the initial 32 week treatment period, 5 received two injections and one patient received a single injection.

Vital Signs, Body Weight, and Physical Examinations:

No clinically or statistically significant changes from baseline values were observed in blood pressure or pulse rate, except for a clinically significant drop in BP for one patient on the day he expired due to metastatic prostate cancer. Mean body weight significantly increased from baseline by 3.1 lbs. ($p=0.004$) at week 16, by 6.3 lbs. ($p<0.001$) at week 32, and by 5.5 lbs. ($p<0.001$) at the "final visit." The sponsor attributes these weight gains to "clinical improvement" during the study, noting the consistency of these findings with those from the 1-month and 3-month depot NDA studies. Testicular atrophy was a clinically significant finding on the physical examinations of 5 patients, and is consistent with the known activity of leuprolide acetate to suppress gonadotropin stimulation of testicular germ cell tissue.

Clinical Laboratory Determinations:

Increased or decreased hemoglobin or clinical chemistry laboratory values were observed in several patients after receiving the 30-mg leuprolide acetate depot formulation. Few of these changes were considered clinically significant, most being attributed by the investigators to the underlying prostate cancer, to the age and clinical status of the individual study subject, or to non-fasting blood specimen collection. On cross-tabulations of serial lab values over time, slight trends were noted for the hemogram parameters and white blood cell counts to decrease to below the normal range, and for prothrombin time, glucose, alkaline phosphatase, lipids, and phosphorus levels to rise to above the normal range. These trends were not considered clinically significant.

After week 32, study visits did not include any required safety laboratory samples; PSA, PAP, and alkaline phosphatase levels (i.e., efficacy parameters) were the only laboratory determinations consistently performed during the long-term treatment phase of the study. Other laboratory tests were only obtained on an "as needed" basis as determined clinically by individual investigators.

Adverse events:

Of the 49 enrolled patients, 39 (80%) reported at least one adverse event during the first 32 weeks of study participation, and 48 (98%) reported at least one adverse event during the entire study duration. Based on this reviewer's analysis of sponsor's Statistical Table 2, Amendment #5, the most frequent event was hot flushes, reported by 24 (49%) of the patients. Adverse events reported by 10% or more patients (rounded to 2 significant figures), regardless of investigator attribution to study drug, included back pain (31%), asthenia (27%), arthralgia (25%), pain (21%), bone pain (16%), constipation (16%), flu syndrome (14%), headache (12%), fever (12%), anemia (12%), hypertension (10%), dyspepsia (10%), dehydration (10%), edema (10%), and peripheral edema (10%). Adverse events reported in

5-10% of the patients (rounded to one significant figure) included myalgia (8%), arthritis (8%), nausea (8%), diarrhea (8%), chest pain (8%), abdominal pain (8%), injection site pain of up to 5 days duration (6%), pelvic pain (6%), anorexia (6%), GI hemorrhage (6%), hyperglycemia (6%), and pathological fracture (6%).

Ascertainment of Symptomatic "Flare" and "Acute-on-Chronic" Reactions:

The sponsor performed an analysis of adverse events occurring within the first 2 weeks of treatment, excluding those considered "not related" to treatment, to ascertain whether the agonist phase of treatment precipitated exacerbated symptoms. In this analysis, hot flushes was the most frequently reported adverse event (14%), followed by back pain (8%, including 2 patients with severe pain: Pt whose severe back and leg pain on treatment day 14 required increased oral narcotic dosage, and Pt whose severe pain and severe arthralgia on treatment day 1 required oral narcotic initiation) and arthralgia (6%).

As requested (FDA letter to sponsor dated 2/21/97), the sponsor also conducted an analysis of adverse events occurring within the first 4 weeks of treatment, both including and excluding those considered "not related" to treatment, to ascertain the adverse event incidence (and possible "flare" reactions) during the agonist phase of leuprolide treatment. Regardless of investigator attribution to study drug, 29 patients (59%) reported an adverse event during this time period, 8 (16%) of which were reported by the investigator to be severe. The most frequently reported adverse events during this period were hot flushes (20%), back pain (8%), arthralgia (8%), and constipation (6%). The severe reactions included Pt and Pt noted above. Although the other severe adverse events during the first 4 weeks of treatment were considered by the investigator to be "not related to study drug," these clinical impressions could not be confirmed due to the absence of control groups in the study for comparison.

During the initial 32-week treatment phase, this reviewer's analysis of sponsor's Appendix E.12 (NDA vol 8.8, pp. 301-349) identified a total of 20 severe events reported by 14 patients. Those marked below with an asterisk (*) occurred within 4 weeks following the first depot injection (8 patients with possible severe symptomatic "flare" reactions due to the agonist phase of treatment). Those marked below with a pound sign (#) occurred within 4 weeks following a subsequent depot injection (8 patients with possible severe symptomatic "acute-on-chronic" responses due to agonist responses to re-injections).

Severe Adverse Events Reported during the Study (Initial 32 week Treatment Period and Long Term Treatment Phase):

<u>Pt #</u>	<u>Age Sex</u>	<u>Rx Day of Onset</u>	<u>Days Since Last Injection at Onset</u>	<u>Reported Event/Action Taken or Treatment Given</u>
81M		704	30	Respiratory failure, sepsis/O ₂ , antibiotics, fluids
		740	66	Respiratory failure, urosepsis/O ₂ , antibiotics
		898	112	Respiratory failure, urosepsis/Nursing home admission
72M		161	48	Exacerbation of pre-existing sinus problem/Seldane
		320	95	Laryngitis/Cough medication
		403	65	Loss of vision right eye/Surgery for blocked carotid
		417	79	Exacerbation of emphysema/Medication
		551	108	Low back pain/Rest
77M		14	13	Shortness of breath/Resolved without treatment
		138	25	Hoarseness/Tylenol
		325	100	Headache/Medications
		423	86	Confusion/Cranial shunt for hydrocephalus
		540	91	Shortness of breath/Medication
		720	47	Generalized weakness/No treatment
60M		377	47	Acute brain syndrome/RT, dexamethasone, Premature D/C study drug
54M		224	111	GI bleed/Hospitalized
		268	42	Pancreatitis/Hospitalized
55M		15	14	Increased back, leg pain/Narcotic analgesic ("Possible flare reaction" per PI)
65M		278	52	Anemia/4 units RBC transfusion
		303	77	Anemia/3 units RBC transfusion
		458	120	Coma, DIC/Hospitalized, transfusions
76M		25	24	Inguinal hernia/Surgical repair
		725	43	Cholecystitis/Cholecystectomy
75M		417	80	Acute MI/Expired
80M		708	49	Low back pain/RT
79M		107	106	Generalized intractable bone pain/Expired

Severe Adverse Events Reported during the Study (Initial 32 week Treatment Period and Long Term Treatment Phase) (continued from previous page):

<u>Pt #</u>	<u>Age</u> <u>Sex</u>	<u>Rx Day</u> <u>of Onset</u>	<u>Days Since</u> <u>Last Injection</u> <u>at Onset</u>	<u>Reported Event/Action Taken or Treatment Given</u>
78M		482	33	Acute cholecystitis/Cholecystectomy
74M		6	5	[Moderately worsened bone pain/Narcotic analgesic, "Probable flare response" per PI]
		16	15	Anemia, dehydration/Hospitalized, transfusion, fluids
66M		226	113	Abnormal liver function tests/Premature Termination of study drug treatment
60M		4	3	Urinary retention/TURP
80M		16	15	3rd nerve palsy, ptosis/RT to large sella turcica mass
		178	65	Hyperglycemia, hypoxia, seizures, pneumonia/ Insulin, antibiotics, anticonvulsant
71M		113	112	Abnormal liver function tests/No treatment
		116	3	Chest pain/MI ruled out
72M		22	21	Worsening urinary retention x 1 week/TURP
71M		252	27	Intermittent hip, leg pain/RT to lumbar spine
		424	87	GI bleed/Hospitalized, transfusion
61M		226	1	Increased shoulder pain/RT ("Definitely related" to study drug, per PI)
78M		266	41	Shortness of breath/Antibiotics for pneumonia
		680	3	Shingles/Medication
68M		131	18	Exacerbation of back pain, wt. loss/ Premature D/C study drug, Medication
64M		62	61	Difficulty urinating/Urethral dilatation
		64	63	Lower back pain/Darvocet
68M		449	7	Low back, hip pain/RT

Severe Adverse Events Reported during the Study (Initial 32 week Treatment Period and Long Term Treatment Phase) (continued from previous page):

<u>Pt #</u>	<u>Age</u> <u>Sex</u>	<u>Rx Day</u> <u>of Onset</u>	<u>Days Since</u> <u>Last Injection</u> <u>at Onset</u>	<u>Reported Event/Action Taken or Treatment Given</u>
56M		2	1	Low back, hip pain/Narcotic analgesic ("Definitely related" to study drug, per PI)
		52	51	Shoulder fracture/Splint, pain medications
76M		493	51	Acute brain syndrome/Hospitalized
		565	4	CVA, seizures, GI bleed/Premature D/C study drug, Anticonvulsant, cimetidine

Premature Terminations due to Adverse Events:

During the initial 32 weeks of the study, 3 patients dropped out due to adverse events or death (see sponsor's Statistical Table 1, Amendment #5):

Pt : Died at week 15 due to prostate cancer.
Pt : Died at week 28 due to prostate cancer.
Pt : Dropped out on day 153 due to increased bone pain
and weight loss.

During the long term treatment phase, 13 additional patients dropped out due to adverse events or death (see sponsor's Statistical Table 1, Amendment #5):

Pt : Died at week 128 due to respiratory failure.
Pt : Died at week 92 due to prostate cancer.
Pt : Died at week 135 due to fall down flight of stairs.
Pt : Died at week 88 due to prostate cancer.
Pt : Died at week 59 due to prostate cancer.
Pt : Died at week 64 due to prostate cancer.
Pt : Died at week 59 due to acute MI.
Pt : Dropped out at week 63 due to abnormal liver function tests.
Pt : Died at week 62 due to prostate cancer.
Pt : Died at week 115 due to prostate cancer.
Pt : Died at week 93 due to unknown cause.
Pt : Died at week 96 due to CVA.
Pt : Died at week 57 due to prostate cancer.

Conclusions regarding Safety Data:

Sponsor concludes that the observed changes in safety parameters were consistent with the known safety profile of leuprolide, with reported adverse events commonly associated with metastatic prostate cancer and its chronic treatment with GnRH analog therapy. Sponsor notes that the statistically significant changes in laboratory parameters were mostly small and clinically insignificant, and that no apparent increase was observed in disease-related symptomatology during the agonist phase of treatment. Based on these findings, sponsor concludes that the 30-mg leuprolide depot formulation administered on a 16-week dosing schedule is safe.

REVIEWER'S COMMENTS: This reviewer concurs with the sponsor's assessment while also noting the frequent occurrence (16% or 8/49 patients in study M93-013) of severe adverse events within 4 weeks following the first injection, of which 6 were clear prostate cancer exacerbations and 3 required surgical or radiation therapy intervention (see pp 34-36 above for specific patient data). Given that most prostate tumors are androgen-dependent, a causal relationship is likely between the increased androgen levels and the clinically significant adverse events reported in these patients; thus, these events likely represent severely symptomatic "flare" reactions due to the agonist phase of Lupron treatment. Given this apparently high "flare" rate, the safety of Lupron during the first month of treatment appears questionable to this reviewer.

Drugs predictably associated with severe, clinically significant adverse reactions in over 15% of treated patients may be considered unsafe, at least during the time interval associated with the highest risk. For Lupron Depot-4 Month 30 mg, the first month of treatment thus appears unsafe for a significant proportion of treated patients. However, higher than usual risk may be considered acceptable for a drug that provides documented benefit to patients with an incurable disease, especially if safer treatment alternatives are not available. In this case, while "medical castration" therapy provides documented palliative benefit for Stage D2 prostate cancer patients, surgical orchiectomy provides equivalent benefit with no associated risk of androgen "flare" reactions. Surgical orchiectomy has other risks, however, including those inherent to any surgical procedure, and remains unacceptable to some patients. For these patients, concomitant androgen receptor blockade (with androgen receptor inhibiting agents) might improve Lupron's safety profile during the first 1-2 months of treatment by reducing or preventing androgen-induced "flare" reactions, provided the antiandrogen drug contributes minimal additive toxicity. While clinical data specifically addressing this question have not been submitted in this application and do not appear to be available to date, the development of such data could elucidate this question and significantly improve future labeling recommendations for this and other related products.

8.1.1.5 Conclusions regarding Efficacy Data

Sponsor's Evaluation: Based on the above data, the sponsor concludes:

1. The 30-mg Lupron Depot formulation "was found to be effective in suppressing serum testosterone to, and maintaining it at, the castrate level over the intended 16-week dosing interval" (NDA vol. 8.9, pg. 020);
2. The pattern of suppression was similar to that observed with the monthly 7.5 mg depot and the 3-month 22.5 mg depot formulations;
3. The clinical response to treatment was comparable to that seen with the monthly and 3-month depot formulations; and
4. There does not appear to be a clinically significant increase in LH or T levels following re-injections that would indicate an stimulation.

REVIEWER'S COMMENTS:

Although the pivotal trial (M93-013) was uncontrolled, the patient population studied was comparable in age, sex, sample size, severity and duration of disease, and concomitant medication use to those studied in previous Phase III trials of other depot leuprolide acetate formulations for this indication (M85-097, M91-583, M91-653). Because of the comparability of patient populations and clinical endpoints assessed, crude historical comparisons may be made of this study's findings with those of previously conducted Phase III studies supporting prior Lupron Depot approvals (1-month and 3-month formulations) for prostate cancer. It should be noted, however, that no concurrently controlled clinical data have been submitted to date which would support directly comparative safety or efficacy claims in labeling or advertising of the various available leuprolide acetate formulations.

It is notable that nearly half the patients in the current clinical studies (M93-013 and M93-012) were African American, while African American men comprised less than 30% of previous prostate cancer clinical trial populations. Since prostate cancer may be a more aggressive disease in Blacks than in Caucasians, this demography provides some assurance that androgen deprivation with Lupron Depot may provide comparable safety and efficacy to prostate cancer patients of both races. Nevertheless, the total number of African American patients studied to date in Lupron Depot clinical trials remains very small.

In view of the above considerations and the 12-year worldwide marketing history of this drug for prostate cancer, the documentation and analysis of results appear sufficient to justify the sponsor's conclusions despite the significant limitations of the submitted pivotal trial. The poor prognosis associated with Stage D2 prostate cancer, and the palliative efficacy of "medical castration" make it ethically unacceptable to require the use of placebo control groups in clinical trials. While active-controlled trials or trials of "add-on" therapy could ethically be utilized, these designs require large sample sizes to yield statistically significant results, a burden that could only be justified for clinical development of a "breakthrough" treatment. Since Lupron Depot-4 month 30 mg is a minor variant of an approved formulation in clinical use for over a decade, such burdensome requirements are not needed to assure the safety and efficacy of the drug. All that is needed is adequate demonstration that

the 4-month dosage form retains the documented safety/efficacy profile of the shorter-acting formulations over the prolonged new dosing interval, and this has been demonstrated by the submitted clinical data. Thus, the submitted documentation is considered sufficient to justify approval.

While no intent-to-treat (ITT) analyses were initially conducted, the results of the requested ITT analyses (Amendments #5 and #6) generally confirmed the findings reported for evaluable patients. This reviewer disagrees with the sponsor's summary statistics regarding "escapes" from suppression, however (and with the associated labeling text based on these analyses, see section 11.0, below) because all analyses submitted to date fail to mention 3 of the 4 patients in study #M93-013 who experienced on-treatment serum T elevations above the castrate range. Also, despite the small sample size, statistical evidence of a small LH effect was found during the first 2 weeks following re-injections. While these small post-re-injection LH increments are of uncertain clinical significance, it is noteworthy but unexplained that 16% of patients reported severe adverse events during the first 4 weeks following re-injections in the absence of detectable increases in post-re-injection T levels (other than the 2 cases described in section 8.1.1.4.2, above).

8.1.2 Reviewer's Trial #2: Sponsor's Protocol #M93-012

This multicenter, open-label, clinical pharmacokinetics (PK) study was conducted in 24 orchiectomized prostate cancer patients at 5 investigational sites to evaluate plasma leuprolide levels following a single IM injection of the Lupron Depot-4 Month 30 mg formulation. Serial plasma leuprolide levels were determined by [redacted] prior to dosing and at serial time points post-injection for 20 weeks. Physical examinations and routine hematology, clinical chemistry, and urinalysis assessments were performed prestudy and at weeks 12 and 20. Because all study participants had undergone prior surgical castration, no LH or T levels were determined and no efficacy endpoints were evaluated. Of 24 enrolled subjects, 50% were African American and 50% Caucasian. Two terminated prematurely from the study (Pt [redacted] due to non-compliance with visit schedule after 96 days; Pt [redacted] due to patient request after 37 days), and 6 had numerous blood samples lost in shipment, leaving only 16 (67%) patients evaluable for the pharmacokinetics analysis. Refer to Biopharmaceutics Review (27/20/97) for review and analysis of PK findings from this study.

Safety data from Study M93-012 included changes in laboratory parameters similar to those observed in study M93-013, i.e., slight trends for the hematologic parameters to decrease below the normal range and for reticulocyte count, prothrombin time, blood glucose, lipids, and phosphorus levels to rise above the normal range. These trends were not considered clinically significant. Mean body weight decreased ($p=0.046$) by 5.5 lbs during the study, with 6 patients losing more than 5% of their baseline body weight. No patient died during the study. The most frequent adverse event was mild injection site pain of up to 9 days duration in 9/24 patients (38%). Other frequent adverse events included anemia (17%), edema (17%), accidental injury (13%), hot flushes, dizziness, hematuria, pain, nocturia, and urinary retention, each reported in 2/24 or 8% of enrolled patients. Severe adverse events of onset during Lupron treatment included spinal cord compression (not attributable to the agonist phase of treatment in the one reported case because the patient was orchiectomized prior to study enrollment) and intestinal obstruction (both events occurred in Patient [redacted], anemia requiring blood transfusion (Pt [redacted]), and bladder carcinoma with gross hematuria (Pt [redacted] who later dropped out). These safety data appear generally consistent with the known safety profile of leuprolide and suggest that the formulation was reasonably well tolerated by the patients studied.

9.0 Overview of Efficacy

Findings are submitted from an ongoing open-label, uncontrolled 8-month study of Lupron Depot-4 Month 30 mg, in which 49 patients with Stage D2 prostate cancer received IM Lupron Depot injections at 112-day intervals with serial monitoring of serum LH and T, physical examinations, and ancillary studies as needed to document metastatic disease and performance status. The supplemental application includes findings from a long term treatment phase beginning at the conclusion of the 32-week treatment period, during which 43/49 enrolled patients continued to receive Lupron Depot injections at 112-day intervals with LH, T, PSA, PAP, and alkaline phosphatase monitoring prior to each dose, and physical exams and ancillary safety/efficacy studies as clinically indicated.

Reported findings include an initial stimulation phase, with increased serum T levels an average of 50% over baseline values, followed by suppression of mean serum T concentrations to the castrate range (ng/dl or less) by week 3 of treatment and maintenance within the castrate range throughout the 32 week treatment period. In an evaluable analysis of 45/49 enrolled subjects, testosterone suppression was achieved by 96% of enrolled patients by week 4, the median onset of castrate T levels was by 22 days, and all patients' serum T levels were suppressed to the castrate range by 43 days. In an ITT analysis, T suppression was achieved by 84% and 94% of the 49 patients at weeks 3 and 4, respectively, and by all patients by day 43, yielding a one-sided lower 95% confidence bound of 94% for the proportion of suppressed patients.

Once achieved, suppression was maintained in all except 4 patients. Two patients (4%) experienced "escapes" from suppression associated with "acute-on chronic" effects (with either transient or sustained T levels above the castrate range) following the week 16 injection, with T levels returning to the castrate range at week 18 in both. In one case, elevated T levels were detected by 12-hours post-dose, with a T level of 87 ng/dl at 72-hours and persistent elevation 1-week post-dose. In the second case, serum T rose to 65 ng/dl at 1-week post-dose (72-hour post-dose sample not drawn), then returned to the castrate range (26 ng/dl) by 2 weeks post-dose. Since the study defined an "escape" as 2 consecutive elevated T values, this transient, minimal T elevation was not considered an "escape" and neither patient reported symptoms in temporal association with these T elevations.

Two other patients experienced late "escapes" from suppression during the long term treatment phase. Since the study design only provided for single pre-dose T measurements at 16-week intervals, only one of these patients strictly met the protocol definition for "escape" (two consecutive T values greater than 50 ng/dl following suppression). In this case, a repeat determination confirmed the high serum T concentration, and the patient subsequently received concomitant flutamide with unexplained return of serum T to the castrate range thereafter. The second patient had only a single documented T level above the castrate range and died of prostate cancer shortly thereafter.

The overall clinical response to treatment for the evaluable population, as assessed by changes in local prostate status, distant metastases, PSA/PAP levels, and performance status, was reportedly "favorable" (i.e., no progression) in 86% of patients at week 16 and in 77% at week 32, with a "best clinical response" rating of "no progression" (defined as complete, partial, or stable response) achieved by 88% of patients (91% by evaluable analysis) at some time point during the first 32 weeks of the

study. This appeared generally comparable to the reported 83% and 87% "best response" ratings of "no progression" in the 3-month depot NDA studies (M91-583 and M91-653), and the 83% reported "no progression" rating in the monthly depot NDA study (M85-097). On ITT analysis, PSA normalized at weeks 16 and/or 32 in 54% of the patients with elevated pre-treatment levels and at least one measurement during treatment.

Although no statistical comparisons of these results were submitted, the sponsor claims that the 4-month depot formulation has comparable efficacy to the currently approved Lupron depot formulations for this indication, based on non-statistical historical comparisons (results of ITT reanalyses of previously submitted efficacy findings). This claim is not adequately supported by the NDA submissions, since a formally historically controlled trial should include statistical analyses directly comparing current and historical outcomes on key efficacy endpoints, using intent-to-treat analyses of study findings.

10.0 Overview of Safety

In response to DRUDP's request for an integrated safety summary that includes all existing safety data for all patients treated with the 4-month formulation to date (FDA letter to sponsor dated 2/21/97), the sponsor submitted an updated safety summary of Studies #M93-012 and M93-013 (Amendment #5), based on a database cut-off date of 9/7/96. According to this summary, all human exposure to the 30 mg depot formulation worldwide through 9/7/96 is accounted for by the total of 49 non-orchietomized and 24 orchietomized prostate cancer patients who received Lupron Depot-4 Month 30 mg in the NDA studies for durations ranging from 20 weeks to 3 years.

10.1 Significant/Potentially Significant Events

During study M93-013, 2 cases of acute urinary retention requiring surgical resection and a case of third nerve palsy requiring radiation therapy to a large sella turcica mass were reported within the first month following treatment initiation. Also, one case of spinal cord compression was reported during study M93-012; this event was unlikely attributable to study drug, however, because the affected patient was orchietomized prior to study enrollment.

10.1.1 Deaths

During the initial 32 week treatment period of study M93-013, 2 patients died of prostate cancer. During the long term treatment phase, 7 additional patients died of prostate cancer and 4 died of other causes (respiratory failure, acute MI, fall down flight of stairs, and unknown cause), for a total of 13 deaths among 49 enrolled patients by the database cutoff date for the safety analysis (9/7/96). No patients died during the 20-week treatment period of study M93-012.

10.1.2 Other Significant/Potentially Significant Events

During study M93-013, 16 of 49 enrolled patients dropped out due to adverse events or death up to the data cutoff date. Of these, 2 patients who died from prostate cancer also had adverse events (brain metastases; fever and thrombocytopenia) which caused them to prematurely terminate from the study. Three other patients dropped out due to adverse events during the long term treatment phase due to CVA, liver function test abnormalities, and increased back and bone pain with weight loss.

Severe adverse events were reported in 16/49 enrolled patients during the initial 32 week treatment period, 8 of which occurred within 4 weeks following the initial injection. During the long term treatment period, severe adverse events were reported in 14/43 enrolled subjects, 8 of which occurred within 4 weeks following a subsequent injection. In summary, 49 severe adverse events occurred by the data cutoff date in 26 of the 49 enrolled patients.

10.1.3 Overdose Experience No pertinent information submitted.

10.2 Other Safety Findings None reported.

10.2.1 ADR Incidence Tables

Of 49 patients in study M93-013, 80% experienced at least one adverse event during the first 32 weeks of study participation and 98% reported one or more ADR's overall. Of the 24 orchiectomized patients in study M93-012, 80% experienced one or more adverse events during the 20 week study. The most frequent event overall was hot flushes, reported by 50% of intact patients and 8% of orchiectomized patients (for an average of 36% overall). Other adverse events reported in 5% or more enrolled patients in either M93-012 or M93-013 were summarized only for those considered by investigators to have possible, probable, definite, or unknown relationship to study drug, as follows: arthralgia (4-6%), asthenia (0-12%), back pain (0-14%), dyspnea (0-6%), edema (4-13%), headache (4-6%), injection site pain (6-38%), pain (0-8%), pelvic pain (0-6%), paresthesia (0-8%), and rash (0-6%). (See attached Table 12: Adverse events occurring at $\geq 5\%$ incidence level in either M93-012 and M93-013, NDA Amendment #5, pg. 73).

