NOA 20-517

AP LETTER

NDA 20-517

TAP Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Regulatory Products Manager
2335 Waukegan Road
Deerfield, IL 60015

DEC 22 1995

Dear Dr. Dabholkar:

Please refer to your December 21, 1994, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot® (leuprolide acetate for depot suspension) 3-Month, 22.5 mg.

We acknowledge receipt of your pre-submission dated October 7, 1994, containing chemistry, manufacturing and controls information, and your amendments dated March 8, April 11 and 21, May 24, June 27, July 28 and 31, August 30, September 11 and 29, December 19 (telefacsimile), and 21 (telefacsimile), 1995.

This new drug application provides for a three-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 draft labeling submitted on October 7, 1994 (vial label), and June 27 (carton and vehicle ampule labels) and December 21 (package insert), 1995. Accordingly, the application is approved.

We remind you of your Phase 4 commitments specified in your submission dated December 21, 1995. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Your Phase 4 commitments are as follows:

1. To perform a multiple-dose (4 doses; 1-year) pharmacokinetic/pharmacodynamic (PK/PD) study including measurements of testosterone. The Division of Pharmaceutical Evaluation II should be contacted to review the protocol prior to the initiation of this study.

2. To perform a 6-month study comparing the 1-month depot vs. the 3-month depot to determine the possible stimulation with reinjection between the two

formulations. The Division should be contacted to review the protocol prior to the initiation of the study.

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 send 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 when it is available.

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:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Name	Title	Signature	Date
Enid Galliers, B.S.	Chief, Project Management Staff		12/21/95
Jean Fourcroy, M.D., Ph.D.	Medical Officer		12/21/95
G. Alexander Fleming, M.D.	Medical Team Leader		12/21/95
Chien-Hua, Ph.D.	Chemist	Stephen Moore for Chienhua Niu	12/21/95
Stephen Moore, Ph.D.	Acting Supervisory Chemist II		12/21/95
Krishan Raheja, D.V.M., Ph.D.	Pharmacologist		12/21/95
Alexander Jordan, Ph.D.	Pharmacology Team Leader		12/21/95
Lisa Rarick, M.D.	Deputy Director II		12-21-95
Solomon Sobel	Division Director		12/22/95

cc:
Original NDA 20-517
HFD-510/Div. files
HFD-2/M.Lumpkin
HFD-102/LRipper (with labeling)
DISTRICT OFFICE
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/S.Sherman (with labeling)
HFD-510/EGalliers/JFoucroy/AFleming/CNiu/SMoore/KRaheja/AJordan/LRarick
HFD-613 (with labeling)
HFD-871 HAhn/JHunt
HF-35/SCruzan (with labeling)

drafted: LPauls/December 20, 1995/N20517AP.001

Concurrences:
see above

APPROVAL

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Division Director's Memo

This NDA will be signed off at the Division level. No memo is required.

LABELING

12/21/95

(No.)

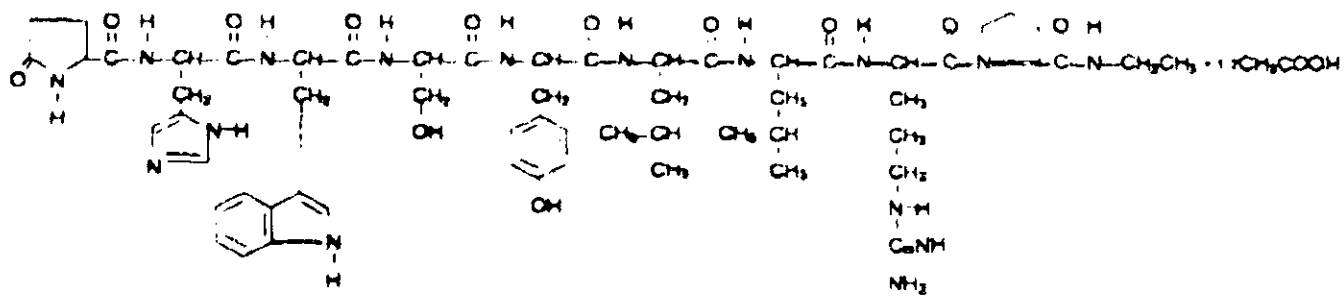
12-21-95

New commodity #
LUPRON DEPOT® - 3 Month 22.5 mg
(leuprolide acetate for depot suspension)

3-MONTH FORMULATION **(STATEMENT TO BE PRINTED IN COLOR)**

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON DEPOT 22.5 mg is available in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS (84 days).**

The single-dose vial of LUPRON DEPOT 22.5 mg contains leuprolide acetate (22.5. mg), polylactic acid (198.6 mg), and D-mannitol (38.9 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (10 mg), D-mannitol (100 mg), polysorbate 80 (2 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 22.5 mg, acetic acid is lost leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon 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 the 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 patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally

PHARMACOKINETICS

Absorption: Following a single injection of the three month formulation of LUPRON DEPOT 22.5 mg in patients, mean peak plasma leuprolide concentration of 48.9 ng/mL was observed at 4 hours and then declined to 0.67 ng/mL at 12 weeks. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Detectable levels of leuprolide were present at all measurement points in all patients. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism: In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on two compartment model.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, pentapeptide (Metabolite I), tripeptide (Metabolite II and III) and dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached mean maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of leuprolide concentrations.
Excretion: Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.
Special Populations: The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

CLINICAL STUDIES

In clinical studies, serum testosterone was suppressed to castrate within 30 days in 87 of 92 (95%) patients and within an additional two weeks in three patients. Two patients did not suppress for 15 and 28 weeks, respectively. Suppression was maintained in all of these patients with the exception of transient minimal testosterone elevations in one of them, and in another an increase in serum testosterone to above the castrate range was recorded during the 12 hour observation period after a subsequent injection. This represents a stimulation of gonadotropin secretion.

An 85% rate of "no progression" was achieved during the initial 24 weeks of treatment. A decrease from baseline in serum PSA of ≥90% was reported in 71% of the patients and a change to within the normal range (≤3.99 ng/ml.) in 63% of the patients.

Periodic monitoring of serum testosterone and PSA levels is recommended, especially if the anticipated clinical or biochemical response to treatment has not been achieved. It should be noted that results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

INDICATIONS AND USAGE

LUPRON DEPOT 22.5 mg is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT 22.5 mg were similar to that of the original daily subcutaneous injection and the monthly depot formulation.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, the monthly formulation of LUPRON DEPOT produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal

malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of LUPRON DEPOT in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** section).

Laboratory Tests: Response to LUPRON DEPOT 22.5 mg should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen and prostatic acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy Category X. (See **CONTRAINDICATIONS** section.)

Pediatric Use: See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness of the monthly formulation in children with central precocious puberty.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS** section).

In two clinical trials of LUPRON DEPOT 22.5 mg, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. **Often, causality is difficult to assess in patients with metastatic prostate cancer.** Reactions considered not drug related are excluded.

	LUPRON DEPOT N=94	(Percent)
Body As A Whole	7	(7.4%)
Asthenia	25	(26.6%)
General Pain	6	(6.4%)
Headache	13	(13.8%)
Injection Site Reaction		
Cardiovascular System		
Hot flashes/Sweats*	55	(58.5%)
Digestive System		
GI Disorders	15	(16.0%)
Musculoskeletal System		
Joint Disorders	11	(11.7%)
Central/Peripheral Nervous System		
Dizziness/Vertigo	6	(6.4%)
Insomnia/Sleep Disorders	8	(8.5%)
Neuromuscular Disorders	9	(9.6%)
Respiratory System		
Respiratory Disorders	6	(6.4%)
Skin and Appendages		
Skin Reaction	8	(8.5%)
Urogenital System		
Testicular Atrophy*	19	(20.2%)
Urinary Disorders	14	(14.9%)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 22.5 mg.

Body As A Whole – Enlarged abdomen, Fever; *Cardiovascular System* - Arrhythmia, Bradycardia, Heart failure, Hypertension, Hypotension, Varicose vein; *Digestive System* – Anorexia, Duodenal ulcer, Increased appetite, Thirst/dry mouth; *Hemic and Lymphatic System* – Anemia, Lymphedema; *Metabolic and Nutritional Disorders* - Dehydration, Edema; *Central/Peripheral Nervous System* - Anxiety, Delusions, Depression, Hypesthesia, Libido decreased*, Nervousness, Paresthesia; *Respiratory System* - Epistaxis, Pharyngitis, Pleural effusion, Pneumonia; *Special Senses* - Abnormal vision, Amblyopia, Dry eyes, Tinnitus; *Urogenital System* - Gynecomastia, Impotence*, Penis disorders, Testis disorders.

Laboratory: Abnormalities of certain parameters were observed, but are difficult to assess in this population. The following were recorded in ≥ 5% of patients. Increased BUN, Hyperglycemia, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Hyperphosphatemia, Abnormal liver function tests, Increased PT, Increased PTT. Additional laboratory abnormalities reported were: Decreased platelets, Decreased potassium and Increased WBC.

The following additional adverse reactions have been reported with other formulations of leuprolide acetate. Reactions considered by the treating physician as not related to drug are excluded.

Body As A Whole - Body odor, Infection/inflammation, Injection site abscess; *Cardiovascular System* – Angina, Congestive heart failure, ECG changes/ischemia, Myocardial infarction, Murmur, Palpitations, Phlebitis/thrombosis, Pulmonary emboli, Transient ischemic attack/stroke; *Digestive System* – Appetite changes, Constipation, Dysphagia, Gastrointestinal bleeding/disturbance, Gingivitis, Hard nodule in throat, Hepatic dysfunction, Peptic ulcer, Rectal polyps; *Endocrine System* – Accelerated sexual maturity, Androgen-like effects, Diabetes, Thyroid enlargement; *Hemic and Lymphatic System* - Lymphadenophathy; *Metabolic and Nutritional disorders* - Growth disorder, Hypoglycemia, Weight gain/loss, *Musculoskeletal System* - Ankylosing spondylosis, Myalgia, Pelvic fibrosis, *Central/Peripheral Nervous System* – Emotional lability, Libido increase, Lethargy, Memory disorder, Numbness, Peripheral neuropathy, Personality disorder, Spinal fracture/paralysis, Syncope/blackouts; *Respiratory System* – Cough, Hemoptysis, Pleural rub, Pulmonary fibrosis, Pulmonary infiltrate, Sinus congestion; *Skin and Appendages* – Acne/Seborrhea, Carcinoma of skin/ear, Dermatitis, Dry skin, Ecchymosis, Erythema Multiforme, Hair loss/Growth/Disorders, Itching, Pigmentation, Skin lesions, Skin striae; *Special Senses* - Hearing disorders, Ophthalmologic disorders, Taste disorders; *Urogenital System* – Bladder spasms, Breast tenderness/pain, Cervix disorder, Lactation, Penile swelling, Prostate pain, Testicular pain, Urinary incontinence, Urinary obstruction, Vaginitis/bleeding/discharge; *Miscellaneous* - Swelling (temporal bone).

Laboratory – Hypoproteinemia, Increased creatinine, Increased calcium, Increased uric acid.
*Physiologic effect of decreased testosterone.

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.

The recommended dose of LUPRON DEPOT 22.5 mg to be administered is one injection every three months **(84 days).** Due to different release characteristics, a fractional dose of this 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given. **(THIS PARAGRAPH TO BE PRINTED IN COLOR)**

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every three months as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 23 gauge needle, withdraw 1.5 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, it is preferable that LUPRON DEPOT 22.5 mg be mixed and used immediately. Reshake suspension if settling occurs.

Although the potency of the reconstituted suspension has been shown to be stable for 24 hours, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

As with other drugs administered by injection, the injection site should be varied periodically.

The vial of LUPRON DEPOT 22.5 mg and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT - 3 Month 22.5 mg (NDC 0300-xxxx-xx) is available in a single use kit. Each kit contains a vial of sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT 22.5 mg is administered as a single IM injection **EVERY THREE MONTHS (84 days).**

No refrigeration necessary. Protect from freezing.

Caution: Federal (U.S.A.) law prohibits dispensing without a prescription.

REFERENCE

1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. Fertil Steril 1987 Sept; 48(3):500-502.

U.S. Patent Nos. 4,005,063, 4,652,441, 4,728,721; 4,849,228; 4,917,893; 4,954,298, and 5,330,767.

TAP

Manufactured for TAP Pharmaceuticals Inc.
Deerfield, IL 60015, U.S.A.
by Takeda Chemical Industries, Ltd.
Osaka, Japan 541

KIT CARTON COPY

Single Dose
Administration Kit
NDC 0300-xxxx-xx

Includes:
One Vial Lurpon Depot®
NDC 0300-xxxx-xx
(Leuprolide Acetate 22.5 mg)
One 2.0 mL Ampule Sterile
Diluent NDC 0300-xxxx-xx
One Syringe with 23 Gauge Needle
One 23 Gauge Needle

Caution:
Federal (USA) law prohibits dispensing without prescription
NO REFRIGERATION NECESSARY
PROTECT FROM FREEZING

LUPRON DEPOT®-3 MONTH
22.5 MG

EXP

LOT

Manufactured for
TAP Pharmaceuticals Inc.
Deerfield IN 60015
by Takeda Chemical Industries Ltd.
Osaka, Japan 541

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

57

6/27/95

CHEM PAC - SUBMISSION 10/7/94

VIAL CARTON COPY

FRONT PANEL

SINGLE DOSE VIAL

LUPRON DEPOT® - 3 Month 22.5 mg
leuprolide acetate for depot suspension

Each vial contains:
leuprolide acetate, 22.5 mg;
polylactic acid, 198.6 mg;
D-mannitol, 38.9 mg.

Usual Dose: After mixing with diluent, administer entire contents of vial by intramuscular injection once every 3 months under physician's supervision. See enclosure for full mixing and prescribing information.

BACK PANEL

NDC 0300-xxxx-xx

SINGLE DOSE VIAL

LUPRON DEPOT® - 3 Month 22.5 mg
leuprolide acetate for depot suspension

leuprolide acetate 22.5 mg
For intramuscular injection after mixing
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

SIDE PANEL

Protect from freezing.
See bottom of carton for expiration date and lot number.

Vial label bears coded expiration date and lot number. Do not use after first day of month/year stamped.

SIDE PANEL

Manufactured for **TAP Pharmaceuticals Inc.**
Deerfield, IL 60015
by Takeda Chemical Industries, Ltd
Osaka, Japan 541

VIAL LABEL COPY

FRONT Of VIAL LABEL

NDC 0300-xxxx-xx
SINGLE DOSE VIAL

LUPRON DEPOT® - 3 Month 22.5 mg
leuprolide acetate for depot suspension

SIDE OF VIAL LABEL

leuprolide acetate 22.5 mg

Usual Dose: After mixing with diluent, administer entire contents of vial by intramuscular injection. See enclosure.

SIDE OF VIAL LABEL

Coded expiration date and lot number.

Manufactured for
TAP Pharmaceuticals Inc.
Deerfield, IL 60015
by Takeda Chemical Industries,
Ltd. Osaka, Japan 541

Commodity #xx-xxxx-xx.

PATENT

EXCLUSIVITY

SUMMARY

Lupron Depot®-3 Month

Patent information on any patent that claims the Drug:

U.S. PATENT NO.	EXPIRATION DATE
4,005,063	January, 1996
4,954,298	March 24, 2004
5,330,767	March 24, 2004
4,652,441	March 24, 2004
4,917,893	March 24, 2004
4,728,721	March 1, 2005
4,849,228	July 18, 2006

EXCLUSIVITY SUMMARY FOR NDA # 20-517 SUPPL #_____

Trade Name Lupron Depot®, 22.5 mg Generic Name (leuprolide acetate)

Applicant Name TAP Holdings, Inc. HFD # 510 CSO: Pauls

Approval Date If Known December 22, 1995

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

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

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

YES /X/ NO /__/

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

_____

_____

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

_____

_____

d) Did the applicant request exclusivity?

YES /__/ NO /_X_/

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

_____

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /__/ NO /_X_/

If yes, NDA #_____ Drug Name _____

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

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

YES /__/ NO /_X_/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X_/ NO /__/

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

NDA	Drug	Dosage Form	Strength	Indication
19-010	Lupron	Injection	1.0 mg	Prostate Cancer
19-732	Lupron	Depot	7.5 mg	Prostate Cancer
19-943	Lupron	Depot	3.75 mg	Uterine Fibroids
20-011	Lupron	Depot	3.75 mg	Endometriosis
20-263	Lupron Lupron	Injection Depot-PED	5.0 mg 7.5, 11.25, & 15.0 mg	Central Precocious Puberty

2. Combination product.

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

YES /__/ NO /__/

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

NDA# _____ _____

NDA#_____ _____

NDA#_____ _____

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

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

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

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

YES /_X_/ NO /__/

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

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

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

YES /_X_/ NO /__/

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

_____

_____

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

YES /__/ NO /_X_/

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

YES /__/ NO /__/

If yes, explain: _____

_____

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

YES /__/ NO /_X_/

If yes, explain: _____

_____

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

M91-587 _____

M91-653 _____

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

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

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

Investigation #1	YES /__/	NO /_X_/
Investigation #2	YES /__	NO /_X_/

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

_____ _____

_____ _____

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

Investigation #1 YES /__/ NO /_X_/

Investigation #2 YES /__/ NO /_X_/

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

_____ _____

_____ _____

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

M91-583 _____

M91-683 _____

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

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

Investigation #1

IND #_ YES /_X_/ ! NO /__/ Explain: _____

! _____

Investigation #2

IND # YES /_X_/ | NO /___/ Explain:_____

_____

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

Investigation #1

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

Lana L. Pauls, M.P.H.

Signature

12/15/95
Date

Title: Regulatory Health Project Manager

Solomon Sobel, M.D.

Signature of Office/
Division Director

12/22/95
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

MEDICAL OFFICER

REVIEW

SUPERVISORY MEDICAL OFFICER NDA REVIEW

NDA: 20,517 Lupron 3 month depot 22.5 mg

Sponsor: TAP Pharmaceuticals
Deerfield, IL

DEC 21 1995

Submission date: December 21, 1994

Date of Review: December 21, 1995

Date of MO Draft review: December 7, 1995

This application presents background, protocols, and results from three trials (one pharmacokinetics study in orchietomized subjects and two pivotal safety/efficacy studies in target populations) to support the requested indication of Lupron (leuprolide acetate) three month depot for the palliative treatment of advanced prostate cancer.

The sponsor currently holds approved applications for this indication for both a subcutaneous formulation of leuprolide and a one month depot formulation.

The Division of Pharmaceutical Evaluation II has extensively reviewed the pharmacokinetics study and recommends approval with labeling changes and phase IV suggestions.

The efficacy/safety trials were open, multicenter (18 total) studies. The first was designed to demonstrate gonadal (testosterone) suppression with a target enrollment of 60 subjects. The second trial was intended to confirm gonadal suppression and to demonstrate equivalence between the pilot study drug product versus the final manufacturing supply in 30 subjects.

In both pivotal trials the depot formulation was administered as an intramuscular injection every 12 weeks. The application addresses the initial 24 weeks of treatment, although all subjects were allowed to continue for as long as clinical benefit was apparent with serum testosterone levels determined every 12 weeks. The procedures were similar between the two studies, although the larger study included a subset of subjects with more vigorous blood level data obtained surrounding the second injection.

Of the 92 evaluable patients, one demonstrated continued non-castrate testosterone levels through week 28 and one through week 14. Three subjects experienced a mild elevation of testosterone level immediately following the second injection at week 12 although some of this apparent elevation may be explained by differences found in the assay methods used.

In terms of tumor response and adverse events, these trials demonstrated similar results to those expected from previous agonist trials. New safety concerns were not raised.

RECOMMENDATION:

As per the draft Medical Officer review (dated Dec. 7, 1995), approval is recommended. Labeling changes and phase IV studies as suggested seem appropriate. It appears that the bulk of the labeling changes could be incorporated into a "clinical studies" section. The Phase IV commitment involves a six month comparison of the one month and three month formulations--specifically evaluating testosterone suppression (or stimulation) surrounding the one monthly and three monthly injections.

I have discussed my comments and suggestions for revision of the Dec. 7th draft medical review with the Medical Officer, Dr. Fourcroy.

Rarick MD 12-21-95

Lisa Rarick, MD
Acting Deputy Director II
DMEDP, HFD-510

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Pediatric Page

This is not an NME, therefore, no information is required.

DEC 2 0 1995

DRAFT

MEDICAL OFFICER REVIEW OF LEUPROLIDE ACETATE NDA

Table of Contents

1.1 Medical Officer's Review - LUPRON Depot 3 month - Leuprolide acetate

1.1.1 NDA 20,517

1.1.2 M.O. Review

1.1.3 Submission December 21, 1994

1.1.4 Review completed December 7, 1995

1.2 Drug name

1.2.1 Generic name leuprolide acetate

1.2.2 Proposed trade name LUPRON Depot 3 MONTH 22.5 MG

1.4 Pharmacologic Category:

Synthetic nonapeptide agonist analog of gonadotropin releasing hormone (GnRH).

1.5 **Proposed Indication:**

Palliative treatment of advanced prostate cancer.

1.6 **Dosage form and route of administration:**

Depot suspension - dose 22.5 mg every 12 weeks (once every 84 days).

The 22.5 mg depot formulation is comprised of a single-dose vial containing lyophilized microspheres of leuprolide (22.5 mg) incorporated into a biodegradable polylactic acid polymer, and a 2 mL ampule of diluent. This dosage is based on 7.5 mg per month over three months. Just prior to each injection, the preparation is to be reconstituted by withdrawing 1.5 mL of the diluent from the ampule and injecting it into the vial containing the lyophilized powder. The resulting suspension is to be withdrawn into a syringe and injected intramuscularly with a 22 gauge needle. Injection sites are to be alternated and the previous injection site is to be examined at the time of the next injection.

1.7 NDA Drug Classification - S

1.8 Important Related Drugs

Both leuprolide and goserelin have been approved for 28 day depot treatment. Both gonadotropins have developed 3 month depot formulations. Leuprolide was originally approved for 1 mg sc daily injections.

LUPRON/leuprolide acetate:

7.5 mg Depot approved in 1988.
- M87-097 7.5 mg monthly intrasmuscular injections. 53 patients were evaluable for efficacy with suppression of gonadal function and demonstrated suppression of gonadal function for up to 12 weeks in 15 patients with stage D2 prostatic carcinoma.

see original review of June 24, 1987

Zoladex/goserelin acetate:

The primary efficacy endpoints for the 3.8 mg 28 day depot were mean serum testosterone levels between week 4 and week 12. The secondary endpoints were mean serum testosterone at weeks 4, 8, and 12, to evaluate maintenance of testosterone suppression.

• leuprolide - LUPRON - approved for medical castration for the treatment of advanced prostate cancer. It is available as 1.0 mg daily subcutaneous injection which was approved April, 9, 1985; the a 7.50 mg 28 day depot was approved January 26, 1989. The 3.75 mg depot was approved March 30, 1995 for the treatment of leiomyoma uteri and October 22, 1990 for the treatment of endometriosis. Injection (5.0 mg) and depot-Ped were approved for the treatment of Central Precocious Puberty on April 16, 1993. TAP currently has a pending NDA (20-517) for the 22.5 mg 3 month depot for the treatment of advanced prostate cancer.

• goserelin - Zoladex - approved for the treatment of advanced prostate cancer using the 3.6 mg monthly implant on December 29, 1989. The 3.6 mg monthly implant was approved February 2, 1993 for the treatment of endometriosis.

• nafarelin - Syntex/Searle NDA 20-109 - Precocious Puberty/Endometriosis

• histrelin - Supprelin - Marketed by Roberts - Precocious Puberty

1.9 Related Reviews see biopharm and pharmacology

2 Table of Contents see first page.

3 Material Reviewed

Electronic submission
Volumes 2.1, 2.5 (91-583), 2.8 (93-653)

4 Chemistry/Manufacturing Controls
see Chemistry review

5 Animal Pharmacology/Toxicology
see Pharmacology review

6 **Clinical Background**

Leuprolide is marketed currently for the following approved indications:

19-732 - Lupron daily subcutaneous injection for palliative treatment of prostate cancer;
20-011 - Lupron Depot 7.5 mg - palliative treatment prostate cancer U.S., Canada
20-263 - Lupron Depot 3.75 mg - endometriosis - U.S., Canada - October 1990 marketed

Lupron Depot-Ped 7.5 mg, 11.25 mg, and 15 mg - Central Precocious Puberty U.D. April 1993 marketed.

Lupron (leuprolide acetate) Injection, administered daily by subcutaneous injection, was released for marketing in April, 1985 for the palliative treatment of advanced prostatic cancer. Subsequently, Lupron depot (leuprolide acetate for depot suspension) was developed, designed to provide continuous release of leuprolide over a four-week period when administered as a monthly intramuscular injection. Lupron Depot (containing 7.5 mg of leuprolide acetate) was released for marketing on January 26, 1989 for the palliative treatment of advanced prostatic cancer. Lupron Depot 3.75 mg (leuprolide acetate for depot suspension) was released for marketing on October 22, 1990 for the management of endometriosis. In addition, Lupron Depot-PED 7.5 mg 11.25 mg, and 15 mg, as well as LUPRON Injection (for pediatric use), were released for marketing on April 16, 1993 for the treatment of central precocious puberty.