This reviewer identified a total of 20 severe events reported by 14 patients (28%) during the initial 32-week treatment phase, and a total of 49 severe events reported by 26 patients (52%) by the database cutoff date. Of these, 16% of patients reported severe events of onset within 4 weeks following the first depot injection and an additional 16% reported severe events of onset within 4 weeks following a subsequent depot injection.

In the sponsor's analysis of adverse events during the first 2 weeks of treatment in study M93-013 (excluding those "not related" to treatment), the most frequently reported adverse event was hot flushes (14%), followed by back pain (8%, half of which were severe) and arthralgia (6%).

In the sponsor's analysis of adverse events during the first 4 treatment weeks in study M93-013, 59% of patients reported an event, nearly a third of which (16% of enrolled patients) were severe per the investigator. These included an 8% incidence of arthralgia (2% severe), 8% back pain (4% severe), 20% hot flushes, and 6% constipation (not severe).

10.2.2 Laboratory Findings, Vital Signs, Physical Findings

Noteworthy changes in individual laboratory values included decreases in the hemogram, elevation in serum lipid and phosphorus levels, and decreases in alkaline phosphatase, all of which are commonly observed in this patient population or with leuprolide treatment. On cross-tabulations of low, normal, and high clinical laboratory variables at baseline with those at weeks 12 and 20 for study M93-012 and with those at weeks 16, 32, and the "final visit" for study M93-013, slight trends were noted for the hemogram parameters and WBC count to decrease to below the normal range, and for prothrombin time, glucose, lipids, alkaline phosphatase, and phosphorus to rise to above the normal range. Although there were statistically significant mean changes from baseline to the end of treatment for many laboratory variables, the changes were mostly of small magnitude and did not indicate clinically significant trends.

In study M93-013, mean body weight increased significantly from baseline by 3.1 lbs. ($p=0.004$) at week 16, by 6.3 lbs. ($p<0.001$) at week 32, and by 6.1 lbs. ($p<0.001$) at the "final visit."

In study M93-012, mean body weight decreased significantly from baseline by 5.5 lbs. ($p=0.046$) at week 20. The sponsor attributes these divergent findings to clinical improvement in the pivotal trial and to various adverse events in the PK study, none of which were considered related to study drug administration.

Blood pressure and pulse rate showed no statistically or clinically significant changes from pretreatment, except for a clinically significant decrease in blood pressure in one patient on the day of his death from metastatic prostate cancer.

Testicular atrophy was a clinically significant finding on the physical examinations of 5/49 (10%) non-orchietomized patients in Study M93-013.

10.2.3 Special Studies	None reported.
10.2.4 Drug-Demographic Interactions	None reported.
10.2.5 Drug-Disease Interactions	None reported.
10.2.6 Drug-Drug Interactions	None reported.
10.2.7 Withdrawal Phenomena/Abuse Potential	None reported.
10.2.8 Human Reproduction Data	None reported.

11.0 Labeling Review

For detailed text of needed revisions to submitted draft labeling, refer to
briefly described below.

The required revisions are

11.1 Description

A prominent statement should be added to this section that this formulation is for use by men only.

11.2 Clinical Pharmacology

Clinical Pharmacology subsection is identical to the currently approved labeling for
Lupron Depot-3 Month 22.5 mg, and is adequate as proposed.

Pharmacokinetics subsection should be revised per recommendations of DPEII, OCPB (refer to
Clinical Pharmacology and Biopharmaceutics Review dated 2/20/97).

Clinical Studies subsection should be rewritten to clearly describe the clinical studies conducted and
their results, based on ITT analyses, including descriptions of all patients with on-treatment serum
T levels outside the castrate range during the study

11.3 Indications and Usage

The last sentence

should be revised and
moved to Clinical Studies subsection, Clinical Pharmacology section,

11.4 Contraindications

Should be revised based on new Lupron label approved 3/97 under NDA #20-708

11.5 Warnings

Should be revised for greater consistency with the currently approved labeling for Zoladex (goserelin
acetate implant 3.6 mg, Zeneca Pharmaceuticals,

11.6 Precautions

Refer to meeting minutes for minor revisions needed based on the new Lupron label.

11.6.2 Information for Patients

Omitted from the submitted draft labeling; draft text should be submitted by the sponsor.

11.6.3 **Laboratory Tests** Minor revision needed.

11.6.4 **Drug Interactions** Minor revision needed.

11.6.5 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

The sentence

should be revised to account for Patient (study M93-013) who developed a 3rd nerve palsy requiring radiation therapy due to a large sella turcica mass.

11.6.6 **Pregnancy** Acceptable as proposed (Pregnancy Category X).

11.6.7 **Labor and Delivery** Appropriately omitted, given the male target population.

11.6.8 **Nursing Mothers** Appropriately omitted, given the male target population.

11.6.9 **Pediatric Use**

Minor revision needed to refer to Lupron Depot-PED labeling for approved indication.

11.7 **Adverse Reactions**

This section needs major revision to describe all adverse reactions reported in all patients treated with Lupron Depot-3 Month 30 mg, regardless of attribution to study drug. Common ADR's should be reported separately for each study to reflect the different patient populations studied in M93-012 (orchiectomized) and M93-013 (intact). Also, new text should be added describing documented bone mineral density changes with Lupron use in premenopausal female patients, based on the new approved Lupron label, and a summary statement should be added describing all available bone mineral density data with Lupron use in men. All reported ADR's during postmarketing surveillance for all Lupron dosage forms should also be included in this section of the labeling.

11.8 **Drug Abuse and Dependence** Appropriately omitted.

11.9 **Overdosage** Revision needed to describe human, not animal, data.

11.10 **Dosage and Administration**

An additional statement is needed to clarify that safety and effectiveness have not been demonstrated for dosing intervals exceeding 112 days (16 weeks).

11.11 **How Supplied** Acceptable as proposed.

11.12 **Annotations** Acceptable as proposed.

12.0 Conclusions

Despite the small sample size and absence of both a concurrent control group and a replicate-pivotal trial, the findings from study M93-013 – considered in the context of the submitted historical clinical data from NDA's 19-732 and 20-517 – demonstrate that Lupron Depot-4 Month 30 mg is safe and effective for the palliative treatment of Stage D2 prostate cancer.

Although frequent adverse events were reported during the study, most were of mild or moderate severity, and the severe events were those commonly associated with advanced stage prostate cancer. During the first 4 weeks of treatment, however, severe adverse events were observed in 16% of enrolled patients, suggesting a causal relationship to the androgen "flare" that follows GnRH analog treatment initiation. Clinically significant adverse events in association with serum T elevations were looked for following re-injections but not found, despite statistically significant serum LH elevations within 24 hours following re-injections. Although symptomatic T elevations were not documented in the study, 16% of enrolled patients reported severe adverse events of onset within 4 weeks of a Lupron re-injection.

The most significant deficiency in the application is the absence of a concurrent control group. Amendments #5 and #6 adequately address the initial omission of ITT efficacy analyses and an integrated safety summary of both clinical studies (M93-013 and M93-012).

The proposed labeling needs revision, as described above (see section 11.0), for better clarification of treatment failures and risks, and to promote greater consistency with the new approved Lupron labeling. Labeling consultation is also needed with the Division of Drug Marketing and Advertising prior to final action on the NDA Supplement.

Further data are needed to determine whether the high risk of "flare" reactions during the first treatment month may be reduced or prevented by concomitant antiandrogen administration during Lupron treatment initiation.

Postmarketing clinical studies are recommended to directly compare the incidence of severe adverse reactions during initiation of Lupron treatment with and without concomitant antiandrogen treatment.

In summary, this small, open-label, uncontrolled clinical trial (M93-013), considered together with the clinical database available from previous TAP-sponsored studies conducted under NDA's 19-010, 19-732 and 20-517, demonstrates the safety and efficacy of the Lupron Depot-4 Month 30 mg formulation for palliative treatment of Stage D2 prostate cancer. To address the safety concern raised by the frequent, severe adverse events associated with treatment initiation, the sponsor should be encouraged to develop well-controlled data regarding potential effectiveness of short-term concomitant antiandrogen treatment to reduce the incidence of severe "flare" reactions during the first 1-2 months of Lupron treatment. For example, the sponsor should be encouraged to conduct a post-approval Phase IV head-to-head study comparing treatment initiation with Lupron alone to initiation of Lupron with short-term antiandrogen treatment during the first dosing interval. During this study, the needed multiple dose PK/PD data, per Clinical Pharmacology and Biopharmaceutics Review, should also be obtained in both treatment groups.

13.0 Recommendations

The NDA is recommended for approval, pending successful resolution of the following deficiencies:

1. The most recent draft labeling should be sent to the Division of Drug Marketing, Advertising, and Communications for consultative review.
2. Revised labeling should be submitted by the sponsor that adequately addresses all modifications requested by DRUDP (communication to the sponsor) and by DDMAC.
3. The sponsor should be encouraged to conduct a postmarketing head-to-head comparative safety study of "flare" reactions with and without short-term concomitant antiandrogen treatment, as a Phase IV commitment. This study should also include serial assessments of leuprolide and testosterone levels after multiple dosing (at least 3 administrations) of the 4-month depot formulation, as recommended by Dr. K. Gary Barnette, DPEII, OCPB, in the Biopharmaceutics Review dated 2/20/97.
4. The sponsor should be encouraged to submit the protocol for the postmarketing Safety/PK/PD study to DRUDP and OCPB/DPEII for comment prior to initiating the study.

Linda J. Golden MD 5/14/97
Linda J. Golden, M.D.
Medical Officer, HFD-580, DRUDP

Concur that application is approvable. H. J. [unclear] M.D. 5/19/97

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ATTACHMENTS:

- Figure 1: Sponsor's Figure 1: Protocol M93-013 Schedule of Procedures (N=40), NDA Vol 8.7, pg 157
- Figure 2: Sponsor's Figure 1: Mean (+ SD) Testosterone, NDA Vol 8.7, pg. 132
- Figure 3: Sponsor's Figure 2: Mean (+ SD) LH, NDA Volume 8.7, pg. 133
- Table 1: Serum Testosterone, NDA Amendment #6, pg. 4
- Table 2: Summary of Testosterone Suppression, NDA Amendment #6, pg. 5
- Table 3: Summary of "Escape" Incidence, NDA Amendment #6, pg. 6
- Table 4: Mean (+/- std. dev) Hormone Levels Immediately Prior to Re-injection and 2-5 Days Post-Injection, NDA Amendment #6, pp. 8
- Table 5: Mean Hormone Levels Immediately Prior to Re-injection and 4, 8 and 12 Hours Post-Injection, NDA Amendment #6, pp. 9
- Table 6: Summary of Injection Delays, NDA Amendment #6, pg. 6
- Table 7: Summary of "Best" Objective Response Rates, NDA Amendment #6, pg. 11
- Table 8: Status of Prostatic Involvement at "Final Visit," NDA Amendment #6, pg. 11
- Table 9: Changes in PSA, NDA Amendment #6, pg. 12
- Table 10: Proportion of Patients with Normalized PSA, NDA Amendment #6, pg. 13
- Table 11: Proportion of Patients with Normalized PAP, NDA Amendment #6, pg. 14
- Table 12: Changes in Performance Status at the "Final Visit," NDA Amendment #6, pg. 16
- Table 13: Adverse events occurring at $\geq 5\%$ incidence level in either M93-012 and M93-013, NDA Amendment #5, pg. 73

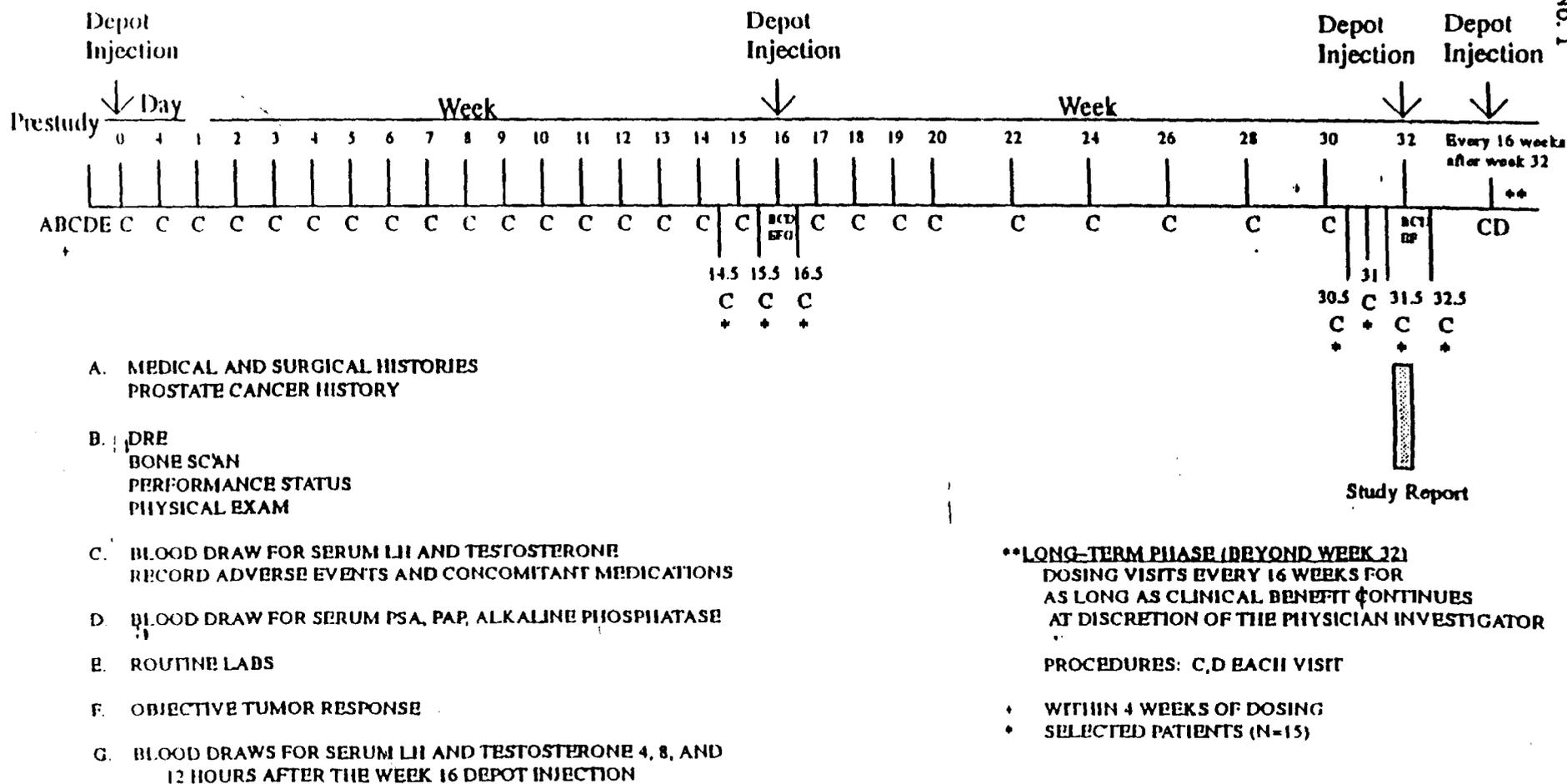
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Revised: 4.30.97; 5.9.97 LGolden/n-20517s.mor

cc: Original NDA Arch
HFD-580
HFD-580/LRarick/HJolson/GBarnette/ADunson
HFD-580/ LGolden (+ attachments)/JFourcroy (+ attachments)

Figure 1.

Protocol M93-013
 Schedule of Procedures
 (N=40)

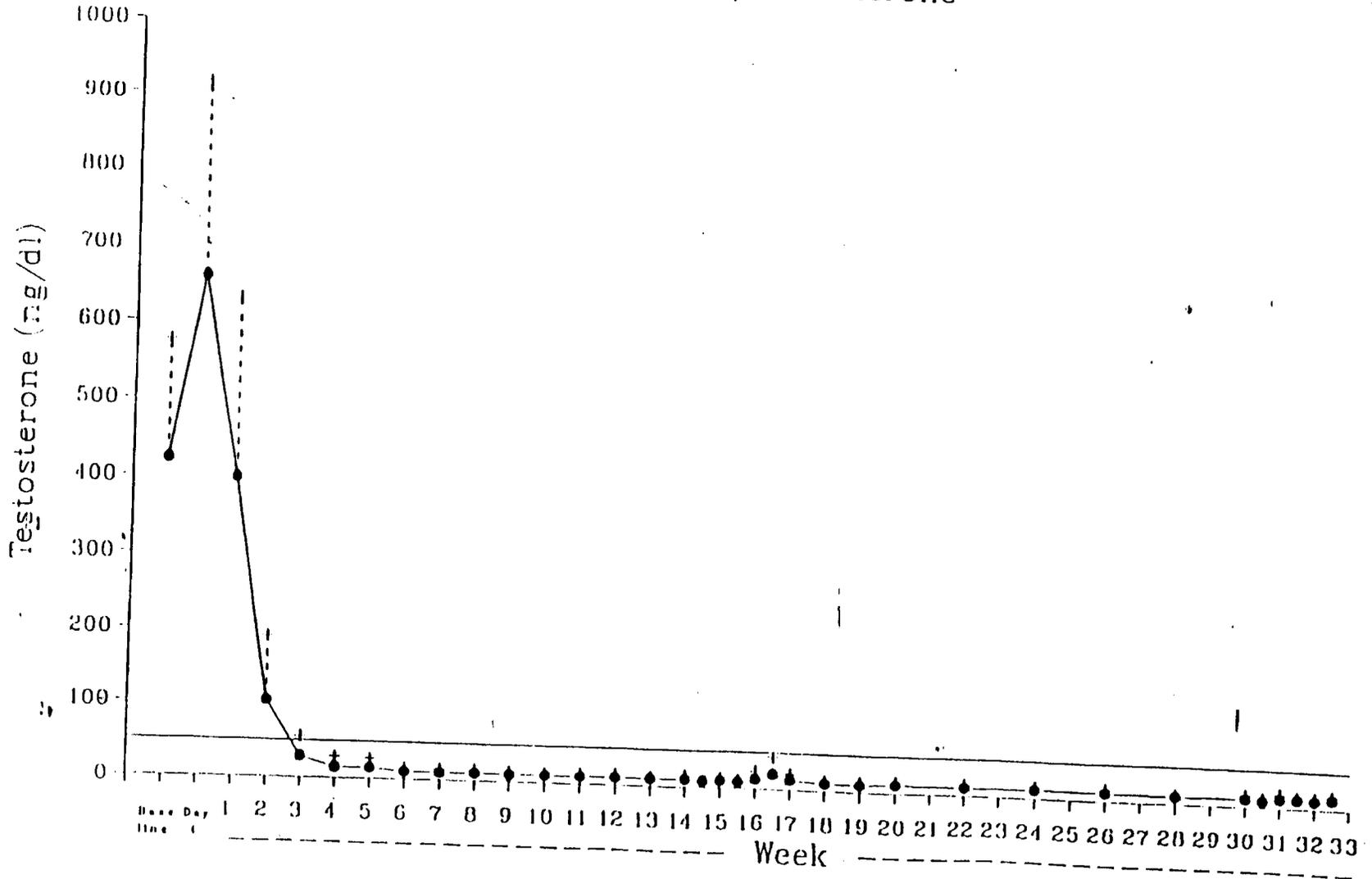


MOR FIGURE 1

157

STUDY M93-013
R&D/05/032

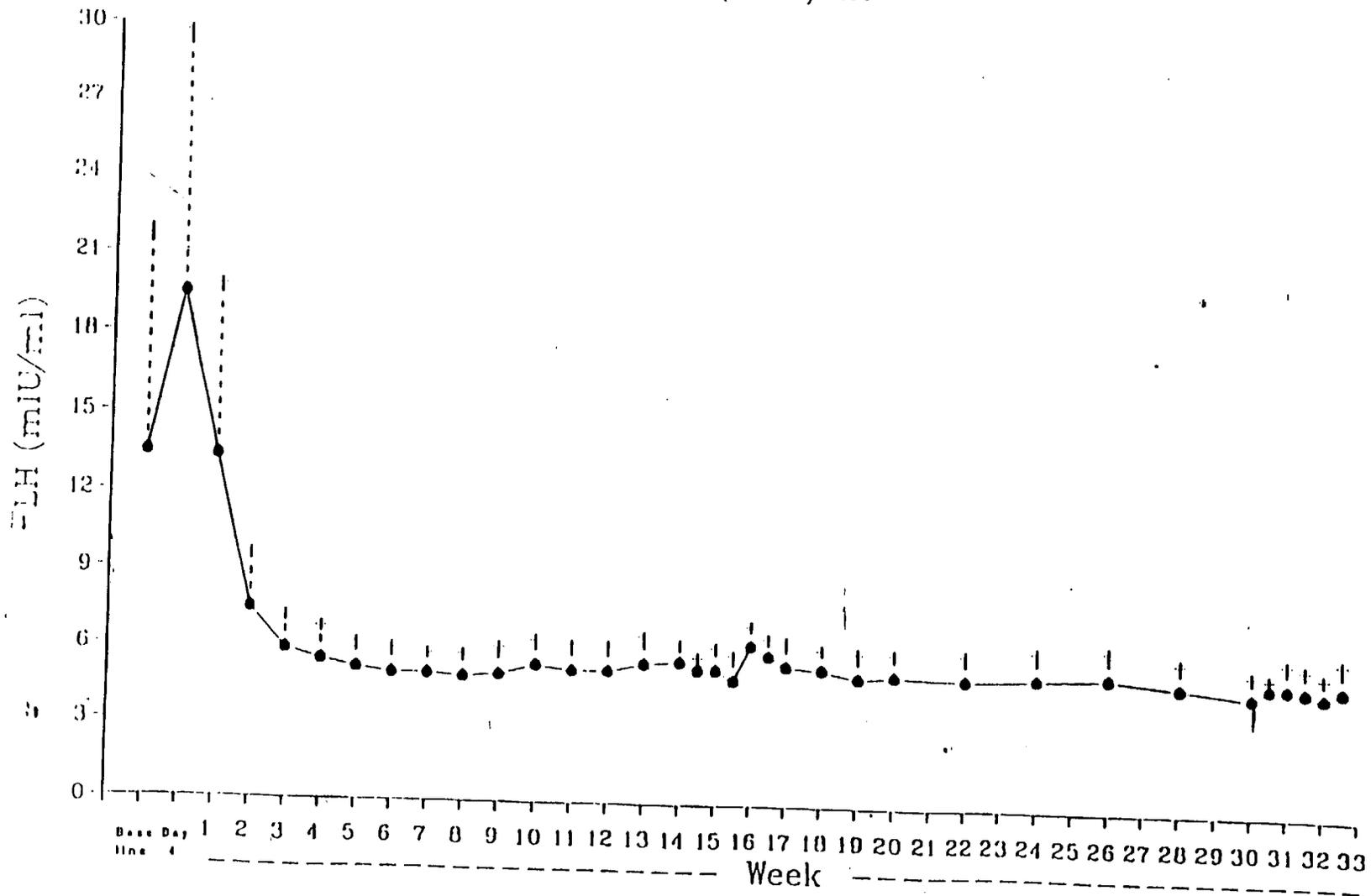
Figure 1
Mean (+ SD) Testosterone



MOR FIGURE 2

STUDY M93 013
RAD/95/032

Figure 2
Mean (\pm SD) LH



MOR FIGURE 3

MOR TABLE 1

SERUM TESTOSTERONE (ng/dL)													
	Week												
	Pre	Day 4	1	2	3	4	8	12	16	20	24	28	32
Study													
M93-013													
N	49	45	44	49	48	47	48	46	45	46	44	43	35
Mean	410.8	633.0	391.9	101.3	29.0	15.6	10.5	10.7	14.1	11.9	12.4	10.2	11.3
M91-583													
N	59	58	52	57	58	58	54	46	52	50	31	--	--
Mean	405.2	571.1	431.4	120.5	46.7	26.3	29.5	35.6	17.5	21.1	22.7	--	--
M91-653													
N	31	29	31	31	32	29	32	30	28	29	25	--	--
Mean	434.8	726.2	436.6	93.6	23.5	11.2	7.6	10.5	8.4	8.5	9.0	--	--
M85-097													
N	56	53	53	53	52	52	54	50	51	48	45	--	--
Mean	372.1	562	344.1	96.6	33.8	17.0	14.5	11.5	13.6	13.4	24.1	--	--

Cross-reference: Statistical Tables 2a-d.

MOR Table 2

Summary of Testosterone Suppression

Study	N	Number (Percent) Patients Suppressed			Median Time (Day of Study) of Onset of Castrate Testosterone Levels (Range)
		By Week 3	By Week 4	By Week 8	
M93-013	49	41 (84%)	46 (94%)	49 (100%)	22
M91-583	61	36 (59%)	56 (92%)	59 (97%) [@]	22 (
M91-653	33	26 (79%)	32 (97%)	32 (97%) [#]	22
M85-097	56	46 (82%)	51 (91%)	53 (95%) [#]	22

- [@] Onset of castrate testosterone levels for remaining 2 patients by Weeks 15 and 28.
- [#] 1 patient unable to reach suppression due to death on Day 6.
- [#] Onset of castrate testosterone levels for 1 patient by Day 66 and 2 patients unable to reach suppression due to not having data beyond Day 4 and Week 2.

NOTE: Time of onset (days) in the statistical tables for Studies M93-013, M91-583, and M91-653 is defined as actual treatment day (Day 1=day of first injection) but is defined as time from first injection (treatment day minus 1) in Study M85-097; time of onset values above for M85-097 are adjusted (by 1 day) for consistency across studies.

Cross-reference: Statistical Tables 3a-d.

MOR TABLE 3

Summary of "Escape" Incidence

Study	N*	No. (%) Patients with "Escapes"	No. of Consecutive Test Values > 50 ng/dL (Weeks)
M93-013	49	0 (0%)	--
M91-583	60	2 (3%)	5 (Week 8-11), 3 (12-13); 4 (Week 12-13)
M91-653	32	0 (0%)	--
M85-097	54	1 (2%)	2 (Week 18, 24)

* Number of patients who reached castrate during 24/32 weeks of treatment.

NOTE: does not include stimulation following reinjection (see next section).

Cross-reference: Statistical Tables 3a-d.

MOR TABLE 4

Mean (+/- std. dev.) Hormone Levels Immediately Prior to
Reinjection and 2-5 Days Post-Injection

Testosterone (ng/dL)

	Inj. 2 (Wk 16, 12, or 4)*				Inj. 3 (Wk 32)*			
	N	Pre	Post	Pre vs. Post p-value	N	Pre	Post	Pre vs. Post P-value
M93-013	9	12.8 (5.6)	21.3 (25.0)	0.250	10	13.5 (5.1)	14.2 (5.4)	0.589
M91-583	13	25.5 (21.0)	28.3 (38.9)	0.633	--	--	--	--
M85-097	17	36.2 (69.6)	41.5 (103.0)	0.538	--	--	--	--

Cross-reference: Statistical Tables 6a-c.

LH (mIU/mL)

	Inj. 2 (Wk 16 or 4)*				Inj. 3 (Wk 32)*			
	N	Pre	Post	Pre vs. Post p-value	N	Pre	Post	Pre vs. Post P-value
M93-013	9	5.6 (0.9)	5.8 (0.6)	0.331	10	4.7 (0.7)	5.2 (1.1)	0.007
M85-097	17	4.6 (2.5)	4.9 (2.0)	0.657	--	--	--	--

- * Weeks 16 and 32 denote M93-013
- Week 12 denotes M91-583.
- Week 4 denotes M85-097.

Cross Reference: Statistical Tables 7a-b.

MOR TABLE 5

Mean Hormone Levels Immediately Prior to Reinjection and
4, 8 and 12 Hours Post-Injection

Hrs. Post-inj.	Testosterone (ng/dL) Injection #2*				Hrs. Post-inj.	LH (mIU/mL) Injection #2*			
	Pre	4	8	12		Pre	4	8	12
<u>M93-013</u>					<u>M93-013</u>				
N	40	39	39	34	N	40	39	39	34
Test	11.7	11.2	12.3	12.6	LH	5.4	6.0	5.9	5.8
<u>M91-583</u>					<u>M91-583</u>				
N	42	42	36	19	N	39	39	35	19
Test	30.6	27.4	31.5	37	LH	4.3	4.7	4.5	4.6
<u>M91-653</u>					<u>M91-653</u>				
N	18	14	16	13	N	19	16	18	14
Test	9.4	8.2	9.4	6.7	LH	5.1	5.4	5.3	5.1
<u>M85-097 (Injs 7-10 combined)</u>									
N	10	10	10	10					
Test	9.2	9.3	9.9	12.4					

* Week 16 for M93-013
 Week 12 for M91-583 and M91-653
 Cross-reference Statistical Tables 8a-d and 9a-c.

MOR TABLE 6

Summary of Injection Delays

No. of Days Between Injections				Inj. Delayed by ≥ 3 days	
Study	<u>Dosing Interval</u> Length/No	Range	Median	No. Pts. /Injections	Corresponding Test. Values > 50 ng/dL
M93-013	112 days/2		112	5/6	0 (1 not available)
M91-583	84 days/2		84	15/16	0 (4 not available)
M91-653	84 days/2		84	4/4	0
M85-097	28 days/5		28	9/11	2

Cross-reference: Statistical Tables 4a-d.

MOR TABLE 7

Summary of "Best" Objective Response Rates

	N	Favorable*	Progression
M93-013	49	88%	12%
M91-583	59	83%	17%
M91-653	31	87%	13%
M85-097	54	83%	17%

* Complete/partial response or stable disease.

Cross-reference: Statistical Tables 11a-d.

MOR TABLE 8

Status of Prostatic Involvement at "Final Visit"

	N	Stable or Improved	>25% Worsened
M93-013	48	100%	0%
M97-583	58	95%	5%
M97-653	30	97%	3%
M85-097	48	98%	2%

Cross-reference: Statistical Tables 12a-d.

MOR TABLE 9

Changes in PSA

	Pretreatment Baseline			Final Visit		
	N	Mean	Median	N	Mean	Median
M93-013	49	1034.6	216.0	47	100.3	3.4
M91-583	51	411.0	69.0	57	24.0	2.9
M91-653	31	844.9	121.0	32	253.7	1.2

Cross-reference: Statistical Tables 13a-c.

MOR TABLE 10

Proportion of Patients with Normalized PSA

	No. (% of Total with Baseline Value) Patients with Elevated Pretreatment PSA and ≥ 1 Treatment Value	No. (% of Patients with Elevated Pretreatment PSA) Patients with Normalized PSA
M93-013	46 (94%)	25 (54%)
M91-583	46 (90%)	29 (63%)
M91-653	27 (87%)	18 (67%)

Cross-reference: Statistical Tables 13a-c.

MOR TABLE 11

Proportion of Patients with Normalized PAP

	No. (% of Total with Baseline Value) Patients with Elevated Pretreatment PSA and ≥ 1 Treatment Value	No. (% of Patients with Elevated Pretreatment PSA) Patients with Normalized PAP
M93-013	35 (71%)	18 (51%)
M91-583	41 (71%)	25 (61%)
M91-653	21 (68%)	11 (52%)
M85-097	24 (67%)	16 (67%)

Cross-reference: Statistical Tables 15a-d.

MOR TABLE 12

Changes in Performance Status at the "Final Visit"

Pretreatment Performance Status	Favorable			Total
	Improved	No Change	Worsened	
Abnormal				
M93-013	7 (35%)	11 (55%)	2 (10%)	20
M91-583	10 (37%)	10 (37%)	7 (26%)	27
M91-653	3 (27%)	8 (73%)	0 (0%)	11
M85-097	13 (41%)	18 (56%)	1 (3%)	32
Normal				
M93-013	N/A	23 (82%)	5 (18%)	28
M91-583	N/A	28 (88%)	4 (13%)	32
M91-653	N/A	17 (81%)	4 (19%)	21
M85-097	N/A	19 (95%)	1 (5%)	20

Cross-reference: Statistical Tables 17a-d

MOR TABLE 13

Adverse Events Occurring at $\geq 5\%$ Incidence Level in Either M93-012 and M93-013

(Possible Probable, Definite or Unknown Relationship to Study Drug)

COSTART	M93-012 (N=24) No. (%)	M93-013 (N=49) No. (%)	Combined Studies (N=73) No. (%)
Arthralgia	1 (4.2)	3 (6.1)	4 (5.5)
Asthenia	0 (0.0)	6 (12.2)	6 (8.2)
Back Pain	0 (0.0)	7 (14.3)	7 (9.6)
Dyspnea	0 (0.0)	3 (6.1)	3 (4.1)
Edema	3 (12.5)	2 (4.1)	5 (6.8)
Headache	1 (4.2)	3 (6.1)	4 (5.5)
Injection Site Pain	9 (37.5)	3 (6.1)	12 (16.4)
Pain	0 (0.0)	4 (8.2)	4 (5.5)
Pelvic Pain	0 (0.0)	3 (6.1)	3 (4.1)
Paresthesia	0 (0.0)	4 (8.2)	4 (5.5)
Rash	0 (0.0)	3 (6.1)	3 (4.1)
Vasodilation	2 (8.3)	24 (49.8)	26 (35.6)

NDA 20-517/S-002

Lupron Depot® (leuprolide acetate for depot suspension)

4-month, 30 mg

Safety Update Review

Included in Medical Officer review dated May 19, 1997.

FEB 20 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA: 20-517

Compound: Lupron® 30 mg 4-month Depot (leuprolide acetate for depot suspension)

Submission Date: 5/30/96

Sponsor: TAP Pharmaceutical, Inc.

Type of Submission: Supplemental NDA (Serial No. 002)

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

I. SYNOPSIS

On May 30, 1996, TAP Pharmaceuticals, Inc. submitted a supplement (Serial No. 002) to NDA 20-517 to support the approval of Lupron Depot®-4 month 30 mg for the palliative treatment of advanced prostate cancer. The active drug (leuprolide acetate) used in the to-be-marketed Lupron Depot®-4 month 30 mg formulation is the same as that used in the previously approved NDAs 19-010 (Lupron Injection), 19-732 (Lupron Depot 7.5 mg), 20-011 and 19-943 (Lupron Depot 3.75 mg), 20-263 (Lupron Depot-PED 7.5, 11.25 and 15 mg) and 20-517 (Lupron Depot-3 month 22.5 mg). The current formulation is intended to deliver the luteinizing hormone, releasing hormone (LHRH) analogue, leuprolide, continuously for 16 weeks for the suppression of serum testosterone levels.

The current submission (Serial No. 002) contains two studies (M93-012 and M93-013). Study M93-012 is a single dose pharmacokinetic study in orchiectomized prostate cancer patients and Study M93-013 is a pharmacodynamic study (no leuprolide blood levels were assessed) in the target population, non-orchiectomized, prostate cancer patients. Study M93-013 was designed to satisfy the clinical requirements for approval of this product and is the only clinical assessment of Lupron Depot®-4 Month 30 mg.

II. RECOMMENDATION

NDA 20-517 submitted on March 30, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II). It should be noted that the multiple dose pharmacokinetics of the Lupron Depot-4 month 30 mg in the target population have-not been assessed.

However, since there is extensive experience with Lupron Depot formulations (1-month and 3-month) where no significant accumulation of leuprolide levels was observed upon chronic dosing, it is the opinion of OCPB/DPE II that the multiple dose pharmacokinetics of this formulation can be assessed in the target population on a post-approval basis, if the Division of Reproductive and Urologic Drug Products (HFD-580) considers that the sponsor has provided sufficient information for approval based on the efficacy and safety of Lupron Depot-4 month 30 mg.

The Phase IV study should include an assessment of both leuprolide and testosterone levels after multiple dosing (at least three administrations) of the 4 month depot and the sponsor is encouraged to submit the protocol for this study to OCPB/DPEII for comment prior to the initiation of the study.

The following change in the **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS** section of the proposed label are recommended.

- ◆ The PHARMACOKINETICS section of the label for the Lupron Depot® 3-month 11.25 mg should be as follows;

The *Absorption*: subsection should be changed to the following;



K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 2/19/97
FT signed by Angelica Dorantes, Ph.D., Team Leader *AD* 2/20/97

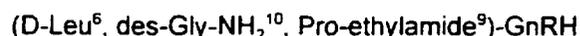
cc: NDA 20-517, HFD-580 (Golden, Dunson), HFD-870 (M.Chen 13B-17, Dorantes, Barnette), Drug file (Millison, HFD-850, WOCII 3010).

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III. BACKGROUND

Leuprolide acts as a gonadotropin inhibitor and is chemically unrelated to the steroids. Leuprolide is often designated by the following with the superscript numbers indicating changes in the GnRH molecule:



Lupron® (leuprolide acetate) Injection, daily subcutaneous injection, has been marketed for the palliative treatment of advanced prostate cancer since April 1985 and for treatment of central precocious puberty since April 1993 by TAP Pharmaceuticals, Inc.

Subsequently, Lupron Depot® (leuprolide acetate for depot suspension) was developed by TAP Pharmaceuticals, Inc., intended to provide continuous release of leuprolide for either 1 or 3 months. The history of Lupron Depot approvals and a recent submission is provided in Table 1.

Table 1

Lupron Depot Approvals and Submissions			
Product	NDA #	Approval Date	Indication
Lupron Depot 7.5 mg	19-732	01/26/89	Palliative Treatment of Advanced Prostate Cancer
Lupron Depot 3.75 mg	20-011	10/22/90	Management of Endometriosis
Lupron Depot-PED 7.5 mg, 11.25 mg and 15 mg	20-263	04/16/93	Treatment of Central Precocious Puberty
Lupron Depot 3.75 mg	19-943	03/30/95	Treatment of Anemia Secondary to Uterine Fibroids
Lupron Depot-3 Month 22.5 mg	20-517	12/22/95	Palliative Treatment of Advanced Prostate Cancer
Lupron Depot-3 Month 11.25 mg	20-708	under review	Management of Endometriosis Treatment of Anemia Secondary to Uterine Fibroids

IV. Formulation and Administration

The formulations of the currently approved Lupron® Depot-3 month 22.5 mg and the 4 month 30 mg depot (reviewed herein) are included in Table 2.

Table 2. Formulation

Ingredient	Lupron® Depot-4 month 30 mg	Lupron® Depot-3 month 22.5 mg
✓ leuprolide acetate	30 mg	22.5 mg
✓ biodegradable polylactic acid polymer	mg	mg
✓ mannitol	mg	mg
Diluent		
✓ sodium carboxymethylcellulose	mg	mg
✓ D-mannitol	mg	mg
✓ polysorbate 80	mg	mg
✓ water for injection, USP	mL	ml

Reviewer Comments:

1. The Lupron® Depot-4 month 30 mg formulation used in Studies M93-012 and M93-013 is the formulation the sponsor intends to market.
2. The Lupron® Depot-4 month 30 mg formulation is NOT compositionally proportional to the currently marketed Lupron® Depot-3 month 22.5 mg.

V. Analytical Methodology

Plasma testosterone levels were estimated (Study M93-013) by a _____ performed by _____
The validation of the _____ for testosterone is provided in Table 3.

Table 3. Testosterone Validation

Sensitivity	3 ng/dl				
Precision, intra-assay					
Mean ± SD	15.5 ± 1.3	37 ± 1.7	256 ± 19	490 ± 25	
% CV	8.1	4.8	7.5	5.2	
n	10	10	10	10	
Precision, inter-assay	100 pg Standard				
Mean ± SD	102.4 ± 8.6	12.5 ± 1.7	34 ± 2.1	235 ± 18	448 ± 33
% CV	8.5	13.4	6.1	7.8	7.3
n	25	25	25	25	25
Specificity	% Cross Reactivity				
Dihydrotestosterone	22				
4-androsten-3β,17β-diol	5.5				
5α-androsten-3β,17β-diol	2.3				
5β-androsten-3α,17β-diol	0.24				
Androsterone	0.8				
Androstenedione	1.4				

Leuprolide acetate levels were determined using a and the validation/quality control of this assay is included in Table 4.

and the validation/quality control of this

Table 4. Leuprolide Acetate Validation

Sensitivity (LLQ)	0.1 ng/ml								
Accuracy	Target (ng/ml)								
	Conc. (ng/ml)								
	% Target	87.0	100.2	101.4	102.4	98.0	98.5	93.8	106.9
Precision (%CV)	17.0	4.3	5.5	2.1	7.0	5.4	13.7	11.8	
Specificity	Not Provided								

Reviewer Comments:

1. The cross-reactivity of the testosterone assay used with dihydrotestosterone (DHT) is 22%.
2. The specificity of the leuprolide is not provided at this time. It is stated in previous reviews of leuprolide formulations (NDAs 19-943 and 20-517 Lupron® Depot-3 month 22.5 mg), that no cross-reactivity was found with TRH and LHRH, but was found with synthetic analogs of leuprolide and a "major metabolite".
3. The assays reviewed herein are identical to those used in the previous NDAs submitted by TAP Pharmaceuticals for leuprolide acetate (see Table 1). Therefore, they are deemed acceptable at this time.

VI. In Vitro Dissolution Testing

The dissolution method proposed for the quality control and release of drug product is as follows;

Apparatus: USP Type II glass (120 ml)

Medium: % polyvinyl alcohol, % polysorbate 80, and mM lactic acid

Procedure:

Specifications:

Time (hours)	Amount Dissolved
	%
	%
	%

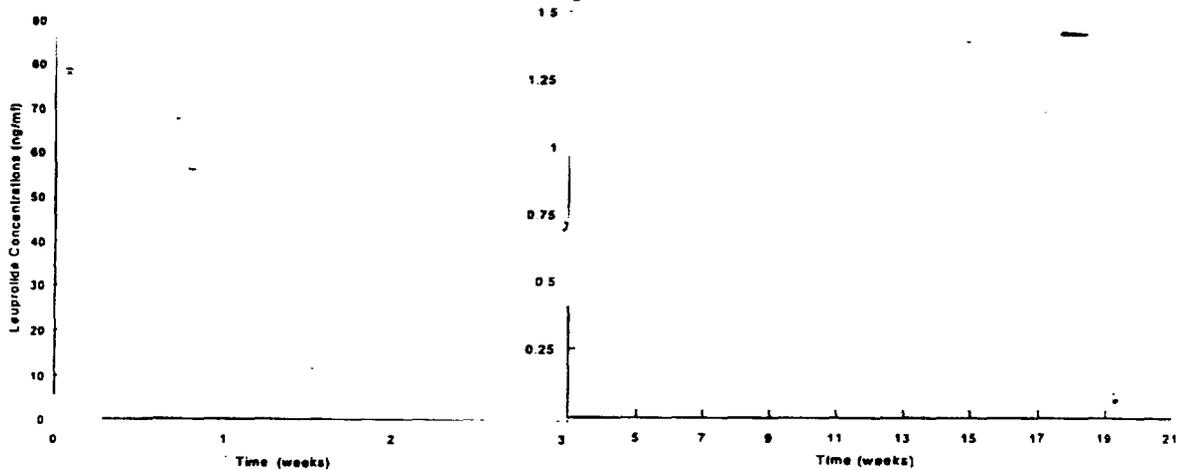
Reviewer Comments:

1. The method and specifications proposed herein are the same as those used for the currently marketed Lupron Depot® 3-month 22.5 mg, indicated for the palliative treatment of advanced prostate cancer (NDA20-517) and Lupron Depot®-3 month 11.25 mg for treatment of endometriosis (NDA 20-708)
2. The dissolution method and specifications proposed herein appear to be acceptable

VII. Pharmacokinetics

The plasma leuprolide levels after a single administration of Lupron® Depot-4 month 30 mg to 24 orchiectomized prostate cancer patients are included in Figure 1.

Figure 1.



It is apparent from Figure 1 that the T_{max} occurred during the first day after dosing. However, the only blood sample taken during this time was at 4 hours post-dose. Therefore, the true C_{max} and T_{max} were not determined from these data. However, these parameters do not provide critical information pertaining to the systemic exposure to leuprolide. Similarly, since a substantial fraction of the AUC_{∞} occurs in the first 24 hours after dosing, a true assessment of AUC_{∞} is not possible from these data and the most appropriate pharmacokinetic parameter demonstrating the systemic exposure of leuprolide is the average plasma concentration of leuprolide from 3 to 16 weeks post-dose. The mean (\pm SD) C_{avg} ($_{3-16}$ weeks) was 0.54 ± 0.27 ng/ml from all 24 subjects and 0.44 ± 0.27 ng/ml for the 16 patients from which complete or near complete data are available.

Table 5 includes a between study (between NDA) comparison of the leuprolide pharmacokinetic parameters from the currently marketed Lupron® Depots, approved for the palliative treatment of advanced prostate cancer

Table 5. Mean Pharmacokinetic Parameters

Depot	Leuprolide concentration at 4 hours post-dose	Steady-State C_{avg} (3-16 weeks)
7.5 mg 1-month#	ng/ml	ng/ml
22.5 mg 3-month#	ng/ml	ng/ml
30 mg 4-month	ng/ml*	ng/ml*

- Currently marketed Lupron® depots for the palliative treatment of advanced prostate cancer.

* - The data presented for the 30 mg-4 month is only from patients with complete or near-complete data.

A. Metabolism

Since leuprolide is a synthetic nonapeptide analogue of luteinizing hormone releasing hormone (LHRH), its metabolism is similar to endogenous LHRH and consists of catabolization into smaller peptide fragments.

B. Special Populations

The effect of hepatic and renal impairment on the pharmacokinetics/pharmacodynamics of leuprolide has not

been determined.

C. Drug Interactions

The potential for pharmacokinetic/pharmacodynamic interaction between leuprolide and other agents has not been assessed, but the likelihood of a clinically significant drug interaction with leuprolide is negligible.

Reviewer Comment:

1. Complete leuprolide levels (i.e. at every sampling time point) are available from only 16 patients. The levels and Cavg presented herein are the mean values of all 24 patients dosed.
2. The subjects used in Study M93-012 were orchiectomized prostate cancer patients and the pharmacokinetics of Lupron® Depot-4 month 30 mg in the target population has not been assessed.

VIII. Pharmacodynamics

The suppression and maintenance of suppression of serum testosterone levels are the clinical endpoints for leuprolide acetate and are used in the pharmacodynamic analysis herein.

Table 6 includes the average testosterone concentration (Cavg) from the time the testosterone level were suppressed to castrate range (<50 ng/dl) to include all testosterone levels thereafter from the intent-to-treat data. These studies represent the pivotal clinical trials that were used in support the approval of the Lupron Injection (NDA 19-010), Lupron Depot 7.5 mg (NDA 19-737) and Lupron Depot-3 month 22.5 mg (NDA 20-517) and the pivotal clinical trial submitted to NDA 20-517 to support the pending approval of the Lupron Depot-4 month 30 mg, reviewed herein.

It should be noted that the assay method used to estimate testosterone levels in Study M91-583 was not as specific as that used in the other studies.

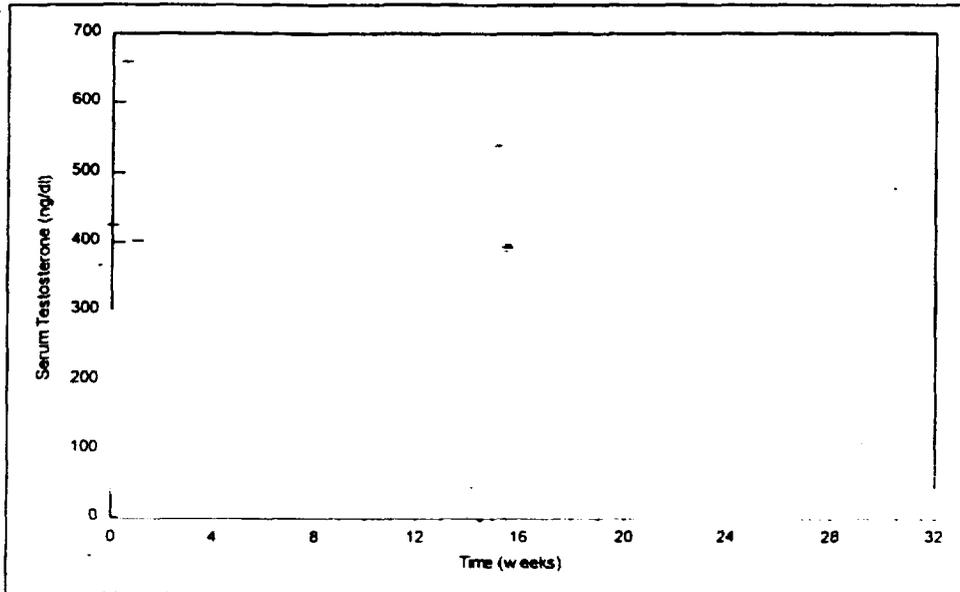
Table 6.

Study #	Formulation	n	Testosterone Cavg (ng/dl)	Time to Castrate (days)	# pts that escaped*
M80-036	daily injection	55			7
M81-017	daily injection	98			14
M85-097	1 month depot	54			8
M88-124	1 month depot	14			1
M91-653	3 month depot	32			0
M91-583	3 month depot	61			7
M93-013	4 month depot	49			4

*some patients escaped more than once.

Mean (+SD) serum testosterone levels from 49 patients with advanced prostate cancer (non-orchiectomized) from Study M93-013 are presented in Figure 2. However, it should be noted that levels were not available from each patient at every time point.

Figure 2.



Reviewer Comments:

1. *The pivotal clinical trial, Study M93-013, was not submitted to the OCPB/DPEII for review.*
2. *The clinical inferences and conclusions from these data will be made by Dr. Linda Golden, Medical Officer, Division of Reproductive and Urologic Drug Products (HFD-580).*
3. *According to these data, the testosterone suppression and maintenance of suppression by the Lupron Depot-4 month 30 mg is similar to that of the currently approved Lupron Injection, Lupron Depot 7.5 mg and Lupron Depot-3 month 22.5 mg.*
4. *As is the case with the previously approved Lupron Depot formulations, no pharmacokinetic/pharmacodynamic correlation could be established.*

IX. Labeling Comments

The proposed label is included in Attachment 1 (page XX)

Reviewer Comments:

The following change in the **CLINICAL PHARMACOLOGY** and **PHARMACOKINETICS** section of the proposed label are recommended.