The incidence of cancer of the prostate has reached an estimated rate of 22% of all malignancies in men (1991).By the age of 50 up to 30% of men are found to have cancer of the prostate. The incidence for white males is estimated to be 88/100,000 white men and 132/100,000 for black men. The mortality rate in the black population is almost double that for white males. In the year 1992 there were 34,999 deaths from prostate cancer and 46,300 deaths for Breast cancer (American Cancer Society). Although geographic differences in prostate cancer are known to exist no clear cause for this difference is known. The incidence of prostate cancer is much higher in black men irrespective of the locality. Androgens and age are the only important risk factors. Family of origin, e.g. father, brother or cousin with prostate cancer, are also strong risk factors. This is why guidelines for prostate cancer screening suggest a Digital Rectal Exam (DRE) and Prostate Specific Antigen (PSA) starting at the age of 50 for white males, 45 for black men and those with a positive family history for cancer. Familial prostate cancer may account for 9% of prostate cancer with an earlier age of onset of disease, and multiple affected family members (Carter, 1992)

Treatment of prostate cancer:

Metastatic PCA must still be considered to be incurable. The purpose of treatment is to improve quality of life, time to progression and perhaps survival. 70% of men with metastatic diseases treated with androgen deprivation will experience a symptomatic and often a clinical regression with androgen deprivation - but most will relapse within 18 to 24 months. Median life The quality of life is the most important endpoint in treatment of prostate cancer; this is rarely evaluated

appropriately. In 1984 Leuprolide was first approved for medical castration but orchiectomy has remained the gold standard and the most economical approach. Labrie and the European community were the first proponents of blockade of the adrenal androgens; this concept was the basis of the NCI 0036 studies comparing leuprolide with flutamide (the first nonsteroidal antiandrogen) to leuprolide with placebo. This combination therapy for total androgen blockade was approved in 1988. There is a continuing dialogue regarding the adrenal androgen contribution, the necessity of total androgen blockade and it's possible advantages and resulted in an international meta-analysis pooling comparable studies. The 1992 preliminary results of this meta-analysis included 5,353 patients from randomized studies that had at least one arm using total androgen blockade. At 5 years there was an overall reduction of 3 percent. It is still not clear that total androgen blockade provides survival benefit; however, it does appear to offer benefits of time to treatment failure or progression time.

In the United States there are only two gonadotropins approved for the treatment of advanced prostate cancer with medical castration: leuprolide (LUPRON - TAP) and goserelin (Zoladex - Zeneca-19-726). Leuprolide (Lupron - 19-732), with a substitution at the 6th position of GnRH, is thought to be 20 times as potent as the natural molecule

Androgen withdrawal and sequelae:

Androgen withdrawal and subsequent cellular apoptosis ultimately results in the relative enrichment of tumors with cells that are more undifferentiated and less responsive to hormonal therapy. Testosterone serum levels have been the gold standard of monitoring castration. Approximately 5 - 7% of the circulating androgens are of adrenal source. If one assumes that castration removes all androgens to the prepubertal status a level of 20 ng/dL (Tanner 1-2) should be attained. If one considers the contribution of the adult adrenal it is reasonable to consider a circulating testosterone level up to 40 ng/dL reflecting the possible metabolism of dehydroepiandrosterone (DHEA) to Testosterone and Dihydrotestosterone. Levels of testosterone greater than this range should be considered inadequate.

Testosterone in normal men

Testosterone is primarily produced by the Leydig cells in the testis and the daily production of testosterone is about 4 to 8 ng daily. 95% of the testosterone is secreted by the Leydig cells in the testis, 5 - 7% of the androgens which are metabolized to testosterone are

secreted by the adrenal gland as dehydroepiandrosterone (DHEA and DHEAs).

Testosterone levels peak in the morning, decreasing during the day (Bremner et al 1983; Nieschlag 1974). The peak and nadir levels differ by approximately 30%. This diurnal rhythm noted early in puberty may be lost with age Supporters of transdermal delivery of testosterone believe that this better approximates the diurnal rhythm in men. There also appears to be significant progressive decreases in total serum testosterone with age (Blackman et al 1988). In the older male this gradual decrease in androgens may be associated with loss of muscle mass and strength, bone density loss and decreased virility. There may be cultural differences in androgen levels, metabolism and the androgen receptors.

Early measurements of testosterone measured urinary ketosteroids. These measurements therefore also included the adrenal components. As much as 70 percent of the androgens originated from precursors secreted by the adrenal cortex (Paulson, 1962). Assay methods have increased in sensitivity in the last 3 decades with radioimmunoassays. Castrate levels - measured in prostate cancer patients post-orchiectomy - have traditionally been considered to be less than 50 ng/dL while early pubertal boys are less than 100 ng/dL. It is probably more accurate to term castrate levels as less than 30 ng/dL and have been reported with medical castration as low as 15 ng/dL.

Conversion Factors - International units v. ng/dl

Hormone	normal parameters	Conversion factors and number
FSH		1 ng = 3 mIU
LH	0 - 18 IU/L	1 ng = 7//8 mIU
Testosterone	m. 300-1000 ng/dL f. 20 - 80 ng/dL	0.0347 m.10.4 - 34.7 nmol/L f. 0.68 - 2.78 nmol/L
Testosterone - free	M. 5.1 - 41. 0 ng/dL	0.0347 0.18 - 1.42 nmol/L
Dihydrotestosterone	M. 30 - 85 ng/dL	0.0344 1.0 - 2.9 nmol/L

source - Becker 1990

Conversion of units of testosterone

Testosterone	50 ng/dL	1.735 nmol/L
	40 ng/dL	1.388 nmol/L
	30 ng/dL	1.041 nmol/L

6.3 Foreign experience

The 22.5 mg has not been marketed anywhere to date.

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

The sponsor states that in pharmacokinetic Study M91-582 plasma leuprolide levels were measured for 20 weeks in patients with prostate cancer following a single intramuscular injection of 22.5 mg depot formulation. At 4 hours post-dosing a mean plasma leuprolide concentration of 48.87 ng/mL was demonstrated and maintained steadily until it reached steady state level during week 3 and maintained for the duration of the 12 week dosing interval with a range of means 46 +/- 0.81 ng/mL. The plasma levels declined very gradually following another 2.5 weeks reaching a minimally detectable level of 0.23 ng/mL by week 20. See Pharmacokinetic review.

6.6 Directions for Use - Sterile lyophilized microspheres mixed with diluent suspension as an intramuscular injection every 12 weeks.

7 Description of Clinical Data Sources

7.1 Study Type and Design

Human pharmnacokinetic study (Protocol M91-582) was conducted in prostate cancer patients to measure plasma leuprolide levels as noted above. Study M91-583 was originally designed as the pivotal study to demonstrate the safety and effectiveness of the 22.5 mg formulation with a target enrollment of 60 men with advanced prostate cancer and a final enrollment of 61. Study M91-653 was designed to demonstrate equivalence between the two supplies of the depot and had a final target enrollment of 30 patients.

7.2 Post-Marketing Experience - none

8 **Clinical Studies**

The sponsor has submitted two pivotal trials submitted M91-583 and M 91-653. The extended-release depot formulation of leuprolide acetate has been developed, containing 22.5 mg of leuprolide, was administered as an intramuscular injection every three months or 84 days. The two clinical studies included in this overview were

conducted to evaluate the effectiveness and safety of this formulation.

Study M91-583 was designed as the pivotal study to demonstrate the safety and effectiveness of the 22.5 mg formulation, with a target enrollment of 60 patients. The supply of study drug used for this study was produced in a pilot plant, which manufactures supplies in limited quantities for investigational purposes. A smaller study was needed to demonstrate equivalence in effectiveness and safety between the two supplies of the 22.5 mg formulation. Study M91-653 was designed to demonstrate equivalence between the two supplies, with an original target enrollment of 15 patients.

There were initial problems in producing and maintaining testosterone suppression in a few patients in M91-583 resulted, following discussions with the FDA, in the target number of patients in study M91-653 being increased to 60. This difficulty was a result of a difference in the column versus extract procedures being used by Following identification of a reason for some of the unfavorable results in M91-583, and after further discussions with the FDA, the target enrollment for M91-653 was reduced to 30 patients.

The 22.5 mg depot formulation was administered in both studies as an intramuscular injection every 12 weeks. The primary efficacy outcome criterion in both studies was suppression of serum testosterone levels to the castrate range (50 ng/dL or less), and maintenance of it at that level, in patients with metastatic (Stage D^2) prostate cancer. The clinical response to treatment, as well as the general safety of the formulation, were also evaluated. Both studies had essentially the same design, with monitoring of serum testosterone levels biweekly or weekly for 24 weeks, and clinical evaluations every twelve weeks. Patients were to continue in the studies for as long as clinical benefit was apparent to the investigator, with serum testosterone determined every 12 weeks. The studies are described in greater detail in the next section. This NDA submission involves data from the initial 24 weeks of treatment for each study. This has been adapted from the sponsor's summary.

Design of Studies and Description of Procedures

The two studies summarized in this overview are both open, multicenter studies conducted at a total of 18 investigative centers. Two of the 18 centers were involved in both studies. The studies were nearly identical in design except that M91-583 included an expanded blood collection schedule (at half-week

intervals during the last two weeks of the first two dosing intervals and following the Week 12 depot injection), for a subset of patients for measurement of serum LH and testosterone, and also, routine clinical laboratory tests were performed during treatment in M91-583 but not in M91-653. Patients received an intramuscular injection of the 22.5 mg depot formulation every 12 weeks.

Patient eligibility and baseline conditions were determined by the following procedures which were performed within four weeks of the initial dose: medical and surgical (including prostate cancer) histories, physical examination, digital rectal examination, ECOG performance status, bone scan (and other imaging procedures if necessary to establish the presence of peripheral metastatic disease), blood collection for serum PSA, LH, testosterone, hematology and chemistries (including alkaline phosphatase and prostatic acid phosphatase), and urinalysis. Blood was also obtained just prior to the initial depot injection for determination of baseline LH and testosterone levels. Once eligibility had been determined, the investigator obtained a patient number assignment from TAP. Blood collection for measurement of serum LH and testosterone levels was performed four and seven days following the initial depot injection and at the end of Weeks 2 through 24, and every 12 weeks thereafter. As mentioned above, additional blood collections were performed for a subset of patients in M91-583, at half-week intervals (at least 72 hours apart) during Weeks 10, 11, 12, 22, and 23, to further characterize the hormonal response to treatment at the end of the first two dosing intervals and several days after the second depot injection (at Week 12). Blood was also to be drawn in all patients at 4, 8, and 12 hours following the Week 12 depot injection to assess if an acute-on-chronic effect due to incomplete pituitary down-regulation was present. Physical examination, digital rectal examination, ECOG performance status, and bone scan (and other imaging procedures if evaluable organ metastases were present at pretreatment) were repeated every twelve weeks to assess the clinical response to treatment. Routine laboratory tests (including alkaline phosphatase and prostatic acid phosphatase) and PSA were also repeated every 12 weeks in M91-583. Routine laboratory tests were performed only at pretreatment in M91-653, and only alkaline phosphatase, prostatic acid phosphatase, and PSA, were performed during treatment. An overall objective response evaluation was also performed at 12-week intervals in both studies.

Serum LH, testosterone, and PSA measurements were performed by

The routine hematology, chemistry (including alkaline phosphatase and prostatic acid phosphatase), and urinalysis tests for M91-583 were performed by

whereas in M91-653 they were performed by the investigator is local laboratory.

Per Amendment No. 1 (M91-583) and No. 3 (M91-653), all procedures except LH, testosterone, PSA, prostatic acid phosphatase, and alkaline phosphatase measurements were deleted from the long-term (beyond Week 24) phase of the protocols. At the time of the amendment many of the patients in M91-583 (and a smaller number of patients in M91-653) still active in the study were well into the long-term phase.

LH and Testosterone Assay Methodology

Blood samples collected for LH and testosterone measurements were centrifuged to obtain the serum and sent to , for assay. Assay methodology for each test consisted of standard RIA methodology. The LH assay is a sequential addition, double-antibody RIA. This method is not specific for bioactive LH, and yields higher results than would be obtained by bioassay. For testosterone in the normal adult male range uses a single-step purification method consisting of simple extraction of testosterone prior to the actual quantitation by RIA (extract method). When testosterone is expected to be at or near castrate levels, a two-step purification method is utilized in which the extracted sample is further purified with column chromatography prior to RIA (column method). This method has greater specificity, and also has higher precision when testosterone levels are in the castrate range, as they are expected to be with leuprolide treatment. The lower limit of sensitivity for the column method is 3 ng/dL compared to 10 ng/dL for the extract method.

also performed LH and testosterone measurements in all of the previous TAP NDA protocols involving the use of the daily subcutaneous injection and the monthly 7.5 mg depot formulations in advanced-stage prostate cancer. Testosterone results for these studies were appropriately generated by the two-step purification method (column method) referred to above. An error in communication between TAP and prior to the initiation of study M91-583 resulted in all serum testosterone levels for the first 24 weeks of treatment for patients in that study and a variable portion of the testosterone values for the first 14 patients enrolled in study M91-653 being measured by the extract method.

Based on the consistently higher than expected (but mostly still in the castrate range) values obtained in both studies, an investigation was conducted to determine the reason for these higher testosterone levels. This included examination of historical and current testosterone values from patients still active in the previous studies and reassay of many samples by the column method by both
to explain and validate the discrepancy in results generated by the two methodologies.

Results of the investigation led to the realization that a different assay had been used in these studies than had been used in previous protocols and that this factor did substantially contribute to the higher values seen in the current studies. Once this was determined, and at TAP's direction, the assay methodology was switched to the column method on August 1, 1993. The samples (all but 4%) that had been assayed with the extract method in M91-653 prior to the method conversion were reassayed by
using the column method.

Patient Selection

All eligible patients had to have histologically-confirmed prostatic adenocarcinoma in Stage D2, i.e., skeletal metastases, nodal metastases above the aortic bifurcation, or metastases to other extra-pelvic sites, such as liver or lung. Patients had to have two or more clinically evaluable lesions (including prostate if present) and be in performance status grades 0, 1, or 2.

Primary endpoint

The primary objective of this study was to demonstrate **suppression of serum testosterone** during the first 24 weeks of treatment or two 2 depot injections.

The serum testosterone determinations were performed by two assay methods (extract and column methods) as discussed above. Since there was a difference in the results obtained by these two methods the results from the two methods will be addressed separately for calculation of mean and median levels and the acute-on-chronic analysis, or combined for calculations of proportions of suppressed patients and patients experiencing escapes from suppression (where the analyses were based on the maximum value regardless of method for each categorized visit). Only data provided by were used in the analyses.

The proportions of patients who achieved testosterone suppression (50 ng/dL for two consecutive tests within eight weeks after the first depot injection) and the

proportion of suppressed patients who experienced escapes (testosterone levels >50 ng/dL for two consecutive tests after suppression had been achieved) were estimated, and one-sided exact 95% confidence bounds were obtained using the exact binomial distribution. Prior to applying these definitions, on days when results from multiple measurements existed, values were reduced to the maximum for the day. This applied to days on which 1) there were both extract and column data, 2)multiple values from reassay using the same assay method existed, or 3) serial data from acute-on-chronic measurements existed. The median time of onset of suppression was estimated using Kaplan-Meier curves. Duration of suppression continued beyond 24 weeks for most patients, so median duration was not estimated.

Summary statistics were provided for testosterone and LH values at each categorized visit without respect to the time of injections. Additional summaries were provided for patients who had samples obtained at 4, 8 and 12 hours following the injections at Week 12 and those that participated in the expanded blood collection schedule. For patients who had data at 10, 10.5, 11, 11.5, and 12 weeks after each injection, repeated measure analysis of variance was used to test for trends across time. Mean testosterone at 12 and 12.5 weeks were analyzed using paired T-tests, as were changes from 0 hour to 4, 8, and 12 hours post-dosing (acute-on-chronic analysis)

The numbers and percentages of patients with graded outcomes are presented for the Week 12 and Week 24 evaluations and for the final visit evaluations for objective tumor response, changes in prostatic involvement, percent changes in PSA and PAP, and changes in performance status.

Ninety-four patients were enrolled and treated across the two studies by 18 investigators. A list of investigators who enrolled patients into each study along with their institutional affiliations and locations and the number of patients enrolled at each center is included in the appendix.

8.1 Trial # **M91-583**

Study	Investigators	Enrolled	Evaluable	continuing
M91-583	13	61	60	51

This study was designed as the pivotal study to demonstrate the safety and effectiveness of the 22.5 mg formulation, with a target enrollment of 60 patients. There were 59 total evaluable patients.

8.1.1 Objective

To demonstrate the safety and effectiveness of the 22.5 mg formulation of leuprolide acetate for the effective castration of the gonadal steroid, testosterone, for the treatment of advanced prostate cancer.

8.1.2 Design

An open, multicenter study. Patients received an intramuscular injection of the 22.5 mg depot formulation every 12 weeks or 84 days. Blood collection schedule included half-week intervals during the last two weeks of the first two dosing intervals and following the week 12 depot injection for a subset of patients.

8.1.3 Protocol

Eligibility of patients included prostate cancer history, Eligible patients had to have histologically-confirmed prostatic adenocarcinoma in Stage D2 with clinically evaluable lesions. Evaluation included physical examination, digital rectal examination, ECOG performance status, bone scan, serum Prostate Specific Antigen (PSA), LH, testosterone, hematology, chemistries and urinalysis. Patient number assignment was received from TAP

Blood collection for LH and Testosterone was performed 4 and 7 days following the initial depot injection, at the end of week 2 through 24, and every 12 weeks thereafter. An overall objective response evaluation was also performed at 12-week intervals.

8.1.3.1 Population, procedures

In both pivotal studies there was an even distribution of age and race. The ages at entry into the study was between 53 and 86 years with a mean of 70.3 years. 67% of the patients were Caucasian, 30% black and 2% Hispanic. Patients in 583 included: 43 Caucasian, 17 Black and 1 Hispanic patient. Approximately 52% of the patients had been diagnosed less than 3 months prior to initiation of treatment 59% of the 92 evaluable patients had no prior treatment for prostate cancer at the time of treatment.

8.1.3.2 Endpoints

Hormonal Responses - **testosterone** and LH suppression.

Objective tumor response - complete, partial or no response.
PSA and PAP

8.1.4 Results

8.1.4.1 Patient Disposition, comparability
Baseline characteristics of patients were comparable.

8.1.4.2 Efficacy endpoint outcomes

- Castration response as measured by testosterone (50 ng/dL)

Peak testosterone levels increased at with the initial agonist effect. Continued treatment resulted in castration levels

M91-583	Pre-Rx	Day 4	Wk 4	wk 8	wk 12
N =	59	57	57	53	46
Mean ng/dL-X	405.2	576.5	26.4	29.7	35.6

Testosterone ≤50 ng/dL was defined as castrate levels. all measurements by above 'extract' assay method. Lower limits of sensitivity differed between the two methods.

2 patients did not achieve castrate levels until weeks 15 and 28, respectively. The first patient, 2016 can be considered suppressed adequately if the extract values of testosterone are used.

2016 - week 8 - through week 13 - normal if extract used.

The second patient clearly was inadequately suppressed and there is no explanation. Abnormal levels of testosterone were demonstrated through week 28. His testosterone fell to 64 ng/dL by week 4 but rose sharply by Week 5, and ranged between 187 to 633 ng/dL through Week 13. By Week 22 it rose to 167 ng/dL and remained outside the castrate range until it fell to 49 ng/dL at Week 28. Since it remained below 50 ng/dL at Week 29 it was considered suppressed at that point. His clinical status remained stable throughout the entire period and patient remains in the study. His PSA was 2.7 at baseline and 2.4 at week 48 and is now becoming elevated.

2032 - week 12 - through week 13

Response to Acute on chronic testing:

The sponsor of this study was asked to identify any possible stimulation of the hypothalamic-pituitary-gonadal axis with the 3-month depot. The protocol included an expanded blood collection schedule around the period of the second depot. Patients were included that were compliant and were represented from many centers.

M91-583	PRE	4 HOURS	8 HOURS	12 HOURS
N=	42	42	36	19
Mean T	30.6	27.4	31.5	37.0
extract assay				

M91-583	PRE	4 HOURS	8 HOURS	12 HOURS
N=	39	39	35	19
LH	4.3	4.7	4.5	4.6

3 patients had important escapes from castrate levels at time of reinjection. This indicated some mild gonadotropin reserve in these patients. (Acute on chronic responses)

2019 - had an escape following the Week 12 injection while preinjection was within the castrate range. However, reevaluation of the testosterone level with extract essay was less than 50 ng/dL

Pt 2003	wk 11	Wk 12(0)	4 HOURS	8 HOURS	12 HOURS	Wk 12.5
T	78 (55)	93(55)	NA	NA	NA	154 (169)
PSA		3.9	-	-	-	-
Leuprolide	NA	NA	NA	NA	NA	NA

Pt 2037	Wk 11	Wk 12 (0)	4 hours	8 hours	12 hours	Wk 13
T	NA	66(52)	74(62)	116(81)	NA	61(53)
PSA	18	-	-	-	-	-

5 other patients had isolated escapes which were acceptable.

2002 - week 9 - 292 - otherwise all normal castrate levels
2017 - week 16 - 52
2021 - week 11 - nl on extract not column
2034 - normal on extract not column
2046 - normal on extract no column

Luteinizing hormone (LH) appeared to be suppressed.

LH

M91-583	Pre	Day 4	Wk 4	wk 8	wk 12
N	56	57	57	52	44
Mean - X	10.5	17.4	5.4	4.3	5.3

Tumor response appeared to be adequate. Over half of the patients had either partial response or stabilization of disease.

Tumor response:

M91-583	CR	PR	Stable	Prog	Total
Week 12	0(0%)	18(33%)	26(48%)	10 (19%)	54
Week 24	0(0%)	23(43%)	20(37%)	11(20%)	54
Best Response	0 (0%)	28(48%)	21(36%)	9(16%)	58

8.1.4.3 Safety comparisons

The major safety issues are also efficacy issues and relate to the possible lack of complete suppression by the gonadotropin agonist. Other safety issues are primarily the result of castration.

10 patients discontinued the study for the following reasons: 1 adverse event, 5 for worsening of disease/symptoms, 2 from death from prostate cancer, 1 from death of myocardial infarction not from prostate cancer. and 1 for non-compliance with visit schedule.

8.1.5 Reviewer's Comments

Although 96.1% of the patients were fully suppressed during the 12 week interval of the first depot there are some problems. Two patients had delayed suppression and one patient in particularly appeared to demonstrate appropriate levels of plasma gonadotropin without evidence of testosterone suppression.

3 other patients demonstrated gonadotropin (LH and T) reserve on restimulation; there was a mild agonist effect at the time of reinjection of second depot. The other five escapes were either an error or error of method and were acceptable.

The safety features of the 3 month depot are quite acceptable.

8.2 Trial # **M91-653**

Study	Investigators	Enrolled	Evaluable	continuing
M91-653	7	33	32	27

8.2.1 Objective

To demonstrate the safety and effectiveness of the 22.5 mg formulation of leuprolide acetate for the effective castration of the gonadal steroid - testosterone for the treatment of advanced prostate cancer.

8.2.2 Design

The design of the two studies was almost identical except for increased blood collection in the previous study. Both studies were open, multicenter studies. Patients received an intramuscular injection of the 22.5 mg depot formulation every 12 weeks. Blood collection schedule included half-week intervals during the last two weeks of the first two dosing intervals and following the week 12 depot injection for a subset of patients.

8.2.3 Protocol

The two protocols were identical except for increased evaluation of patients in protocol M91-583 at time of reinjection.

Eligibility of patients included prostate cancer history, physical examination, digital rectal examination, ECOG performance status, bone scan, serum PSA, LH, testosterone, hematology, chemistries and urinalysis. Patient number assignment was received from TAP

Blood collection for LH and Testosterone was performed 4 and 7 days following the initial depot injection, at the end of week 2 through 24, and every 12 weeks thereafter. An overall objective response evaluation was also performed at 12-week intervals. The column method was used primarily in this protocol of it's greater specificity at castrate levels.

8.2.3.1 Population, procedures

Histologically-confirmed prostatic adencocarcinoma in Stage D2 with skeletal metastases, nodal metastases or other extra-pelvic sites. Patients had to have two or more clinically evaluable lesions and be in ECOG performance status grades 0,1, or 2.

8.2.3.2 Endpoints - the same endpoints of testosterone, LH and tumor respouse were used in this protocol.

8.2.4 Results

8.2.4.1 Patient Disposition, comparability

The disposition and comparability of the patients was the same ie studies. The mean age was 69.3 with a range of 55 - 82. The mean time from diagnosis of prostate cancer to enrollment was 1.2 years.

8.2.4.2 Efficacy endpoint outcomes

All patients demonstrated testosterone suppression by week 8 without escape. Levels of testosterone suppression also appeared to be lower.

Serum testosterone (ng/dL)

M91-653	Pre	Day 4	Wk 4	wk 8	wk 12
N =	30	28	29	32	30
Mean	443.7	739.3	11.2	7.6	10.5

Testosterone ≥50 ng/dL defined as castrate levels.

LH (MIU/ML)

M91-653	Pre	Day 4	Wk 4	wk 8	wk 12
N	31	28	29	32	30
Mean	9.8	16.5	5.3	5.0	5.3

M91-653	PRE	4 hours	8 hours	12 hours	
Testosterone					
N	18	14	16	13	
Mean	9.4	8.2	9.4	6.7	
LH					
N	18	14	16	13	
Mean	5.1	5.4	5.3	5.1	

(Volume 2.8)

Tumor response evaluation

M91-653	CR	PR	Stable	Prog	Total
Wk 12	0(0%)	5(16%)	21(68%)	5(16%)	31
Wk 24	1(3%)	2(7%)	20(69%)	6(21%)	29
Best response	1(3%)	5(16%)	(68%)	4(13%)	31

There appeared to be a better tumor response in study 583 but the number of patients between the two studies is too small to make any conclusions.

8.2.4.3 Safety comparisons

There were no major safety problems that were not related to disease or related to gonadal steroid suppression. Importantly there were no delays in suppression or escape from suppression.