- ◆ The **PHARMACOKINETICS** section of the label for the Lupron Depot® 3-month 11.25 mg should be as follows;

8 Pages (9-16)

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Attachment 2: Individual Study Summary

M93-012

Study Number: M93-012

Title: Pharmacokinetics of a Four-Month Depot Formulation of Leuprolide in Prostate Cancer Patients

Objectives: The objectives of this study were to determine plasma leuprolide levels for 20 weeks following a single injection of a 30 mg depot formulation of leuprolide and to monitor the safety of this formulation.

Investigators:

Study Design and Dose Administration: This was a single dose, open, multicenter pharmacokinetic study in orchiectomized prostate cancer patients.

Patients: The mean \pm SD age of the 24 patients enrolled in the study was 73.3 ± 7.2 years (range: yrs), the mean \pm SD weight was 89.0 ± 14.9 kg (range: kg), and the mean \pm SD height was 177 ± 7 cm (range: cm). Two patients did not complete the study. One patient prematurely terminated due to personal reasons with his last sample obtained on Week 5. One patient did not complete the study for lack of compliance with the sampling schedule. No samples were obtained between Week 14 and 19, but the patient returned for the last sample on Week 20.

Formulation:

The formulation used in Study M93-012 is included in Table 7 and is the to-be-marketed formulation of the Lupron® 30 mg 4-month depot.

Table 7. Formulation

Ingredient	Lupron 30 mg
leuprolide acetate	30 mg
biodegradable polylactic acid polymer	mg
mannitol	mg
	Diluent
sodium carboxymethylcellulose	mg
D-mannitol	mg
polysorbate 80	mg
water for injection, USP	mL

Blood Collection: Blood samples (4 mL) for the determination of plasma leuprolide concentrations were obtained prior to dosing (0 h) and at 4 h post dosing on Day 0, on Days 1, 2, 4, and 7, twice a week (at least three days apart) during Weeks 1.5 through 4, once a week at the end of Weeks 5 through 12, twice a week (at least three days apart) during Weeks 12.5 through 16, and then weekly through Week 20.

Analytical Methods: Plasma leuprolide acetate concentrations were determined at using a procedure. The lower limit of quantitation for this study was ng/mL with a sample volume of mL.

Pharmacokinetic Methods: Leuprolide concentrations less than ng/mL were reported as and were treated as for all calculations. The area under the plasma concentration-time curve (AUC_t) for leuprolide acetate concentrations was calculated using the linear trapezoidal rule.

Results

Pharmacokinetics

As was the case with other Lupron depot formulations (7.5 mg, 1-month and 22.5 mg, 3-month), the apparent peak concentrations occurred during the first 24 hours post-dose. Since leuprolide concentration were only taken 4 h post-dose during this time interval (0-24 h post-dose) the actual C_{max} was not assessed (see Figure 3). Additionally, since 42% of the total measured AUC was during the first week and the valid C_{max} was not properly characterized, the reported AUC_{total} values probably underestimate the actual AUC_{total}. Since, leuprolide concentrations were relatively constant from Week 3.5 to Week 16 (the proposed dosing interval), the most adequate measure of systemic exposure of leuprolide acetate from Lupron® 30 mg 4-month depot is the average plasma concentration from 3.5-16 weeks.

A second peak leuprolide level (1.89 ng/mL) was apparent at Week 2 after dosing in the mean concentration-time profile mainly caused by one patient who had a high leuprolide acetate concentration at that time (22.30 ng/mL). Another patient had a high leuprolide concentration at Week 1.5 with a value of 13.69 ng/mL.

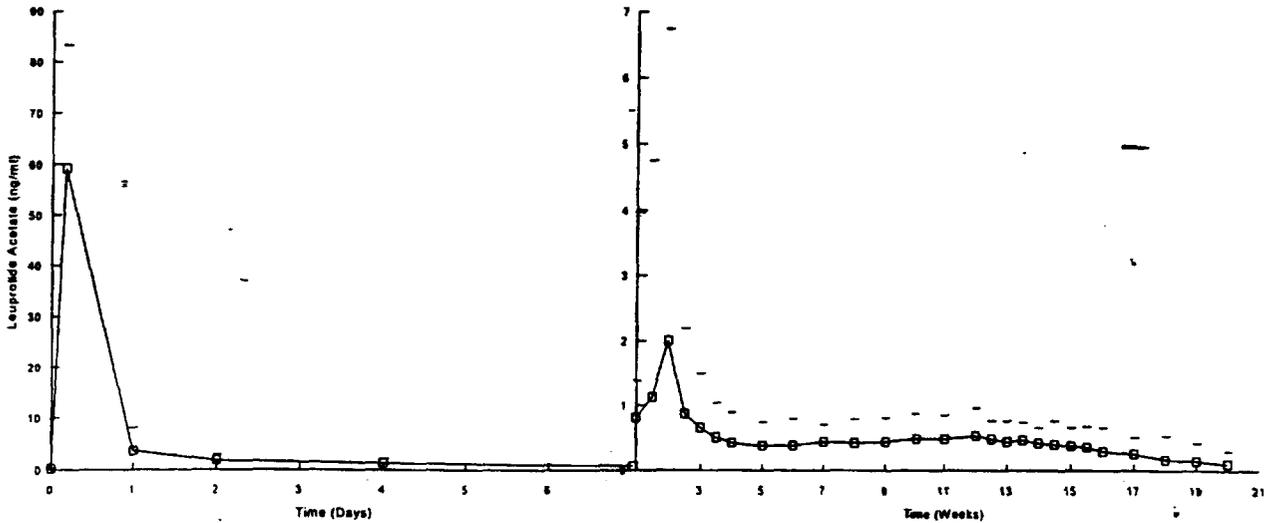
A summary of mean plasma leuprolide concentrations and AUC values at each week after dosing is provided as follows.

Mean ± SD Leuprolide Acetate Concentrations and AUC			
Week	All Patients [†]	Patients with Complete Data [‡]	
	Conc (ng/mL)	Conc (ng/mL)	AUC (ng•h/mL)
1	0.93 ± 0.45	0.80 ± 0.35	973 ± 258
2	1.89 ± 4.86	1.99 ± 5.43	222 ± 376
3	0.71 ± 0.78	0.67 ± 0.83	172 ± 320
4	0.54 ± 0.36	0.43 ± 0.24	91 ± 77
5	0.47 ± 0.28	0.39 ± 0.21	70 ± 36
6	0.48 ± 0.31	0.38 ± 0.22	65 ± 34
7	0.48 ± 0.22	0.46 ± 0.24	70 ± 35
8	0.51 ± 0.28	0.43 ± 0.19	74 ± 33
9	0.53 ± 0.28	0.45 ± 0.25	74 ± 37
10	0.56 ± 0.31	0.49 ± 0.26	80 ± 42
11	0.55 ± 0.30	0.50 ± 0.30	81 ± 48
12	0.61 ± 0.35	0.53 ± 0.31	83 ± 51
13	0.51 ± 0.25	0.46 ± 0.26	83 ± 44
14	0.46 ± 0.21	0.42 ± 0.21	75 ± 38
15	0.44 ± 0.22	0.38 ± 0.19	69 ± 32
16	0.39 ± 0.28	0.30 ± 0.20	58 ± 34
17	0.31 ± 0.21	0.25 ± 0.20	46 ± 33
18	0.27 ± 0.27	0.18 ± 0.23	36 ± 35
19	0.22 ± 0.20	0.16 ± 0.18	28 ± 35
20	0.15 ± 0.15	0.12 ± 0.15	25 ± 27

[†] N = 19 to 22 patients

[‡] N = 16 patients with complete or nearly complete data.

Figure 3. Mean (SD) Leuprolide Acetate Concentrations



A between study comparison of the release rates of the three different formulations (currently marketed 7.5 mg 1-month and 22.5 mg 3-month depots and the 30 mg 4-month depot) by plotting the percent AUC relative to AUC at the end of the intended therapeutic duration vs. time as percent of the intended therapeutic duration (one, three or four months) are similar (data not shown). Additionally, mean pharmacokinetic parameters from the aforementioned depot formulations are included in Table 8, below.

Table 8. Mean Pharmacokinetic Parameters

Depot	Leuprolide concentration at 4 hours post-dose	Steady-State Cavg
7.5 mg 1-month#	20 ng/ml	0.70 ng/ml
22.5 mg 3-month#	49 ng/ml	0.60 ng/ml
30 mg 4-month	59 ng/ml	0.44 ng/ml

- Currently marketed Lupron® depots for the palliative treatment of advanced prostate cancer.

Sponsor's Conclusions

Following the initial burst of leuprolide from the formulation which is characteristic of this type of preparation, the 30 mg Lupron Depot formulation provided a relatively constant release rate of the drug during the intended 16-week treatment duration. Excluding the initial release, leuprolide acetate concentrations averaged 0.44 ± 0.20 ng/mL between Weeks 3.5 and 16 in the 16 patients in which complete or near complete data was available.

Sponsor's Comments:

- Three patients (Patients _____) had detectable leuprolide concentrations in the pre-dose sample, with respective concentrations of 0.28, 0.19, and 0.18 ng/mL, possibly due to nonspecific binding with the radioimmunoassay. These predose concentrations were used in calculations of AUC.
- Sixteen missing or lost plasma concentrations were replaced using linear interpolation (Patient _____ Day 4, Patient _____ Weeks 12 and 12.5; Patient _____ Weeks 3, 14, 15, 15.5, and 16; Patient _____

Weeks 12.5, 13, and 13.5; Patient Weeks 1 and 1.5; Patient #910, Week 15; Patient Week 12.5; Patient Week 2). One missing concentration on Day 1 (Patient was replaced using the predicted value from the linear regression estimated from Day 1 and Day 2 values of the patients with data. Several missing values could not be estimated (Patient Weeks 14 to 19; Patient Weeks 6 to 20) and were not replaced. Patient was out of town between Weeks 14 and 19 but returned for his final sample on Week 20, and Patient withdrew from the study after Week 5.

3. Several samples were lost during shipping. These came from Patient Weeks 7 to 20; Patient Predose to Week 7; Patient Predose to Week 7; Patient Predose to Week 4; Patient Predose to Week 3; Patient Week 15; and Patient Predose to Week 1. With the exception of Patient at Week 15, concentrations were not estimated for these samples.

Reviewer Comments:

1. *It is of significance that Study M93-012 was conducted in orchiectomized males and no pharmacodynamic assessment (testosterone suppression) was possible in this study and the pharmacokinetics of Lupron® Depot-4 month 30 mg in the target population has not been assessed.*
2. *It was stated by Dr. Aruna Dabholkar, Regulatory Affairs, TAP Pharmaceuticals, Inc. that boxes containing the samples listed in Sponsor's Comment #3, above, were lost during shipping. When the boxes arrived at the analytical site, they were thawed and the samples were not assayed.*

JUN 14 1996

N20517.S-C02

6-18-1996

NDA 20-517
S-002

TAP Holdings Inc.
Deerfield, IL

Submission dated: 5-30-1996

Received at HFD-510: 5-31-1996

Pharmacology Review of NDA Supplement
S002

Drug: Lupron depot 3 months 22.5 mg (proprietary name);
leuprolide acetate for depot suspension (established name); TAP-
144-SR(3M) & Abbott-43818 (code names).

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

Also designated as D-leu-6, des-gly-NH₂, 10, pro-ethylamide-9-
GnRH.

Dosage form: Sterile depot suspension for injection.

Route of administration: intramuscular injection.

Proposed indication: palliative treatment of advanced prostatic
cancer.

Related INDs and NDAs: IN NDA 19-010
(Lupron injection for treatment of prostate cancer); NDA 19-943
(for treatment of anemia secondary to uterine fibroids); NDA 19-
732 (Lupron Depot 7.5 mg for palliative treatment of advanced
prostate cancer); NDA 20-011 (Lupron Depot 3.75 mg for management
of endometriosis); NDA 20-263 (Lupron Depot-PED for treatment of
precocious puberty); NDA 20-708 (Lupron Depot-3 Month 11.25 mg
for the management of endometriosis and anemia secondary to
uterine fibroids).

The proposed product TAP-144-SR(4M) injection microspheres
incorporates leuprolide into a biodegradable depot formulation
which uses the same vehicle as used with the approved Lupron
Depot-3 month-22.5 mg product.

A single vial of Lupron Depot- 4 Month 30 mg contains leuprolide acetate (30 mg), polylactic acid (mg), and D-mannitol (mg). The accompanying ampule of diluent contains caboxymethylcellulose sodium (mg), D-mannitol (mg), polysorbate 80 (mg), water for injection, USP and glacial acetic acid, USP to control pH. The later is lost during the depot manufacturing.

Preclinical pharmacology and toxicology: is referred to previous approved products of similar composition under various NDAs as mentioned under related INDs/NDAs sub-heading.

Previous human experience with the proposed product: An overview of clinical studies of a four month depot formulation of leuprolide in patients with stage D2 prostatic adenocarcinoma (Scientific report No. R&D/96/285) showed that after an initial burst of leuprolide, it provided constant release rate of drug during the intended 16 week treatment period. Leuprolide concentrations averaged 0.44 ± 0.20 ng/ml between weeks 3.5 and 16.

The release pattern of the 30 mg leuprolide depot during the 16 weeks following dosing was similar to the pattern observed during the 4 and 12 weeks following dosing with the monthly 7.5 mg and the 3-month 22.5 mg formulations, respectively.

It was also stated that the formulation was well tolerated and safety data was consistent with the known safety profile of leuprolide.

Summary: In conclusion the sponsor stated that the microsphere [TAF-144-MC(3M)] powder used for Lupron Depot-4-Month 30 mg product is the same as that used for the approved product Lupron Depot-3 Month 22.5 mg, with the exception of the additional quantity of the drug is used to provide adequate leuprolide blood levels over 16 weeks. It is manufactured by the same materials, methods and procedures as those of Lupron Depot-3 Month 22.5 mg approved under NDA 20-517.

The PK and clinical studies conducted with Lupron Depot-4 Month 30 mg supported the use of the product every 16 weeks with the known safety profile of leuprolide.

N20517.S-002

Labeling: Labeling is similar to that approved as part of NDAs 19-010, 19-732, 20-011, 20-263 and 20-517 and is applicable to present NDA 20-517 supplement 002.

Recommendations: Based on the extensive experience, both preclinical and clinical with leuprolide depot formulation and the present formulation being similar to that approved before under NDA 20-517 for similar indication, Pharmacology recommends approval of NDA 20-517 supplement 002. (Lupron Depot-4 Month 30 mg) for the palliative treatment of advanced prostatic cancer.

Krishan L. Raheja, DVM, PhD
Krishan L. Raheja, DVM, PhD

A. Jordan
6/18

Original NDA 20-517 S002
HFD-3454
HFD-510
HFD-510/A. Jordan
HFD-510/K. Raheja, 6-18-1996, N20517.S-002

APR 25 1997

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-580

2. NDA Number
20-517

3. Name and Address of Applicant

TAP Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

4. Supplement

S-002
5-30-96

5. Name of Drug

Lupron Depot, 4-month, 30mg

6. Nonproprietary Name

Leuprolide acetate for depot suspension

7. Supplement Provides For

A new strength (30mg) for 4 months treatment

8. Amendment

9. Pharmacological Category

Gonadorelin agonist/Palliative treatment
of prostate cancer

10. How Dispensed

Rx

11. Related

12. Dosage form

Lyophilized powder to be reconstituted for injection (IM)

13. Potency

30mg

14. Chemical Name and Structure

5-oxo-L-Pro-L-His-L-Trp-L-Ser-L-Tyr-D-Leu-L-Leu-L-Arg-N-ethyl-L-Prolinamide acetate

15. Comments:

This efficacy supplement describes a new strength of 30mg for the increased duration of palliative treatment of prostate cancer from 3 months to 4 months. The drug product is the same as previously approved 22.5mg for 3 months, except for the increased amount of lyophilized microspheres in the same vial.

The submission contains information on **drug substance** (manufacturers, methods of manufacturer and packaging, process controls, specifications and analytical methods for the bulk drug substance, and stability) and **drug product** (specifications and analytical methods for ingredients, manufacturer, method of manufacturing, container and closures, stability, and certificates of analysis) and they are essentially cross-referencing to previously approved information for 22.5mg for 3 months, except for stability data.

Six months stability data at 25oC and 40oC for a clinical batch (Z304501) were provided together with a stability protocol as well as 3 months stability data for four production scale batches (Z304503, Z304504, Z304505, and Z304506).

Two-year expiration date was proposed and considered to be reasonable.

16. Conclusion and Recommendation

This supplement can be approved from the chemistry point of view.

17. Name

Moo-Jhong Rhee, Ph.D.

Reviewer's Signature

Date

4-25-97

Distribution

R/D initialed by

s20517.002

Original Jacket

Reviewer

Division File

MJR
4/25/97

**ENVIRONMENTAL ASSESSMENT
AND FINDING OF NO SIGNIFICANT IMPACT
FOR**

**Lupron Depot, 4-month, 30mg
Leuprolide Acetate for Depot Suspension
NDA 20-517, S-002**

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Division OF Reproductive and Urologic Drug Products
(HFD-580)**

FINDING OF NO SIGNIFICANT IMPACT
NDA 20-517, S-002
Lupron Depot- 4 month, 30mg
Leuprolide acetate
For Depot Suspension

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process. The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their supplemental new drug application for Lupron Depot, 4-Month, 30mg, TAP Holdings Inc., has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Leuprolide acetate is a chemically synthesized peptide drug which is administered as intramuscular injection every four months for the management of prostate cancer. The drug substance will be manufactured by

The drug product will be manufactured by
and may be

tested and packaged for marketing by

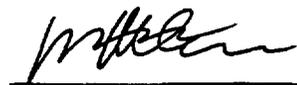
The finished drug product will be used in hospitals and clinics throughout the United states.

Leuprolide acetate, a peptide expected to have extremely low toxicity, is metabolized in vivo to inactive metabolites. Any excreted metabolites that enter public water and sewage treatment facilities are expected to be rapidly biodegraded by soil and water microbial organisms.

Off specification lots of bulk drug substance from facility will be treated as a special pharmaceutical waste and sent to an incineration site. Any unused drug product that is returned to will be also separated and will be treated as special pharmaceutical waste and sent an incinerator.

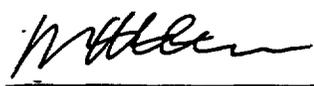
The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

4/30/97
DATE



PREPARED BY
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
HFD-820 Assigned to HFD-580

4/30/97
DATE



DIVISION CONCURRENCE
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
HFD-820 Assigned to HFD-580

5/9/97
DATE



CONCURRED
Nancy B. Sager
Environmental Assessment Team Leader
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Certification stating that EA is FOIable
Material Safety Data Sheets for Drug Substances

cc:

Orig. NDA 20-517

HFD-580/Division File

HFD-580/MRhee/ADunson

337 HFD-004/FONSI File 20-517

337 HFD-004/FONSI File *direct*

215 HFD-049/FOI COPY

NON-CONFIDENTIAL

Environmental Assessment of Lupron Depot® - 4 Month 30 mg

**TAP Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015**

The Environmental Assessment (EA) being submitted by TAP Holdings Inc. on this product is a nonconfidential document and has appendices A, B, and C. These are: 1) Non-Confidential, Appendix A containing Material Safety Data Sheets (MSDS); 2) Non-Confidential, Appendix B containing references; and 3) Confidential, Appendix C which is the full EA for review by FDA.

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1 DATE

May 15, 1996

2 NAME OF APPLICANT

TAP Holdings Inc.

3 ADDRESS

Bannockburn Lake Office Plaza

2355 Waukegan Road

Deerfield, Illinois 60015

4 DESCRIPTION OF THE PROPOSED ACTION

4.1 REQUESTED APPROVAL

TAP Holdings Inc. is seeking an approval through this Supplemental New Drug Application for the manufacture, packaging, and distribution of Lupron Depot[®]-4 Month 30 mg, for the palliative treatment of advanced prostate cancer, pursuant to Section 505(b) of the Food, Drug, and Cosmetic Act. The drug product is a leuprolide acetate suspension designated for one intramuscular injection, every four months containing 30 mg of the active ingredient, leuprolide acetate (also referred to in the Environmental Assessment as leuprolide). This dosage form consists of leuprolide acetate enveloped in a polymer comprised of polylactic acid. The drug-polymer microspheres are mixed at the time of use with a sterile diluent and the resulting suspension is injected intramuscularly, providing 4 months of sustained leuprolide release into the tissues.

The drug product is administered with the help of an administration kit that includes: 1) a single dose glass vial [a colorless 9 mL silicone-baked vial of highly resistant, boro-silicate glass . . . glass)] containing the drug product which is the biodegradable 4-month depot comprising sterile, white, and odorless formulated microspheres [designated TAP-144-SR (4M) 30 mg] containing leuprolide acetate (30 mg), polylactic acid (264.8 mg), and D-mannitol (51.9 mg); the glass vial has a . . . rubber stopper with an aluminum cap which has a dark blue . . . cover which can be taken off easily; 2) a 2-mL glass ampule [colorless, highly resistant, boro-silicate glass . . . glass)] containing the diluent which is clear, colorless, and slightly viscous liquid [designated TAP-144-SR(4M) Vehicle] for reconstitution; 3) one . . . syringe with . . . Needle for withdrawing the vehicle from the glass ampule and placing it in the vial containing the drug product; and 4) one extra . . . Needle used along with the syringe for intravenous injection. The administration kit is packaged in a . . . container.

A five year forecast for the quantity of the drug substance that will be required to manufacture the drug product Lupron Depot® - 4 Month 30 mg from 1997 (******) to 2001 (******) is presented in Appendix C.

The bulk drug, leuprolide acetate, manufactured by . . . has been the subject of a first and previously approved new drug application (NDA 19-010, approved April 9, 1985) for Lupron® Injection, list 3626. Subsequently, the following NDAs have also been approved:

Lupron Depot® 7.5 mg, list 3629 (NDA 19-372 in January 1988)

Lupron Depot® 3.75 mg, list 3639 (NDA 20-011 in October 1990)

Lupron Depot®-PED 11.25 mg, list 2270 (NDA 20-263 in April 1993)

Lupron Depot® 3.75 mg, list 3639 (NDA 19-943 in March 1995)

Lupron Depot® - 3 Month 22.5 mg list 3336 (NDA 20-517 in December 1995)

A request for approval of an NDA (#20-708) for Lupron Depot® 3 Month 11.25 mg has been submitted on March 6, 1996, and is under review by FDA.

The format of the EA for Lupron Depot®-4 Month 30 mg, is arranged as required in 21 CFR 25.31a "Environmental Assessment for Proposed Approvals of FDA-regulated Products", and "Guidance for the Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements" provided in the guidance document from Center for Drug Evaluations Research (CDER) of FDA (1995). Using the formula recommended in this FDA, CDER guidance document, the Expected Introduction Concentration (EIC) was estimated to be ***** (***) which is several orders of magnitude below the one (1) part per billion (1 ppb) limit set in the guidance document. Because leuprolide acetate, being a peptide is readily biodegradable to CO₂, and the EIC is less than *** ***, an abbreviated Environmental Assessment (EA), excluding items 7-11 is presented based on the FDA, CDER (1995) guidance document. Supporting documents for the items discussed in this EA have been organized as Appendices A to C.

4.2 NEED FOR ACTION

Leuprolide acetate is a long-acting GnRH analog. It is a nonapeptide synthesized sequentially in solution using the classical method of blocking, coupling, and

deblocking of the aminoacids. All the aminoacids are levo-rotatory (L-) except for the leucine in the sixth position which is dextro-rotatory (D-) (Appendix C). Administration of leuprolide acetate results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing results in decreased secretion of gonadal steroids. Consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible through discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of reproductive organs.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment and castrate levels of testosterone in prostatic cancer patient have been demonstrated for periods of up to five years (TAP Pharmaceuticals Inc., 1995).

Leuprolide acetate is not active when given orally. However, the intramuscular injection of the biodegradable Lupron Depot® formulation provides 4 months of sustained leuprolide release into the tissues. The subject of this NDA and the

Environmental Assessment prepared in this document is Lupron Depot®-4 Month, 30 mg, which will be used for the palliative treatment of advanced prostate cancer.

4.3 PRODUCTION LOCATIONS AND THEIR ENVIRONMENTAL SETTINGS

The bulk drug, leuprolide acetate, is manufactured by _____ and is the subject of a previously approved New Drug Application (19-010), approved April 10, 1985). _____ will be the primary supplier of the bulk drug substance. _____ is an alternate bulk drug supplier.

The bulk drug is shipped from _____

_____ for manufacture of the final dosage form. Both the drug product (microspheres) and diluent are manufactured by _____ from where they are packaged in the primary containers and shipped to _____ for labeling and final packaging. The sites of manufacture of bulk drug and the drug product and the diluents, as well as the packaging (Figure 4-1) are listed below along with their addresses. The drug is distributed within the United States by TAP Pharmaceuticals Inc., Bannockburn Lake Office Plaza, 2355, Waukegan Road, Deerfield, Illinois 60015, USA.

A brief description of the environments at and adjacent to the manufacturing and packaging facilities involved in the drug substance and the drug product manufacture and packaging of drug product are provided after the listing of the production locations.

4.3.1 Synthesis and Production of Bulk Drug Substance

The synthesis scheme of leuprolide acetate powder is described in Appendix C. Production of the bulk drug substance, leuprolide acetate is conducted at the following locations:

ATTACHMENTS

- 15-1 Environmental Laws and Regulations of Japan**
- 15-2 Statement of General Environmental Compliance for** —

- 15-3 Certificate of Environmental Compliance for the Manufacture of Bulk Drug, Leuprolide Acetate, at**

- 15-4 Certificate of Environmental Compliance from Plant General Manager of _____ for the Manufacture of Bulk Drug Leuprolide Acetate**
- 15-5 Certificate Environmental Compliance for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg), at _____ From the Managers of Environmental Pollution Control, Water Quality Control and Industrial Waste Guidance Departments, Government, Japan**
- 15-6 Certificate of Environmental Compliance from Plant General Manager of _____ Plant for the Manufacture of Drug Product, and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)**
- 15-7 Certificate of Environmental Compliance from the Mayor of _____ for the Manufacture of Drug Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg)**
- 15-8 Certificate of Environmental Compliance from the Director of _____**

1.

(Primary Location)

2.

(Alternate Location)

4.3.2 Manufacture of the Final Dosage Form (Drug Product and Diluent)

1.

2.

4.3.3 Packaging of the Final Dosage Form (Drug Product and Diluent)

1.

4.3.4

The manufacturing of drug substance, leuprolide acetate, is conducted at the

The southern part of is

bordered by the Seto Inland National Park, and the northern side is adjacent to a commercial

and residential area. The plant has a total area of about 0.37 square miles. The

climate of City is characterized by warm summers (71 to 95°F) and cold to moderate

winters (28 to 55°F). The average annual rainfall is 67 inches. Most industries and

residences in City obtain potable water from the City of municipal water

supply. The source of the municipal water supply is the Shimata river, which passes from

the City from north to south and flows down into Seto Inland Sea. The Plant uses municipal water only. Wastewater is sewerred to an on site water treatment facility.

4.3.5

The method of manufacture of the drug product, Lupron Depot[®], 4 month, 30 mg [TAP-144-SR(4M) Injection 30 mg] is described in the Appendix C. The plant of the is the site of drug product, leuprolide manufacture and is located in the northwestern part of City. It is situated approximately 650 yards from the Yodo river and is more than 0.07 square miles in area. Drainage is dominantly to the south toward the river. The climate of City is characterized by warm summers (75 to 95°F) and cold to moderate winters (36 to 50°F). The average rainfall is 52 inches. Most industries and residences in City obtain potable water from the City of municipal water supply. The source of municipal water supply is the Yodo River flowing from Lake Biwa. The Plant uses municipal water only. Wastewater is sewerred to an on site water treatment facility.

4.3.6

The method of manufacture of drug product and the vehicle (diluent) at located at the is described in Appendix C. Most industries and residences in obtain potable water from the municipal water supply. The source of municipal water supply is the Sagami River flowing from Lake Sagami. The Plant uses municipal water only. Wastewater is sewerred to an onsite water treatment facility.

4.3.7

The synthesis of bulk drug (Appendix C) and the packaging of final dosage form (drug product and vehicle) is conducted at

The properties of the [redacted] are located within Lake County, Illinois. The North Chicago property lies 600 to 1000 feet west of Lake Michigan at an elevation of ten to fifteen feet above the average 580 foot mean sea level elevation of the lake. There are no other significant geographic features, such as mountains, lakes (aside from Lake Michigan) or rivers in proximity to the manufacturing site. The area is topographically flat and slopes very gently to the east, toward Lake Michigan. Drainage is dominantly to the east-southeast, again toward the lake. The climate of northeastern Illinois is characterized by warm summers (74 to 94°F) and cold winters (20 to 32°F). The average annual rainfall is 32 inches; wind directions are highly variable.

Most industries and residences near the [redacted] facility are served by the City of North Chicago municipal water supply. The source of the municipal water supply is Lake Michigan. The [redacted] facility currently uses municipal water. Wastewater is sewered to the treatment facility of the North Shore Sanitary District. Land use (zoning) near the North Chicago facility is primarily residential and industrial. The portion of Lake County in which it is located is part of the Chicago metropolitan area.

The physiographic features and near surface deposits of northeastern Illinois are the result of the late Pleistocene Wisconsinian glaciation, the most recent of four episodes of continental glaciation. Glacial deposits of the Lake County area consist of lake sediments (clay, silt and sand) of the Equality Formation, and clayey to silty glacial till of

the Lake Border Morainic System. From 50 to 200 feet of Pleistocene glacial sediments unconformably overlie Silurian dolomite in this area. The Paleozoic stratigraphic section in this area from top to bottom includes Silurian dolomite, Ordovician shale, dolomite, and sandstone, and Cambrian sandstone. The Paleozoic section unconformably overlies Precambrian crystalline rocks. Three dominant aquifer systems, the Basal Bedrock, Midwest Bedrock, and Upper Bedrock, underlie northeastern Illinois. Principal water producing zones include sandstone of the Eau Claire and Mount Simon Formations for the Basal Bedrock system, the Iron-ton-Galesville and Glenwood-St. Peter (Ansell aquifer) sandstones for the Midwest Bedrock System, and the Silurian Dolomite aquifer for the Upper Bedrock system. Locally, Pleistocene deposits may yield large quantities of water (greater than 1000 gpm); however, development of this aquifer is limited. Municipal and industrial water wells in the Chicago region tap the deeper aquifer systems.

4.4 LOCATIONS OF USE

The Lupron Depot®-4 Month 30 mg, will be administered under the direction of physicians to patients afflicted with advanced prostrate cancer. The locations of use are, therefore, mainly hospitals and clinics throughout the United States.

4.5 DISPOSAL SITES

The disposal of the components of the administration kit after administering it to the patient will be consistent with disposal practices of hospitals and clinics. Generally, needles, syringes, vials and ampules are treated and disposed of as special hospital wastes in a certified landfill.

Leuprolide acetate is metabolized extensively in the human body. The excipients used in the drug product, as well as the components of the diluent are easily biodegradable. Negligible quantities of the drug substance and its metabolites or excipients are excreted by patients which will enter municipal treatment systems through domestic sewage.

Off specification lots of bulk drug substance from facility will be treated as a special pharmaceutical waste and sent to an incineration site. Any unused drug product that is returned to (beyond expiration date) will be separated; the vials with drug will be treated as special pharmaceutical waste and sent to an incinerator. All other components are sent to a landfill. Details of mode of disposal of wastes are discussed in Section 6.0.

5 IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Information on the drug substance, leuprolide acetate, is provided below to allow for accurate location of data about the chemical in scientific literature and to allow for identification of closely related compounds. The information is taken from the Chemistry and Manufacturing Controls Section of this supplemental application.

5.1 NOMENCLATURE

5.1.1 Established Name (United States Adopted Name - USAN)

Leuprolide Acetate

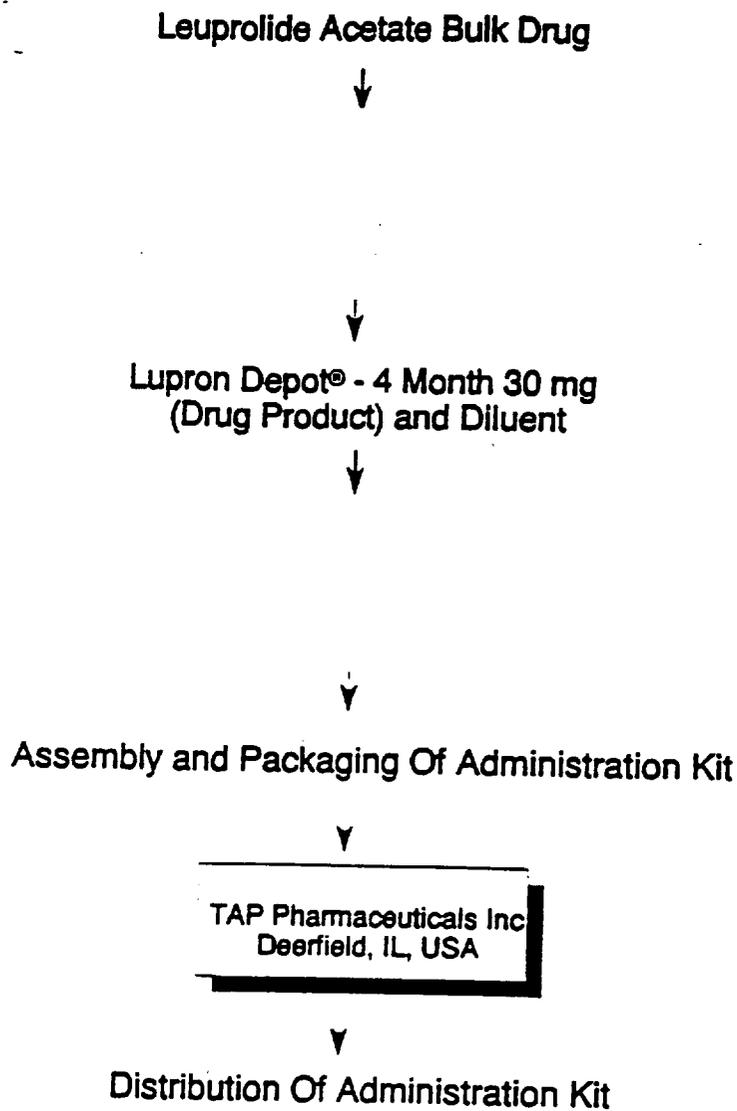


Figure 4-1
Sites Relevant to the Manufacture,
Packaging, and Distribution of Lupron Depot® -
4 Month 30 mg

5.1.9 Physical Description

White Powder

5.2 ADDITIVES

The excipients of the drug product and the vehicle are listed in Appendix C.

Most of the components are readily biodegradable.

5.3 IMPURITIES

Approximately impurities i.e., %); unknown
%); and

%) have been identified (Adjei and Hsu, 1993; Appendix B) and total amount of the five impurities combined did not exceed % and, therefore, further elaboration of these impurities have not been made in the EA, as per CDER, FDA (1995) guidance document.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

This section discusses the introduction of the substances into the environment and the controls exercised during the manufacturing and packaging operations. The manufacturing facilities of cities in Japan are governed by the Environmental Laws and Regulations of Japan (Attachment 15-1). The manufacturing of bulk drug and the packaging operations for the drug product at are governed by Environmental Laws and Regulations promulgated under the National Environmental Policy Act (NEPA).

6.1 Synthesis and Production of Bulk Drug Substance at

(Primary Location)

6.1.1 Substances Expected to be Emitted

Atmospheric Emissions

The facility at is equipped with Air Pollution Controls.

The drug substance will be manufactured in a closed system. Particulate emissions will be negligible as the synthesis of leuprolide acetate involves the use of a variety of solvents (Appendix C). An examination of the details of synthesis (Appendix C) shows that the most likely volatiles emitted will be acetone, acetic acid and alcohol. The only potential exposure to the air could be during the dispensing of the bulk drug for export to Japan, which is also conducted carefully in specially packed containers which are housed in drums.

Aqueous Wastes

Losses during formulation as aqueous waste are insignificant since the total quantity of the drug substance produced for this indication will be *** ** (*****). Any small amounts in the aqueous water are deactivated and then sewerred. If any significant amount of drug substance is left in the process tanks, it will be contained and disposed of as a special pharmaceutical waste. Any final synthesis waste such as intermediates during the synthesis process will also be disposed of as a special pharmaceutical waste. Wastewater from equipment and room cleaning is directed to the chemical sewer which goes to the

Wastewater Treatment Plant. After pre-treatment at North Chicago, the wastewater is discharged Wastewater Discharge Control Document (Permit) No. 95-5A] to the sewer system of the North Shore Sanitary District (NSSD) and

from there to Gurnee Wastewater Treatment Plant of the NSSD. The other waste streams (eg., solvents) some containing water are: 1) recovered; 2) recycled; 3) incinerated; or 4) used as a boiler fuel.

Solid Wastes

Solid wastes from manufacturing of bulk drug as leuprolide acetate are expected to be minimal since the peak yearly production of the drug substance for this indication is *****. Packaging rejects, air filter cartridges, and protective clothing worn by employees will be collected in drums and disposed of off-site. These solid wastes will be transported to Waste Management of Wisconsin, Bristol, Wisconsin (Permit No. 3062). Unused drug substance, past expiration date will be disposed of as a special pharmaceutical waste, and incinerated using the contractors listed in Table 6-1.

6.1.2 Controls Exercised on Residuals and Emissions

Air emissions are controlled as required by the Operating Permit of the Illinois Environmental Protection Agency (IEPA). Record of emissions are maintained and available for inspection. All air emissions are within the permitted limits. Solid wastes are disposed of at permitted waste facilities. Wastes are sent for recycling into fuels at the waste facilities discussed in Table 6-1. Special Pharmaceutical wastes discussed above are sent for incineration (Table 6-1).

6.1.3 Compliance of Proposed Action with Applicable Emission Requirements

Since particulate and VOC emissions are insignificant [Illinois EPA (IEPA) Definition: less than 0.1 lb./hr. and 0.44 tons per year], at _____ facility, manufacturing of less than ***** of bulk drug will be in compliance with IEPA requirements.

Only tank residuals and fill line residuals will be sewerred. In the event some amount of drug substance is left in the process tanks for disposal, it will be drummed up and disposed of as a special pharmaceutical waste. Particulate emissions from the drug-substance manufacturing facility at _____ is regulated under a permit issued by the Illinois Environmental Protection Agency. Wastewater from manufacturing must meet the General Pretreatment Standards in 40 CFR Part 403 and the Effluent Guidelines and standards for Pharmaceutical Manufacturing in 40 CFR Part 439. The prohibitions and limitations for discharge into the sewer system of the North Shore Sanitary District (NSSD) are listed in NSSD Wastewater Discharge Control Document No. 95-5A. Solid wastes will be landfilled by Waste Management of Wisconsin under Permit No. 3062 from the State of Wisconsin, Department of Natural Resources.

A Certificate of General Environmental Compliance with applicable emission requirements for the manufacture of drug at _____ is provided in Attachment 15-2.

6.1.4 Effect of the Proposed Action on Compliance with Current Emission Requirements

Emissions and releases from the manufacture of drug substance will not exceed the limitations of current permits. Manufacturing of this product will be scheduled to fit within the existing framework of activities for which current emission requirements are applicable. No additional facilities are required to facilitate the manufacture of bulk drug for this indication.

6.2 Packaging of the Final Dosage Form at

Unused administration kits, or those kits past expiration dates will be returned to _____ where the drug product and the diluent, syringes and needles will be sorted out. Vials with the drug are treated as special waste and put in fiber or plastic drums and are sent for incineration at approved medical waste incinerators (Table 6-1). All other components of the kit are shredded in garbage hopper and treated as non-hazardous solid waste and go to the landfill managed by Waste Management of Wisconsin.

6.3 Synthesis of Bulk Drug, Leuprolide Acetate at

A certificate of compliance of _____ with local and national environmental regulations for the synthesis of bulk drug, leuprolide acetate by the Director of

Table 6-1

Waste Disposal Contractors and Their USEPA Registration Numbers*

<u>Contractor</u>	<u>USEPA ID#</u>	<u>Function</u>
	UTD98152177	Incineration
	ARD981057878	Fuels
	3062	Solid Wastes

*This is a current list of contractors and is subject to change.

Environmental Protection Division, Environmental Protection and Public Health Department, Yamaguchi Prefectural Government, Japan is provided in the Attachment 15-3. As required by the FDA, CDER (1995), EA guidelines for those manufacturing sites located outside the United States, a letter from the General Manager of _____ Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-4.

6.4 Manufacture of Drug Product and Diluent at

A certificate of compliance of _____ Plant with local and national environmental regulations for the manufacture of Lupron Depot® (Drug Product and Diluent) by the Manager of Environmental Pollution Control, Water Quality Control and Industrial Waste Guidance Departments, Osaka City Government, Japan is provided in Attachment 15-5. As required by the FDA, CDER (1995), EA guidelines for those manufacturing sites located outside the United States, a letter from the General Manager of _____ Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-6.

6.5 Manufacture of Drug Product and Diluent at

A certificate of compliance of _____ with local and national environmental regulations for the manufacture of Lupron Depot® (Drug Product and Diluent) by the Mayor of Fujisawa City is provided in Attachment 15-7. As required by the FDA, CDER (1995), EA guidelines for those manufacturing sites located outside the United States,

a letter from the General Manager of Plant certifying that the facility is in compliance with all local and National regulations is provided in Attachment 15-8.

6.6 OCCUPATIONAL SAFETY

At the facility, chemicals used in manufacture of the drug substance, leuprolide acetate, are regulated by the Occupational Safety and Health Administration. Employees are trained in the proper operation of equipment in order to minimize potential safety, health and environmental risks. Extensive safety training is mandated, and Material Safety Data Sheets (Appendix A) are available to personnel for chemicals handled in the manufacturing area. Employee training is conducted on the chemical hazards associated with manufacturing.

Specified personal protective equipment (e.g., gloves, safety shoes, eye protection, respirators, etc.) and engineering controls designed for the equipment (e.g., exhausts to remove dust) are adequate to protect the employees. Specific procedures for gowning and degowning and spill containment are in place and all employees working in leuprolide acetate manufacturing facility are trained to follow these procedures.

The safe transport of all drug-related materials is ensured by following protocols which include formal qualification of vendors, training of personnel, and rigid specification of containers and materials. Access to drug substance is restricted to authorized personnel.

6.7 AMOUNT OF SUBSTANCES ENTERING THE ENVIRONMENT

Human drugs find their way into the environmental compartments (eg. soil, air, water) through manufacture, use, disposal and accidental spills. The two major sources

of environmental exposure of the drug are: 1) the patients who use the drug product; the drug product and/or its metabolites are discharged into the domestic sewer through excreta of the patients; and 2) release of the drug or its precursors or by-products through wastewater from the manufacturing plants. In either case the municipal sewage in the wastewater treatment plant could be the main recipient of these contaminant sources. The concentrations and releases in the subsections below are estimated without taking into consideration any degradation of the drug or its products at the manufacturing plants or during transport in the municipal sewage to the wastewater treatment plant (WTP), and, therefore, are worst case scenarios.

6.7.1 Human Elimination

The drug product, Lupron Depot[®] - 4 Month 30 mg, is administered as intramuscular injection. Over a 4-month period sustained release of leuprolide acetate, the active ingredient, is facilitated. As it is released and metabolized within the human body, the drug product is biodegraded. Information available on the metabolism in the human body is provided below to understand the products that are eliminated (or excreted) from patients using this drug.

Leuprolide acetate (TAP-144) has mostly naturally occurring amino acids comprising in its structure (5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-arginyl-N-ethyl-L-prolinamide) with the exception of D-leucine. Amino acids that are naturally occurring can be metabolized by microbes to CO₂. Naeshiro et al (1990) used carbon-14 labeled leuprolide to study its metabolism in rats and dogs. Biotransformation of leuprolide in rats and dogs is consistent with what might be expected for a small peptide i.e.,

it involves the hydrolysis of amide bonds, followed by the excretion of smaller peptides in urine or bile and/or further catabolism of component amino acids. The metabolic pathways of leuprolide are summarized in Figure 6-1. Leuprolide is metabolized in rats and dogs through hydrolysis to form the M-I pentapeptide (Tyr-D-Leu-Leu-Arg-N-ethyl-prolinamide) and the M-III tripeptide (Tyr-D-Leu-Leu-OH). Further hydrolysis of M-I leads to the M-II tripeptide (Tyr-D-Leu-Leu-OH), while M-III is hydrolyzed to M-IV dipeptide (5-oxo-Pro-His-OH). Some of the metabolites are further catabolized as evidenced by the loss of label in the expired air and/or the apparent incorporation of carbon-14 into methanol-insoluble components in tissues. Naeshiro et al (1990) also demonstrated that most natural amino acids could metabolize to $^{14}\text{CO}_2$, unless they are unnatural amino acids, such as D-leucine present in leuprolide acetate. For example, when leuprolide was labeled with carbon-14 in the oxo-proline moiety, about half the label was eliminated in the expired air, presumably after having been completely catabolized to $^{14}\text{CO}_2$. Labelling in the D-leucine, which is the only unnatural amino acid in the leuprolide molecule, afforded the retention of the label but some radioactivity was still eliminated in the expired air. Leuprolide labeled with carbon-14 in the oxo-proline moiety metabolized and approximately 47% was eliminated in the expired air ($^{14}\text{CO}_2$), and 49% of ^{14}C was excreted in urine (49%), only 1% was recovered in feces during a four day study period. In urine, the unchanged leuprolide accounted for 12% of the ^{14}C -dose, while M-III, a tripeptide from the amino side of the molecule (5-oxo-Pro-His-Trp-OH) represented 10% and M-IV, a dipeptide (5-oxo-Pro-His-OH) accounted for 17% of the dose. The metabolites of leuprolide do not contribute to the pharmacological activity of the compound nor the metabolism of leuprolide shown to be of any toxicological concern.

In patients given three 1 month depot injections of 3.75 mg/dose at 4 week intervals, the urinary recoveries of leuprolide and its M-I metabolite averaged 1.2% and 0.4%, respectively, within 24 hours after the first dose and increased to 2.9% and 1.5% after 27 days. Based on these results it can be concluded that leuprolide is metabolized extensively in the human body, possibly leading to ultimate degradation to $^{14}\text{CO}_2$, which may be released in the expired air. Since CO_2 is a natural component of air, this expired air has no environmental impact. The components of the drug product such as polylactic acid and D-manitol are readily biodegradable to CO_2 and H_2O (Literature Review on the Polymers of Lactic and Glycolic Acid, Reference 5, Appendix B).

For the estimations of Expected Introduction Concentration (EIC) from use, it is assumed that all the drug forecasted for production in the United States (Appendix C), which is approximately ***** in the fifth year of production, will be ingested and eliminated by the U.S. population. This worst case estimate also assumes that there will be no metabolism of leuprolide acetate in the human body and that there will be no degradation in the domestic sewage receiving human excreta containing the drug product.

Typical minimum and maximum flow rates for wastewater treatment systems are set by Federal and State agencies to range from 280 to 1,500 L/person/day (Metcalf & Eddy, Inc., 1979). The 1990 Census gives the population of the United States as 250,378,000. The worst case concentration of the drug expected to be found in WTP is estimated from the dilution of the total drug produced in the year of maximum production (*****) in the total wastewater produced in the United States.

The Expected Introduction Concentration (EIC) from use at the WTP can be estimated from the following equation:

$$EIC = \frac{\text{Total drug produced (fifth year production)}}{\text{Total waste water in the United States}}$$

Total leuprolide acetate produced [peak year (1998) production estimate] = *****

(**) = or ***** x 10⁹ µg

Total wastewater produced in the United States per year:

Liters of waste water per person = 280 L/day

Population of the United States = 250 million

Days in a year = 365 days

= 280 x 250 million x 365 = Liters of total waste water per year

Therefore the EIC for leuprolide acetate at the WTP will be:

$$\frac{***** \times 10^9}{280 \times 250 \times 10^6 \times 365} = ***** (***) = \text{or } \frac{*****}{***** (***)}$$

An equivalent method for calculating the concentration of drug that would be expected at the WTP is given in Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA (PMA, 1991) which estimates the EIC in ppm as follows:

$$ppm = (A) (B) (C) (D) (E) (F)$$

A = pounds/year production

B = year/365 days

C = day.person/280 L (74 gallons)

D = 1/250 million persons

E = gallons/8.34 pounds

F = one million ($\times 10^6 = \text{ppb}$)

Leuprolide acetate at WTP in ppb = ***** (Kg) (A) \times 1/365 (B) \times 1/74 (C) \times 1/(250 $\times 10^6$) (D) \times 1/8.34 (E) $\times 10^6$ (F) = ***** or *****.

A method for calculating the expected introduction concentration (EIC) of the drug at the WTP is given in "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements" published by the Center for Drug Evaluation Research (CDER), FDA, in November 1995 (FDA 1995). The estimate of the EIC in ppm based on this method is as follows.

$$\text{EIC-Aquatic (ppm)} = (A) (B) (C) (D)$$

A = Kg/year production

B = 1/Liters per day entering WTP

C = year/365 days

D = 10^6 mg/Kg (conversion factor)

EIC of leuprolide acetate at WTP in ppm = ***** (A) \times 1/1.115 $\times 10^{11}$ (B) \times 1/365 (C) $\times 10^6$ (D) = ***** or *****.

The worst case EIC estimation for leuprolide in WTP calculated three different ways ranges from ***** to ***** ***. This is several orders below the 1 ppb cutoff limit suggested in the FDA CDER (1995) EA guidelines.