Patients who withdrew from study:

5 patients discontinued from the study for the following reasons: 1 adverse event, 3 worsening of disease and/or

symptoms, 1 death heart failure and 1 from uncertainty regarding protocol and continuation.

8.2.5 Reviewer's Comments

In this study there was no evidence of any escape or lack of complete testosterone suppression. Al patients suppressed appropriately at excellent castration levels of testosterone.

8.3 Trial # **M91-582**

This was not a pivotal trial but was conducted in prostate cancer patients to measure plasma leuprolide levels for 20 weeks following a single intramuscular injection of the 22.5 mg depot formulation in order to determine the pharmacokinetic profile, and to assess the safety of the formulation.

This study was an open, single-dose pharmacokinetic study in 23 orchiectomized prostate cancer patients. The depot formulation was supplied as a single-dose vial containing lyophilized powder with leuprolide incorporated into a biodegradable polylactic acid polymer, accompanied by a 2 mL ampule of diluent. Following the intramuscular injection, plasma leuprolide levels were determined four hours post-injection, and then on Days 1, 2, 4, twice weekly (at least three days apart) during Weeks 1 through 16, and then weekly during Weeks 17 through 20. Plasma leuprolide levels were determined using radioimmunoassay. A physical examination as well as specimen collection for routine hematology, chemistries, and urinalysis were performed prestudy, and repeated at Weeks 12 and 20. Twenty-three patients were enrolled across three investigative centers. Six patients prematurely terminated from the study. Five of these patients did not supply sufficient data to be included in the pharmacokinetic analysis, and, therefore, the analysis was based on data from 18 patients.

Following the intramuscular administration of the 22.5 mg dose, there was an initial burst of leuprolide in the plasma which is characteristic of this type of depot formulation. This was observed at four hours post-dosing, at which time a mean plasma leuprolide concentration of 48.87 ng/mL was achieved. The mean concentration then declined steadily until it reached a steady-state level during Week 3 that was maintained for the duration of the intended 12-week dosing interval (range of means 0.46 to 0.81 ng/mL), indicating a steady release of drug from the depot during this time. Detectable levels of leuprolide were present in all patients at all measurement points during this period. After Week 12 the mean concentration changed little for

another 2.5 weeks, after which it declined very gradually, reaching a minimally detectable concentration by Week 20 (mean = 0.23 ng/mL).

Adverse events generally reflected the prostate cancer, with generalized pain having been the most frequently-reported event. Only two patients experienced injection site reactions (pain), and these were both mild and of short duration (three days).

The similarity in the pattern of release of leuprolide during the 12 weeks following dosing with the 22.5 mg formulation with the pattern during the four weeks following dosing with the monthly 7.5 mg formulation, and the maintenance of therapeutic leuprolide plasma levels throughout the intended 12-week dosing interval, indicate that the 22.5 mg formulation is suitable for administration as a three month-depot. Safety data indicated that the formulation was well-tolerated and were consistent with the known safety profile of leuprolide. This has been adapted from the sponsor's summary.

9 Overview of Efficacy -

The aim of these two studies was to demonstrate that serum testosterone was effectively suppressed in a range similar to that observed with surgical castration and the previous leuprolide monthly studies. In addition to testosterone suppression by medical castration, the sponsor also included clinical response to androgen deprivation e.g. complete or partial response of androgen dependent tumor to medical castration. The numbers are very small on which to base any conclusions but response appeared to be as expected. (In the 7.5 mg depot studies the no progression rate was 81%.)

Patients enrolled in the two studies.

	M91-583	M91-653
N=enrolled Evaluable Continuing - 3rd depot	61 60 51	33 32 27
Start date	11/8/91	
Premature termination	10	6
Investigators	13	7
Total 2 studies N=94 18 investigators		

Tumor response:

M91-583	CR	PR	Stable	Prog	Total
Week 12	0(0%)	18(33%)	26(48%)	10 (19%)	54
Wee' 24	0(0%)	23(43%)	20(37%)	11(20%)	54
Best Response	0(0%)	28(48%)	21(36%)	9(16%)	58

M91-653	CR	PR	Stable	Prog	Total
Wk 12	0(0%)	5(16%)	21(68%)	5(16%)	31
Wk 24	1(3%)	2(7%)	20(69%)	6(21%)	29
Best response	1(3%)	5(16%)	(68%)	4(13%)	31

Testosterone endpoint

Rapid suppression of testosterone by gonadotropin suppression is very important. Castration levels of testosterone need to be maintained without escape. Gonadotropin secretion should remain completely suppressed; the reinjection of the next depot should not have a stimulatory effect on the pool of gonadotropins and produce an agonist effect or an "acute on chronic effect". The first trial demonstrated that there are patients who have an acute on chronic effect from the reinjection of the depot. Three patients were identified with a mild agonist response at the time of the repeat depot. One of these can be excluded if the "extract assay" is used. This would suggest that approximately 3 out of 100 men have sufficient gonadotroph reserves to increase the testosterone. These men will clearly benefit from the addition of an antiandrogen to block androgen activity.

One patient was not suppressed until week 28 although supposedly had subjective response to medical castration. (pt 2032) and a second patient had an escape between suppression and second depot. In one of the patients level of plasma gonadotropin were identified. There is no rationale for this type of escape and these patients should be managed in other ways, e.g. surgical castration.

Isolated events of T elevation were noted in 5 other patients; 3 were normal on extract assay, 1 was within a normal range and 1 was an isolated event that could have been a laboratory error.(see table). These were all acceptable.

In M91-583 96.6% of the patients were suppressed through week 12 of 60 evaluable patients. In study M91-653 all 100% of the patients were suppressed at 12 weeks. <u>There was no evidence of lack of suppression in M91-653.</u> The median time to onset of castrate levels in all three studies was 22 days with a range of 13 to 169 days for the two pivotal trials. (In the goserelin study of a comparable 3 month depot suppression was maintained in 94.3% of the 35 evaluable patients on the 3 month depot and 91.4%

in 32 of the 35 evaluable patients on the 1 month depot in the first 12 weeks study 0001)

Nonsuppressed patients at some point during study:

Study N91-583

Pt #	type	date reached Castrate	T level	Investigator
	FAILED PATIENTS - DELAYED SUPPRESSION			
2016*	week 4 - 46 ng rise week 5 - 14 elevated on extract; acceptable on column assay	week 14		Patterson
2032*	64 ng week 4 -elevated until	week 28	187-633	Sharafi
	MILD ELEVATION AT TIME OF REINJECTION OF DEPOT			
2003	escape week 8-11 12,12.5 and 13	week 3	>50	Sharafi
2019	acute on chronic	week 4	**nl on extract**	Brawer
2037	61-116 ng/dL during week 12 serial measurements	week 3	52-81 escape end of depot	Kabalin
	ISOLATED EVENTS - ALL OTHER NORMAL			
2002	isolated event	week 3	292 at wk9	Stephenson
2017	acceptable	week 2	52 wk 16	Crawford
2021	acceptable	week 4	nl on extract	Dreicer
2034	acceptable	week 3	nl on extract	Patterson
2046	acceptable	week 5	nl on extract	Sharafi

Summary of the non-suppressed patients:

2016: The testosterone initiallly fell to 46 ng/dL by Week 4 but then began to rise and was within the 50 - 86 ng/dL range from week 5 through week 14 after which it fell to within the castrate range with the exception of 67 ng/dL at week 18. Patient experienced a partial response at Weeks 12 and 24 with PSA at 0.7 at Week 24.

2032. Testosterone fell to 64 ng/dL by week 4 and then rose sharply by week 5 ranging between 187 and 633 ng/dL through Week 13. Following the second injection at Week 12, it fell sharply to 91 ng/dL by week 13 and then declined to slightly above the castrate range (48-69 ng/dL through Week 21. By week 22 it rose to 167 ng/dL and remained outside the castrate range until it fell to 49 ng/dL at week 28. It remained at castrate levels after than. Patient is still receiving depot.

The following patients were excluded from efficacy analysis

- pt M91-583 - no pretreatment testosterone
- pt M 91-653 discontinued day 6 insufficient data.
- 16 pts terminated from study prematurely - most common worsening or death from prostate cancer.

59% of 92 evaluable patients had no prior treatment.

10 Overview of Safety

The agonist effect of a gonadotropin agonist rather than the down-regulation of the gonadotropins remains an important safety issue in the treatment of advanced prostate cancer. Presumably testosterone elevation could result in excaberation of the disease. Three out of 42 patients tested demonstrated some stimulatory effect (583) with reinjection of the second depot. This was discussed with the sponsor and will be followed as a Phase IV commitment.

The following patients had an important adverse event:

Graham - 2030 week 42 severe phlebitis
Stein - 2036 week 49 due to foot hypothesis possibly related to spinal cord compression.

97% of the patients in the combined studied received concomitant medications during the initial 24 week treatment. 8 patients were on flutamide following the 2nd depot.

Safety Uptdate of April 24, 1995.

The safety update was satisfactory and there were no changes from the original submission.

11 **Labeling Review**

The sponsor will be submitting changes and additions to the label as it now stands. To be included in the label will be a better description of the possible agonist effect with depot re-injection, differences in testosterone assays and the possible escapes from suppression. The sponsor will include specific data from the acute on chronic study, leuprolide plasma levels during the 3 month depot and identification of non-suppressed patient. The label should include some statement regarding the importance of monitoring patient for complete androgen suppression and consideration of other methods of treatment if patient demonstrates any agonist effect or lack of suppression. This has been discussed with the sponsor (December 5, 1995)

11.1 Description - satisfactory

11.2 Clinical Pharmacology - satisfactory

11.3 Indications and Usage - satisfactory and identical to previous label.

11.4 Contraindications - satisfactory

11.5 Warnings - should include either in this section or precautions problems regarding the agonist effect with reinjection of depot as well as lack of suppression.

11.6 Precautions - satisfactory but must include agonist effect with re-injection and possible escape from suppression.

"In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

11.7 - 11.9 - satisfactory

11.10 Dosage and Administration - satisfactory but should read 84 days as well as 3 months. There is no safe window beyond 84 days for all patients.

"The recommended dose of LUPRON DEPOT 22.5 mg to be administered is one injection every three months. Due to different release characteristics, a fractional dose of this 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given."

11.11 How Supplied - satisfactory

12 Conclusions

The New Drug Application for leuprolide acetate 3-month depot is satisfactory and approvable. There are several major concerns which will be addressed by the sponsor, TAP, as label changes and Phase IV commitments. The label must identify the patient with delayed suppression (2032 - study 583) and a summary of the agonist effect in three patients with reinjection of depot. The importance of evaluating the patient and his testosterone suppression during therapy should be clearly identified. The release characteristics of the depot should be included in the label. This facts should be included in the advertising of the depot.

A phase IV study should be initiated by the sponsor to further identify possible agonist effect of leuprolide and to compare the acute on chronic response between the 1 month (28 day) and the three month (84 day) depot.

13 Recommendations

The 3-month leuprolide acetate depot is approvable dependent on Phase IV commitments and label changes as noted above.

Jean L. Fourcroy, M.D., PhD
Medical Officer
December 7, 1995

See my note

12/29/95

Appendix

1. Investigators

2. Testosterone levels - 4 studies

Study	Investigator	Institution	Location	Number of Patients
M91-583	M. Brawer, MD	V.A. Medical Center	Seattle, WA	2
	A. Cohen, MD	Peninsular Testing	Miami, FL	3
	E. Crawford, MD	Univ. of Colorado	Denver, CO	2
	J. deKernion, MD	U.C.L.A.	Los Angeles,CA	1
	R. Dreicer, MD	Univ. of Iowa	Iowa City, IA	3
	S. Graham, MD	Emory Clinic	Atlanta, GA	5
	P. Hudson, MD	V.A. Medical Center	Bay Pines, FL	8
	J. Kabalin, MD	V.A. Medical Center	Palo Alto,CA	4
	A. Patterson, MD	Univ. of Tennessee	Memphis, TN	3
	R. Sharifi, MD	Univ. of Illinois	Chicago, IL	15
	J. Smith, MD	Vanderbilt Univ.	Nashville, TN	4
	B. Stein, MD	Rhode Island Hosp.	Providence, RI	9
	R. Stephenson, MD	Univ. of Utah	Salt Lake City, UT	2
M91-653	R. Bruskewitz, MD	Univ. of Wisconsin	Madison, WI	7
	M. Gittelman, MD	S. Fla. Med. Research	N.Miami, FL	8
	L. Gomella, MD	Jefferson Med. College	Philadelphia, PA	2
	S. Graham, MD	Emory Clinic	Atlanta, GA	2
	P. Reddy, MD	V.A. Medical Center	Minneapolis, MN	1
	R. Sharifi, MD	Univ. of Illinois	Chicago, IL	10
	A. Tully, MD	Urology Associates	Birmingham, AL	3

DEC 2 1 1995

NDA 20-517
TAP/Leuprolide 3 month depot
December 21, 1995

The safety update for the 3 month depot was received in April. There have been no additional safety concerns since that time and no additional safety information is needed.

Jean A. Fourcroy
Medical Officer

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Safety Update Review

Included in the medical review dated December 7, 1995.

STAT REVIEW

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I. Clinical Data Summary and Results of Statistical Analyses

1. Clinical Pharmacology

For information on the clinical pharmacology of leuprolide acetate, please refer to New Drug Applications 19-010 and 19-732.

A. Study M91-582

A human pharmacokinetic study (Protocol M91-582) was conducted in prostate cancer patients to measure plasma leuprolide levels for 20 weeks following a single intramuscular injection of the 22.5 mg depot formulation in order to determine the pharmacokinetic profile, and to assess the safety of the formulation. The complete study report is submitted in Section VI of this New Drug Application. The study design and results are summarized below.

This study was an open, single-dose pharmacokinetic study in 23 orchiectomized prostate cancer patients. The depot formulation was supplied as a single-dose vial containing lyophilized powder with leuprolide incorporated into a biodegradable polylactic acid polymer, accompanied by a 2 mL ampule of diluent. Following the intramuscular injection, plasma leuprolide levels were determined four hours post-injection, and then on Days 1, 2, 4, twice weekly (at least three days apart) during Weeks 1 through 16, and then weekly during Weeks 17 through 20. Plasma leuprolide levels were determined using radioimmunoassay. A physical examination as well as specimen collection for routine hematology, chemistries, and urinalysis were performed prestudy, and repeated at Weeks 12 and 20.

Twenty-three patients were enrolled across three investigative centers. Six patients prematurely terminated from the study. Five of these patients did not supply sufficient data to be included in the pharmacokinetic analysis, and, therefore, the analysis was based on data from 18 patients.

Following the intramuscular administration of the 22.5 mg dose, there was an initial burst of leuprolide in the plasma which is characteristic of this type of depot formulation. This was observed at four hours post-dosing, at which time a mean plasma leuprolide concentration of 48.87 ng/mL was achieved. The mean concentration then declined steadily until it reached a steady-state level during Week 3 that was maintained for the duration of the intended 12-week dosing interval (range of means 0.46 to 0.81 ng/mL), indicating a steady release of drug from the depot during this time. Detectable levels of leuprolide were present in all patients at all measurement points during this period. After Week 12 the mean concentration changed little for another 2.5 weeks, after which it declined very gradually, reaching a minimally detectable concentration by Week 20 (mean = 0.23 ng/mL).

Changes in laboratory parameters included a slight trend for the hemogram parameters to decrease to below the normal range, and a slight trend for elevations of LDH to above the normal range. These were generally attributed by the investigator to the underlying prostate cancer. Adverse events generally reflected the prostate cancer, with generalized pain having been the most frequently-reported event. Only two patients experienced injection site reactions (pain), and these were both mild and of short duration (three days).

The similarity in the pattern of release of leuprolide during the 12 weeks following dosing with the 22.5 mg formulation with the pattern during the four weeks following dosing with the monthly 7.5 mg formulation, and the maintenance of therapeutic leuprolide plasma levels throughout the intended 12-week dosing interval, indicate that the 22.5 mg formulation is suitable for administration as a three month-depot. Safety data indicated that the formulation was well-tolerated and were consistent with the known safety profile of leuprolide.

2. Overview of Clinical Studies

A. Introduction

Lupron® (leuprolide acetate) Injection, administered daily by subcutaneous injection, was released for marketing in April, 1985 for the palliative treatment of advanced prostatic cancer. Subsequently, Lupron Depot ® (leuprolide acetate for depot suspension) was developed, designed to provide continuous release of leuprolide over a four-week period when administered as a monthly intramuscular injection. Lupron Depot® (containing 7.5 mg of leuprolide acetate) was released for marketing on January 26, 1989 for the palliative treatment of advanced prostatic cancer. Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension) was released for marketing on October 22, 1990 for the management of endometriosis. In addition, Lupron Depot-PED® 7.5 mg 11.25 mg, and 15 mg, as well as Lupron® Injection (for pediatric use), were released for marketing on April 16, 1993 for the treatment of central precocious puberty.

Studies involving the treatment of metastatic prostate cancer patients with the daily subcutaneous as well as the monthly intramuscular (depot) dosage forms of leuprolide acetate have shown that serum testosterone is effectively suppressed, after two to four weeks of treatment, to a range similar to that observed in surgically castrated patients. This is accomplished by desensitization of the pituitary to native GnRH stimulation, resulting in decreased pituitary gonadotropin release and resultant suppression of gonadal testosterone production, leading to a marked reduction in serum testosterone to castrate levels. This androgen deprivation can result in slowing, stabilization, or regression of androgen-dependent tumor (primary and metastatic) proliferation, associated with a reduction in pain produced by metastatic skeletal lesions. Favorable objective responses to treatment were observed in 72% to 86% of the patients treated in these studies, and most patients showed improvement or stabilization of performance status.

An extended-release depot formulation of leuprolide acetate has been developed, containing 22.5 mg of leuprolide, to be administered as an intramuscular injection every three months. The two clinical studies included in this overview were conducted to evaluate the effectiveness and safety of this formulation.

B. Design of Studies

Study M91-583 was designed as the pivotal study to demonstrate the safety and effectiveness of the 22.5 mg formulation, with a target enrollment of 60 patients. The supply of study drug used for this study was produced in a pilot plant, which manufactures supplies in limited quantities for investigational purposes. Since the marketed supply of the 22.5 mg formulation would be produced in a production plant, which manufactures supplies on a larger scale, a study was needed to demonstrate equivalence in effectiveness and safety between the two supplies of the 22.5 mg formulation. Study M91-653 was designed to demonstrate equivalence between the two supplies, with an original target enrollment of 15 patients. Unexpected difficulty in producing and maintaining testosterone suppression in a few patients in M91-583 resulted, following discussions with the FDA, in the target number of patients in study M91-653 being increased to 60 (Amendment No. 2). Following identification of a reason for some of the unfavorable results in M91-583, and after further discussions with the FDA, the target enrollment for M91-653 was reduced to 30 patients (Amendment No. 3)

The 22.5 mg depot formulation was administered in both studies as an intramuscular injection every 12 weeks. The primary efficacy outcome criterion in both studies was suppression of serum testosterone levels to the castrate range (≤50 ng/dL), and maintenance of it at that level, in patients with metastatic (Stage D2) prostate cancer. The clinical response to treatment, as well as the general safety of the formulation, were also evaluated. Both studies had essentially the same design, with monitoring of serum testosterone levels biweekly or weekly

for 24 weeks, and clinical evaluations every twelve weeks. Patients were to continue in the studies for as long as clinical benefit was apparent to the investigator, with serum testosterone determined every 12 weeks. The studies are described in greater detail in the next section. This NDA submission involves data from the initial 24 weeks of treatment for each study.

3. Open-Label Clinical Trials

A. Design of Studies and Description of Procedures

The two studies summarized in this overview are both open, multicenter studies conducted at a total of 18 investigative centers (two of the 18 centers conducted both studies). They were nearly identical in design except that M91-583 included an expanded blood collection schedule (at half-week intervals during the last two weeks of the first two dosing intervals and following the Week 12 depot injection), for a subset of patients for measurement of serum LH and testosterone, and also, routine clinical laboratory tests were performed during treatment in M91-583 but not in M91-653. Patients received an intramuscular injection of the 22.5 mg depot formulation every 12 weeks.

Patient eligibility and baseline conditions were determined by the following procedures which were performed within four weeks of the initial dose: medical and surgical (including prostate cancer) histories, physical examination, digital rectal examination, ECOG performance status, bone scan (and other imaging procedures if necessary to establish the presence of peripheral metastatic disease), blood collection for serum PSA, LH, testosterone, hematology and chemistries (including alkaline phosphatase and prostatic acid phosphatase), and urinalysis. Blood was also obtained just prior to the initial depot injection for determination of baseline LH and testosterone levels. Once eligibility had been determined, the investigator obtained a patient number assignment from TAP.

Blood collection for measurement of serum LH and testosterone levels was performed four and seven days following the initial depot injection and at the end of Weeks 2 through 24, and every 12 weeks thereafter. As mentioned above, additional blood collections were performed for a subset of patients in M91-583, at half-week intervals (at least 72 hours apart) during Weeks 10, 11, 12, 22, and 23, to further characterize the hormonal response to treatment at the end of the first two dosing intervals and several days after the second depot injection (at Week 12). Blood was also to be drawn in all patients at 4, 8, and 12 hours following the Week 12 depot injection to assess if an "acute-on-chronic" effect due to incomplete pituitary down-regulation was present.

Physical examination, digital rectal examination, ECOG performance status, and bone scan (and other imaging procedures if evaluable organ metastases were present at pretreatment) were repeated every twelve weeks to assess the clinical response to treatment. Routine laboratory tests (including alkaline phosphatase and prostatic acid phosphatase) and PSA were also repeated every 12 weeks in M91-583. Routine laboratory tests were performed only at pretreatment in M91-653, and only alkaline phosphatase, prostatic acid phosphatase, and PSA, were performed during treatment. An overall objective response evaluation was also performed at 12-week intervals in both studies.

Serum LH, testosterone, and PSA measurements were performed by The routine hematology, chemistry (including alkaline phosphatase and prostatic acid phosphatase), and urinalysis tests for M91-583 were performed by whereas in M91-653 they were performed by the investigator's local laboratory.

Per Amendment No. 1 (M91-583) and No. 3 (M91-653), all procedures except LH, testosterone, PSA, prostatic acid phosphatase, and alkaline phosphatase

measurements were deleted from the long-term (beyond Week 24) phase of the protocols. At the time of the amendment many of the patients in M91-583 (and a smaller number of patients in M91-653) still active in the study were well into the long-term phase.

Detailed descriptions of procedures can be found in the respective protocols (Appendix B in each individual study summary). A schematic representation of the study designs is shown in each protocol.

(1.) <u>LH and Testosterone Assay Methodology</u>

Blood samples collected for LH and testosterone measurements were centrifuged to obtain the serum and sent to for assay. Assay methodology for each test consisted of standard RIA methodology. The LH assay is a sequential addition, double-antibody RIA. This method is not specific for bioactive LH, and yields higher results than would be obtained by bioassay. For testosterone in the normal adult male range uses a single-step purification method consisting of simple extraction of testosterone prior to the actual quantitation by RIA ("extract" method). When testosterone is expected to be at or near castrate levels, a two-step purification method is utilized in which the extracted sample is further purified with column chromatography prior to RIA ("column" method). This method has greater specificity, and also has higher precision when testosterone levels are in the castrate range, as they are expected to be with leuprolide treatment. The lower limit of sensitivity for the "column" method is 3 ng/dL compared to 10 ng/dL for the "extract" method. Technical descriptions of each assay can be found in Appendix C in each individual study summary.

. also performed LH and testosterone measurements in all of the previous TAP NDA protocols involving the use of the daily subcutaneous injection and the monthly 7.5 mg depot formulations in

advanced-stage prostate cancer. Testosterone results for these studies were appropriately generated by the two-step purification method ("column" method) referred to above. An error in communication between TAP and prior to the initiation of study M91-583 resulted in all serum testosterone levels for the first 24 weeks of treatment for patients in that study and a variable portion of the testosterone values for the first 14 patients enrolled in study M91-653 being measured by the "extract" method. Based on the consistently higher than expected (but mostly still in the castrate range) values obtained in both studies, an investigation was conducted to determine the reason for these higher testosterone levels. This included examination of historical and current testosterone values from patients still active in the previous studies and reassay of many samples by the "column" method by both to explain and validate the discrepancy in results generated by the two methodologies.

Results of the investigation led to the realization that a different assay had been used in these studies than had been used in previous protocols and that this factor did substantially contribute to the higher values seen in the current studies. Once this was determined, and at TAP's direction, the assay methodology was switched to the "column" method on August 1, 1993. The samples (all but 4%) that had been assayed with the "extract" method in M91-653 prior to the method conversion were reassayed by using the "column" method. The effect of this on the testosterone results and analyses of those results in each study is detailed in the individual study summaries, and a complete summary of the entire investigation into the matter, including the reassay data generated during the investigation, can be found in Appendix C of the M91-583 summary. The effect on the analyses of testosterone results presented in this overview is described in detail in the description of statistical methods (Section I.3.D).

B. **Study Drug Dosage and Administration**

The 22.5 mg depot formulation is comprised of a single-dose vial containing lyophilized microspheres of leuprolide (22.5 mg) incorporated into a biodegradable polylactic acid polymer, and a 2 mL ampule of diluent. This dosage is based on 7.5 mg per month over three months. Just prior to each 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. The resulting suspension was withdrawn into a syringe and, using a 22 gauge needle, injected intramuscularly. Injection sites were alternated and the previous injection site was examined at the time of the next injection.

C. **Patient Selection**

Eligible patients had to have histologically-confirmed prostatic adenocarcinoma in Stage D2, i.e., skeletal metastases, nodal metastases above the aortic bifurcation, or metastases to other extra-pelvic sites, such as liver or lung. Patients had to have two or more clinically evaluable lesions (including prostate if present) and be in performance status grades 0, 1, or 2, as defined below:

Grade	Performance
0	Fully active, able to carry on all usual activities without restriction and without the aid of analgesics.
1	Restricted in strenuous activity but ambulatory and able to carry out light work or pursue a sedentary occupation. This group also contains patients who are fully active, as in Grade 0, but only with the aid of analgesics.
2	Ambulatory and capable of all self-care but unable to work; up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, unable to carry out any self-care and confined totally to bed or chair.

The prestudy serum testosterone level had to be ≥150 ng/dL and the patient must have recovered from the effects of any major surgery. Patients were excluded if they did not have an intact hypothalamic-pituitary-gonadal axis (orchiectomy, hypophysectomy, adrenalectomy were excluded) or if they had received anti-cancer medication (e.g. estrogen, anti-estrogen, progestogen, antiandrogen, other steroid treatment, chemotherapy or GnRH analogs) within four weeks preceding the initial depot injection, or if they required antineoplastic medication during the study. Initially, patients were excluded if they required antiandrogen (flutamide) treatment during the study, but per Amendment Nos. 1 (M91-583) and 3 (M91-653) antiandrogen treatment (flutamide) was permitted after Week 24. Radiation treatment (including implants) was not permitted at the time of study entry. Patients needed to have a life prognosis of at least 12 months, and could not have any underlying disease that would place them in additional jeopardy by participating in the study. Details of remaining selection criteria can be found in Sections 4 (M91-583) and 5 (M91-653) of the respective protocols.

D. Statistical Methods

Data were summarized using the Statistical Analysis System (SAS Institute, Inc. {Version 6.08}).

Tests resulting in p-values less than or equal to 0.050 (when rounded to three digits) were reported as "significant" in the text.

For any variable, the final value obtained before the start of study drug administration was used as the baseline value for that variable unless otherwise indicated. Data obtained after the start of study drug administration were grouped into time intervals (categorized visits) determined by the midpoints between scheduled visits or collections times. These intervals were defined to have been exhaustive and mutually exclusive for each variable, so that the intervals varied based on how frequently the variable was collected. If multiple values were obtained in an interval, the value closest to the scheduled collection time was used in analysis, except for hormones. For the hormone data the maximum value in an interval was used. If multiple PSA values existed for a day, the maximum for that day was used in analysis.

Since this report covers the first 24 weeks of treatment, the data used in analysis, unless otherwise specified, was cut off using conventions as to the number of days after the second (or last for patients terminating earlier) injection. The duration of treatment of any injection was defined to be 84 days. Therefore, all data used in analysis for any laboratory variable (hormones, hematology, chemistries, urinalysis) was obtained no later than 84 + 14 = 98 days after the second injection, while data for all clinical response variables (objective response, digital rectal exam, performance status) were obtained no later than 84 + 42 = 126 days after the second injection. Except where indicated, the timing of injections is ignored.

Baseline characteristics

Summary statistics were calculated for demographic characteristics (race, age, height, and weight) and disease status at baseline (time since diagnosis of prostate cancer, prior treatments for prostate cancer, results of the digital rectal examination, and performance status).

Primary endpoint

The primary objective of this study was to demonstrate suppression of serum testosterone during the first 24 weeks of treatment.

As previously stated, serum testosterone determinations were performed by two assay methods ("extract" and "column" methods). Since there was a difference in the results obtained by these two methods [see Section 3.A.(1)], the results from the two methods will be addressed separately for calculation of mean and median levels and the "acute-on-chronic" analysis, or combined for calculations of proportions of suppressed patients and patients experiencing "escapes" from suppression (where the analyses were based on the maximum value regardless of method for each categorized visit). Only data provided by were used in the analyses.

The proportions of patients who achieved testosterone suppression (≤50 ng/dL for two consecutive tests within eight weeks after the first depot injection) and the proportion of suppressed patients who experienced "escapes" (testosterone levels >50 ng/dL for two consecutive tests after suppression had been achieved) were estimated, and one-sided exact 95% confidence bounds were obtained using the exact binomial distribution. Prior to applying these definitions, on days when results from multiple measurements existed, values were reduced to the maximum for the day. This applied to days on which 1) there were both "extract" and "column" data, 2) multiple values from reassay using the same assay method existed, or 3) serial data from "acute-on-chronic" measurements existed. The

median time of onset of suppression was estimated using Kaplan-Meier curves. Duration of suppression continued beyond 24 weeks for most patients, so median duration was not estimated.

Summary statistics were provided for testosterone and LH values at each categorized visit without respect to the time of injections. Additional summaries were provided for patients who had samples obtained at 4, 8 and 12 hours following the injections at Week 12 and those that participated in the expanded blood collection schedule. For patients who had data at 10, 10.5, 11, 11.5, and 12 weeks after each injection, repeated measure analysis of variance was used to test for trends across time. Mean testosterone at 12 and 12.5 weeks were analyzed using paired T-tests, as were changes from 0 hour to 4, 8, and 12 hours post-dosing (acute-on-chronic analysis).

Additional Efficacy Variables

The numbers and percentages of patients with graded outcomes are presented for the Week 12 and Week 24 evaluations and for the "final visit" evaluations for objective tumor response, changes in prostatic involvement, percent changes in PSA and PAP, and changes in performance status.

E. Clinical Results - Efficacy

(1.) Patient Enrollment, Evaluable Patients, and Premature Terminations

Ninety-four patients were enrolled and treated across the two studies by 18 investigators (two investigators conducted both studies). A list of investigators who enrolled patients into each study along with their institutional affiliations and locations and the number of patients enrolled at each center is presented below:

Study	Investigator	Institution	Location	Number of Patients
M91-583	M. Brawer, MD	V.A. Medical Center	Seattle, WA	2
	A. Cohen, MD	Peninsular Testing	Miami, FL	3
	E. Crawford, MD	Univ. of Colorado	Denver, CO	2
	J. deKernion, MD	U.C.L.A.	Los Angeles,CA	1
	R. Dreicer, MD	Univ. of Iowa	Iowa City, IA	3
	S. Graham, MD	Emory Clinic	Atlanta, GA	5
	P. Hudson, MD	V.A. Medical Center	Bay Pines, FL	8
	J. Kabalin, MD	V.A. Medical Center	Palo Alto,CA	4
	A. Patterson, MD	Univ. of Tennessee	Memphis, TN	3
	R. Sharifi, MD	Univ. of Illinois	Chicago, IL	15
	J. Smith, MD	Vanderbilt Univ.	Nashville, TN	4
	B. Stein, MD	Rhode Island Hosp.	Providence, RI	9
	R. Stephenson, MD	Univ. of Utah	Salt Lake City, UT	2
M91-653	R. Bruskewitz, MD	Univ. of Wisconsin	Madison, WI	7
	M. Gittelman, MD	S. Fla. Med. Research	N.Miami, FL	8
	L. Gomella, MD	Jefferson Med. College	Philadelphia, PA	2
	S. Graham, MD	Emory Clinic	Atlanta, GA	2
	P. Reddy, MD	V.A. Medical Center	Minneapolis, MN	1
	R. Sharifi, MD	Univ. of Illinois	Chicago, IL	10
	A. Tully, MD	Urology Associates	Birmingham, AL	3

The first patient (No. 2001, M91-583) to enter either of the studies began treatment on November 8, 1991 and the last patient (No. 33, M91-653) to complete the initial 24 weeks of treatment (portion of each study submitted in this report) in either study did so on August 16,1994.

Two patients (one from each study) were excluded from the efficacy analysis. The M91-583 patient did not have a pretreatment (qualifying) testosterone level; the M91-653 patient discontinued from the study at Day 6, and therefore did not have sufficient data to be included. Patients were considered to have prematurely terminated from a study if they did not receive the third depot injection. Sixteen patients terminated from the study prematurely (10 in M91-583 and 6 in M91-653). These patients, along with all the reasons given

for their termination, are listed in End-of-Text Table 1. The primary reasons for termination and the respective numbers of patients are summarized below:

Primary Reasons for Discontinuation From Study
During the First 24 Weeks for All Patients

Reason	M91-583 (N=61)	M91-653 (N=33)	Combined (N=94)
Adverse event	1	1	2
Worsening of disease/symptoms	5	3	8
Death from prostate cancer	2	0	2
Death not from prostate cancer	1	1	2
Non-compliance with visit schedule	1	0	1
Uncertainty re: protocol continuation	0	1	1

Although not always considered the primary reason, six patients terminated, at least in part, due to an adverse event. This included two deaths from heart disease and two patients whose adverse event reflected worsening of disease symptoms (one of these patients also developed symptoms of progressive lung cancer, which was present prior to treatment), as well as intolerable hot flashes and chronic obstructive pulmonary disease, the last two having been considered the primary reason for termination in one patient each. Disease progression usually consisted of worsening of skeletal metastatic disease and consequent increase in pain. Two additional patients in M91-583 died from prostate cancer. One patient in M91-583 terminated due to non-compliance with the visit schedule and one patient terminated in M91-653 due to uncertainty as to the continuation of development of the 22.5 mg formulation.

The following table summarizes the number of patients enrolled, the number who were efficacy evaluable, and the number who continued in the study beyond the initial 24 weeks of treatment.

Summary of Patients Enrolled, Evaluable, and Continuing Treatment

Study	No. of Investigators	No. of Enrolled Patients	No. of Evaluable Patients	Patients Continuing*
M91-583	13	61	60	51
M91-653	7	33	32	27

* received third Lupron Depot injection

(2.) Patient Demographics and Prostate Cancer History

Patients in the two studies were fairly evenly matched for the demographic variables of race, age, weight and height. Overall, 67% of the patients were Caucasian, 30% were Black, and 2% were Hispanic. Ages at study entry ranged from 53 to 86 years, with a mean of 70.3 years. Heights ranged from 61 to 75 inches, with a mean of 68.6 inches. Weights ranged from 90 to 252 lbs., with a mean of 170.7 lbs.

The time interval between the initial diagnosis and the start of treatment (first depot injection) for the 92 evaluable patients ranged from 7 days to 7.6 years (median 83 days). Approximately half (52%) of the patients had been diagnosed less than three months prior to initiation of treatment and 84% had been diagnosed within three years.

Overall, 59% of the 92 evaluable patients had no prior treatment for prostate cancer at the time of the initiation of treatment. The remaining patients had had prostatic resection (TURP), radical prostatectomy, radiation, hormonal treatment (GnRH analogs or DES), pelvic lymphadenectomy, or a combination of these. A summary of demographic characteristics, by study, for the 92 evaluable patients is presented in the following table:

Summary of Demographic Characteristics for the Efficacy Evaluable Patients

Variable	M91-583 (N=60)	M91-653 (N=32)	Combined (N=92)
Race			
Caucasian	42 (70%)	20 (63%)	62 (67%)
Black	17 (28%)	11 (34%)	28 (30%)
Hispanic	1 (2%)	1 (3%)	2 (2%)
Age at Study Start			
mean (s.d.) in years	70.8 (7.2)	69.3 (7.2)	70.3 (7.2)
range in years	53-86	55-82	53-86
Height at Study Start			
mean (s.d.) in inches	68.6 (2.7)	68.5 (2.8)	68.6 (2.7)
range in inches	63-75	61-74	61-75
Weight at Study Start			
mean (s.d.) in lbs.	170.3 (33.2)	171.4 (29.2)	170.7 (31.7)
range in lbs.	100-252	90-232	90-252
Time Since Diagnosis			
< 3 months	34 (57%)	14 (44%)	48 (52%)
3 months to <1 year	11 (18%)	5 (16%)	16 (17%)
1 year to <3 years	5 (8%)	8 (25%)	13 (14%)
3 years to <5 years	5 (8%)	4 (13%)	9 (10%)
> 5 years	5 (8%)	1 (3%)	6 (7%)
mean (s.d.) time in years	1.1 (1.9)	1.2 (1.7)	1.2 (1.8%)
Previous Treatment for Prostate Cancer			
no prior treatment	40 (67%)	14 (44%)	54 (59%)
resection (TURP) only	5 (8%)	6 (19%)	11 (12%)
radical prostatectomy only	2 (3%)	1 (3%)	3 (3%)
radiation only	5 (8%)	4 (13%)	9 (10%)
hormonal only	2 (3%)	0 (0%)	2 (2%)
pelvic lymphadenectomy only	1 (2%)	0 (0%)	1 (1%)
combination of treatments	5 (8%)	7 (22%)	12 (13%)

(3.) Hormonal Response

a) Serum Testosterone

The response of serum testosterone to treatment was similar in the two studies (see Figure 1). Following the initial depot injection, the characteristic increase in mean testosterone over the pretreatment level occurred on Day 4, followed by a steady decline to the castrate range by Week 3 (see table below). The peak mean testosterone levels observed on Day 4 were similar to that observed for the monthly 7.5 mg depot in NDA (19-732) study M85-097. In M91-583, mean levels (by "extract" method) fluctuated between 24 and 36 ng/dL at the weekly visits between Weeks 4 and 13, followed by a further decline, fluctuating between 18 and 23 ng/dL at the weekly visits between Weeks 14 and 24. These levels were slightly inflated by the presence of "outlier" values for one patient, as well as the assay method by which they were obtained [see Section I.3.(1.)]. In M91-653, mean levels (by "column" method) fluctuated between 8 and 11 ng/dL at the weekly visits between Weeks 4 and 24. Mean values at various points during the 24-week treatment period are presented below:

Serum Testosterone (ng/dL)

			Week No.								
	Pre	Day 4	1	2	3	4	8	12	13	18	24
M91-583*											
N	59	57	52	56	58	57	53	46	42	48	31
Mean	405.2	576.5	431.4	121.3	46.7	26.4	29.7	35.6	30.1	18.7	22.7
M91-653*											
N	30	28	31	31	32	29	32	30	31	29	24
Mean	443.7	739.3	436.6	93.6	23.5	11.2	7.6	10.5	9.1	8.7	8.9

* M91-583 results by "extract" assay method and M91-653 results by "column" assay method

The first of two consecutive visits at which testosterone levels were ≤50 ng/dL was considered to be the "onset" of castrate levels for individual patients. If this occurred by Week 8, the patient was considered to be

"suppressed." All patients in M91-653 and all but two patients in M91-583 [98% of total number of patients (and a one-sided lower 95% confidence bound of 93%)] were suppressed. The remaining two patients achieved onset of castrate levels at Weeks 15 and 28. Onset of castrate levels of testosterone was achieved within 30 days of the initial depot injection in all patients in M91-653 and in all but five of the patients in M91-583 (95% of the total number of patients). This was comparable to the 96% of patients in the monthly depot NDA study achieving castrate levels within this time period. The median time to onset of castrate levels in all three studies was 22 days [range 13 to >169 days (M91-583 and M91-653)].

Two (2%) of the 90 evaluable patients who had been suppressed (combined studies) experienced an "escape" (testosterone levels > 50 ng/dL for two consecutive tests after suppression had been achieved) from the castrate level. The one-sided 95% upper confidence bound for the proportion of patients with an escape was 7%. These were both in M91-583. The "escape" occurred at Week 8 for one patient and at Week 12 (prior to the depot injection) for the other patient, and continued through Week 13 for both patients. There were no further "escapes" for either patient at least through Week 120. The "escape" values were mostly under 100 ng/dL (highest 154 ng/dL).

One additional M91-583 patient had three consecutive testosterone values >50 ng/dL, but this was limited to the serial measurements taken during the 12 hours following the Week 12 depot injection, and is therefore more accurately classified as an "acute-on-chronic" response.

Testosterone was above 50 ng/dL on single occasions following suppression in four additional patients and on two non-consecutive occasions in one patient in M91-583. An additional non-castrate value

occurred for one patient in M91-653. None of these values was expected to have clinical significance. The range was 51-61 ng/dL for all but one, and the remaining value (292 ng/dL) was likely due to incorrect sample identification since all other values for this patient were well within the castrate range.

As previously mentioned [Section L3.(1)] and detailed in Appendix C of the M91-583 summary, many of the non-castrate testosterone values which occurred following suppression or in patients having delayed suppression in that study were originally obtained by the "extract" method and were reassayed using the "column" method. When these values from reassay were substituted for the original values, the incidence of non-castrate values decreased markedly (from 53 to 37, with 12 unavailable for reassay) and also resulted in favorable reclassification of five of the ten patients in whom these 53 non-castrate values occurred. This included one "failure-to-suppress" reclassified as an "escape", one "acute-on-chronic stimulation" reclassified as an "isolated high value", and three "isolated high values" no longer existing. The single value >50 ng/dL (by "extract" method) in M91-653 also fell to within the castrate range when reassayed by the "column" method.

Testosterone suppression was sustained throughout each 84-day dosing interval. After falling to the castrate range, mean testosterone remained well within the castrate range throughout each interval. The end of each dosing interval theoretically represents the weakest control point in the treatment cycle. With the exception of the two patients who experienced "escapes" and the two patients in whom the onset of castrate levels was delayed, referred to above, testosterone was within the castrate range just prior to the injections at Week 12 and 24 in all other evaluable patients. Testosterone was determined at half-week intervals during the last two

weeks of each dosing interval in a subset (N=13 at Week 12 and N=7 at Week 24) of patients in M91-583 who had values at each measurement point. There was no significant linear trend in the mean testosterone values obtained at these measurement points for either dosing interval.

Compliance with the 84-day dosing interval was generally good, with the number of days between injections ranging from 77 to 98 days (median = 84 days). The depot injection at Week 12 or 24 was delayed by >3 days in 16 of the 92 evaluable patients. Testosterone values, however, just prior to the injection on these "late" injection days, as well as the next time measured (if performed), were all within the castrate range (including any values excluded from analysis).

b) **Serum LH**

As mentioned in Section I.3.(1), LH was assayed using RIA methodology which is not specific for bioactive LH, resulting in higher levels than would be obtained by bioassay. The response pattern was the same for both studies, and was similar to that observed for serum testosterone, with an initial increase to above pretreatment level on Day 4, followed by a decline to below the pretreatment level by Week 2, and a further decline to the lower end of the normal range (3-10 mIU/mL) by Week 4, where it remained throughout the 24-week treatment period, as seen below:

Serum LH (mIU/mL)

			Week No.								
	Pre	Day 4	1	2	3	4	8	12	13	18	24
M91-583											
N	56	57	51	55	57	57	52	44	40	47	29
Mean	10.5	17.4	11.3	7.4	5.9	5.4	4.3	5.3	4.5	4.3	3.9
M91-653											
N	31	28	31	31	32	29	32	30	30	29	24
Mean	9.8	16.5	10.9	7.1	6.0	5.3	5.0	5.3	5.0	5.2	5.4

c) **"Acute-On-Chronic" Response**

Stimulation of the hypothalamic-pituitary-gonadal axis, and a consequent increase in serum LH and testosterone over pre-treatment levels within the initial week of treatment, is known to occur with GnRH analogs. This is occasionally associated with a transient exacerbation of symptoms. Although this initial increase in serum LH and testosterone was observed in the monthly 7.5 mg depot NDA study (M85-097), exacerbation of symptoms during the two weeks following the initial depot injection was not observed, nor was there a transient rise in serum LH or testosterone following subsequent depot injections.

As previously discussed, mean serum LH and testosterone did increase considerably above pretreatment levels on Day 4 following the initial injection of the 22.5 mg depot formulation. To determine whether this effect was present after subsequent depot injections ("acute-on-chronic" effect) of the 22.5 mg formulation, testosterone levels were determined 2-5 days after the depot injection at Week 12 for a subset of patients in M91-583, and LH and testosterone were also determined 4,8, and 12 hours after this injection for a larger group of patients in M91-583 and M91-653. These values were compared with the values obtained just prior to the Week 12 depot injection.

The change in mean testosterone from just prior to the depot injection to 2-5 days after the injection was not statistically ($p=0.633$) or clinically significant (see below), and only one patient had a post-injection testosterone value (154 ng/mL) that was higher than the pre-injection value and that was also outside the castrate range. This patient, however, one of the previously referred to patients who experienced an "escape" from suppression, had non-castrate testosterone values for three weeks prior to Week 12.

Mean (s.d.) Testosterone Levels (ng/dL) Immediately Prior to the Week 12 Depot Injection and 2-5 Days Post-Injection
[(from M91-583) N=13]

Pre-Injection	Post-Injection
25.5 (21.0)	28.3 (38.9)

Changes in mean LH and testosterone from pre-injection to 4, 8, and 12 hours following the Week 12 depot injection were not clinically significant, but were statistically significant at a few points as indicated below:

Mean LH (mIU/mL) and Testosterone (ng/dL) Levels Prior to and at Indicated Times Following the Week 12 Depot Injection

	Pre	4 hours	8 hours	12 hours
LH				
M91-583				
N	39	39	35	19
Mean	4.3	4.7*	4.5*	4.6*
M91-653				
N	18	14	16	13
Mean	5.1	5.4	5.3	5.1
Testosterone				
M91-583+				
N	42	42	36	19
Mean	30.6	27.4	31.5	37.0
M91-653+				
N	18	14	16	13
Mean	9.4	8.2	9.4	6.7*

*p<0.05 vs. pre-injection
+M91-583 results by "extract" assay method and M91-653 results by "column" assay method

The above mean testosterone values for M91-583 are slightly inflated due to the presence of "outlier" values for the patient previously described, for whom onset of castrate levels did not occur until Week 28.

Serial LH and testosterone measurements were inadvertently performed on four and six patients, respectively, following the Week 24 depot injection in

M91-583, but these results did not differ from the above results. See the individual study summary for these data.

Based on the above data, there does not appear to be an acute-on-chronic stimulation following subsequent depot injections.

(4.) **Objective Tumor Response**

A total of eighty-nine evaluable patients had at least one objective tumor response evaluation at Week 12 and/or 24. With respect to the combined data, 82% of the patients had a favorable (CR, PR, or NC) rating at Week 12, and 80% at Week 24. Considering only the best objective response obtained for each patient during the treatment period, an 84% "no progression" (CR + PR + NC) rate was achieved during the 24-week treatment period for M91-583 and an 87% rate for M91-653, resulting in an overall "no-progression" rate of 85% for the combined data, as detailed below:

Summary of Best Objective Response Rates

	Number (%) of Patients				
	Complete Response (CR)	Partial Response (PR)	Stable (NC)	Progression (P)	Total
M91-583	0 (0%)	28 (48%)	21 (36%)	9 (16%)	58
M91-653	1 (3%)	5 (16%)	21 (68%)	4 (13%)	31
Combined	1 (1%)	33 (37%)	42 (47%)	13 (15%)	89

These results are comparable to the 81% "no-progression" rate seen in the NDA study for the monthly 7.5 mg depot.

(5.) **Prostatic Involvement**

A total of eighty-eight patients who had both a pretreatment and at least one (at Week 12 and/or 24) digital rectal examination of the prostate during treatment were evaluable for analysis of change in prostate status. Nearly all patients improved or remained stable during treatment. For the combined

data, 98% of the patients had a favorable (returned to normal, >50% improved, or similar to baseline) evaluation at Week 12 and 97% at Week 24. At the "final visit" only three (3%) patients had significant progression with respect to prostate status. The "final visit" results are summarized below:

Summary of Changes in Prostate Status During Treatment at the "Final Visit"

	Number (%) of Patients				
	Returned to Normal	>50% Improved	Similar to Baseline	>25% Worsened	Total
M91-583	13 (22%)	20 (34%)	22 (38%)	3 (5%)	58
M91-653	6 (20%)	6 (20%)	18 (60%)	0 (0%)	30
Combined	19 (22%)	26 (30%)	40 (45%)	3 (3%)	88

(6.) <u>Prostate-Specific Antigen (PSA)/Prostatic Acid Phosphatase (PAP)</u>

With respect to the combined data, pretreatment PSA was elevated (>3.9 ng/mL) in 75 (93%) of the 81 evaluable patients with pretreatment values. PAP was elevated (>3.99 mcg/L) in 64 (74%) of the 87 patients with pretreatment values. The PSA and PAP responses to treatment were similar in the two studies, as PSA and PAP normalized or decreased in nearly all patients in each study who had at least one follow-up value obtained during treatment, as summarized in the table below:

Changes in PSA and PAP at the "Final Visit" in Patients with Elevated Pretreatment Values

	Number of Patients					
	Pre-Rx	Elevated Pre-Rx	Elevated Pre-Rx and ≥1 Rx Value	Normalized	Decreased But Not Normalized	Increased
M91-583						
PSA	51	48 (94%)	45	28 (62%)	16 (36%)	1 (2%)
PAP	57	43 (75%)	41	25 (61%)	13 (32%)	3 (7%)
M91-653						
PSA	30	27 (90%)	27	17 (63%)	9 (33%)	1 (4%)
PAP	30	21 (70%)	21	11 (52%)	8 (38%)	2 (10%)
Combined						
PSA	81	75 (93%)	72	45 (63%)	25 (35%)	2 (3%)
PAP	87	64 (74%)	62	36 (58%)	21 (34%)	5 (8%)

Pretreatment PSA was normal in a total of six patients and was elevated in one of these patients during treatment (one patient had no subsequent data). PAP was normal at pretreatment in 23 patients and was elevated in three of these patients during treatment (one had no subsequent data).

A total of 11 patients did not have a pretreatment PSA value and PSA was elevated in six of these during treatment. Pre-treatment PAP was not available in five patients and was elevated during treatment in three of these patients.