6.7.2 Expected Introduction Concentration from Disposal

Synthesis of the drug substance and packaging of drug product is conducted at

Manufacture of the drug product is conducted in

No air emissions are expected during synthesis or packaging at

The drug product is administered under the directions of a physician. Therefore, it will not be entering the environment through patient use. Less than % of the kit ingredients (other than the drug product) may be disposed of in the landfill as part of unused, rejected or expired drug product and the drug product is itself incinerated. Thus, emissions from introduction into the environment through disposal would be negligible and no environmental impact is anticipated.

7 **FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT**

The environmental fate of the emitted substances is not presented because the worst case EIC for the drug is less than **** ***, which is several orders below the cutoff limit of 1 ppb suggested by FDA, CDER (1995).

8 **EFFECT OF EMITTED SUBSTANCES IN THE ENVIRONMENT**

See Sections 4.1 and 7

9 **USE OF RESOURCES AND ENERGY**

See Sections 4.1 and 7.

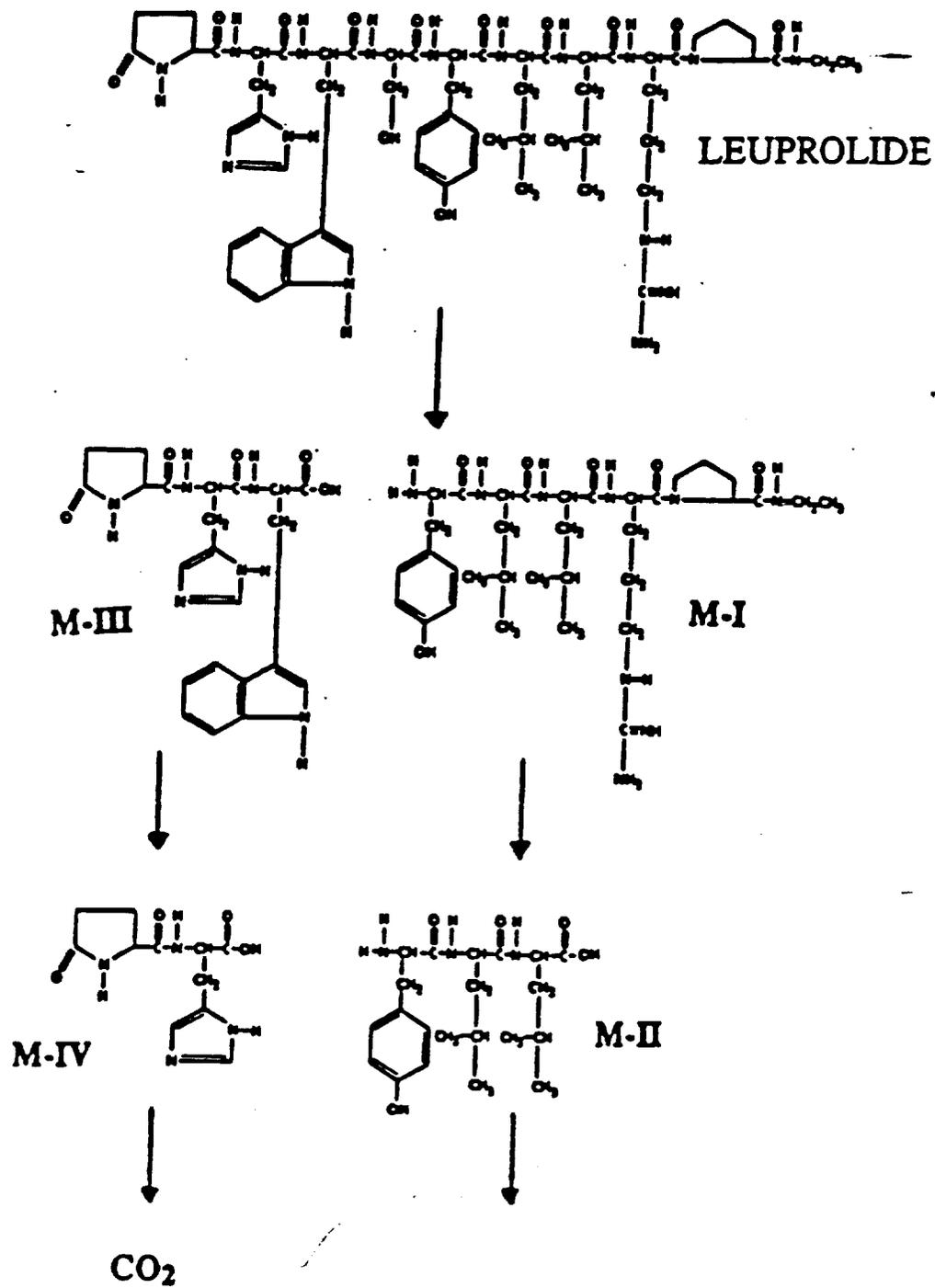


Figure 6-1
Proposed Pathway of Leuprolide Metabolism

10 MITIGATION MEASURES

See Sections 4.1 and 7.

11 ALTERNATIVES TO THE PROPOSED ACTION

See Sections 4.1 and 7

12 PREPARER

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Columbia, Missouri 65202

The undersigned certify that the information presented is true, accurate, and complete for preparation of the Environmental Assessment Report in accordance with 21 CFR 25.31(a).

Signature Ranga Velagaleti Date 5-17-96

Title: Director, Pharmaceutical Manufacturing Support & Environmental Compliance
Division

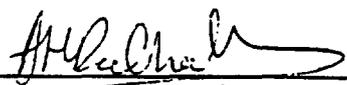
13

CERTIFICATION

The undersigned official certifies that the information presented herein and provided to Ranga Velagaleti by TAP Holdings Inc. (applicant) is true, accurate, and complete to the best of our knowledge.

The undersigned official certifies that the EA summary document and Appendices A and B contain non-confidential information and acknowledges that the non-confidential information will be made available to the public in accordance with 40 CFR part 1506.6. Appendix C includes confidential and proprietary information and is not for public disclosure.

Signature



Date

5/21/96

Title: Regulatory Products Manager

14

REFERENCES

1. Adjei, L.A. and Hsu, L. 1993. Leuprolide and Other LH-RH Analogues. In Stability and Characterization of Protein and Peptide Drugs. Case Histories. Ed. Y. John Wang and Rodney Pearlman, Plenum Press, New York.
2. Metcalf & Eddy, Inc., 1979. Wastewater Engineering: Treatment, Disposal, Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.

3. Naeshiro, S.K., Mitani, S., Yoshida, K., Kobahashi, H., Kimura, T., Shimomura, S. and Tanayaura, S. 1990. Metabolic Fate of TAP-144, An LH-RH Agonist in Rats and Dogs. Japanese Journal of Therapeutics-18: 35-56.
4. Pharmaceutical Manufacturers Association (PMA). 1991. Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. Washington, D.C., July 1991. *Reference not included in Appendix B.
5. U.S. Food and Drug Administration. 1995. Guidance for the Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation Research, (CDER), FDA, Washington, D.C. *Reference not included in Appendix B.
6. Literature Review of the Polymers of Lactic and Glycolic Acids.

15

ATTACHMENTS

15-1 Environmental Laws and Regulations of Japan

15-2 Statement of General Environmental Compliance for

15-3 Certificate of Environmental Compliance for the Manufacture of Bulk Drug, Leuprolide Acetate, at

**Division, Environmental Protection and Public Health Department,
Yamaguchi Prefectural Government, Japan**

- 15-4 **Certificate of Environmental Compliance from Plant General Manager
of Plant for the Manufacture of Bulk Drug Leuprolide Acetate**
- 15-5 **Certificate Environmental Compliance for the Manufacture of Drug
Product and Vehicle (Lupron Depot® - 3 Month, 11.25 mg), at
From the Managers of
Environmental Pollution Control, Water Quality Control and Industrial
Waste Guidance Departments, City Government, Japan**
- 15-6 **Certificate of Environmental Compliance from Plant General Manager
of Plant for the Manufacture of Drug Product, and Vehicle
(Lupron Depot® - 3 Month, 11.25 mg)**
- 15-7 **Certificate of Environmental Compliance from the Mayor of
City for the Manufacture of Drug Product and Vehicle (Lupron Depot®
- 3 Month, 11.25 mg)**
- 15-8 **Certificate of Environmental Compliance from the Director of**

ATTACHMENT 15-1

Environmental Laws and Regulations of Japan

JAPAN

INTRODUCTION

The Japanese system of environmental law is complicated because, in a great many cases, one single ministry or agency is not the sole administrator of a law. Thus, to ascertain which government bodies or public officials are responsible in a particular instance, it is often necessary to narrow one's enquiry down to the relevant part of that particular law.

Some laws include the names of responsible government agencies. Not listed are other responsible entities such as the Prime Minister's Office and prefectural governments.

Additionally, the Environment Agency, itself, in most cases, is not the final authority when dealing with environmental matters. Actual administrative powers are vested in a number of ministries, agencies, and officials, with the responsible authorities being determined by the content of each particular law.

The Environment Agency

During the rapid economic growth of the 1940s, serious pollution began to manifest itself. A number of laws and regulations were legislated to deal with the situation.

In 1964, the Liaison Council for Environmental Pollution Control was established, and in 1965 the Ministry of Health and Welfare established the Environmental Pollution Inquiry Committee.

Late that same year, the Industrial Pollution Control Special Committee was organized in the Diet. A government agency headed by the Prime Minister, the Central Headquarters for Environmental Pollution Control, was set up in 1970 and, during that same year, in a landmark legislative session known as the "pollution Diet," fourteen pollution-related laws were enacted. These were the events leading to the formation of the Environment Agency.

The Environment Agency was established on July 1, 1971, under the provisions of the Environment Agency Establishment Law (Law No. 88 of May 31, 1971; last amended by Law No. 97 of 1967). Article 3 of this law describes the agency's duties thus:

"The principal duties of the Environment Agency are to comprehensively promote government administration pertaining to environmental preservation in order to control pollution, protect and maintain the natural environment, and provide for environmental preservation in other ways, as well as to contribute to securing a healthful and cultural life for the citizens" (*Kanryo Roppo*, 1968, p. 13).

The Environment Agency, headed by a director-general ranking as a minister of state, can be roughly divided into the Minister's Secretariat, the Planning and Coordination Bureau, the Environmental Health Department, the Nature Conservation Bureau, the Air Quality Bureau, and the Water Quality Bureau, to which have been added other functions, including training institutes and councils. The powers of the director-general include making recommendations to the heads of other government agencies, or requesting information and explanations from them, concerning matters important to environmental preservation.

The general duties of the agency include the formulation and promotion of fundamental environmental policies, coordination of budgeting policies for pollution-control expenditures, the management of appropriations for environmental research and development, and overall coordination of the various government agencies responsible for environmental protection.

Some of the major laws whose enforcement is within the jurisdiction of the agency are the Air Pollution Control Law, the Water Pollution Control Law, the Nature Conservation Law, the Natural Parks Law, the Wildlife Protection and Hunting Law, and the Law Relating to the Regulation of Transfer of Special Birds. The agency also establishes "environmental quality standards." These standards are benchmark values thought to represent desirable maximum levels for certain pollutants, and are usually meant to be attained within a specified length of time. However, the standards themselves are not legally binding.

General descriptions of the various bureaus follow.

The Minister's Secretariat

The functions of the Minister's Secretariat can be classified and described in the following manner: (1) Accounting; (2) personnel administration; (3) public relations and information concerning environmental administration; (4) surveys of local environmental situations and the gathering/cataloging of pertinent data; (5) promotion of international cooperation; (6) general supervision of the agency's duties; and (7) the general affairs of the Central Council for Environmental Pollution Control.

Through the Secretariat the Environment Agency is directly concerned with the following international conventions:

- Ramsar Convention
- Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES)
- Convention on the Prevention of Marine Pollution by the Dumping of Waste and other Matter; and
- Protocol of 1973 relating to the International Convention for the Prevention of Pollution from Ships

Furthermore, bilateral cooperation for the protection of the natural environment and wildlife is conducted with the countries of the United States, the Federal Republic of Germany, France, Canada, Australia, the People's Republic of China, the Republic of Korea, the EC, and ASEAN.

Planning and Coordination Bureau

The bureau is responsible for (1) the formulation and implementation of basic environmental policy; (2) coordinating management, budgets, and research on environmental conservation as assigned to the ministries and agencies associated with environmental protection; (3) expressing opinions concerning national land use and development, and offering guidance in the preparation of regional pollution control programs; (4) the planning, formulation, and promotion of basic policies for environmental impact assessment; (5) preparation of an annual report on environmental quality by the bureau's Office of Planning and Research; and (6) the administration, by the Planning and Coordination Division, of the Environmental Pollution Control Service Corporation, which provides loans for the pollution-control facilities of small- and medium-sized enterprises, as well as the management of the National Institute for Environmental Studies and the Training Institute for Environmental Pollution Control.

With regard to environmental impact assessments, the Planning and Coordination Bureau formulates and promotes the basic policy for assessments, and coordinates related work for assessments among the agencies concerned. The bureau includes an Environmental Impact Assessment Division that handles the scientific and technical questions arising

ing with assessments, as well as the examination of assessments and the provision of guidance in their preparation. Environmental assessments will be dealt with in greater detail below.

Environmental Health Department

This department was created to insure full enforcement of the Pollution-Related Health Damage Compensation Law. Through its two divisions, the Planning Division and the Health and Welfare Division, the Environmental Health Department administers the National Institute for Minamata Disease, which conducts medical research on Minamata disease, carries on scientific research regarding the diseases caused by pollution, and, through prefectural and local government, provides pollution victims with compensation benefits. Some of the well-known pollution diseases with which the department is concerned are "Itai-itai disease" (cadmium poisoning in Toyama Prefecture), "Minamata disease" (organic mercury poisoning in Kumamoto, Kagoshima, and Niigata prefectures), "Yokkaichi asthma" (a severe respiratory ailment caused by factory air pollution in Yokkaichi City, Mie Prefecture), and chronic arsenic poisoning in the Torokai district of Miyazaki Prefecture.

Additionally, the department, through either of its two divisions: (1) supervises the Pollution-Related Health Damage Compensation Association; (2) performs clerical work for the Pollution-Related Health Damage Compensation Grievance Board; (3) scientifically determines the causes of pollution-related health damage; (4) performs duties related to enforcing the Interim Law Concerning Special Measures for the Promotion of Minamata Disease Certification; and (5) performs work associated with designating the items to be tested for new chemicals pursuant to the Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances.

Nature Conservation Bureau

This bureau concerns itself with a number of areas including: (1) Planning of basic policies for the protection and conservation of the natural environment; (2) surveys of Japan's natural environment by way of the "Green Census," a national survey of the environment, the results of which are employed in the formation of conservation measures; (3) the designation of national parks, quasi-national parks, marine parks, and natural areas requiring conservation; (4) the implementation of measures for the protection, management, and maintenance of natural parks; and (5) the protection and breeding of wildlife. The bureau is responsible for the enforcement of the Natural Parks Law, the Hot Springs Law, the Wildlife Protection and Hunting Law, the Ramsar Convention, and CITES.

There are 27 national parks totaling 2,072,162 hectares in size and 54 quasi-national parks totaling 1,298,776 hectares.

Air Quality Bureau

This bureau is concerned with: (1) The establishment of environmental quality standards, considered desirable in protecting human health and preserving the human living environment, regarding air and noise pollution, vibration, and offensive odors; (2) regulating the amount of soot and dust emitted by factories, and specifying the maximum permissible limits for automobile exhaust emissions (actual regulation of emissions is the province of the prefectural governments); (3) designation of pollution-related areas, regulation of working hours, and specifying permissible automobile noise limits for the purpose of protecting residential environments from the noise and vibration of factories, construction work, and traffic (actual designation is the

province of the prefectural and municipal governments); (4) the control of offensive odors from factories (actual control is the province of the prefectural and municipal governments); and (5) the promotion of comprehensive measures to prevent motor vehicle pollution. For this last purpose the bureau established the Automotive Pollution Control Division and the Office of Traffic Pollution Control.

Water Quality Bureau

This bureau is concerned with: (1) The regulation of factory effluents, the establishment of environmental water quality standards for the protection of human health, the preservation of residential environment, and the prevention of water pollution (actual regulation is the province of prefectural governments); (2) the planning and implementation of comprehensive measures for conserving the environment of the Seto Inland Sea, including the maintenance of water quality; (3) the designation of lakes in which water quality has degraded, and the implementation of measures to maintain lake water quality; (4) the specification of waste disposal criteria; (5) the protection of agricultural land from soil pollution, the specification of remedial measures to be implemented in the event of soil contamination, and restrictions on the use of agrochemicals; (6) nationwide surveys of ground subsidence and regulation of groundwater use by industry and construction (actual duties performed by prefectural governments); (7) establishing standards for waste disposal and sewage sludge treatment; and (8) assisting in the planning for river basin sewer construction.

Ground subsidence is the province of the Planning Division, which is responsible for enforcing the Industrial Water Law and the Law Concerning the Regulation of Pumping-Up of Groundwater for Use in Buildings.

The bureau established a Soil and Agricultural Chemicals Division to control soil contamination and the use of agrochemicals. This division determines environmental quality standards for soil contamination, and enforces the Agricultural Land Soil Pollution Prevention Law.

Water pollution is specifically the charge of the bureau's Water Quality Management Division and Water Pollution Control Division, and this includes the duties specified in the Law Concerning Special Measures for Conservation of the Environment of the Seto Inland Sea, for which purpose the Water Pollution Control Division established the Office of Seto Inland Sea Environmental Conservation.

Auxiliary Organs

These eight bodies are as follows: National Institute for Environmental Studies, National Institute for Minamata Disease, Training Institute for Environmental Pollution Control, Pollution-Related Health Damage Compensation Board, Central Council for Environmental Pollution Control, Nature Conservation Council, Seto Inland Sea Environmental Conservation Council, and Special Certification Council for Minamata Disease.

The most important of these with respect to the formulation of environmental policy are:

The Central Council for Environmental Pollution Control, which has a maximum of 90 members appointed by the prime minister for a term of two years. The council deliberates upon important matters relating to environmental measures, and expresses its views, including advice and suggestions, to the prime minister and the director-general of the Environment Agency. It was established on July 1, 1971.

The Nature Conservation Council, which has a maximum of 45 members likewise appointed by the prime minister.

for a term of two years. The council investigates and deliberates upon matters of importance to the conservation of the natural environment, and expresses its views to the director-general or other ministers. It was established on April 12, 1972; and

The Setsu Inland Sea Environmental Conservation Council, which has a maximum of 24 members appointed by the prime minister for a two-year term. The council investigates and deliberates upon matters of importance to the conservation of the Setsu Inland Sea, and expresses its views to the director-general or other ministers. It was established on November 2, 1972.

Corporations

The Environment Agency also supervises two environment-related corporations, the Environmental Pollution Control Service Corporation, which funds corporate relocations and pollution-control facilities at low interest rates, and the Pollution-Related Health Damage Compensation Association, which collects money from polluting industrial facilities and pays this as compensation (through local governments) to pollution patients under the Pollution-Related Health Damage Compensation Law.

Environmental Impact Assessment System

Although efforts at legislation for a national environmental impact assessment (*konkyo eikyō hyōka*) law failed in the Diet, assessments are now normally prepared for large-scale public works projects throughout Japan.

Development of the environmental impact assessment procedures in Japan were initiated with the Cabinet decision of June, 1972 called Environmental Preservation Countermeasures for Public Works Projects, and since that time environmental impact assessments have been conducted on the basis of certain laws such as the Public Waters Landfill Law, the administrative guidance of government agencies, and municipal ordinances and guidelines.

Later, on August 21, 1984, a Cabinet decision passed the Implementation of Environmental Impact Assessments, thereby establishing the Guidelines for the Implementation of Environmental Impact Assessments. In this way the government established a set of uniform procedures to be employed in assessing the impact of large-scale projects with which the national government is associated. The kinds of projects covered include roads, dams, railways, airports, landfills, and land development for urban or industrial use.

The process of preparing an assessment can be roughly divided into four steps and described as follows:

- The developer (i.e., the person or persons undertaking the project), pursuant to the policies established by the concerned minister after conferring with the director-general of the Environment Agency, performs a survey, makes predictions, assesses the impact of the project, and prepares a draft Environmental Impact Statement (EIS). The draft includes the following items: Name and address of developer, purpose and description of project, a summary of the findings obtained in surveys and studies, and an assessment of the project's impact, including proposed pollution control measures.

- The developer publishes the draft, circulating it among concerned parties, and conducts an explanatory meeting. The draft should be made available for public scrutiny for at least one month.

- The developer endeavors to ascertain the opinions of people residing in the affected region and then encourages

the mayors of the municipalities in this region to state their opinions to the prefectural governor.

- The developer then revises the draft and prepares the final assessment based upon these various opinions.

The resulting document is then employed by the concerned government officials in making decisions affecting the proposed development project. When deemed necessary, these officials may seek the opinion of the Environment Agency's director-general with respect to the assessment.

Environmental impact assessments implemented on the basis of laws such as the Harbor Law and the Public Waters Landfill Law have included projects such as harbor planning, landfills, locating electric generating plants, and urban planning.

Local governments have also concerned themselves with the need for assessments and, as of 1984, 26 local governments had passed ordinances or instituted guidelines for the preparation of assessments. Four local governments (Hokkaido Prefecture, the Tokyo Metropolitan Government, Kanagawa Prefecture, and Kawasaki City) have ordinances; the other 22 local governments (19 prefectures and 3 cities) have instituted guidelines.

Summaries of Major Laws

General environmental quality is the province of the Basic Law for Environmental Pollution Control. The law sets out the responsibilities of developers or those who operate business or industrial enterprises, the national government, local governments, and individual citizens with regard to maintaining the general quality of the environment.

Specifically, the national government is to establish environmental quality standards for air, water, soil contamination, and noise, and enact measures to see that these standards are met. In addition, the government must control land use and the installation of facilities causing pollution; promote the establishment of facilities such as buffer zones, waste disposal plants, and sewage systems to prevent pollution; monitor the state of the environment; conduct surveys to plan measures for pollution control and disseminate information to the citizens to increase their consciousness concerning the need to prevent environmental pollution. Local governments are to enact the same measures in their local areas.

The law also provides for the formulation of Environmental Pollution Control Programs by the prefectures, the settlement of pollution disputes by the government, and the payment of costs for pollution control.

Chapter IV establishes the Conference on Environmental Pollution Control and the various Councils on Environmental Pollution Control. The latter include prefectural and local councils in addition to the Central Council on Environmental Pollution Control (see "Auxiliary Organ," above).

Water Quality

The purpose of the Water Pollution Control Law is to prevent the pollution of public waters (i.e., rivers, lakes, ports, harbors, irrigation channels, and coastal ocean areas) by wastes discharged from business and industrial facilities, and to effect compensation for damage to human health from water pollution.

Standards for effluents and thermal pollution, specifying maximum permissible amounts for each regulated substance, are established by an ordinance of the Prime Minister's Office. The director-general of the Environment Agency

cy may also advise prefectures to establish or modify their own standards to be in accordance with this law.

The prime minister is to establish policies to reduce the pollution loads for designated large, nearly closed bodies of water that are subject to considerable amounts of pollution due to heavy population or industrialization. These policies set out objectives, including target dates and amounts by which the pollution loads are to be reduced. The governors of affected prefectures are to establish, on the basis of these policies, their own plans for the attainment of objectives outlined in the government policies.

The law also places restrictions on industrial facilities which discharge certain substances (specified by Cabinet order) into designated bodies of water, and prefectural governors are empowered to order the enactment of remedial measures when a specified facility fails to comply with standards. Governors are also responsible for the monitoring of water quality within their prefectures.

Provisions for compensation have also been included to cover instances in which human health has been damaged by water pollution from industrial facilities.

The Law Concerning Special Measures for the Preservation of Lake Water Quality (Clean Lakes Law), enacted and promulgated on July 27, 1984, provides for the establishment of the basic policy for the preservation of lake water quality by the national government, as well as the drafting of a lake conservation plan for each lake designated under the law, by which actions for lake protection can be implemented, such as the construction of sewage facilities, or the initiation of regulatory actions to reduce pollutants. The law also provides well-defined regulations to control pollution sources and makes it possible to enact special measures for protecting lakes requiring immediate action to meet the Environmental Water Quality Standards of December 15, 1982. Lakes are designated by the prime minister, after which the governor of the affected prefecture prepares a plan for the preservation of lake water quality.

The Law Concerning Special Measures for Conservation of the Inland Sea promotes the conservation of the Seto Inland Sea by establishing a basic plan for conservation of the environment of the Seto Inland Sea by the national government, and "prefectural plans" to be established by the adjoining prefectures for the parts of the Inland Sea off their shores. Furthermore, special conservation measures place restrictions on the establishment of industrial facilities and their effluents; permission must be obtained from prefectural governors before building facilities of a certain type and scale.

Other sections of the law place restrictions on substances such as phosphorus to prevent eutrophication, or provide for the designation of "natural seashores" by the prefectures to protect sand beaches, reefs, or public swimming areas.