Changes in PSA and PAP during treatment were also assessed according to graded outcomes. In this analysis (combined data), PSA decreased by at least 50% in 96% of the patients and PAP decreased by more than 50% in 84% of the patients with elevated pretreatment values and at least one treatment value, as summarized below:

PSA Changes in Patients with Elevated Pretreatment PSA
and ≥1 Treatment PSA Value at the "Final Visit"

	>95% Decrease	90-95% Decrease	50 to <90% Decrease	<50% Decrease	No Change or Increase	Total
M91-583	23 (51%)	9 (20%)	12 (27%)	0 (0%)	1 (2%)	45
M91-653	13 (48%)	5 (19%)	7 (26%)	1 (4%)	1 (4%)	27
Combined	36 (50%)	14 (19%)	19 (26%)	1 (1%)	2 (3%)	72

PAP Changes in Patients with Elevated Pretreatment PAP
and ≥1 Treatment PAP Value at the "Final Visit"

	>50% Decrease	25-50% Decrease	Within 25% of Baseline	25-50% Increase	>50% Increase	Total
M91-583	35 (85%)	1 (2%)	2 (5%)	2 (5%)	1 (2%)	41
M91-653	17 (81%)	1 (5%)	1 (5%)	0 (0%)	2 (10%)	21
Combined	52 (84%)	2 (3%)	3 (5%)	2 (3%)	3 (5%)	62

(7.) **Performance Status**

A total of 91 evaluable patients had a pretreatment performance status assessment and at least one assessment during the treatment period. The majority of patients in each study had a normal performance status prior to treatment, although the proportion differed slightly between studies, as summarized below:

	Total Evaluable Patients	Pretreatment Performance Status	
		Abnormal	Normal
M91-583	59	27 (46%)	32 (54%)
M91-653	32	11 (34%)	21 (66%)
Combined	91	38 (42%)	53 (58%)

Overall, a favorable response to treatment ("improved" or "no change" for patients with abnormal pretreatment status and "no change" for patients with normal pretreatment status) was achieved in 85% of the patients. The

aa

proportion of patients achieving a favorable response was comparable in the two studies, and regardless of pretreatment performance status, as summarized below:

Changes in Performance Status

	Pre-Rx Performance Status	Favorable: Improved	Favorable: No Change	Worsened	Total
M91-583	abnormal	10 (37%)	10 (37%)	7 (26%)	27
	normal	N/A	28 (88%)	4 (13%)	32
M91-653	abnormal	3 (27%)	8 (73%)	0 (0%)	11
	normal	N/A	18 (86%)	3 (14%)	21
Combined	abnormal	13 (34%)	18 (47%)	7 (18%)	38
	normal	N/A	46 (87%)	7 (13%)	53

N/A=not applicable

(8.) Conclusions - Efficacy

The 22.5 mg depot formulation was found to be effective in suppressing serum testosterone to, and maintaining it at, the castrate level, in a manner similar to that seen with the monthly 7.5 mg depot formulation. This was true for both the pilot plant supply (M91-583) as well as the production plant supply (M91-653) of the formulation. The clinical response to treatment was also similar to that of the monthly depot.

F. Clinical Results - Safety

(1.) Statistical Methods

Data from all patients who received leuprolide were included in the safety analysis. All p-values reported for the safety analysis are based on two-tailed tests.

Changes in vital signs and clinical laboratory variables from baseline to each visit were analyzed using paired t-tests. Crosstabulations of low, normal, and

high (with respect to the normal range) clinical laboratory results at baseline with those at each treatment visit are presented.

The prevalence of adverse events during the 24-week treatment period was summarized using COSTART Coding Symbols for Thesaurus of Adverse Reaction Forms, 3rd Edition, Department of Health and Human Services. Adverse events that ended before the start of treatment were not included. All other adverse events were included unless 1) for patients who received a depot injection at Week 24, the event(s) occurred more than 87 (84 + 3) days after the Week 12 injection; 2) for all other patients, the event(s) occurred more than 126 (84 + 42) days after the last injection.

(2.) Patient Accountability/Treatment Exposure

A total of ninety-four patients received the 22.5 mg leuprolide depot formulation in studies M91-583 and M91-653. Seventy-eight (83%) completed the first 24 weeks of treatment and continued with the long-term phase of the study. Sixteen (17%) patients discontinued from the study prior to receiving the third injection. All but four patients received the second depot injection.

The number of injections received is as follows:

	No. of Injections			
	1	2	3*	Total
M91-583	1	5	27	33
M91-653	3	7	51	61
Combined	4	12	78	94

* patients continuing in the study beyond the first 24 weeks of treatment

(3.) Patient Demographics

Race, age, height, and body weight for all patients enrolled into the two efficacy and safety studies is summarized below. Sixty-eight percent of the

patients were Caucasian, 30% were Black, and 2% were Hispanic. Ages ranged from 53 to 86 years (mean 70.3 years), heights from 61 to 75 inches (mean 68.6 inches), and body weights from 90 to 252 lbs. (mean 171.1 lbs.).

Summary of Demographic Characteristics for All Patients

Variable	M91-583 (N=61)	M91-653 (N=33)	Combined (N=94)
Race			
Caucasian	43 (70%)	21 (64%)	64 (68%)
Black	17 (28%)	11 (33%)	28 (30%)
Hispanic	1 (2%)	1 (3%)	2 (2%)
Age at Study Start			
mean (s.d.) in years	70.6 (7.2)	69.7 (7.4)	70.3 (7.3)
range in years	53-86	55-82	53-86
Height at Study Start			
mean (s.d.) in inches	68.7 (2.7)	68.5 (2.8)	68.6 (2.7)
range in inches	63-75	61-74	61-75
Weight at Study Start			
mean (s.d.) in lbs.	170.7 (33.0)	171.9 (28.9)	171.1 (31.8)
range in lbs.	100-252	90-232	90-252

(4.) **Vital Signs and Body Weight**

Systolic and diastolic blood pressures, pulse rates, and body weights are listed for each patient in Appendix E.6 in each of the individual study summaries, and corresponding summary statistics can be found in End-of-Text Table 2.

There were no statistically or clinically significant changes from pretreatment in mean systolic or diastolic blood pressure. Mean pulse rate decreased by 4.0 and 4.2 bpm at Week 24 and at the "final visit" in M91-583; these changes were statistically significant ($p<0.05$), but not indicative of a clinically significant trend. With respect to the combined data, the mean pulse rate at the "final visit" decreased by 2.9 bpm and this was statistically significant ($p<0.05$), but, again, not indicative of a clinically significant trend.

Changes from pretreatment in mean body weight were statistically significant at Weeks 12 and 24, and at the "final visit", in both studies. With respect to the combined data, mean body weight increased by 3.1, 5.9, and 5.6 lbs. at Weeks 12, 24, and the "final visit" respectively. These changes were all significant ($p<0.001$). These results were not unexpected, since patients generally showed clinical improvement with treatment during the study. These increases in mean body weight paralleled the results obtained in the NDA study for the monthly depot formulation.

(5.) **Clinical Laboratory Determinations**

Pretreatment and treatment hematology, blood chemistry, and urinalysis results are listed for each patient in M91-583 in Appendices E.8, E.9, and E.10, respectively, in the individual summary for that study. These tests (with the exception of alkaline phosphatase) were performed only at pretreatment in M91-653, and these results can be found in the same appendices in the individual summary for that study.

Changes in mean values for M91-583 can be found in End-of-Text Table 3. End-of-Text Table 4 displays cross-tabulations of low, normal, and high laboratory results at baseline with those at Weeks 12, 24, and the "final visit" for M91-583. This table indicates shifts from normal values prior to treatment to out-of-range values in laboratory variables during treatment, as well as laboratory variables which were outside the normal range prior to treatment and remained there during treatment.

There were no major adverse or unexpected trends apparent in either of these analyses. There appeared to be a slight tendency toward decreases in the hemogram parameters, WBC, and % basophils, and elevations in total, HDL-, and LDL-cholesterol, triglycerides, SGPT, phosphorus, sodium, and glucose, as statistically significant increases in mean values for these variables (except

triglycerides) occurred and the changes for most of these variables were reflected in the cross-tabulation tables. These increases, however, were not of the magnitude to be indicative of a clinically-significant trend, and were often attributed, by the investigator, to the underlying disease state, to non-fasting blood collection, or as being consistent with the age and status of the patient population studied.

As expected, pretreatment levels of alkaline phosphatase reflected the presence of bony metastatic disease. Changes during treatment reflected the continuing presence of, and presumably the treatment-related reduction in, bony metastatic disease. In M91-583, mean pretreatment alkaline phosphatase was elevated well above the normal range, but decreased considerably with treatment, although remaining above the normal range. In both M91-583 and M91-653, alkaline phosphatase was within the normal range and remained there during treatment in the majority of patients, but, as can be seen in the cross-tabulation tables, cases in which it increased to above the normal range or decreased to within the normal range during treatment, or was above the normal range prior to treatment and remained there during treatment, were common.

(6.) Adverse Events

a) Adverse Events During the First 24 Weeks of Treatment

Adverse events were summarized using COSTART coding symbols from the Thesaurus of Adverse Reactions Forms (3rd edition) prepared by the Department of Health and Human Services. All adverse events (including severity, duration, pattern, and etiology) reported during the first 24 weeks of treatment for each patient, and the corresponding medical, COSTART, and body system terms used for summarization, are listed in Appendix E.11 in each of the individual study summaries. A list of the COSTART terms

by body system used in the studies, and the original medical terms from the raw data listings associated with them, are provided in End-of-Text Table 6.

A summary of all adverse events which occurred during the first 24 weeks of the study for each patient, regardless of severity or relationship to treatment, is presented, by body system, for each study separately, and then combined, in End-of-Text Table 7. The sum of the numbers of patients experiencing the various events within a given body system may exceed the marginal column total ("Patients with one or more symptoms") for that body system because a patient may have been included in the count for more than one COSTART term (symptom).

Adverse events were reported by 90 (96%) of the 94 total patients in the two studies. This proportion was similar in the two studies. Twenty-three (25%) patients reported severe adverse events. End-of-Text Table 8 summarizes the incidences of severe adverse events occurring within the first 24 weeks of treatment, regardless of relationship to treatment. The most common adverse event was VASODILATATION (COSTART), or hot flashes, occurring in 59% of the patients. Only one of these cases was severe. The following table summarizes the adverse events (regardless of relationship to treatment) that occurred in 10% or more of the patients.

Summary of Adverse Events Occurring at the ≥10% Incidence Level
for the Combined Studies (N=94)
(Disregarding Relationship to Treatment)

COSTART	No.(%) Patients	No.(%) Patients with Severe Events
VASODILATATION	55 (58.5)	1 (1.1)
PAIN	25 (26.6)	4 (4.3)
TESTICULAR ATROPHY	20 (21.3)	0 (0.0)
BACK PAIN	15 (16.0)	1 (1.1)
ARTHRALGIA	14 (14.9)	0 (0.0)
ASTHENIA	11 (11.7)	0 (0.0)
CONSTIPATION	11 (11.7)	0 (0.0)
INJECTION SITE PAIN	10 (10.6)	0 (0.0)

The incidence of adverse events which occurred during the first 24 weeks, excluding those judged by the investigator to definitely not be treatment-related, is summarized in End-of-Text Table 9. End-of-Text 10 provides the incidence of severe events within this category. In this analysis, 77 (82%) of the 94 total patients reported one or more adverse events. The incidence of hot flashes remained the same at 59%. The following table summarizes the adverse events which occurred in 5% or more of the patients when events definitely not treatment-related are excluded. Patients with severe events are also summarized for COSTART terms meeting this criterion.

Summary of Adverse Events Occurring at the ≥5% Incidence Level for the Combined Studies (N=94) (Excludes Events Definitely Not Related to Treatment)

COSTART	No.(%) Patients	No.(%) Patients with Severe Events
VASODILATATION	55 (58.5)	1 (1.1)
TESTICULAR ATROPHY	19 (20.2)	0 (0.0)
PAIN	14 (14.9)	1 (1.1)
ARTHRALGIA	11 (11.7)	0 (0.0)
INJECTION SITE PAIN	10 (10.6)	0 (0.0)
ASTHENIA	7 (7.4)	0 (0.0)
CONSTIPATION	6 (6.4)	0 (0.0)
HEADACHE	6 (6.4)	1 (1.1)
NAUSEA	6 (6.4)	1 (1.1)
SOMNOLENCE	6 (6.4)	0 (0.0)
URINARY FREQUENCY	6 (6.4)	0 (0.0)
BACK PAIN	5 (5.3)	0 (0.0)
HEMATURIA	5 (5.3)	0 (0.0)
HYPERTONIA	5 (5.3)	0 (0.0)

The overall incidence of severe events (excluding those judged by the investigator as definitely not treatment-related) was low (8 patients, 9%), with no single event having had a disproportionate number of occurrences. Each of the ten severe events was reported by only one patient each. All of the above events are either consistent with symptoms commonly seen in metastatic prostate cancer patients (COSTART: PAIN, ASTHENIA, URINARY FREQUENCY, BACK PAIN, AND HEMATURIA), expected with leuprolide treatment (COSTART: VASODILATATION, TESTICULAR ATROPHY, and INJECTION SITE PAIN), or generally consistent with the population studied (including testicular atrophy).

Thirteen (14%) patients reported one or more injection site events (discomfort, tenderness, soreness, swelling, pain, or nodule) (COSTART: INJECTION SITE REACTION, INJECTION SITE PAIN, OR INJECTION SITE MASS), with a total of 18 such events during the first 24 weeks of treatment. All but three were mild in severity, with the

remainder having been moderate in severity. None of these required treatment for the reaction, and all but two resolved within seven days of onset.

A display of the grouping of COSTART terms for the package insert can be found in End-of-Text Table 13. A summary of adverse events, by body system, with definite probable, possible, or unknown relationship to treatment with COSTART terms grouped for the package insert, is presented in End-of-Text Table 14.

b) <u>Adverse Events During the First Two Weeks of Treatment</u>

During the agonist phase of leuprolide treatment, occurring shortly after the initiation of treatment, an increase in serum testosterone to above pretreatment levels usually occurs. This has been seen with both the daily injection and monthly depot formulations, as well as with the 22.5 mg formulation as reported earlier. This effect usually peaks within the first week after the initial depot injection, and may theoretically result in a transient exacerbation of disease-related symptoms, especially bone pain. For this reason the appearance of new adverse events and adverse events increasing in severity level during the first two weeks of treatment with the 22.5 mg formulation were examined.

A summary of adverse event incidence by body system during this period is presented in End-of-Text Table 11. Forty-six (49%) of the 94 total patients experienced one or more adverse events during the initial two weeks of treatment. Seven (7%) of the patients experienced severe events. These all involved different events, and only one involved pain. Hot flashes was again the most frequently (13%) reported event during this time.

Sixteen (17%) patients reported new onset pain (includes COSTART codes PAIN, PELVIC PAIN, BACK PAIN, AND BONE PAIN) during the initial two weeks and four (4%) reported exacerbation of existing pain. Only one of these cases (which was apparently not related to prostate cancer) resulted in hospitalization. Two (2%) patients experienced an increase in urinary frequency (COSTART: URINARY FREQUENCY); there was one (1%) case of urinary retention (COSTART: URINATION IMPAIRED) which was unrelated to prostate cancer. There were no cases of spinal cord compression. None of the percentages for the individual events mentioned above during this period accounted for the majority of the total percentage of occurrence during the 24-week treatment period for that event.

c) <u>Premature Terminations Due to Adverse Events</u>

A total of six patients terminated prematurely at least in part due to an adverse event, three from M91-583 and three from M91-653. The adverse event was not the primary reason for termination in four of these cases (two from M91-583 and two from M91-653). In M91-583 one patient died from a myocardial infarction, one patient terminated from the study due to pleural effusion secondary to lung cancer, and the third patient experienced exacerbation of chronic obstructive pulmonary disease which was present prior to treatment. In M91-653 one patient died from heart failure, one patient experienced an increase in back pain (secondary to progression of bony metastatic disease), and one patient discontinued due to intolerable hot flashes. The investigator indicated that, with the exception of the last event, none of these events was related to treatment.

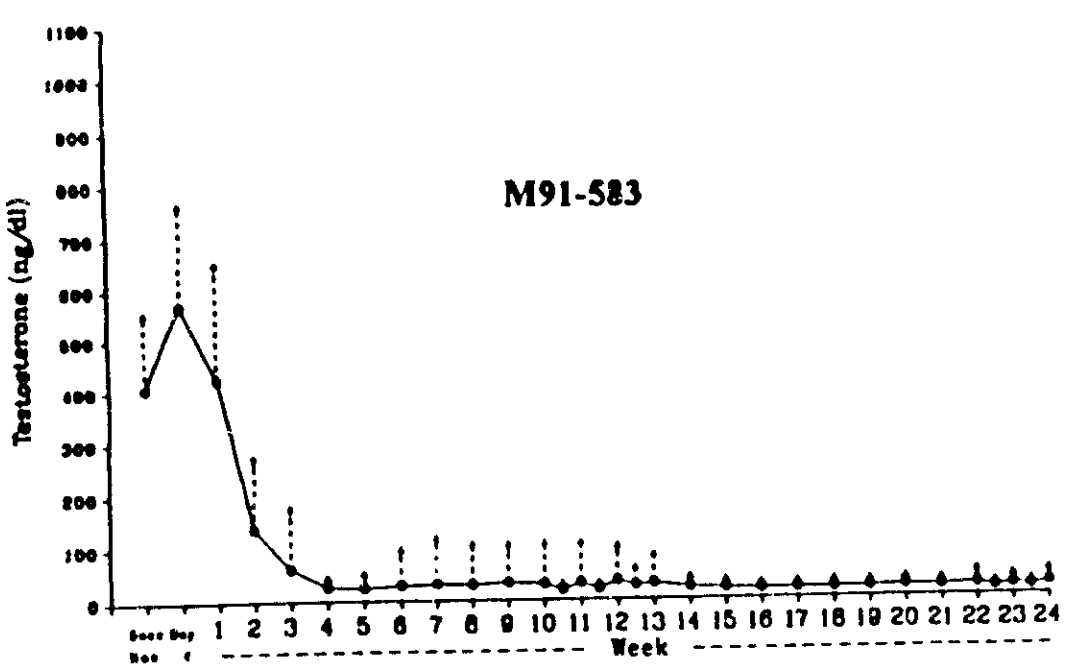
Two patients in M91-583 died from prostate cancer during the treatment period.

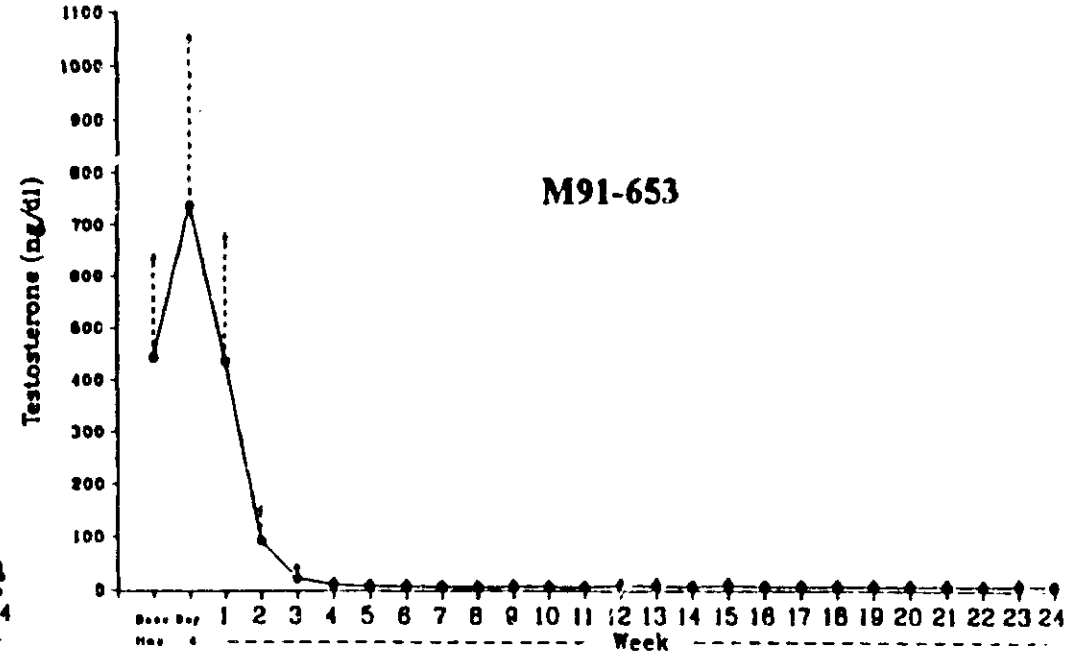
(7.) **Conclusions - Safety**

Changes in safety parameters were consistent with the known safety profile of leuprolide. The statistically significant changes observed in laboratory parameters were mostly small and clinically insignificant. The tendency toward elevations in serum lipid levels is also consistent with changes expected with treatment with GnRH analogs. Adverse events experienced by patients in the studies are those commonly seen in metastatic prostate cancer patients or in association with hypoandrogenism. The injection site reactions observed were mostly mild (none were severe) and were generally of short duration. There did not appear to be an increase in disease-related symptomatology during the agonist phase of treatment. The leuprolide 22.5 mg formulation appears to be safe when administered every 12 weeks.

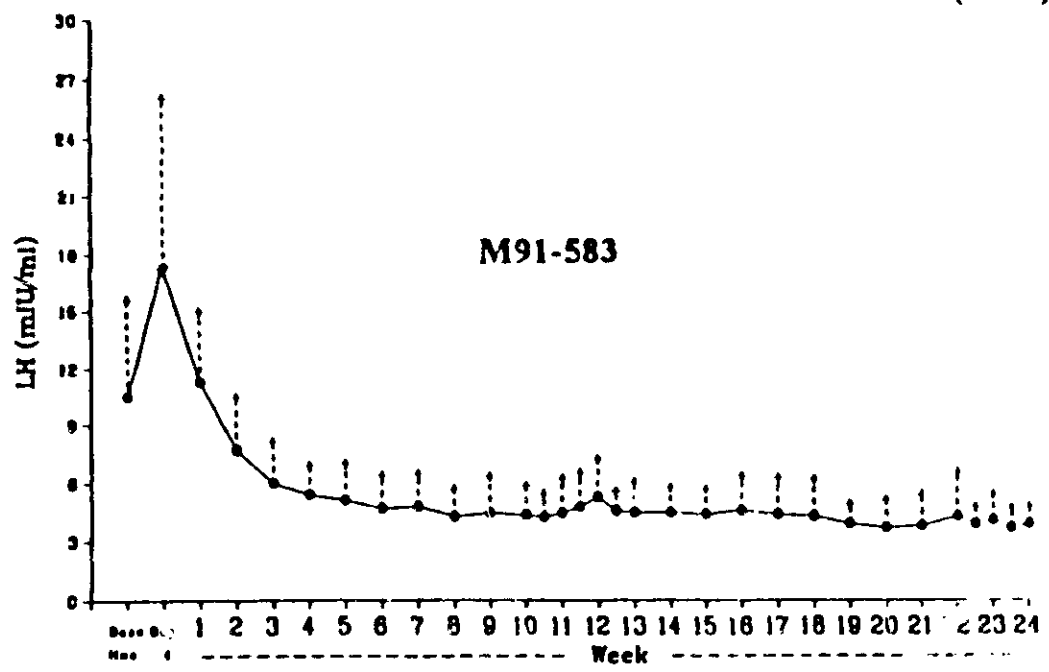
Figure 1

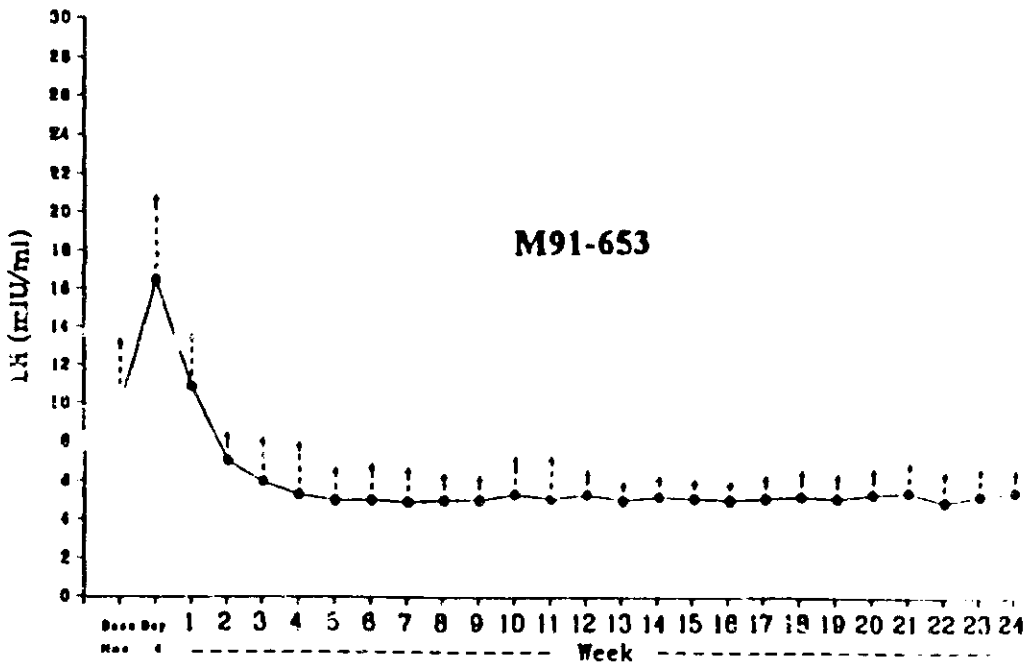
Mean (+ SD) Testosterone





Mean (+ SD) LH





MEMORANDUM OF CONSULTATION

DATE: April 6, 1995

BETWEEN: Jean L. Fourcroy, M.D. (HFD-510)

AND: Daniel N. Marticello (HFD-713)

SUBJECT: NDA 20-517 Lupron Depot - 3 month 22.5mg submitted December 21, 1994

As we discussed, the sponsor's submission consists of two open non-comparative multicenter studies which were submitted in support of the safety and efficacy of Lupron 22.5mg (a formulation change to the currently marketed Lupron Depot 7.5mg) for the palliative treatment of advanced prostatic cancer.

Consequently, as we agreed, we will not be conducting a formal statistical review of this submission.

However, as we discussed, we will certainly be available to address statistical issues as they arise in your review of the submission.

Daniel N. Marticello
Mathematical Statistician

cc:
ARCH NDA 20-517
HFD-510
HFD-510/SSobel
HFD-510/GFleming
HFD-510/JFourcroy
HFD-510/LPauls
HFD-344/ALisook
HFD-713/SDubey[File: DRU 1.3.2 NDA]
HFD-713/Group 2 File
HFD-713/DMarticello

This memorandum consists of 1 page of text.

PHARM REVIEW

DEC 19 1995

12-18-1995

NDA 20-517

TAP Pharmaceuticals Inc.
Deerfield, IL

Submission dated: 12-21-1994 Received at CDER: 12-23-1994

Pharmacology Review of Original NDA Submission

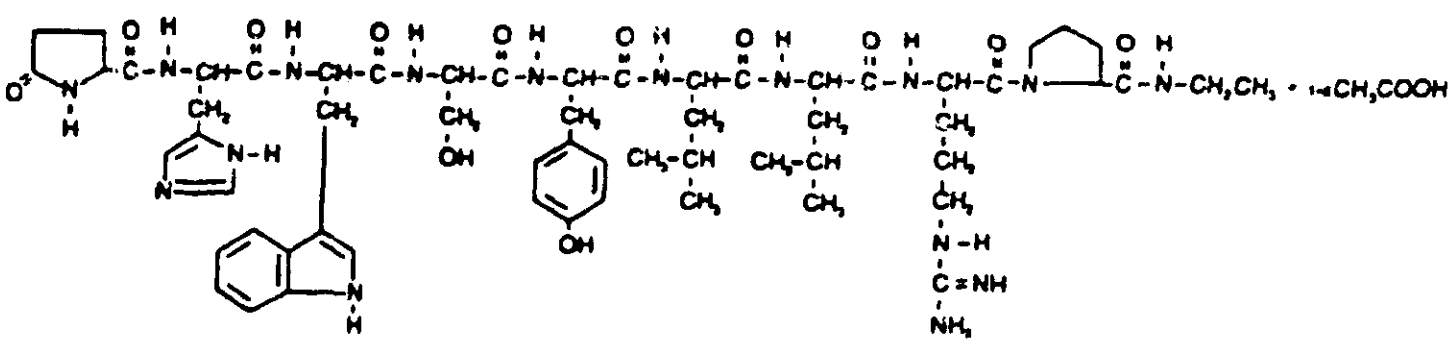
Drug's established name: Leuprolide acetate for depot suspension.

Proprietary name: Lupron Depot-3 month 22.5 mg

Code names: TAP-144-SR (3M), Abbott-43818

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.
(D-Leu , des-Gly-NH2 , Pro-ethylamide)-GnRH.

Structural formula:



Dosage form: Sterile suspension for injection

Route of administration: Intramuscular injection

Proposed indication: Palliative treatment of advanced prostatic cancer.

Related INDs and NDAs: IND (Lupron Depot); NDA 19-010 (Lupron injection), NDA 19-943 (Uterine fibroids), NDA 19-732 (Lupron Depot 7.5 mg), NDA 20-011 (Lupron Depot 3.75 mg) and NDA 20-263 (Lupron Depot-PED).

Lupron Depot 3 month 22.5 mg is the product which incorporates leuprolide into a biodegradable depot formulation as suspended at the time of use. It comes as a single dose vial containing sterile lyophilized microspheres. The vial contents composition is as follows:

leuprolide acetate, 22.5 mg
polylactic acid, 198.6 mg
D-mannitol, 38.9 mg

Each ampule of the sterile diluent used for suspension contains D-mannitol 100 mg; carboxymethylcellulose sodium, 10 mg; polysorbate 80, 2 mg; distilled water for injection, USP; and glacial acetic acid, USP to control pH.

The sponsor has stated that this product is similar to Lupron Depot 7.5 mg (Approved NDA 19-732) and uses the same drug substance (leuprolide acetate). The biodegradable polymer (polylactic acid) used in the manufacturing process of Lupron Depot 3 Month 22.5 has a different molecular weight (ranging from , resulting in leuprolide release over a more extended duration. Accordingly the quantity of the drug incorporated in the microspheres is three times (22.5 mg) to be released over the longer duration.
The amount of drug loaded in the microspheres also influenced the release profiles: microsphere loaded with drug at 9-12% gave a similar linear release of drug after s.c. injection but those loaded with 15 and 18% produced large initial burst. The amount of drug loaded was therefore set at 11%.

Preclinical studies:

The present Lupron Depot 3 month formulation was evaluated for drug release characteristics and pharmacologic effectiveness in rats and dogs and for potential to cause tissue irritation upon injection in rabbits.
These studies were conducted by the R&D division of Takeda Chemical Industries Ltd.

TAP-144-SR(3M) animal studies for drug release and pharmacological activities in rats and dogs after a single injection (T-2-1631).

It was reported that when rats were injected s.c. with

microspheres of polylactic acid of various molecular weights, there was a linear release of Lupron over 12-13 weeks with microspheres composed of _____ when measured in terms of % remaining in the microshperes from injection site excised skin.

When 5 male rats were injected a dose of 4.5 mg microcapsule/rat (approximately 100 ug/kg/day for 90 days) and 5 male dogs were given Lupron depot 3-month equivalent to 25.6 ug Lupron/kg/day (18.5 mg of drug in 1.5 ml of vehicle for a dog weighing 8 kg calculated over 90 day period), after an initial spike of Lupron which lasted for 2 days (about 6 ng/ml in rat and 3.5 ng/ml in the dog), Lupron concentrations were sustained in serum at about 0.5 ng/ml in the rat and 0.5-1.0 in the dog) for at least 15-16 weeks.

Serum testosterone measured in same dogs used to determine Lupron level, showed that after an initial spike (about 6 ng/ml) testosterone which lasted about 1-2 days, essentially comp[illegible] suppression of testosterone was observed for 15-16 weeks. Testosterone levels recovered to normal by 20 weeks after injection.

When serum testosterone was measured in groups of 5 rats given i.m. injections of 0.45, 1.35 and 4.5 ng microcapsule/rat, the results were similar to those seen in the dogs.

In an other study,, groups of 5 rats each were given s.c. injections of 4.5 mg microcapsules/rat. Testosterone response to 100 ug/kg injection of aqueous Lupron was determined at various times after microcapsule injection over a period of 18 weeks.

Results showed that complete suppression was achieved over the first 8 weeks and was sig suppressed over the entire 19 week period. Beginning week 13 after injection slight recovery of testosterone response was seen.

Using the same dose levels as described above, groups of 5 rats were used to see the effect on reproductive organs at various intervals after treatment as compared to age matched (10 week at the time of treatment) untreated controls.

Results showed that testis weights were suppressed by even the lowest dose of Lupron depot 3 month, while weights of prostate

and seminal vesicle were suppressed by the 3 higher doses during the period of 2-18 weeks after injection.

From results of the above studies, the sponsor concluded that Lupron depot 3-month exhibited the required characteristics of drug release and pharmacologic activity in rats and dogs over a period of 3 months after a single injection.

Intramuscular and subcutaneous irritation study of TAP-144-SR(3M) in rabbits (T-2-1656).

This study was conducted in accordance with FDA-GLP Regulations.

Composition for 1 g of TAP-144-SR(3M) was as follows: TAP-144 81.9 mg, polylactic acid 767.7 mg and D-mannitol 150.4 mg. Composition per ampule of the vehicle was same as outlined before.

Twelve 13-week old male Japanese white rabbits were administered I ml/site of Lupron depot 3 month intramuscularly and subcutaneously. The amount of microcapsules powder administered was 11.25 mg for intramuscular injection in the left lateralis muscle and 5.64 mg for s.c. injection in the abdominal region. An additional group of 12 rabbits were similarly administered vehicle.
Animals were observed for general clinical signs and examined for signs of local irritation at various time intervals after treatment. 3 animals/group were euthanized at 2 days, and 2, 13 and 21 weeks after injection for gross and histological evaluation of the injection sites.

Results: Muscle weight ratio (comparing treated left and untreated right muscle as indication of muscle swelling) was not affected (99.5-106.2 for control and 102.5-108.4 for treated). At necropsy, hemorrhage and test article like substance was seen at the i.m. injection site 2 days after treatment. Hemorrhage was not seen after 21 weeks test article like substance after 21 weeks. This was confirmed by histological examination. Vesicles thought to contain test compound were observed throughout the 21 week observation period. Fibrin deposition and muscle fiber degeneration were seen 2 days after injection but not at later. Granulation tissue and multinucleated giant cells were observed by 2 weeks after injection and these changes declined in severity 13 and 21 weeks after injection.

After s.c. injection, erythema at injection site was seen only on the first day of injection and swelling was observed through week 16. Upon necropsy, test article like substance was seen at 2 days and 2 weeks after injection and pale brown discoloration at 2 weeks and thereafter. Presence of test like article was observed histologically throughout the observation period. In addition macrophage and neutrophil infiltration were seen 2 days after injection. Granulation tissue with multinucleated giant cells were seen 2 weeks after injection but diminished in severity throughout the remainder of the 21 week observation period.
The observed changes were concluded to be of mild nature and were characterized mainly by foreign body reactions caused by the persistence of the microcapsule formulation.

Note: It is not clear why the sponsor has interchangeably used microspheres and microcapsule formulation.

Sponsor has submitted reprints of 2 publication which show that tissue reaction to biodegradable polylactic acid suture is similar to the reaction observed in present studies.

Clinical experience: The sponsor has conducted a PK study (Protocol M91-582) to measure plasma leuprolide levels for 20 weeks in prostate cancer patients following a single i.m. injection of a 22.5 mg depot formulation of leuprolide in order to determine PK profile and assess the safety of the formulation.

Results of this study showed that the pattern of release of leuprolide during the 12 weeks following dosing with the 22.5 mg formulation was similar with the pattern during the 4 weeks following dosing with the monthly 7.5 mg formulation. Also maintenance of measurable leuprolide plasma levels throughout the 12 week dosing interval indicate that the 22.5 mg formulation is suitable for administering as a 3 month depot.

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

Recommendations: Based on the extensive experience, both preclinical and clinical with leuprolide depot and the present formulation being essentially similar to that approved before under various NDAs, Pharmacology recommends approval of NDA 20-517 for Lupron Depot - 3 Month 22.5 mg for palliative treatment of advanced prostate cancer.

Krishan L. Raheja 12/15/95

Krishan L. Raheja, D.V.M., Ph.D

A Jordan 12/19

Original NDA 20-517
HFD-. 15
HFD-510
HFD-510/A.Jordan
HFD-510/K.Raheja, 12-18-1995, N20517.ori

CHEM REVIEW

AUG - 7 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 20-517
Chemistry Review #: 2

Date Reviewed: August 7, 1995

Submission Type	Document Date	CDER Date	Assigned Date
Pre-submission	10/11/94	10/12/94	10/20/94
Original	12/23/94	12/27/94	1/6/95
Amendment	6/27/95	6/28/95	6/30/95
	7/28/95	7/31/95	8/2/95
	7/31/95	8/1/95	8/2/95

Name & Address of Applicant:

TAP Pharmaceuticals, Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Drug Product Name:

Proprietary: Lupron Depot 3 month 22.5 mg
Nonproprietary/Established/USAN: leuprolide acetate depot for suspension

Code Name: TAP-144-SR (3M)(22.5 mg)
Chem.Type/Ther.Class: 3S

Dosage Form: Lyophilized powder containing 22.5 mg leuprolide acetate imbedded in polylactic acid (PLA)

Strengths: 22.5 mg leuprolide acetate/vial

Conclusions and Recommendation:

The sponsor and the DMF holders have properly responded to chemistry deficiencies. Moreover, the established cGMP of Hikari Plant and Shonan Plant, Takeda Chemical Industries, Japan and Abbott Laboratories, USA is acceptable by the Office of Compliance. Because there are no more pending CMC issues, this application is approvable from chemistry viewpoint.

Chien-Hua Niu, Ph.D.
Review Chemist

cc: Org. NDA
HFD-510/Division File
HFD-510/CHNiu/8/7/95/Disc #2/NDA20517.002
HFD-510/LPauls
HFD-510/YYChiu
R/D init by: 8/7/95

Pauls

MAY 4 1995

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 20-517
Chemistry Review #: 1 Date Reviewed: May 3, 1995

Submission Type	Document Date	CDER Date	Assigned Date
Pre-submission	10/11/94	10/12/94	10/20/94
Original	12/23/94	12/27/94	1/6/95

Name & Address of Applicant: TAP Pharmaceuticals, Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Drug Product Name:

Proprietary:	Lupron Depot, 22.5 mg
Nonproprietary/Established/USAN:	Leuprolide acetate Depot for Suspension
Code Name:	TAP-144-SR (3M)(22.5 mg)
Chem.Type/Ther.Class:	3S
Pharmacological Category/Indication:	Palliative treatment of advanced prostatic cancer
Dosage Form:	Lyophilized powder containing 22.5 mg leuprolide acetate imbedded in polylactic acid (PLA)
Strengths:	22.5 mg leuprolide acetate/vial
Route of Administration:	Intramuscular injection

Conclusions and Recommendation:

The application is approvable from chemistry viewpoint provided that (1)the facilities are found be in compliance with cGMP regulations and (2) the chemistry deficiencies listed in the draft letters for the NDA along with DMFs are properly answered.

Chien-Hua Niu, Ph.D.
Review Chemist

cc: Org. NDA
HFD-510/Division File
HFD-510/CHNiu/5/3/95/Disc #2/NDA20517.001
HFD-510/LPauls
HFD-510/YYChiu
R/D init by:

5/4/95

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Environmental Impact Assessment Report (EIAR)

Included in the chemistry review dated August 7, 1995.

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Microbiology Review

No microbiology review is required for this application.

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

DSI Investigations

No DSI investigations were required per Medical Officer, Dr. Jean Fourcroy.

INTEGRATED

SUMMARY OF

SAFETY

Section VIII.F Integrated Summary of Safety

TABLE OF CONTENTS

END-OF-TEXT TABLES — No. of Pages

Section VIII.F Integrated Summary of Safety

TABLE OF CONTENTS (CONTINUED)

Section VIII.F Integrated Summary of Safety

1. Introduction

The clinical studies summarized in this NDA were designed to demonstrate the safety and efficacy of the 22.5 mg leuprolide depot formulation in the palliative treatment of advanced-stage prostate cancer patients. This section of the NDA summarizes the safety information for the first 24 weeks of treatment from two open-label studies. The 22.5 mg depot formulation was administered in both studies as an intramuscular injection every 12 weeks.

Patients continue treatment in the protocols for as long as clinical benefit continues.

Study M91-583 was designed as the pivotal study to demonstrate the safety and effectiveness of the 22.5 mg formulation, with a target enrollment of 60 patients. The supply of study drug used for this study was produced in a pilot plant, which manufactures supplies in limited quantities for investigational purposes. Since the marketed supply of the 22.5 mg formulation would be produced in a production plant, which manufactures supplies on a larger scale, a study was needed to demonstrate equivalence in effectiveness and safety between the two supplies of the 22.5 mg formulation. Study M91-653 was designed to demonstrate equivalence between the two supplies, with an original target enrollment of 15 patients. Unexpected difficulty in producing and maintaining testosterone suppression in a few patients in M91-583 resulted, following discussions with the FDA, in the target number of patients in study M91-653 being increased to 60 (Amendment No. 2). Following identification of a reason for some of the unfavorable results in M91-583, and after further discussions with the FDA, the target enrollment for M91-653 was reduced to 30 patients (Amendment No. 3).

2. Statistical Methods

Data from all patients who received leuprolide were included in the safety analysis. All p-values reported for the safety analysis are based on two-tailed tests.

Changes in vital signs and clinical laboratory variables from baseline to each visit were analyzed using paired t-tests. Crosstabulations of low, normal, and high (with respect to the normal range) clinical laboratory results at baseline with those at each treatment visit are presented.

The prevalence of adverse events during the 24-week treatment period was summarized using COSTART Coding Symbols for Thesaurus of Adverse Reaction Forms, 3rd Edition, Department of Health and Human Services. Adverse events that ended before the start of treatment were not included. All other adverse events were included unless 1) for patients who received a depot injection at Week 24, the event(s) occurred more than 87 (84 + 3) days after the Week 12 injection; 2) for all other patients, the event(s) occurred more than 126 (84 + 42) days after the last injection.

3. Patient Accountability/Treatment Exposure

A total of ninety-four patients received the 22.5 mg leuprolide depot formulation in studies M91-583 and M91-653. Seventy-eight (83%) completed the first 24 weeks of treatment and continued with the long-term phase of the study. Patients were considered to have prematurely terminated from a study if they did not receive the third depot injection. Sixteen (17%) patients discontinued from the study prior to receiving the third injection. All but four patients received the second depot injection.

The number of injections received is as follows:

	No. of Injections			
	1	2	3*	Total
M91-583	1	5	27	33
M91-653	3	7	51	61
Combined	4	12	78	94

* patients continuing in the study beyond the first 24 weeks of treatment

End-of-Text Table 1 lists the 16 patients who prematurely terminated, along with all the reasons given for their termination. The primary reasons for premature termination and the respective numbers of patients are summarized below:

Primary Reasons for Discontinuation From Study
During the First 24 Weeks for All Patients

Reason	M91-583 (N=61)	M91-653 (N=33)	Combined (N=94)
Adverse event	1	1	2
Worsening of disease/symptoms	5	3	8
Death from prostate cancer	2	0	2
Death not from prostate cancer	1	1	2
Non-compliance with visit schedule	1	0	1
Uncertainty re: protocol continuation	0	1	1

Although not always considered the primary reason, six patients terminated, at least in part, due to an adverse event. This included two deaths from heart disease and two patients whose adverse event reflected worsening of disease symptoms (one of these patients also developed symptoms of progressive lung cancer, which was present prior to treatment), as well as intolerable hot flashes and chronic obstructive pulmonary disease, the last two having been considered the primary reason for termination in one patient each. Disease progression usually consisted of worsening of skeletal metastatic disease and consequent increase in pain. Two additional patients in M91-583 died from prostate cancer. One patient in M91-583 terminated due to non-compliance

with the visit schedule and one patient terminated in M91-653 due to uncertainty as to the continuation of development of the 22.5 mg formulation.

The following table summarizes the number of patients enrolled, the number who were efficacy evaluable, and the number who continued in the study beyond the initial 24 weeks of treatment.

Summary of Patients Enrolled, Evaluable, and Continuing Treatment

Study	No. of Investigators	No. of Enrolled Patients	No. of Evaluable Patients	Patients Continuing*
M91-583	13	61	60	51
M91-653	7	33	32	27

* received third Lupron Depot injection

4. Patient Demographics

Race, age, height, and body weight for all patients enrolled into the two efficacy and safety studies is summarized below. Sixty-eight percent of the patients were Caucasian, 30% were Black, and 2% were Hispanic. Ages ranged from 53 to 86 years (mean 70.3 years), heights from 61 to 75 inches (mean 68.6 inches), and body weights from 90 to 252 lbs. (mean 171.1 lbs.).

Summary of Demographic Characteristics for All Patients

Variable	M91-583 (N=61)	M91-653 (N=33)	Combined (N=94)
Race			
Caucasian	43 (70%)	21 (64%)	64 (68%)
Black	17 (28%)	11 (33%)	28 (30%)
Hispanic	1 (2%)	1 (3%)	2 (2%)
Age at Study Start			
mean (s.d.) in years	70.6 (7.2)	69.7 (7.4)	70.3 (7.3)
range in years	53-86	55-82	53-86
Height at Study Start			
mean (s.d.) in inches	68.7 (2.7)	68.5 (2.8)	68.6 (2.7)
range in inches	63-75	61-74	61-75
Weight at Study Start			
mean (s.d.) in lbs.	170.7 (33.0)	171.9 (28.9)	171.1 (31.8)
range in lbs.	100-252	90-232	90-252

5. Vital Signs and Body Weight

Systolic and diastolic blood pressures, pulse rates, and body weights are listed for each patient in Appendix E.6 in each of the individual study summaries, and corresponding summary statistics can be found in End-of-Text Table 2.

There were no statistically or clinically significant changes from pretreatment in mean systolic or diastolic blood pressure. Mean pulse rate decreased by 4.0 and 4.2 bpm at Week 24 and at the "final visit" in M91-583; these changes were statistically significant ($p<0.05$), but not indicative of a clinically significant trend. With respect to the combined data, the mean pulse rate at the "final visit" decreased by 2.9 bpm and this was statistically significant ($p<0.05$), but, again, not indicative of a clinically significant trend.

Changes from pretreatment in mean body weight were statistically significant at Weeks 12 and 24, and at the "final visit", in both studies. With respect to the combined data,

mean body weight increased by 3.1, 5.9, and 5.6 lbs. at Weeks 12, 24, and the "final visit" respectively. These changes were all significant ($p<0.001$). These results were not unexpected, since patients generally showed clinical improvement with treatment during the study. These increases in mean body weight paralleled the results obtained in the NDA study for the monthly depot formulation.

6. Clinical Laboratory Determinations

Pretreatment and treatment hematology, blood chemistry, and urinalysis results are listed for each patient in M91-583 in Appendices E.8, E.9, and E.10, respectively, in the individual summary for that study. These tests (with the exception of alkaline phosphatase) were performed only at pretreatment in M91-653, and these results can be found in the same appendices in the individual summary for that study.

Changes in mean values for M91-583 can be found in End-of-Text Table 3. End-of-Text Table 4 displays cross-tabulations of low, normal, and high laboratory results at baseline with those at Weeks 12, 24, and the "final visit" for M91-583. This table indicates shifts from normal values prior to treatment to out-of-range values in laboratory variables during treatment, as well as laboratory variables which were outside the normal range prior to treatment and remained there during treatment.

There were no major adverse or unexpected trends apparent in either of these analyses. There appeared to be a slight tendency toward decreases in the hemogram parameters, WBC, and % basophils, and elevations in total, HDL-, and LDL-cholesterol, triglycerides, SGPT, phosphorus, sodium, and glucose, as statistically significant increases in mean values for these variables (except triglycerides) occurred and the changes for most of these variables were reflected in the cross-tabulation tables. These increases, however, were not of the magnitude to be indicative of a clinically-significant trend, and were often attributed, by the investigator, to the underlying disease state, to non-fasting blood collection, or as being consistent with the age and status of the patient population studied.

As expected, pretreatment levels of alkaline phosphatase reflected the presence of bony metastatic disease. Changes during treatment reflected the continuing presence of, and presumably the treatment-related reduction in, bony metastatic disease. In M91-583, mean pretreatment alkaline phosphatase was elevated well above the normal range, but decreased considerably with treatment, although remaining above the normal range. In both M91-583 and M91-653, alkaline phosphatase was within the normal range and remained there during treatment in the majority of patients, but, as can be seen in the cross-tabulation tables, cases in which it increased to above the normal range or decreased to within the normal range during treatment, or was above the normal range prior to treatment and remained there during treatment, were common.

7. Adverse Events

A. Adverse Events During the First 24 Weeks of Treatment

Adverse events were summarized using COSTART coding symbols from the Thesaurus of Adverse Reactions Forms (3rd edition) prepared by the Department of Health and Human Services. All adverse events (including severity, duration, pattern, and etiology) reported during the first 24 weeks of treatment for each patient, and the corresponding medical, COSTART, and body system terms used for summarization, are listed in Appendix E.11 in each of the individual study summaries. A list of the COSTART terms by body system used in the studies, and the original medical terms from the raw data listings associated with them, are provided in End-of-Text Table 6.

A summary of all adverse events which occurred during the first 24 weeks of the study for each patient, regardless of severity or relationship to treatment, is presented, by body system, for each study separately, and then combined, in End-of-Text Table 7. The sum of the numbers of patients experiencing the various events within a given body system may exceed the marginal column total ("Patients

with one (or more symptoms") for that body system because a patient may have been included in the count for more than one COSTART term (symptom).

Adverse events were reported by 90 (96%) of the 94 total patients in the two studies. This proportion was similar in the two studies. Twenty-three (25%) patients reported severe adverse events. End-of-Text Table 8 summarizes the incidences of severe adverse events occurring within the first 24 weeks of treatment, regardless of relationship to treatment. The most common adverse event was VASODILATATION (COSTART), or hot flashes, occurring in 59% of the patients. Only one of these cases was severe. The following table summarizes the adverse events (regardless of relationship to treatment) that occurred in 10% or more of the patients.

Summary of Adverse Events Occurring at the ≥10% Incidence Level
for the Combined Studies (N=94)
(Disregarding Relationship to Treatment)

COSTART	No.(%) Patients	No.(%) Patients with Severe Events
VASODILATATION	55 (58.5)	1 (1.1)
PAIN	25 (26.6)	4 (4.3)
TESTICULAR ATROPHY	20 (21.3)	0 (0.0)
BACK PAIN	15 (16.0)	1 (1.1)
ARTHRALGIA	14 (14.9)	0 (0.0)
ASTHENIA	11 (11.7)	0 (0.0)
CONSTIPATION	11 (11.7)	0 (0.0)
INJECTION SITE PAIN	10 (10.6)	0 (0.0)

The incidence of adverse events which occurred during the first 24 weeks, excluding those judged by the investigator to definitely not be treatment-related, is summarized in End-of-Text Table 9. End-of-Text 10 provides the incidence of severe events within this category. In this analysis, 77 (82%) of the 94 total patients reported one or more adverse events. The incidence of hot flashes remained the same at 59%. The following table summarizes the adverse events which occurred in 5% or more of the patients when events definitely not

treatment-related are excluded. Patients with severe events are also summarized for COSTART terms meeting this criterion.