The law also requires the national government to organize a system to deal with oil spills in the Inland Sea, to ascertain the mechanism by which algae blooms occur (specifically, the "red tide"), and to provide relief for fishermen who suffer losses because of oil spills or the red tide.

Marine pollution and accidents at sea are to be prevented by the Law Relating to the Prevention of Marine Pollution and Maritime Disaster. The law prohibits, except in certain cases, the discharge of oils or oily mixtures, various liquid substances (other liquids designated by Cabinet order), or wastes from vessels at sea, and stipulates the kinds of equipment and facilities that seagoing vessels are to have, as well as their methods of operation and record-keeping. The minister of transport is responsible for carrying out periodic inspections of the marine pollution prevention facilities (bilge discharge prevention facilities, water ballast

discharge prevention facilities, and a segregated ballast tank), and may order modifications or repairs to such when it is found that they do not conform with standards.

The law also prohibits the discharge of oil and wastes into the sea from offshore facilities and aircraft, and provides for controls on the incineration of oil, various liquid substances, or wastes on board ship or at offshore facilities. In addition, the minister of transport is given the responsibility for issuing permits to operate waste oil disposal businesses.

The law outlines procedures for the prevention of marine pollution and maritime disaster, as well as for dealing with oil spills, fires, collisions, and other accidents and disasters at sea.

A Maritime Pollution Prevention Center is also incorporated under the law to prevent or deal with maritime disasters, and to protect human life and property.

The Industrial Water Law provides for measures to assure a water supply for industrial development, to promote the conservation of groundwater resources, and prevent ground subsidence.

The law controls the use of groundwater by industries within areas designated by Cabinet order. Such areas are designated when, due to the excess use of groundwater, the level of the water table has become extremely low, ground subsidence has occurred, or when salt water or foul water has invaded the groundwater supply. Permission for the use of wells is granted by prefectural governors.

Another law whose purpose is to prevent ground subsidence is the Law Concerning the Regulation of Pumping-Up of Underground Water for Use in Buildings. This law controls the use of groundwater for industrial use pursuant to the Industrial Water Law, above, and for other kinds of facilities designated by Cabinet order, such as air conditioning and flush toilets.

Similar to the foregoing law, areas in which groundwater use is to be regulated are designated by Cabinet order. Persons wishing to draw and use underground water in designated areas must receive permission from prefectural governors, city mayors, or other public officials.

Air Quality

The Air Pollution Control Law sets maximum permissible limits for motor vehicle exhausts and other emissions, and regulates industrial soot and smoke emissions. Regulated emissions include sulfur oxides, oxides, chlorine, hydrogen fluoride, lead, particulate matter, carbon monoxide, and hydrocarbons produced by combustion, synthesis, mechanical processes, or resolution. However, the law is not applicable to air pollution caused by radioactive materials.

Emission standards for facilities emitting soot and smokes are set by the Prime Minister's Office, while the maximum permissible limits on motor vehicle emissions are established by the director-general of the Environment Agency, who may also recommend emission standards for industrial facilities to prefectural governors. Prefectural governors are responsible for measuring the concentration of motor vehicle exhaust gases in areas with heavy traffic, for periodically monitoring the general level of air pollution, and for publicly announcing the extent of air pollution in their prefectures. Governors are also empowered to enact measures when necessary in order to reduce air pollution when human health is endangered.

Businesses and industries are required to provide compensation for damage to human health as a result of their emissions, and the law also provides for fines or imprisonment for violators.

Unpleasant odors produced by industrial or business facilities are subject to regulation by the *Offensive Odor*

Control Law. Substances covered by the law are the eight substances listed in the Cabinet Order, including ammonia, methyl mercaptan, hydrogen sulfide, and styrene.

Prefectural governors are required, after consultation with the mayors of local governments, to designate areas in which orders are to be regulated, as well as the regulation standards. Maximum concentrations in the air are set for pollutants produced at ground level, emitted from smoke stacks, and discharged in aqueous effluents. Governors are also charged with measuring concentrations of the stipulated substances within designated areas.

In the event of an accident in which the stipulated substances are discharged into the environment to the extent that regulation standards are exceeded, businesses are required to take immediate remedial action.

The law also prohibits burning in the open air large quantities of substances such as rubber, hides, and synthetic resins in densely populated areas.

Pollution Control

Specific punishments for pollution related offenses, including fines and imprisonment, are stipulated by the *Law for the Punishment of Crimes Relating to the Environmental Pollution which Adversely Affects the Health of Persons*. Both representatives or employees of a business or corporation, and the business entity itself, may be subject to punishment when, either with intent or through negligence, it is found to be adversely affecting human health, endangering human life, or causing death through the discharge of harmful substances.

Business and industries are required by the *Pollution Control Public Works Cost Allocation Law* to install facilities for the prevention of pollution, or to undertake projects to repair pollution-caused damage, such as dredging, sludge removal, or topsoil replacement. The law specifies the procedures by which is determined the percentage of the costs that a business or industry shall pay, and the methods for their payment.

Compensation for Pollution Victims

The *Pollution-Related Health Damage Compensation Law*, a major piece of legislation for redressing the damage of pollution to human health, provides for the designation, by Cabinet order, of regional and diseases, and the payment of seven types of compensation benefits to pollution victims or their survivors. The benefits are: (1) Medical care benefits and expenses, (2) compensation for handicaps, (3) compensation for survivors, (4) lump-sum compensation payments for survivors, (5) child compensation allowances, (6) medical care allowances, and (7) funeral expenses. Prefectural governors follow detailed criteria in certifying pollution victims, who then become eligible for benefits. According to the law, each prefecture and city located within a designated region must establish a Pollution-Related Health Damage Certification Council, consisting of a maximum of 15 persons, which assists the implementation of the law in each locality. The Pollution-Related Health Damage Compensation Association (established by Chapter 3 of the law, see the section "Corporations" under the Environment Agency, above) is to collect levies from industrial facilities producing soot and smoke, and these funds are used to pay benefits. Eighty percent of all benefits awarded under this system are obtained from these levies, and the other 20 percent are derived from automobile tonnage tax. In addition, the law provides for the establishment of a Pollution-Related Health Damage Compensation Grievance Board (see "Envi-

ronmental Health Department" under the Environment Agency, above) to handle complaints from persons who are dissatisfied with the action taken on their behalf.

A major amendment was effected on March 1, 1986 when the regional designations for air pollution-related health damage established under the law were completely canceled, the reason being that air pollution has decreased substantially, thereby no longer constituting the principal cause of disorders such as asthma. In addition, facilities in all parts of Japan that emit sulfur oxides had been subject to levies, even if they were outside the designated regions. In view of the increasing number of certified patients, and the concomitant increasing total amount of benefits, as well as the fact that nearly 70 percent of the costs were being borne by undesignated regions, the Central Council on Environmental Pollution Control recommended, among other measures, that (1) all designations be canceled, (2) compensation benefits continue to be paid to certified patients, and (3) stronger measures be implemented to prevent air pollution. The amendment provides for the continuing payment of benefits to patients already certified, with the amount of levies on SO₂-emitting facilities being determined on the basis of their emissions over a certain amount of time prior to the cancellation of regional designations.

A total of 41 regions in 10 prefectures (19 of them Tokyo wards) had been designated, and the number of certified patients throughout Japan had grown from 19,300 at the beginning of the program to 102,523 as of January, 1981. Paid benefits for FY 1986 totaled approximately ¥100 billion (US\$400 million).

Food and Chemicals

The purpose of the *Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances* is to prevent environmental contamination by chemical substances which decompose with difficulty, and which may present a danger to human health. To this end, new chemical substances are screened prior to manufacture or importation to determine their properties, and to place any necessary controls on their manufacture, importation, or use. Chemical substances subject to controls under this law exclude radioactive substances and those controlled by other laws, such as poisons, stimulants, and narcotics.

The purpose of the *Food Sanitation Law* is to prevent harm arising from food sanitation problems. It requires that all foods sold are sanitary, including all implements and containers used for their collection, manufacture, processing, use, preparation, storage, transport, display, and transfer, and in general prohibits the handling or sale of contaminated, unsafe, unsafe, or decayed foods, as well as meat and other parts and products from wild or domestic animals that have died of illness. The law also makes provisions for prohibiting the sale of newly developed foods and food additives which have not been approved. In addition, the Minister of Health and Welfare is empowered to establish criteria and standards for the manufacture, processing, use, preparation, and preservation of foods and food additives, as well as their containers and packaging.

Agriculture and Agricultural Chemicals

The purpose of the *Agricultural Land Soil Pollution Prevention Law* is to prevent harm to crops and human health by preventing or removing harmful substances which contaminate agricultural land. Prefectural governors are empowered to designate certain areas of agricultural land,

the agricultural produce of which has been found to contain certain levels of harmful substances (cadmium, copper, arsenic, and their compounds), as "agricultural land soil pollution policy areas." Governors then formulate plans for these areas which provide for appropriate land use, construction of, or modifications in, drainage or irrigation facilities in order to prevent soil contamination, and projects designed for the purpose of eliminating soil contamination.

The *Agricultural Chemicals Regulation Law* establishes a registration system, and regulates the sale and use of agrochemicals (including natural enemies used for pest control).

Official standards for the amounts of active ingredients and harmful ingredients are set by the Minister of Agriculture, Forestry, and Fisheries. The Minister also grants registrations to agrochemical manufacturers and importers (including foreign manufacturers who export to Japan), who may not sell manufactured, imported, or processed chemicals in Japan without registration. Proper labeling is also required for sale.

The government may also designate agrochemicals as those which tend to show residual properties in soil or crops, or which contaminate water supplies. The government may institute certain controls over agrochemicals thus designated.

This law does not apply to any agrochemicals which are manufactured, processed, or sold for the purpose of export.

Waste Disposal

The disposal of both domestic and industrial wastes is the province of the *Waste Disposal and Refuse Collection Law*.

The law requires businesses and industry to correctly dispose of the industrial wastes generated in their operations, as well as to recycle their wastes to the greatest extent possible in order to reduce the total amount. They must also endeavor to see that the subsequent disposal of the discarded products or containers used in manufacturing, processing, and sales shall not present them with undue difficulties. Municipalities may dispose of industrial wastes when those wastes are of a kind which may be disposed of with domestic wastes. Prefectural governors are responsible for planning industrial waste disposal.

The law specifies that municipal governments are responsible for collecting and disposing of domestic wastes in their areas, and also outlines the procedures for establishing and operating domestic waste disposal plants, as well as private waste disposal tank cleaning businesses.

Noise and Vibration

The *Noise Regulation Law* sets maximum permissible levels for motor vehicle noise, and regulates the noise generated by industrial and construction sites.

Areas subject to industrial noise level controls are designated by prefectural governors after consulting with city, town, and village mayors in the areas concerned. Such areas are those with, for example, schools, hospitals, or densely populated residential districts. Governors then establish regulatory standards, with respect to certain hours and zones, for the businesses and industries (determined by Cabinet order) located in these areas.

In the event that levels of noise in a designated area are found to be unsatisfactory with respect to the regulatory standards, prefectural governors are empowered to recommend improvements to ameliorate noise, and, if these rec-

ommendations are not followed within a stipulated period of time, issue an executive order requiring the implementation of such improvements.

Maximum permissible levels for motor vehicle noise are set by the director-general of the Environment Agency, and these levels must be observed by the minister of transport when regulating motor vehicle noise under the *Road Transportation Vehicles Law*.

The *Vibration Regulation Law* controls the vibration caused by industrial and construction sites, and provides a channel for requests by prefectural governors regarding road improvements for the control of road traffic vibration.

As with the *Noise Regulation Law*, prefectural governors designate areas and then establish regulatory standards for vibration from industrial facilities and construction sites.

If levels of vibration in a designated area are found to be unsatisfactory with respect to the regulatory standards, prefectural governors are empowered to recommend improvements to ameliorate vibration, and, if these recommendations are not followed, issue an order requiring the implementation of such improvements.

If monitoring results indicate that road traffic vibration has exceeded the limits set by an ordinance of the Prime Minister's Office, prefectural governors are empowered to ask the road administrator or the Prefectural Public Safety Commission to take appropriate remedial action.

Nature Protection

The *Nature Conservation Law* states the obligations of the national government, local governments, business and industry, and the citizens in conserving the natural environment and establishes a Nature Conservation Council in the Environment Agency. The council discusses and conducts studies on matters related to the provisions of this law and others concerned with wildlife protection (see "Auxiliary Organs" in the section on the Environment Agency).

The law provides for the designation of wilderness areas by the director-general of the Environmental Agency, and conservation plans for these areas are established upon consultations with prefectural governors and the Nature Conservation Council. All development, mineral exploitation, capturing or collection of wildlife, use of powered vehicles, and other such activities are prohibited.

The director-general may also designate nature conservation areas in parts of the country that are in need of preservation due to their special or unique qualities. A conservation plan for each such area is formulated by the Director-General, and certain development activities are prohibited within the areas.

In addition to these areas, the director-general is empowered to create "wildlife protection districts" and "special marine areas" for reasons of conservation. These districts and areas too are subject to certain restrictions on development and other activities.

The purpose of the *Natural Parks Law* is the protection of places of scenic beauty, and the promotion of their use, thereby contributing to the health, recreation, and cultural education of the citizens. Natural parks include national parks, quasi-national parks, and prefectural national parks. National parks and quasi-national parks are designated by the director-general of the Environment Agency after consultations as specified by this law. Prefectural national parks are designated by the respective prefectural governments. Marine park areas may also be designated by the director-general. The law provides for the protection, maintenance, and utilization of natural parks, as well as prescribing certain activities within park boundaries.

The purposes of the *Wildlife Protection and Hunting Law* are to improve the living environment of the citizens and to provide agriculture, forestry, and fisheries by implementing projects for the protection of wildlife, providing for appropriate hunting, and controlling "harmful wildlife."

Prefectural governments are to establish plans for wildlife protection projects, in accordance with standards set by the director-general of the Environment Agency, which provide for propagation, hunting, habitat surveys, and the control of harmful wildlife. The law also makes provisions for the various classes of hunting licenses and the requirements for their acquisition, as well as the establishment and management of hunting areas.

Regulatory measures for the protection of endangered species of birds are provided for by the *Law Relating to the Regulation of Transfer of Special Birds*. "Special birds" and their eggs, i.e., birds in danger of extinction in either Japan or other countries, and designated as such by the Prime Minister's Office, may not be imported, exported, or otherwise transferred unless permission has been granted by the director-general of the Environment Agency or, in the case of imports, unless a certificate granting permission has been obtained from the government of the exporting country.

The *Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora* was created as a domestic law to work in conjunction with the Convention on International Trade in Endangered Species of Flora and Fauna (CITES), and prohibits the purchase, sale, or other transfer of rare species of flora and fauna, including their eggs, seeds, and derivatives, as defined by Cabinet order. The law provides for several exceptions to this provision, as when, for example, the director-general of the

Environment Agency allows such transfer for scientific research or breeding.

Public display of rare species of flora and fauna is prohibited, and specimens that have been commercially bred or are covered by a Cabinet order must be officially registered. Registration certificates are issued by the director-general of the Environment Agency. When a registered specimen is purchased, sold, or otherwise transferred, the registration certificate must accompany the specimen.

The director-general is further empowered to direct inspections of registered specimens and the conditions under which they are kept, and to offer advice pertaining to the improvement of such conditions.

Land Use and Development

The *Public Waters Landfill Law* makes provision for obtaining a license from the prefectural governor in order to landfill or otherwise reclaim a part of a river, the sea, or a lake (i.e., "public waters," or those in the possession of the national government), for occupation when the landfill operation prevents effective use of the concerned area of water, and for the procedures to be observed in the operation.

The *Harbor Law* stipulates that creation of a harbor should not degrade the surrounding environment, and that the residential environment of people living in the vicinity should be preserved, or degradation kept to a minimum. The law provides that the developer may be required to pay part of the expenses incurred in this environmental preservation. See the section on the Environmental Impact Assessment System.

DIRECTORY OF AGENCIES

Administering Agencies

Many Japanese government ministries, agencies, and offices are in some way, directly or indirectly, involved in environmental administration, but the major government bodies are as follows:

Environment Agency (Kankyō-chō)

No. 5 Joint Government Building (19th to 22nd Floors)
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100
Telephone: (03) 381-3331

Ministry of International Trade and Industry (Taishōsan-gyō-shō or Tōsōan-shō)

2-1 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 501-1311

Industrial Location and Environmental Protection Bureau, Industrial Location Guidance Division, Industrial Water Division, Safety Division, Chemical Products Safety Division, Machinery and Information Industries Bureau, Consumer Goods Industries Bureau.

Ministry of Health and Welfare (Kōsei-shō)

2-2 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 503-1711

Food Sanitation Division, Environmental Health Bureau, Veterinary Sanitation Division, Food Chemistry Division, Water Supply and Environmental Sanitation Department, Waste Management Division, Pharmaceuticals and Chemicals Safety Division, Pharmaceuticals Affairs Bureau.

Ministry of Agriculture, Forestry, and Fisheries (Nōrin-sanshō)

2-1 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111

Regional Planning Division, Planning Department, Agricultural Structure Improvement Bureau, Crop Production Division, Agricultural Production Bureau, Plant Protection Division, Processing Industry Division, Food and Marketing Bureau.

Ministry of Construction (Kōsōtsum-shō)

1-3 Kasumigaseki 2-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 348-4311

Building Land Development Division, Economic Affairs Bureau, City Planning Division, City Bureau, Parks and Greens Division, Sewerage and Sewage Purification Division, River-Basin Sewerage Division, Public Sewerage Division, Water Administration Division, River Bureau (this bureau administers landfill operations), Development Division, Road Administration Division, Road Bureau.

National Land Agency (Kokudo-chō)

2-2 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 303-3311

Land Use Planning and Control Division, Land Bureau, Water Resources Planning Division, Water Resources Department, Regional Development Bureau, Urban Area Development Division.

Prime Minister's Office (Sōriju)

1-4-1 Nagata-chō
Chiyoda-ku, Tokyo 100
Telephone: (03) 341-2301

National Public Safety Commission (National Police Agency) (Keisatsu-chō)

1-2 Kasumigaseki 2-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 381-8141

Pollution Control Division, Safety Department, Criminal Investigation Bureau (this agency is responsible for the enforcement of regulations according to the Basic Law for Environmental Pollution Control).

Environmental Disputes Coordination Commission (Kōgai-to Chōsei Inkai)

1-4-1 Nagata-chō
Chiyoda-ku, Tokyo 100
Telephone: (03) 341-2301

General Affairs Division, Investigations.

Forestry Agency (Rinya-chō)

2-1 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111

Planning Division, Private Forest Department, Siliculture Division, Forest Road Division, Forest Protection Division.

Fisheries Agency (Suisan-chō)

2-1 Kasumigaseki 1-chōme
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-3111

Fishing Port Planning Division, Fishing Port Department, Fishing Ground Preservation Division.

Science and Technology Agency (Kagakugijutsu-chō)

2-2-1 Kasumigaseki
Chiyoda-ku, Tokyo 100
Telephone: (03) 341-3271

Responsible for radioactive wastes (the Environment Agency is not connected in any way with radioactive waste management).

JAPAN

LIST OF SELECTED LAWS AND REGULATIONS

Major Laws, Orders, Enforcement Rules

General

Basic Law for Environmental Pollution Control (Law No. 132 of 1967; last amended by Law No. 73 of 1973).

Law for the Punishment of Crimes Relating to the Environmental Pollution which Adversely Affects the Health of Persons (Law No. 103 of 1970).

Air Pollution and Odors

Air Pollution Control Law (Law No. 91 of 1962; last amended by Law No. 65 of 1976; Environment Agency, National Police Agency, Ministry of Transport, and Ministry of International Trade and Industry).

Cabinet Order for Implementation of the Air Pollution Control Law (Law No. 229 of 1962; last amended by Cabinet Order No. 102 of 1963).

Enforcement Regulation of the Air Pollution Control Law (Ministry of Health and Welfare and Ministry of International Trade and Industry Ordinance No. 1 of June 22, 1971; last amended by Prime Minister's Office Ordinance No. 53 of 1987).

Offensive Odor Control Law (Law No. 91 of 1971; Environment Agency, Ministry of Agriculture, Forestry, and Fisheries).

Cabinet Order and Ordinance of the Prime Minister's Office for the Offensive Odor Control Law (Cabinet Order No. 207 of 1972; amended by Ordinance of Prime Minister's Office No. 69 of 1976).

Environmental Quality Standards Regarding Air Pollution (Environment Agency Notification No. 25, May 2, 1973; amended by Notification No. 67 of 1981).

Environmental Quality Standard for Nitrogen Dioxide (Environment Agency Notification No. 32, 1978).

Noise and Vibration

Regulatory Standards for Noise Emitted from Specified Factories (Notification No. 1 of November 27, 1963, from the Ministry of Health and Welfare, Ministry of Agriculture, Forestry and Fisheries, Ministry of International Trade and Industry, and Ministry of Transport; amended by Environment Agency Notification No. 11 of 1966).

Standards for Noise from Special Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 27, 1964; amended by Environment Agency Notification No. 12 of 1987).

Environmental Quality Standards for Noise (Cabinet Decision of May 21, 1981).

Environmental Quality Standards for Shinkansen Superelectric Railway Noise (Environment Agency Notification No. 46 of July 23, 1978).

Environmental Quality Standards for Aircraft Noise (Environment Agency Notification No. 154 of December 27, 1973).

Noise Regulation Law (Law No. 98 of 1962; last amended by Law No. 83 of 1972; Environment Agency, National Police Agency, Ministry of Transport).

Cabinet Order for Implementation of the Noise Regulation Law (Cabinet Order No. 214 of 1962; last amended by Cabinet Order No. 23 of 1986).

Vibration Regulation Law (Law No. 64 of 1976; Environment Agency, National Police Agency).

Cabinet Order for the Implementation of the Vibration Regulation Law (Cabinet Order No. 230 of 1976; amended by Cabinet Order No. 23 of 1986).

Regulatory Standards for Vibration Emitted from Specified Factories (Environment Agency Notification No. 90 of November 10, 1971; amended by Environment Agency Notification No. 23 of 1986).

Standards for Vibration Emitted from Specified Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 22, 1964; amended by Environment Agency Notification No. 1 of 1986).

Water Pollution

Water Pollution Control Law (Law No. 120 of 1970; last amended by Law No. 90 of 1982; Environment Agency, Ministry of Transport).

Cabinet Order for Implementation of the Water Pollution Control Law (Cabinet Order No. 184 of 1972; last amended by Cabinet Order No. 89 of 1987).

Water Pollution Control Law Enforcement Regulations (Order No. 2 of June 18, 1971 of the Prime Minister's Office, and the Ministry of International Trade and Industry; last amended by Prime Minister's Office Order No. 67 of 1986).

Law Concerning Special Measures for the Preservation of Lake Water Quality (Law No. 61 of 1981; amended by Law No. 69 of 1984; commonly known as the "Clean Lakes Law"; Environment Agency, Ministry of Transport).

Enforcement Order of the Law Concerning Special Measures for the Preservation of Lake Water Quality (Cabinet Order No. 37 of March 28, 1983; last amended by Cabinet Order No. 214 of 1987).

Enactment Regulations of the Law Concerning Special Measures for the Preservation of Lake Water Quality (Prime Minister's Office Order No. 7 of March 28, 1983; amended by Prime Minister's Office Order No. 44 of 1985).

Law Concerning Special Measures for Conservation of the Environment of the Seto Inland Sea (Law No. 110 of October 2, 1972; last amended by Law No. 69 of June 12, 1978; Environment Agency, Ministry of Transport).

Soil Contamination, Agricultural Chemicals

Agricultural Land Soil Pollution Prevention Law (Law No. 129 of 1970; last amended by Law No. 67 of 1972; Environment Agency, Ministry of Agriculture, Forestry, and Fisheries).

Cabinet Order for Implementation of the Agricultural Land Soil Pollution Prevention Law (Cabinet Order No. 204 of 1971; last amended by Cabinet Order No. 103 of 1973).

Agricultural Chemicals Regulation Law (Law No. 82 of 1948; last amended by Law No. 23 of 1984; Environment Agency, Ministry of Health and Welfare, Ministry of Agriculture, Forestry, and Fisheries, Ministry of International Trade and Industry).

Cabinet Order for Implementation of the Agricultural Chemicals Regulation Law (Cabinet Order No. 56 of 1971; last amended by Cabinet Order No. 60 of 1987).

Ground Subsidence

Law Concerning the Regulation of Pumping-Up of Underground Water for Use in Buildings (Law No. 100

of 1962; last amended by Law No. 88 of 1971; Environment Agency, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Law Concerning the Regulation of Pumping-Up of Under-ground Water for Use in Buildings (Cabinet Order No. 335 of 1962; last amended by Cabinet Order No. 243 of 1974).

Industrial Water Law (Law No. 146 of 1954; last amended by Law No. 88 of 1972; Environment Agency, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Industrial Water Law (Cabinet Order No. 142 of 1957; last amended by Cabinet Order No. 34 of 1967).