Summary of Adverse Events Occurring at the ≥5% Incidence Level for the Combined Studies (N=94) (Excludes Events Definitely Not Related to Treatment)

COSTART	No.(%) Patients	No.(%) Patients with Severe Events
VASODILATATION	55 (58.5)	1 (1.1)
TESTICULAR ATROPHY	19 (20.2)	0 (0.0)
PAIN	14 (14.9)	1 (1.1)
ARTHRALGIA	11 (11.7)	0 (0.0)
INJECTION SITE PAIN	10 (10.6)	0 (0.0)
ASTHENIA	7 (7.4)	0 (0.0)
CONSTIPATION	6 (6.4)	0 (0.0)
HEADACHE	6 (6.4)	1 (1.1)
NAUSEA	6 (6.4)	1 (1.1)
SOMNOLENCE	6 (6.4)	0 (0.0)
URINARY FREQUENCY	6 (6.4)	0 (0.0)
BACK PAIN	5 (5.3)	0 (0.0)
HEMATURIA	5 (5.3)	0 (0.0)
HYPERTONIA	5 (5.3)	0 (0.0)

The overall incidence of severe events (excluding those judged by the investigator as definitely not treatment-related) was low (8 patients, 9%), with no single event having had a disproportionate number of occurrences. Each of the ten severe events was reported by only one patient each. All of the above events are either consistent with symptoms commonly seen in metastatic prostate cancer patients (COSTART: PAIN, ASTHENIA, URINARY FREQUENCY, BACK PAIN, AND HEMATURIA), expected with leuprolide treatment (COSTART: VASODILATATION, TESTICULAR ATROPHY, and INJECTION SITE PAIN), or generally consistent with the population studied (including testicular atrophy).

Thirteen (14%) patients reported one or more injection site events (discomfort, tenderness, soreness, swelling, pain, or nodule) (COSTART: INJECTION SITE REACTION, INJECTION SITE PAIN, OR INJECTION SITE MASS), with a

total of 18 such events during the first 24 weeks of treatment. All but three were mild in severity, with the remainder having been moderate in severity. None of these required treatment for the reaction, and all but two resolved within seven days of onset.

A display of the grouping of COSTART terms for the package insert can be found in End-of-Text Table 13. A summary of adverse events, by body system, with definite probable, possible, or unknown relationship to treatment with COSTART terms grouped for the package insert, is presented in End-of-Text Table 14.

B. <u>Adverse Events During the First Two Weeks of Treatment</u>

During the agonist phase of leuprolide treatment, occurring shortly after the initiation of treatment, an increase in serum testosterone to above pretreatment levels usually occurs. This has been seen with both the daily injection and monthly depot formulations, as well as with the 22.5 mg formulation as reported earlier. This effect usually peaks within the first week after the initial depot injection, and may theoretically result in a transient exacerbation of disease-related symptoms, especially bone pain. For this reason the appearance of new adverse events and adverse events increasing in severity level during the first two weeks of treatment with the 22.5 mg formulation were examined.

A summary of adverse event incidence by body system during this period is presented in End-of-Text Table 11. Forty-six (49%) of the 94 total patients experienced one or more adverse events during the initial two weeks of treatment. Seven (7%) of the patients experienced severe events. These all involved different events, and only one involved pain. Hot flashes was again the most frequently (13%) reported event during this time.

Sixteen (17%) patients reported new onset pain (includes COSTART codes PAIN, PELVIC PAIN, BACK PAIN, AND BONE PAIN) during the initial two weeks

and four (4%) reported exacerbation of existing pain. Only one of these cases (which was apparently not related to prostate cancer) resulted in hospitalization. Two (2%) patients experienced an increase in urinary frequency (COSTART: URINARY FREQUENCY); there was one (1%) case of urinary retention (COSTART: URINATION IMPAIRED) which was unrelated to prostate cancer. There were no cases of spinal cord compression. None of the percentages for the individual events mentioned above during this period accounted for the majority of the total percentage of occurrence during the 24-week treatment period for that event.

C. <u>Premature Terminations Due to Adverse Events</u>

A total of six patients terminated prematurely at least in part due to an adverse event, three from M91-583 and three from M91-653. The adverse event was not the primary reason for termination in four of these cases (two from M91-583 and two from M91-653). In M91-583 one patient died from a myocardial infarction, one patient terminated from the study due to pleural effusion secondary to lung cancer, and the third patient experienced exacerbation of chronic obstructive pulmonary disease which was present prior to treatment. In M91-653 one patient died from heart failure, one patient experienced an increase in back pain (secondary to progression of bony metastatic disease), and one patient discontinued due to intolerable hot flashes. The investigator indicated that, with the exception of the last event, none of these events was related to treatment.

Two patients in M91-583 died from prostate cancer during the treatment period.

8. *Conclusions - Safety*

Changes in safety parameters were consistent with the known safety profile of leuprolide. The statistically significant changes observed in laboratory parameters were mostly small and clinically insignificant. The tendency toward elevations in

serum lipid levels is also consistent with changes expected with treatment with GnRH analogs. Adverse events experienced by patients in the studies are those commonly seen in metastatic prostate cancer patients or in association with hypoandrogenism. The injection site reactions observed were mostly mild (none were severe) and were generally of short duration. There did not appear to be an increase in disease-related symptomatology during the agonist phase of treatment. The leuprolide 22.5 mg formulation aprears to be safe when administered every 12 weeks.

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Advertising Material

No advertising material has been submitted.

CORRESPONDENCE

NDA 20-517

Aruna Dabholkar, M.D.
Regulatory Products Manager

Items required from TAP Holdings, Inc. before approval of the application may be granted.

1. Phase 4 Commitments:

   a. To perform a multiple-dose (4 doses; 1-year) pharmacokinetic/ pharmacodynamic (PK/PD) study including measurements of testosterone. The Division of Pharmaceutical Evaluation II should be contacted to review the protocol prior to the initiation of this study.

   b. To perform a 6-month study comparing the 1-month depot vs. the 3-month depot to determine the possible stimulation with reinjection between the two formulations. The Division should be contacted to review the protocol prior to the initiation of the study.

2. Labeling revisions:

   a. DESCRIPTION section (page 1)

      In the second paragraph after the phrase "ONCE EVERY THREE MONTHS", the phrase "(84 days)" should be added in bold face type.

   b. CLINICAL STUDIES section (page 3)

      1. In the first paragraph, the end of the first sentence of the that currently reads ". . . in three patients", a new sentence that reads "One patient did not suppress for 28 weeks" should be added.

      2. In this same paragraph, at the end of the second sentence that reads ". . . a subsequent injection", a new sentence that reads "This represents a stimulation of gonadotropin secretion" should be added.

   c. DOSAGE AND ADMINISTRATION section (page 7)

      In the first paragraph after the phrase "one injection every three months", the phrase "(84 days)" should be added in bold face type.

Please contact me at 301-443-3510 with any questions. A fax with the complete package insert (with revisions) along with a cover letter committing to perform the Phase 4 studies will be sufficient.

NDA 20-517

MAY 17 1995

Tap Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your pending December 23, 1994, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron® (leuprolide acetate) Depot, 22.5 mg.

We have completed our review of the Manufacturing/Quality Control section of your submission and have identified the following deficiencies:

Polylactic Acid:

Deficiencies in the manufacturing and chemistry controls for polylactic acid (DMF will be communicated directly to the manufacturer,

Reference Standard for the Drug Substance:

1. During preparation of the reference standard, four different lots of bulk leuprolide acetate were used (Vol 1.1, p. 144, October 11, 1994 submission). Do these lots have different purities to begin with?

2. Although the reference standard was characterized by elemental analysis, UV, amino acid analysis and proton-NMR, this standard should be sequenced to ensure that it has correct amino acid sequence. To determine the peptide sequence, either mass spectrometry or amino acid sequencing can be used. If mass spectrometry is employed, the fragmentation pattern of leuprolide acetate should be clearly illustrated.

Manufacturing and Processing for Lupron Depot, 22.5 mg:

1. The results from the differential scanning calorimetry (DSC) study of PLA indicate that the glass transition temperature of polylactic acid (PLA) is between (see Fig. 5, p. 49, Vol. 1.1, submission dated October 11, 1994). In addition, the stability data also indicate that changes in appearance, drug release, and molecular weight of PLA were observed when TAP-144-SR (3M; 22.5 mg) was stored at However, in the manufacture of TAP-144-SR (3M; 22.5 mg), '

3. It is possible that leuprolide acetate may react with PLA to form a drug-polymer product during the manufacturing and processing of Lupron Depot, 22.5 mg. Therefore, the same analytical method that was developed for monitoring the complex in Lupron Depot, 7.5 mg, to characterize and determine the drug polymer product in TAP-144-SR(3M)(22.5 mg) should be employed.

4. In the package insert (p. 10, Vol. 2.2, submission dated December 21, 1994) you indicate that "During the manufacturing of Lupron Depot, 22.5 mg, acetic acid is lost leaving the peptide". Experimental evidence should be provided to support this statement.

Stability:

Please propose an expiration date based on the stability data provided.

Labeling:

Please submit the carton label for the kit containing a microsphere vial and a vehicle ampule.

Environmental Impact:

In your environmental assessment, you indicate that both the drug product and vehicle are manufactured in Shonan Plant (Fujisawa City, Kanagawa, Japan). Please provide a letter issued by the Japanese government authority certifying that the manufacturing site is in compliance with Japan's environmental laws.

Please note, additional chemistry information has been requested from Takeda Chemical Industries, Ltd. concerning their DMF

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

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

G Troendle 5-16-95
for

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-517
HFD-510/Div. Files
HFD-510/CSO/L.L.Pauls
HFD-510/CNiu/YYChiu
DISTRICT OFFICE

drafted: LPauls/May 10, 1995/N20517IR.chm

Concurrences:
CNiu, YYChiu 05.15.95

INFORMATION REQUEST (IR)

LLP 5/15/95

NDA 20-517

OCT 19 1994

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

Dear Dr. Dabholkar:

We have received your presubmission of chemistry, manufacturing and controls information for the following:

Name of Drug Product: Lupron Depot® (leuprolide acetate for depot suspension), 22.5 mg

Date of Application: October 7, 1994

Date of Receipt: October 11, 1994

Our Reference Number: NDA 20-517

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. Should you have any questions regarding this information, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Our willingness to accept your pre-submission is based upon the condition that the full application will be submitted no sooner than 90 days nor later than 120 days from the date of your submission.

Please cite the NDA number assigned to this application at the top of the first page of every communication concerning this application.

Sincerely yours,

10/18/94

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc:
Orig. NDA
DISTRICT OFFICE
HFD-510
HFD-510/YYChiu
HFD-511/LPauls/10.14.94/N20517AK.PRE
PRESUBMISSION ACKNOWLEDGEMENT (AC)

NDA 20-517

JAN 25 1994

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

Dear Dr. Dabholkar:

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

Name of Drug Product: Lupron Depot® (leuprolide acetate for depot suspension), 22.5 mg

Therapeutic Classification: S

Date of Application: December 21, 1994

Date of Receipt: December 23, 1994

Our Reference Number: NDA 20-517

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 21, 1995, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

elmg 1/5/94

Enid Galliers
Chief, Project Management Staff
Division of Metabolism
and Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc
Orig. NDA
DISTRICT OFFICE
HFD-80/RBrown
HFD-510
HFD-510/JFourcroy/YYChiu/CNiu/AJordan
HFD-510/LPauls/01.05.94/N20517.ACK

ACKNOWLEDGEMENT - AC

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Arrowsmith Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

1.4 NDA
12/21/95

December 21, 1995

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517

Dear Doctor Sobel:

Attached is a final draft of the package insert.

The revised package insert incorporates all the changes recommended by the Medical and Biopharmaceutics reviewers. All revisions are underlined.

TAP Holdings Inc. also commits to perform the two Phase 4 studies as indicated in your facsimile December 21, 1995.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc.

Lincolnshire Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

December 19, 1995

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Lana Pauls

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517

Dear Ms. Pauls:

Enclosed is a diskette (Wordperfect 6.0) containing the revised package insert. Please note that we have added the CLINICAL STUDIES Section after PHARMACOKINETICS Section to address the issues mentioned in Dr. Fourcroy's fax today.

I am faxing a copy to Dr. Fourcroy for her review.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

ORIGINA

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Bannockburn Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

September 29, 1995

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517
Amendment No. 007

Dear Doctor Sobel:

Pursuant to 21 CFR §314.60, the Sponsor, TAP Holdings Inc., submits this amendment to NDA 20-517 submitted on December 21, 1994.

This amendment contains the response (data) to a question asked by the Biopharmaceutics reviewer (Dr. Ahn). The data submitted here are the two additional tables (4A and 5A) for the Drug Metabolism Report (Appendix B) of the Summary of the Pharmacokinetic study M91-582. The Tables 4A and 5A present the weight-normalized plasma concentrations and AUC respectively.

The percent CV for plasma concentrations and AUC values increased when normalized with body weight. This indicates that body weight likely is not a contributing factor for the variability of the data.

A desk copy of these data and a Macintosh diskette was sent to Dr. Ahn on September 21, 1995.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

REVIEWS COMPLETED

CSO ACTION:

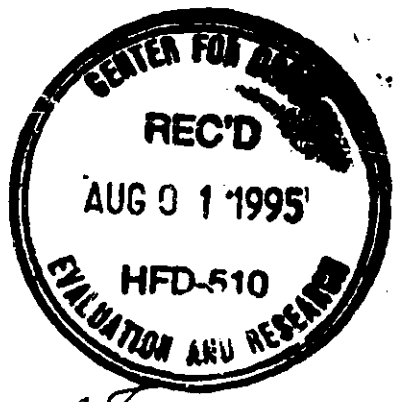
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Lannockburn Lake Office Plaza
355 Waukegan Rd
Deerfield, IL 60015

ORIGINAL



July 31, 1995

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Filed
Review completed
(see also Rev. #2.)
C Niu 8/3/95

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517
Amendment No. 004
Response to Question on CMC Section

Dear Doctor Sobel:

The Sponsor, TAP Holdings Inc., submits this amendment pursuant to CFR § 314.60.

This amendment to the referenced NDA contains response to one question that chemistry reviewer (Dr. Niu) asked over the telephone.

Attached is the response and information required for this amendment.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

ORIGINAL

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Shnockburn Lake Office Plaza
355 Waukegan Rd
Deerfield, IL 60015

July 28, 1995

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted
Reviewer copy left
(Lee Clem Rev. #2)
8/2/95

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517
Amendment No. 003

Dear Doctor Sobel:

The Sponsor, TAP Holdings Inc., submits this amendment pursuant to CFR § 314.60.

The information submitted in this amendment was requested over the phone by the chemistry reviewer (Dr. Niu).

A desk copy is mailed directly to Dr. Niu.

Attached is the information required for this amendment.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

ORIGINAL

CRIC ARCHIVE COPY

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

annockburn Lake Office Plaza
2355 Waukegan Rd
Deerfield, IL 60015

June 27, 1995

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-03, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Attn: Doctor Sobel

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517
Amendment No. 002
Response to Deficiency Letter

Noted
Chem. Rev. completed
(See Chem. Rev. #2)
6/7/95

Dear Doctor Sobel:

Attached please find the response to the deficiency letter dated May 17, 1995, regarding the Chemistry, Manufacturing and Controls section of the application.

Two copies of the response and appropriate attachments are enclosed. A desk copy of this submission is being mailed directly to the chemistry reviewer.

The sponsor, TAP Holdings Inc. requests to amend the NDA No. 20-517 and to continue your evaluation of the NDA.

Attached is the information required for this amendment.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachment

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 28 1995
HFD-510

TAP PHARMACEUTICALS INC.

ORIGINAL

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

March 8, 1995

ORIG AMENDMENT

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Mailed
Cliti
Mailed - 8/7/95.
3-13-95

Dear Doctor Niu:

I am sending you seven publications on Depot that we had in-house. I have also requested more information through Abbott's library. This may take about a week to receive. I will forward any additional information to you as soon as I receive it.

As I mentioned on the phone, the CMC section of NDA 20-517 (Lupron Depot 22.5 mg) has two publications attached at the end.

I hope this helps in your preparation of the abstract and the presentation.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

Attachments

CENTER FOR DRUG
REC'D
MAR 0 9 1995
HFD-510
EVALUATION AND RESEARCH

REVIEWS COMPLETED
CSO
DATE

TAP PHARMACEUTICALS INC.

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

NI CLINICAL DATA PER THASSALI 3/9/95

December 21, 1994

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Rockville, MD 20857

RE: NDA 20-517
Lupron Depot®-3 Month 22.5 mg for Palliative Treatment of Advanced Prostate Cancer (leuprolide acetate for depot suspension)

Gentlemen:

The sponsor, TAP Pharmaceuticals Inc., submits information for a New Drug Application (NDA) under the provision of Section 505(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR§ 314.50.

Pursuant to CFR §314.50 (d)(i)(iv), TAP Pharmaceuticals submitted the complete Chemistry, Manufacturing and Controls (CMC) section for this New Drug Application on October 7, 1994.

This submission consists of 17 volumes numbered 2.1 to 2.17, containing clinical study summaries, data, a summary report for the pharmacokinetics study, and Preclinical Study Summaries.

As previously requested, desk copies of the Clinical Summaries and Statistical tables are being submitted in appropriate software packages. The SAS data files for the two clinical studies are also being appended as desk copies for the statistician.

The check for the initial user fees ($104,000.00) was mailed on December 20, 1994.

TAP Pharmaceuticals certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306 (a) or (b)], in connection with this application.

Please direct any questions you may have on this application to my attention.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp

TAKEDA CHEMICAL INDUSTRIES, LTD.

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

October 7, 1994

ORIGINAL

Division of Metabolism and Endocrine Products, HFD-510
Document Control Room 14B-03
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Noted
Lli 8/7/95

RE: Drug Master File for TAP-144-SR(3M), Type II, DMF

Dear Sirs:

We hereby authorize the FDA to refer to the above Drug Master File for TAP-144-SR(3M) and all amendments, in the review of TAP Pharmaceuticals Inc., NDA 20-517 for this new depot formulation, submitted on October 7, 1994.

We hereby state that we commit to comply with the statements made in the DMF referenced above.

Appended is the authorization for me to act as a representative for Takeda Chemical Industries, Ltd., in the United States.

REVIEW COMPLETED

Sincerely,

Toshikazu Ban
Manager, Technical Liaisons
TAP Pharmaceuticals Inc.

cc
Takeda Chemical Industries, Japan
TAP Pharmaceuticals, Inc.

TB/jn

CENTER FOR DRUGS REC'D
OCT 14 1994
HFD-510
EVALUATION AND RESEARCH

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Advisory Committee Minutes

This NDA was never taken to an Advisory Committee.

NDA 20-517
Lupron Depot® (leuprolide acetate)
TAP Holdings, Inc.

Federal Register Notices

No notices appeared in the Federal Register for this application.

NDA 20517

3 month foem

Pk + Bio Rv

DRAFT

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-517
Lupron® Depot- 3 month
Leuprolide acetate 22.5 mg

SUBMISSION DATE: December 21, 1994
August 30, 1995
September 11, 1995
September 29, 1995

TAP Pharmaceuticals
Deerfield, IL

REVIEWER: Hae-Young Ahn, Ph.D.

TYPE OF SUBMISSION: New NDA

Code: 3S

SYNOPSIS: The sponsor has submitted a new NDA for Lupron Depot 3 month 22.5 mg for the palliative treatment of advanced prostate cancer. Lupron Depot 3 month 22.5 mg is intended as an intramuscular injection to be given once every three months.

The sponsor conducted a single dose pharmacokinetic study (Study M91-582) to support this NDA. (**Note:** There was no filing meeting for this NDA.) A method) was employed to measure the plasma levels of leuprolide. However, as stated in a bio-review of NDA 19-943 for Lupron Depot 3.75 mg (stamp dated 03/01/95), the method could not differentiate between intact leuprolide and one of the metabolites. Therefore, the plasma levels of leuprolide in this study should be considered as those of intact leuprolide and a metabolite.

There seems no relationship between body weights and plasma levels and/or AUC values. Simulation data for the plasma profile of leuprolide following 5 multiple doses was submitted upon request and it appears that accumulation is minimal.

RECOMMENDATION:
The Division of Pharmaceutical Evaluation II (HFD-870) has reviewed NDA 20-517 with its submissions of 12/21/94, 8/30/95, 9/11/95 and 9/29/95. HFD-870 feels that a multiple-dose pharmacokinetic study in patients is needed but it could be conducted post-approval if the NDA is approved based on clinical efficacy and safety data. Leuprolide plasma samples should be analyzed with the echnique which can identify intact leuprolide and metabolite.

Please convey the Recommendation and the Labeling Comment to the sponsor.

BACKGROUND: Lupron® (leuprolide) Injection was approved by the Agency in April, 1985 for the palliative treatment of advanced prostate cancer as a single daily subcutaneous injection. Since then, Lupron® Depot (leuprolide depot suspension) products designed for monthly intramuscular injections were approved by the Agency. Lupron® Depot 7.5 mg was approved under NDA 19-732 for the palliative treatment of advanced prostate cancer in 1989. Lupron® Depot 3.75 mg was approved for the management of endometriosis (NDA 20-011) in 1990 and for the treatment of leiomyomata uteri (NDA 19-943) on March 30, 1995. Leuprolide's therapeutic effect is related to suppressing gonadotropin hormon systemic plasma levels.

Study M91-582

Objective: To measure plasma leuprolide levels for 20 weeks in prostate cancer patients following a single intramuscular injection of a 22.5 mg depot formulation of leuprolide.

Study Design: An open, single-dose pharmacokinetic study.

1. **Population:**
   Twenty-three orchiectomized prostate cancer patients participated in the study. Eighteen patients had sufficient plasma concentration measurements for phamacokinetic analyses. The mean age of the 18 patients was 73 yr. (range: 61-84), the mean weight was 81 kg (range: 62-132) and the mean height was 175 cm (range: 163-188).

2. **Test Preparation:**
   The leuprolide depot formulation was supplied as a lyophilized powder, 22.5 mg (Lot No. 55-136-AR), which consists of leuprolide incorporated into a biodegradable lactic acid polymer in a single-dose vial, accompanied by a 2 mL ampoule of diluent (Lot No. 55-137-AR). This formulation was the to-be-marketed formulation.

3. **Drug Administration:**
   The leuprolide powder was reconstituted by adding 1.5 mL of the diluent to the powder. This suspension was then withdrawn from the vial using a 22 gauge needle and injected intramuscularly.

4. **Blood Collection for Leuprolide Plasma Level Determination:**
   Blood samples were collected during the following visits: just prior to the depot injection, four hours post-injection, at Days 1, 2, 4, twice weekly (at least three days apart) during Weeks 1 through 16, and then weekly during Weeks 17 through 20.

5. **Assay Methodology**

6. **Pharmacokinetic Methods**
   The area under the plasma concentration-time curve (AUCt) was calculated using the linear trapezoidal rule

Results

Premature Termination

Six patients prematurely dropped from the study. Two patients (numbers 208 and 211) dropped out within the first two days of the study due to an anticipated inability to remain compliant with the visit schedule. Patient 203 completed 19 weeks of the study and was unable to return for the Week 20 visit. Patient 204 was discontinued from the study at Week 4.5 due to progression of prostate cancer. Patient 301 died from prostate cancer at Week 19 of the study and Patient 403 discontinued at Week 12.5 due to hospitalization for heart failure.

Concomitant Medications

Twenty-one of the 23 patients enrolled in the study received concomitant medication. Medications most frequently taken were analgesics, antihypertensives, laxatives/cathartics/stool softeners, diuretics, antidepressants, and antibiotics. It was claimed by the sponsor that none of the medications taken should have interfered with the absorption or metabolism of leuprolide.

Pharmacokinetics

Of the 23 patients who participated in the study, 18 were included in the pharmacokinetic analysis and five were excluded on the basis of having insufficient data. (**Note:** Four patients prematurely discontinued in an early stage and were excluded in the data analyses. Although 2 patients could not complete the study, plasma levels were available up to 18 and 19 weeks and they were included in the data analyses. One patient who completed the study who had half of blood samples below assay sensitivity and/or missing samples was excluded in the data analyses.)

Commencing 4.5 weeks post-dosing, plasma leuprolide concentrations for one patient (212) were considerably higher than those for the other study patients, and therefore analyses were performed with and without this patient's data. The total AUC for this patient was approximately 2.6 fold higher than the mean AUC excluding his. The sponsor stated that several hepatic enzymes were substantially elevated prior to dosing and continued to rise during the study in this patient, and these relatively high leuprolide levels could possibly be attributed to non-specific liver pathology which might have interfered with the metabolism of leuprolide. Mean plasma leuprolide levels are displayed graphically in Figure 1 with this patient's data being included. In Figure 2 his data was excluded.