Wastes and Marine Pollution

Waste Disposal and Refuse Collection Law (Law No. 137 of 1970; last amended by Law No. 87 of 1967; Environment Agency, Ministry of Health and Welfare).

Cabinet Order for Implementation of the Waste Disposal and Refuse Collection Law (Cabinet Order No. 300 of September 21, 1971; last amended by Cabinet Order No. 292 of 1967).

Law Relating to the Prevention of Marine Pollution and Maritime Disaster (Law No. 126 of 1970; last amended by Law No. 40 of 1967; Environment Agency, Ministry of Transport, Maritime Safety Agency).

Cabinet Order for Implementation of the Law Relating to the Prevention of Marine Pollution and Maritime Disaster (Cabinet Order No. 281 of June 22, 1971; last amended by Cabinet Order No. 115 of 1967).

Chemical Substances

Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances (Law No. 117 of October 16, 1973; last amended by Law No. 44 of 1964; Environment Agency, Ministry of Health and Welfare, Ministry of Agriculture, Forestry, and Fisheries, Ministry of International Trade and Industry).

Cabinet Order for the Implementation of the Law Concerning the Screening and Regulation of the Manufacture of Chemical Substances (Cabinet Order No. 302 of June 7, 1973; last amended by Cabinet Order No. 49 of 1967).

Food Sanitation Law (Law No. 233 of December 24, 1947; last amended by Law No. 104 of 1972; Ministry of Health and Welfare).

Compensation, Settlement of Disputes

Pollution-Related Health Damage Compensation Law (Law No. 111 of October 1, 1972; last amended by Cabinet Order No. 368 of November 4, 1967; Environment Agency, Ministry of International Trade and Industry).

Enforcement Order of the Pollution-Related Health Damage Compensation Law (Cabinet Order No. 295 of August 20, 1970; last amended by Cabinet Order No. 368 of 1967).

Pollution Disputes Settlement Law (Law No. 108 of June 1, 1970; last amended by Law No. 90 of 1963; Environmental Disputes Coordination Commission).

Costs and Assistance

Pollution Control Public Works Cost Allocation Law (Law No. 123 of December 23, 1970; amended by Law No. 43

of 1967; Environment Agency, Ministry of Finance, Ministry of Health and Welfare, Ministry of Construction, Ministry of Home Affairs).

Cabinet Order for Implementation of the Pollution Control Public Works Cost Allocation Law (Cabinet Order No. 106 of May 8, 1971; last amended by Cabinet Order No. 214 of 1960).

Nature Conservation

Nature Conservation Law (Law No. 85 of 1972; last amended by Law No. 28 of 1967; Environment Agency).

Natural Parks Law (Law No. 161 of 1967; last amended by Law No. 67 of 1972; Environment Agency).

Wildlife Protection and Hunting Law (Law No. 23 of April 4, 1912; last amended by Law No. 63 of 1962; Environment Agency).

Cabinet Order for the Implementation of the Wildlife Protection and Hunting Law (Cabinet Order No. 254 of August 21, 1952; last amended by Cabinet Order No. 106 of April 14, 1973).

Enforcement Regulation for the Wildlife Protection and Hunting Law (Ordinance of the Ministry of Agriculture and Forestry No. 108 of September 30, 1952; last amended by Ordinance of the Prime Minister's Office No. 65 of 1963).

Law Relating to the Regulation of Transfer of Special Birds (Law No. 45 of 1972; amended by Law No. 85 of 1972; Environment Agency).

Order for the Implementation of the Law Relating to the Regulation of Transfer of Special Birds (Cabinet Order No. 465).

Implementation Ordinance for Law Relating to the Regulation of Transfer of Special Birds (Ordinance of Prime Minister's Office No. 71 of November 27, 1972; last amended by Ordinance of the Prime Minister's Office No. 62 of 1963).

Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Law No. 58 of June 2, 1967; Environment Agency).

Implementation Ordinance for the Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Cabinet Order No. 373 of November 6, 1967).

Enforcement Regulations for the Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Ordinance of the Prime Minister's Office No. 35 of December 1, 1967).

Basic Policy on Conservation of the Natural Environment (Prime Minister's Office Notification No. 20 of November 6, 1973).

Land Use and Urban Planning

Urban Planning Law (Law No. 100 of June 13, 1962; last amended by Law No. 66 of 1967; National Land Agency, Ministry of Transport, Ministry of Construction).

Public Waters Land/III Law (Law No. 57 of 1921; last amended by Law No. 5 of 1973).

Harbor Law (Law No. 218 of May 31, 1950; amended by Law No. 87 of 1967).

APPENDIX A

Material Safety Data Sheets

MATERIAL SAFETY DATA SHEET

aaaaaaaaaaaa ABBOTT LABORATORIES
a CHEMICAL & AGRICULTURAL PRODUCTS DIVISION
aaaaaaaaaaaa a NORTH CHICAGO, ILLINOIS 60064
a a EMERGENCY TELEPHONE 1-708-937-6100
a ABBOTT a CHEMTREC 1-800-424-9300
aaaaaaaaaaaa

ISSUE DATE:08/19/94 TSCA STATUS:Exempt

APPROVAL: _____

LIST/CODE:5375,5508,3626/41450,
41558,41559

PRODUCT NAME: Leuprolide Acetate

CHEMICAL NAME: 6-D-Leucine-9-(N-ethyl-L-prolinamide)-10-
deglycinamidyluteinizing hormone-releasing factor monoacetate; C61N88F16014

DOT CLASSIFICATION: Not Regulated

HAZARDOUS INGREDIENTS/IDENTITY INFORMATION

Table with 4 columns: NAME (CAS NO.), OSHA PEL, ACGIH TLV, ABBOTT LIMIT. Row 1: Leuprolide Acetate*(74381-53-6) EL EL ..

** - Internal Guideline 0.01 mcg/m3 (8-hr TWA). In the event that the exposure limit cannot be demonstrated by air monitoring, biological monitoring to assess exposure (specific program designed and

administered through Corporate Employee Health) should be used.

PHYSICAL PROPERTIES

Appearance: white, flocculent powder

Solubility: completely soluble in water

Boiling Point: N/A

pH: N/A

Vapor Density: N/A

Viscosity: N/A

Melting Point: N/D

Vapor Pressure: N/A

Density: N/A

FIRE AND EXPLOSION DATA

Flash Point: N/A

PRODUCT NAME: Leuprolide Acetate

FIRE AND EXPLOSION DATA (cont)

Extinguishing Media: Use appropriate media for underlying cause of fire.

Special Fire Fighting Procedures: wear protective clothing and self-contained breathing apparatus

Unusual Fire and Explosion Hazards: N/D

REACTIVITY

Incompatibility: Hypochlorite solutions

Hazardous Decomposition or By-products: N/D

Conditions to Avoid: N/D

HEALTH HAZARD DATA

Routes of Entry: Inhalation - YES Skin - Yes Ingestion - Yes

Oral Toxicity: N/D. Oral administration has produced pharmacologic responses in men at a dose of 10 mg

Dermal Toxicity: N/D. LD50 > 100 mg/kg (SC) in rats and mice. Skin application has produced pharmacological responses in humans and animals.

Inhalation Toxicity: N/D. Intranasal application has produced pharmacologic responses in men and women at doses of 50 mcg or more

Corrosiveness: N/D

Dermal Irritation: N/D

Ocular Irritation: N/D

Dermal Sensitization: N/D

Special Target Organ Effects: In clinical use, subcutaneous doses of 1 mg/day act as potent, but reversible, inhibitors of GnRH secretion by the pituitary resulting in inhibition of ovarian and testicular function. In contrast, doses as low as 0.16 mcg or more stimulate gonadotropin release. In rabbits, subcutaneous dosages as low as 0.1 mcg/kg/day produced embryolethality while dosages of 10 mcg/kg/day produced fetal resorptions in rats. Materials similar to leuprolide have the potential to exert a contraceptive effect in pregnant women if administered 5-8 days after the LH surge.

Carcinogenicity: NTP - NL IARC - NL OSHA - NL ACGIH - NL

PRODUCT NAME: Leuprolide Acetate

HEALTH HAZARD DATA (cont)

Carcinogenicity (cont): Benign pituitary hyperplasia and tumors were found in carcinogenicity studies in rats (0.6-4 mg/kg/day). A study in mice at dosages up to 60 mg/kg/day was negative and no comparable effect has been found in man at doses up to 20 mg/day

Signs and Symptoms of Exposure: n/d. In clinical use, the initial response to leuprolide acetate is an increase in LH, FSH and male and female sex hormones (e.g. testosterone and estrogens). Continued use leads to reductions in these hormones to castrate or post-menopausal levels. Other adverse reactions include hot flashes, edema, GI upset, dizziness, headache, bone pain, weakness.

Medical Conditions Aggravated by Exposure: n/d. Data suggest preexisting pituitary, ovarian or testicular dysfunction. Metastatic vertebral lesions and/or urinary tract obstruction

Emergency and First Aid Procedures: Remove from source of exposure. If skin or eye contact occurs flush with copious amounts of water. If irritation persists or signs of toxicity occur, seek medical attention. No known antidote. Provide symptomatic/supportive care, monitoring hormone/sexual function, as necessary

SPECIAL PROTECTION INFORMATION

Ventilation: Use inside hood or glovebox

Respirator: supplied air respirator

Gloves: wear 2 pair; Latex inside, thicker outside

Eye Protection: Full face respirator

Other Protection: wear fullbody tyvek coverings with hood and shoe covers

SPECIAL HANDLING AND STORAGE

Special Precautions: Wash thoroughly after handling this compound. Keep latex gloves on until all potentially contaminated personal protective equipment is removed

Spill or Release Procedures: Wet material before cleanup to prevent dust generation. Utilize ventilation and personal protective equipment during cleanup. Avoid dust. Place in appropriate container for disposal. Ventilate and wash spill area.

Waste Disposal: Dispose of material in accordance with applicable federal, state, and local regulations

Other Handling: n/d

PRODUCT NAME:Leuprolide Acetate

Legend

- N/A = NOT APPLICABLE
- N/D = NOT DETERMINED
- NL = Not Listed
- L = Listed
- C = Ceiling
- S = Short Term
- (R) = A registered trademark of Abbott Laboratories
- (TM) = A registered trademark of Abbott Laboratories

The information and recommendations contained herein are based upon tests believed to be reliable. However, Abbott Laboratories does not guarantee their accuracy or completeness NOR SHALL ANY OF THIS INFORMATION CONSTITUTE A WARRANTY, WHETHER EXPRESSED OR IMPLIED, AS TO THE SAFETY OF THE GOODS, THE MERCHANTABILITY OF THE GOODS, OR THE FITNESS OF THE GOODS FOR A PARTICULAR PURPOSE. Adjustment to conform with actual conditions of usage may be required. Abbott Laboratories assumes no responsibility for results obtained or for incidental or consequential damages arising from the use of these data. No freedom from infringement of any patent, copyright or trademark is to be inferred.

APPENDIX B

References

- B1. Akwete Lex Adjei and L. Hsu. Leuprolide and Other LH-RH Analogues. In Stability and Characterization of Protein and Peptide Drugs. Case Histories. Ed. Y. John Wang and Rodney Pearlman, Plenum Press, New York.
- B2. Metcalf & Eddy, Inc. Wastewater Engineering: Treatment Disposal Reuse. Revised by G. Tchobanoglous. New York: McGraw-Hill Book Company.
- B3. Naeshiro, S. Kondo, S. Mitani, K. Yoshida, H. Kobayshi, T. Kimura, S. Shimomura and S. Tanayama. Metabolic Fate of TAP-144. An LH-RH Agonist In Rats and Dogs. Japanese Journal of Therapeutics 18:35-56.
- B4. Pharmaceutical Manufacturers Association (PMA), 191. Interim Guidance of the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA. PMA, Washington, D.C. *Reference not included in Appendix B.
- B5. U.S. Food and Drug Administration. 1995. Guidance for the Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. FDA, Washington, D.C. *Reference not included in Appendix B.
- B6. Literature Review of the Polymers of Lactic and Glycolic Acids.

JAN 24 1997

REVIEW FOR HFD-580
MICROBIOLOGIST'S REVIEW #1 OF SUPPLEMENT
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY REVIEW STAFF

22 January 1997

NDA/Supplement Number: 20-517/SEZ-002

Document Date: 30 May 1996

Date Assigned for Review: 15 July 1996

Amendments and Others: none

Name and Address of Applicant: TAP Pharmaceuticals
2355 Waukegan Rd.
Deerfield Illinois, 60015

Name of Drug: Lupron Depot[®]-4 Month 30 mg (leuprolide acetate for depot suspension)

Supplement Provides For: This is an efficacy supplement to change the dosage and administration from 22.5 mg every 3 months to 30 mg every 4 months.

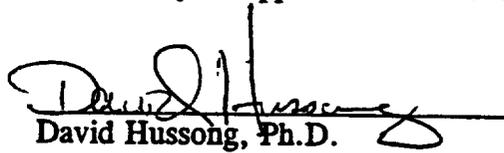
Pharmacological Category: Synthetic gonadotropin secretion inhibitor

Dosage Form: Vials filled with lyophilized powder (dry fill process) and packaged with diluent solution. The suspensin is for intramuscular injection.

Related Documents: NDA 20-517/S-001

Comments: The submission states that the aseptic fill information is unchanged from supplement 001. Supplement 001 was reviewed and recommended for approval by Dr. Brenda Uratani (reviews dated 05/22/96 and 06/13/96).

Conclusions and Recommendations: No action is indicated by microbiology on this supplement and the submission may be approved for sterility assurance issues.


David Hussong, Ph.D.

1-22-97

pkc 1/24/97

cc:

Original NDA 20-517/SEZ-002
HFD 160/Consult File
HFD 580/CSO/L. Pauls
HFD 580/Chemist/
HFD 805/D. Hussong

Drafted by: D. Hussong, 01/22/97
R/D initialed by: P. Cooney

Filename, c:\nda\s\20-517r1.s02



NDA 20-517/S-002

Food and Drug Administration
Rockville MD 20857

FEB 21 1997

Tap Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your pending May 30, 1996, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot® (leuprolide acetate for depot suspension) 4-month, 30 mg.

To complete our review of the Clinical section of your submission, we request the following information:

1. Intent-to-treat analyses for all efficacy endpoints. These should form the basis for all labeled efficacy claims.
2. An integrated summary of safety that includes all existing safety data for all patients treated with the 4-month Lupron Depot formulation to date. This should include the safety data from all treated patients in studies M93-012 and M93-013, as well as any other available clinical safety data from foreign marketing and/or other known sources.
3. Revised labeling that reflects the findings of the above efficacy and safety re-analyses and describes all known cases of "escape" from testosterone suppression during treatment with the 4-month depot formulation.
4. If you plan to include labeling statements comparing the effects of the 4-month depot formulation with other Lupron formulations approved for this indication, these statements should be based on intent-to-treat analyses of all endpoints described in labeling from the current and prior clinical studies (M-93-013, M91-583, M91-653, M85-097).
5. A summary and evaluation of all available clinical data (whether or not considered "related" to treatment) that may be used to estimate the incidence of severe adverse reactions associated with initiation of Lupron treatment (i.e., "flare" reactions of onset within the first 3-4 weeks of Lupron treatment). This summary should include any existing data that directly compare the incidence of "flare" reactions with and without concomitant antiandrogen administration.
6. A specific description of any foreign experience with the clinical use of the 4-month Lupron Depot.

NDA 20-517/S-002

Page 2

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

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,



Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

Original NDA 20-517
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/LGolden/HJolson/LRarick/LPauls

Drafted by: ADunson/February 12, 1997/n20517s2ir

Concurrences:

LPauls2.12.97/LGolden, HJolson2.13.97/LRarick2.18.97

INFORMATION REQUEST (IR)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUN 12 1996

NDA No. 20-517

TAP HOLDINGS INC.
2355 Waukegan Road
Deerfield, IL 60015

Attention: Aruna Dabholkar, M.D., Regulatory Products Manager

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: LUPRON DEPOT ⁴ 3 Month 22.5 mg

NDA Number: 20-517

Supplement Number: S-002

Date of Supplement: MAY 30, 1996

Date of Receipt: MAY 31, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on JUL 30 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research



TAP HOLDINGS INC.

part of TAP Pharmaceuticals Inc.

Pharmaceutical Division
2100 Wilson Blvd
Rockville, MD 20857

May 30, 1997

**Division of Reproductive and Urologic Drug Products
Document Control Room 17B-20, HFD-580
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857**

**RE: Lupron Depot®-4 Month 30 mg
NDA 20-517, S-002
Amendment No. 011**

Dear Dr. Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application S-002.

Attached are the revised labeling and the patient package insert as requested today via telephone communication.

Sincerely,

**Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893**

AD/mea

Attachment





TAP HOLDINGS INC.

May 29, 1997

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

RE: Lupron Depot®-4 Month 30 mg
NDA 20-517, S-002
Amendment No. 010

Dear Dr. Rarick:

Pursuant to 21 CFR 314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application S-002.

Attached is the revised labeling as requested in your letter dated May 29, 1997. The only revision that is not incorporated in this revision is the change suggested in the last line of the *Changes in Bone Density* section (Page 7 of labeling).

Also attached is the Patient Package insert which has been revised to incorporate all the changes recommended by the Division this afternoon.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/mea

Attachment



TAP HOLDINGS INC.

parent of TAP Pharmaceuticals

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

May 27, 1997

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

**RE: Lupron Depot®-4 Month 30 mg
NDA 20-517, S-002
Amendment No. 009**

Dear Dr. Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application S-002.

Attached is the revised labeling as requested in your letter dated May 23, 1997. Also enclosed is the annotated labeling explaining the revisions. Attachment #1 contains the 3500A forms for all the reported cases of spontaneous abortions as requested.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/mea

Attachment



TR

TAP HOLDINGS INC.

ORIGINAL

ORIG AMENDMENT

522-002
BC

May 9, 1997

Division of Reproductive and Urologic Drug Products, HFD-580.
Document Control Room 17B-20
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

*rec'd
5-19-97*

NDA 20-517, S-002
(Lupron Depot® - 4 Month 30 mg)
(leuprolide acetate for depot suspension)
Amendment No. 008

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
AD	5/27/97
CSO INITIALS	DATE

Dear Doctor Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application 002.

The amendment contains the response to the request for information for the Environmental Assessment portion of the application. This request was conveyed to the sponsor via a teleconference this morning with Mr. Alvis Dunson, Jr. and Dr. Nancy Sager.

FONSI was signed off on May 9, 1997 by Nancy Sager. Miller 5/23/97

Following requested information is attached:

1. Calculation for the entire product line of Lupron (Injection and Depot).
2. Certifications from Abbott Laboratories for bulk manufacturing and for finishing.

Please note that the product still qualifies for a Tier 0 Claim.

A copy is being sent to Dr. Sager via a telefacsimile.

Sincerely,

Aruna Dabholkar

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp

Attachment



TR

TAP HOLDINGS INC.

noted - refer to minutes of internal meeting held 5/22/97 for comments on this draft labeling
YJH 5/23/97

ORIGINAL

ORIG AMENDMENT
SE2-0023L

May 8, 1997

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

RE: Lupron Depot®-4 Month 30 mg
NDA 20-517, S-002
Amendment No. 007

Dear Dr. Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application S-002.

Attached is the revised labeling as requested in your letter dated May 1, 1997. Also enclosed is the annotated labeling explaining the revisions. All attachments mentioned in the annotations are submitted including a draft patient information pamphlet. The same attachment also contains the printed information pamphlets used with Lupron Depot 7.5 mg. and Lupron Depot - 3 Month 22.5 mg., for easy reference.

We request the Division to continue the review of this efficacy supplement.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893



AD/mea

Attachment

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

RP

TAP HOLDINGS INC.

ORIGINAL

April 7, 1997

ORIG AMENDMENT

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

NDA 20-517, S-002 (Lupron Depot^o - 4Month 30 mg)
Amendment No. 006

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Dear Doctor Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application 002.

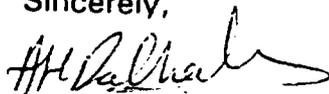
Attached is the response to the item number 4 from your letter dated February 21, 1997 requesting information for clinical section. The data presented demonstrate that the three formulations of leuprolide acetate are similar in safety and efficacy.

Responses to all other items in the letter were submitted on March 20, 1997 (Amendment No. 005).

The summary document is submitted on a WordPerfect diskette.

We request the Division to continue the review of this efficacy supplement.

Sincerely,



Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp

Attachment





TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

ORIGINAL

Win Lake Office Plaza
Jackson Rd
Baltimore

ORIG AMENDMENT

March 20, 1997

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

EM

NDA 20-517, S-002 (Lupron Depot - 4Month 30 mg)
Amendment No. 005

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS
DATE

Dear Doctor Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application 002.

Attached is the response to your letter dated February 21, 1997 requesting information for clinical section.

Responses to all items except item number 4 are submitted. We are analyzing (intent-to-treat) the databases for clinical studies in support of monthly and 3-Month depot formulations and all requested information will be submitted in the first week of April 1997.

Please note that all summaries and the revised package insert are also submitted on Word Perfect diskettes for the Medical reviewer (desk copy). All statistical tables are submitted on Excel as requested before.

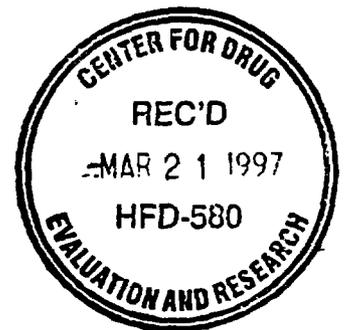
We request the Division to continue the review of this efficacy supplement.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

AD/pjp

Attachment





TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

*noted
3/18/97*

ORIGINAL

SE2-002

SUPPL NEW CORRESP

Rockburn Lake Office Plaza
Waukegan Rd.
Deerfield, IL 60015

March 4, 1997

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

*noted
3/19/97*
*noted
3/19/97*
*noted
3/13/97*

**RE: Lupron Depot®-4 Month 30 mg
NDA 20-517, S-002
Amendment No. 004**

Dear Dr. Rarick:

We have reviewed your letter dated February 21, 1997, requesting additional information to complete the review.

The requested information is being prepared. We plan to submit a response with all data and if required revised labeling by March 21, 1997.

We request the Division to continue the review of this efficacy supplement.

Sincerely,

Aruna Dabholkar

Aruna Dabholkar, M.D.
Regulatory Products Manager
(847) 317-4893

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
<i>AD</i>	<i>3/20/97</i>
CSO INITIALS	DATE

AD/pjp

Attachment





TAP HOLDINGS INC.

Division of TAP Pharmaceuticals

Orig

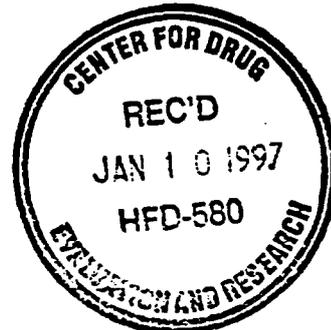
*Noted
1/5/97*

*Noted
1/29/97*

SBZ

January 9, 1997

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



RE: NDA 20-517, S-002
Amendment 003 (CRFs and Stability Data)

Dear Doctor Rarick:

The Sponsor, TAP Holdings Inc., submits this Amendment to Application under the provisions of Section 505(l) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.60.

Enclosed are the complete case report forms for the four patients nos. as requested by the medical reviewer.

Note that three of these patients have discontinued from the study M93-013 for following reasons

<u>Patient Nos.</u>	<u>Reasons for Discontinuation</u>
	Patient Request
	Patient Request
	Non-Compliance

Patient no. is still in the study. However, his data were excluded from efficacy analysis due to insufficient evidence of metastatic disease.

REVIEWS COMPLETED

CSO ACTION:
 LETTER N.A.I. MEMO

CSO INITIALS _____ DATE _____



Please note that additional stability data (12 months) for Lupron Depot-4 Month 30 mg are also submitted in a separate volume for the chemistry reviewer. These data are for the same lots as those submitted in the original application on May 30, 1996.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893

TAP HOLDINGS INC.
a subsidiary of TAP Pharmaceuticals Inc.

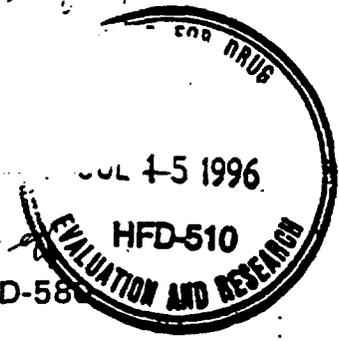
ORIGINAL

NDA SUPPL AMENDMENT

552-0210

July 12, 1996

started
MPL 7/29/96



Division of Reproductive and Urologic Drug Products, HFD-580
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted
Kizakaya
5/1/96

NDA 20-517, S-002 (Lupron Depot-4Month 30 mg)
Amendment No. 1

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> H.A.I.
<input type="checkbox"/> MEMO	
AD	4/2/97
CSO INITIALS	DATE

Dear Doctor Rarick:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application 002 with the following debarment statement. Please forward the copies to the Chemistry reviewer.

The sponsor, TAP Holdings Inc. certifies that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306 (a) or (b)], in connection with this application.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(847) 317-4893

AD/pjp

Attachment