Figure 1. Mean (±SD) Plasma Leuprolide Concentrations After a Single Intramuscular Injection of a 3-Month 22.5 Mg Lupron Depot Formulation

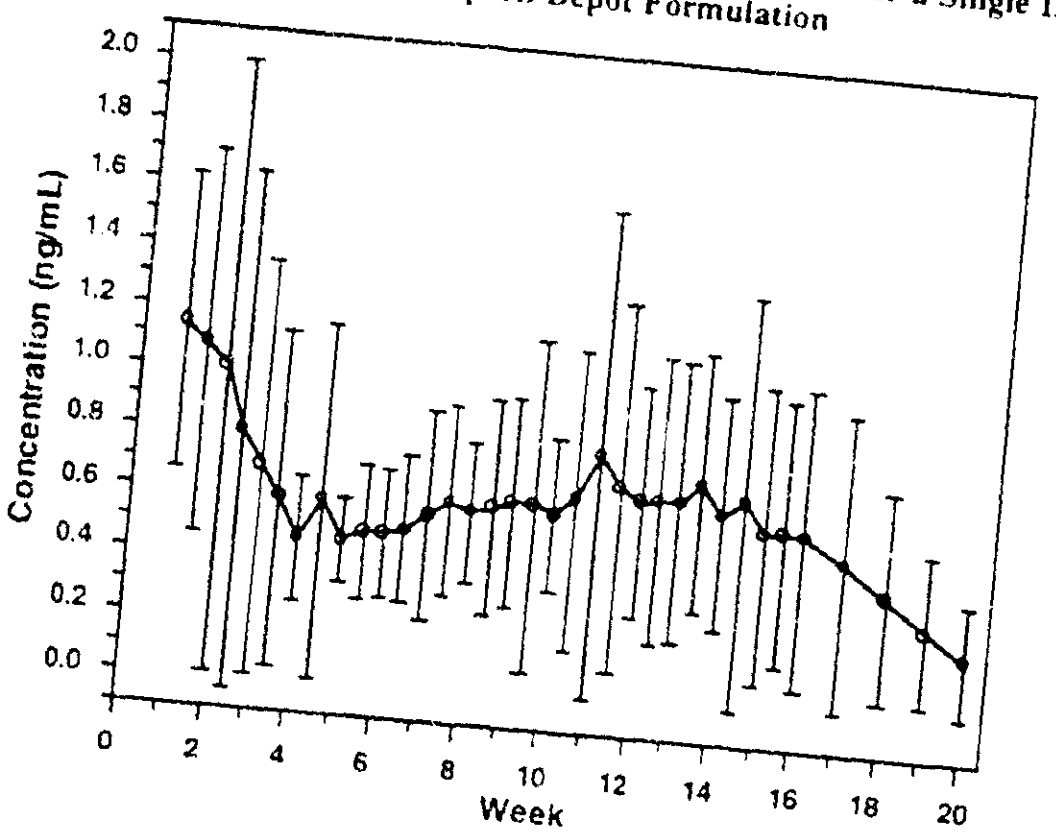
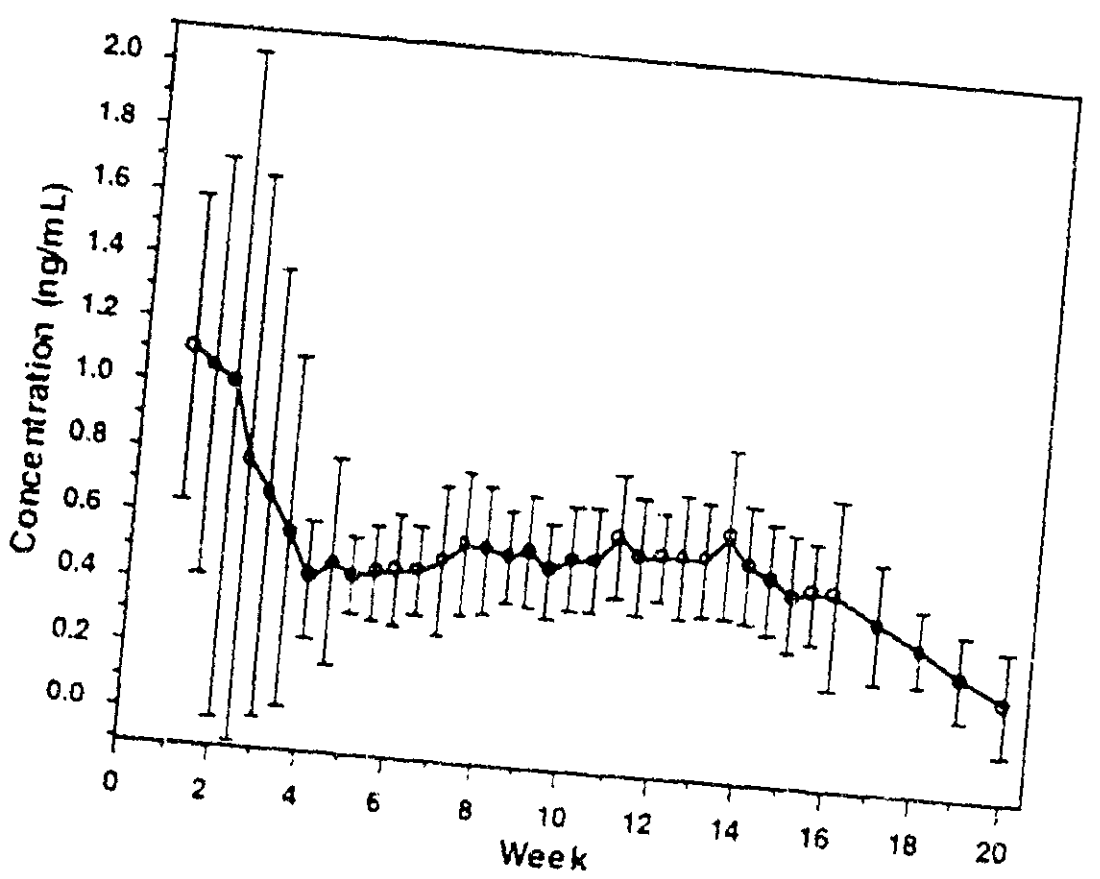


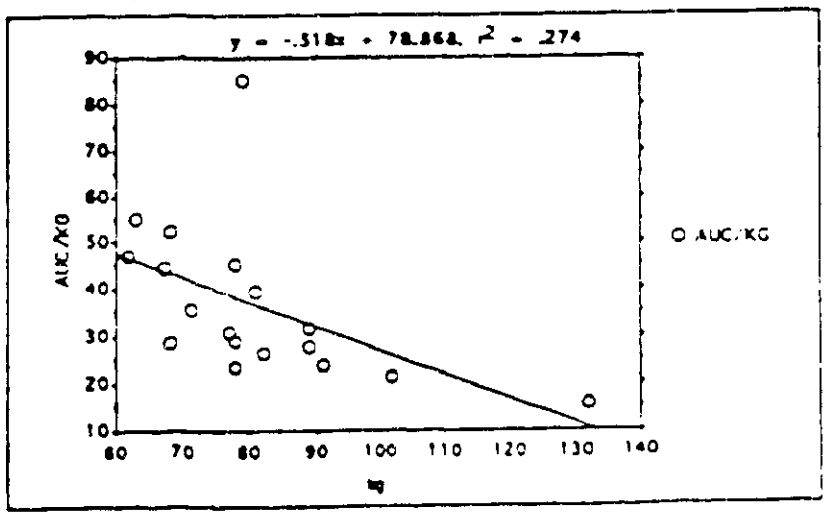
Figure 2. Mean (±SD) Plasma Leuprolide Concentrations After a Single Intramuscular Injection of a 3-Month 22.5 Mg Lupron Depot Formulation (Excluding Patient 212)

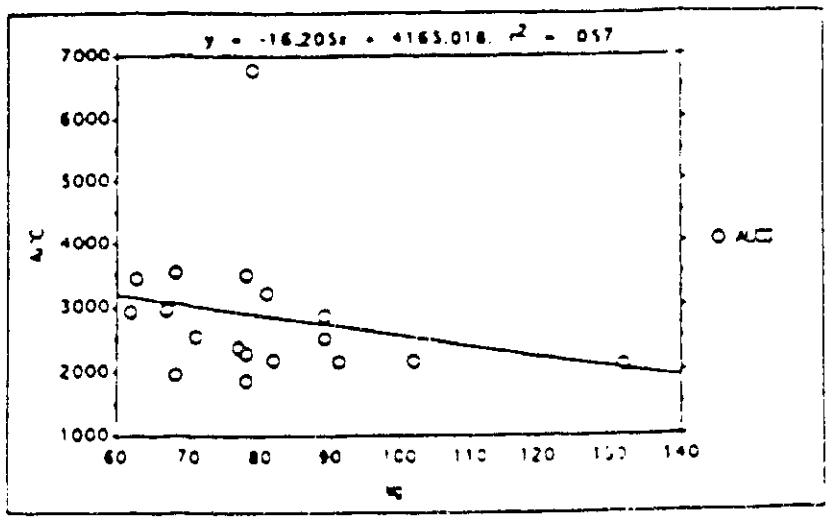


Following the administration of a single 22.5 mg intramuscular injection of leuprolide, the first plasma leuprolide level was measured at 4 hours post dosing when a mean plasma leuprolide level was 48.87 ng/mL. (Note: An initial plasma leuprolide level might be higher during the first few hours post dosing.) Following this initial burst of leuprolide in the plasma, which was also observed with the monthly depot formulations, the mean plasma leuprolide level declined to 4.86 ng/mL (4.75 ng/mL excluding Patient 212) 24 hours post-dosing and to 1.01 ng/mL (same excluding Patient 212) after two weeks. By Week 3, it had declined to 0.69 ng/mL (0.68 ng/mL excluding Patient 212) and remained relatively stable for the duration of the intended 12-week dosing interval, with mean plasma concentrations ranging from 0.46 to 0.81 ng/mL (0.43 to 0.63 ng/mL excluding Patient 212). After Week 12, the mean concentration changed little for another 2.5 weeks, after which it declined very gradually to a concentration of 0.23 ng/mL (0.20 ng/mL excluding Patient 212) by Week 20.

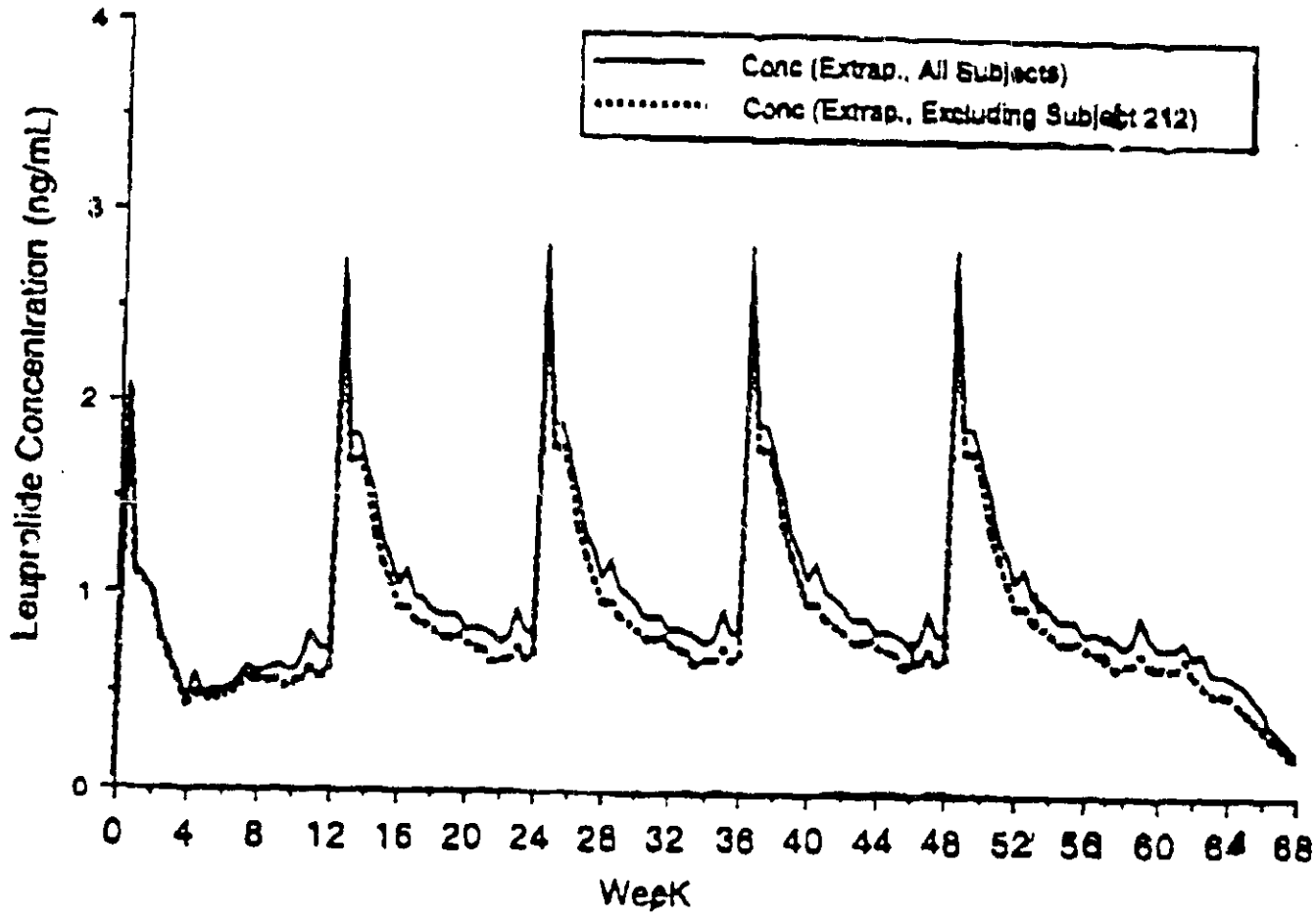
Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing, providing steady plasma concentrations through the intended 12-week dosing interval. The initial burst, followed by the rapid decline to this steady-state level, was similar to the release pattern seen with the monthly leuprolide depot 7.5 mg formulation as well as the 3.75 mg formulation.

Body Weight Normalization:
Upon request the sponsor normalized the plasma concentrations of leuprolide (plus a metabolite) and AUC values, based on patients' body weight. It did not appear that there was a relationship between body weights and pharmacokinetic parameters (Cmax and AUC). The percent CV for plasma concentrations and AUC values increased when normalized with body weights, which indicates that body weight may not be a contributing factor for the variability of the data.





Simulation for Multiple Doses:
The sponsor also conducted a simulation for the estimation of leuprolide acetate concentrations after five doses of the 22.5 mg leuprolide depot formulation. Since concentrations beyond Week 20 were not measured after the single dose, concentrations during Weeks 20 to 30 were estimated by linear extrapolation. The initial burst at hour 4 was ignored in the simulation because this transiently high concentration does not have any effects on the outcome of simulation.



Concentrations for Weeks 20.5 to 30 after a single dose were estimated by linear extrapolation.

It appears that accumulation is minimal. However, it is suggested that the sponsor conduct a multiple-dose pharmacokinetic study in patients.

PK/PD Analysis:
Since orchiectomized prostate cancer patients participated in the study, plasma testosterone levels could not be measured. Therefore, PK/PD analysis could not be conducted.

LABELING COMMENT:

1. Under the Pharmacokinetic section of the Clinical Pharmacology section of the package insert the following statement:

> "*Absorption*: Following.....Leuprolide appeared to be released at a constant rate following the onset of steady state levels during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. Detectable levels of leuprolide were present....."

should be changed to

> "*Absorption*: Following.....Leuprolide appeared to be released at a constant rate following the onset of steady state levels during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. Detectable levels of leuprolide were present....."

Hae-Young Ahn, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by J. Hunt 12/13/1995

FT initialed by John Hunt

cc: NDA 20-517, HFD-510 (Fourcroy, Pauls), HFD-860(Malinowski), HFD-870(Ahn, M. Chen), HFD-880(Fleischer), HFD-850(Lesko, Drug, Chron, Reviewer), HFD-205(FOI)

Table 1. Demographic Data of Patients and Time of Dose

PATIENT NUMBER	AGE (YEARS)	WEIGHT (KG)	HEIGHT (CM)	DATE OF DOSE	TIME OF DOSE
201					
202					
203					
204&					
205					
206					
207					
208&					
209					
210					
211&					
212					
213&					
301					
302					
303					
304					
305					
401					
402					
403&					
404					
405					
ALL PATIENTS					
MEAN	74	80	175		
MEDIAN	74	78	175		
S.D.	6	15	8		
LOW					
HIGH					
PATIENTS INCLUDED IN ANALYSIS					
MEAN	73	81	175		
MEDIAN	74	78	173		
S.D.	5	16	8		
LOW					
HIGH					

& - PATIENT NOT INCLUDED IN ANALYSIS

27MAY93 <M91582DE SAS T55KJP>

Table 4. Plasma Leuprolide Acetate Concentrations (ng/mL) Following Intramuscular Injection of a 22.5 Mg Leuprolide Acetate (Abbott-43818) Three Month Depot Formulation in Men

PATIENT NUMBER	PRE-DOSE	HOUR 4	DAY 1	DAY 2	DAY 4	WEEK 1	WEEK 1.5	WEEK 2	WEEK 2.5	WEEK 3	WEEK 3.5	WEEK 4
201												
202												
203												
~~204~~												
205												
206												
207												
~~208~~												
209												
210												
~~211~~												
212												
~~213~~												
301												
302												
303												
304												
305												
401												
402												
~~403~~												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	17	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.04	48.87	4.86	2.36	1.77	1.14	1.08	1.01	0.80	0.69	0.59	0.46
MEDIAN	0.0	49.9	4.6	2.3	1.8	1.1	1.0	0.7	0.6	0.5	0.5	0.4
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	16	17	17	17	17	17	17	17	17	17	17	17
MEAN	0.04	48.80	4.75	2.37	1.74	1.11	1.06	1.01	0.78	0.68	0.56	0.43
MEDIAN	0.0	49.6	4.5	2.4	1.8	1.0	0.9	0.6	0.6	0.5	0.4	0.4
S.D.												
CV												
LOW												
HIGH												

@ - MISSING VALUE ESTIMATED USING LINEAR INTERPOLATION FROM ACTUAL COLLECTION TIMES
& - PATIENT NOT INCLUDED IN SUMMARY STATISTICS

Table 4. Plasma Leuprolide Acetate Concentrations (ng/ml) Following Intramuscular Injection of a 22.5 Mg Leuprolide Acetate (Abbott-43818) Three Month Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
201												
202												
203												
~~204~~												
205												
206												
207												
~~208~~												
209												
210												
~~211~~												
212												
~~213~~												
301												
302												
303												
304												
305												
401												
402												
~~403~~												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.59	0.47	0.50	0.50	0.52	0.57	0.62	0.59	0.61	0.63	0.63	0.60
MEDIAN	0.4	0.5	0.4	0.4	0.5	0.5	0.6	0.5	0.5	0.6	0.6	0.6
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	0.48	0.45	0.46	0.47	0.48	0.51	0.57	0.56	0.54	0.56	0.51	0.55
MEDIAN	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.6	0.6
S.D.												
CV												
LOW												
HIGH												

@ - MISSING VALUE ESTIMATED USING LINEAR INTERPOLATION FROM ACTUAL COLLECTION TIMES
& - PATIENT NOT INCLUDED IN SUMMARY STATISTICS

Table 4. Plasma Leuprolide Acetate Concentrations (ng/mL) Following Intramuscular Injection of a 22.5 Mg Leuprolide Acetate (Abbott-43818) Three Month Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16
201												
202												
203												
~~204~~												
205												
206												
207												
~~208~~												
209												
210												
~~211~~												
212												
~~213~~												
301												
302												
303												
304												
305												
401												
402												
~~403~~												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.66	0.81	0.71	0.67	0.68	0.68	0.74	0.65	0.69	0.59	0.60	0.53
MEDIAN	0.6	0.6	0.6	0.6	0.6	0.6	0.7	0.6	0.5	0.5	0.5	0.5
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	0.55	0.63	0.57	0.58	0.58	0.58	0.66	0.57	0.53	0.49	0.50	0.50
MEDIAN	0.6	0.6	0.6	0.6	0.6	0.5	0.6	0.5	0.5	0.4	0.5	0.4
S.D.												
CV												
LOW												
HIGH												

@ - MISSING VALUE ESTIMATED USING LINEAR INTERPOLATION FROM ACTUAL COLLECTION TIMES
& - PATIENT NOT INCLUDED IN SUMMARY STATISTICS

Table 4. Plasma Leuprolide Acetate Concentrations (ng/mL) Following Intramuscular Injection of a 22.5 Mg Leuprolide Acetate (Abbott-43818) Three Month Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 17	18	19	20
201				
202				
203				
~~304~~				
205				
206				
207				
~~308~~				
209				
210				
~~311~~				
212				
~~313~~				
301				
302				
303				
304				
305				
401				
402				
~~403~~				
404				
405				
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY				
N	18	18	18	18
MEAN	0.52	0.42	0.32	0.23
MEDIAN	0.4	0.4	0.3	0.2
S.D.				
CV				
LOW				
HIGH				
SUMMARY STATISTICS EXCLUDING PATIENT 212				
N	17	17	17	17
MEAN	0.42	0.35	0.27	0.20
MEDIAN	0.4	0.3	0.3	0.2
S.				
CV				
LO				

@ - MISSING VALUE ESTIMATED USING LINEAR INTERPOLATION FROM ACTUAL COLLECTION TIMES
# - MISSING VALUE ESTIMATED USING LINEAR EXTRAPOLATION FROM ACTUAL COLLECTION TIMES (ESTIMATED VALUES <0 SET EQUAL TO)
& - PATIENT NOT INCLUDED IN SUMMARY STATISTICS

Table 5. Cumulative Areas Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men

PATIENT NUMBER	HOUR	DAY			WEEK						
	4	1	2	4	1	1.5	2	2.5	3	3.5	4
201											
202											
203											
205											
206											
207											
209											
210											
212											
101											
102											
301											
304											
305											
401											
402											
404											
405											
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY											
N	18	18	18	18	18	18	18	18	18	18	18
MEAN	94	623	710	792	910	988	1090	1154	1224	1266	1319
MEDIAN	93	603	699	789	919	976	1036	1079	1111	1136	1170
S.D.											
CV											
LOW											
HIGH											
SUMMARY STATISTICS EXCLUDING PATIENT 212											
N	17	17	17	17	17	17	17	17	17	17	17
MEAN	94	621	707	788	904	981	1082	1144	1214	1253	1304
MEDIAN	92	599	693	769	887	959	1028	1062	1095	1123	1162
S.D.											
CV											
LOW											
HIGH											

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <M91582C1 SAS T55KJP>

Table 5. Cumulative Areas Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
201												
202												
203												
205												
206												
207												
209												
210												
212												
301												
302												
303												
304												
305												
401												
402												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	1357	1407	1442	1490	1529	1581	1622	1682	1726	1785	1829	1889
MEDIAN	1196	1241	1274	1333	1372	1428	1473	1537	1584	1647	1690	1741
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	1337	1380	1414	1458	1494	1541	1578	1634	1675	1726	1764	1815
MEDIAN	1189	1240	1271	1324	1353	1401	1437	1490	1531	1582	1618	1654
S.D.												
CV												
LOW												
HIGH												

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <M91582C1 SAS T55KJP>

Table 5. Cumulative Areas Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16
201												
202												
203												
205												
206												
207												
209												
210												
212												
301												
302												
303												
304												
305												
401												
402												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	1934	2007	2060	2125	2176	2237	2291	2361	2406	2473	2507	2572
MEDIAN	1792	1852	1893	1947	1996	2060	2104	2153	2191	2263	2277	2340
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	1855	1914	1956	2009	2055	2106	2153	2213	2253	2308	2334	2391
MEDIAN	1702	1750	1779	1810	1853	1914	1961	2005	2047	2156	2162	2259
S.D.												
CV												
LOW												
HIGH												

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 ·M215820I SAS T55K1F·

Table 5. Cumulative Areas Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 17	18	19	20
201				
202				
203				
205				
206				
207				
209				
210				
212				
301				
302				
303				
304				
305				
401				
402				
404				
405				
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY				
N	18	18	18	18
MEAN	2662	2747	2810	2856
MEDIAN	2361	2453	2491	2530
S.D.				
CV				
LOW				
HIGH				
SUMMARY STATISTICS EXCLUDING PATIENT 212				
N	17	17	17	17
MEAN	2463	2532	2584	2625
MEDIAN	2262	2400	2448	2506
S.D.				
CV				
LOW				
HIGH				

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <M91582C1 SAS TYSK 1P>

Table 6. Percent of Total Area Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men

PATIENT NUMBER	HOUR 4	DAY 1	DAY 2	DAY 4	WEEK 1	WEEK 1.5	WEEK 2	WEEK 2.5	WEEK 3	WEEK 3.5	WEEK 4
201											
202											
203											
205											
206											
207											
209											
210											
212											
301											
302											
303											
304											
305											
401											
402											
404											
405											
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY											
N	18	18	18	18	18	18	18	18	18	18	18
MEAN	3.5	23.2	26.3	29.3	34	36	40	42	44	46	48
MEDIAN	3.5	23.9	26.5	29.4	32	36	40	42	44	45	47
S.D.											
CV											
LOW											
HIGH											
SUMMARY STATISTICS EXCLUDING PATIENT 212											
N	17	17	17	17	17	17	17	17	17	17	17
MEAN	3.6	24.0	27.2	30.3	34.7	37.6	41.2	43.4	45.9	47.3	49.1
MEDIAN	3.6	24.0	26.9	29.7	32.6	36.0	40.2	42.5	45.3	47.0	48.8
S.D.											
CV											
LOW											
HIGH											

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <M91582C2 SAS T55KJP>

Table 6. Percent of Total Area Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10
201												
202												
203												
205												
206												
207												
209												
210												
212												
301												
302												
303												
304												
305												
401												
402												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	49.0	50.6	51.9	53.6	55.0	56.8	58.2	60.3	61.8	63.9	65.4	67.4
MEDIAN	48.2	50.0	51.7	53.9	55.6	57.6	59.4	61.7	63.4	65.6	67.3	69.1
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	50.4	52.0	53.3	55.0	56.3	58.1	59.6	61.7	63.2	65.2	66.7	68.7
MEDIAN	49.9	51.5	53.4	55.3	56.6	58.4	59.7	62.0	63.9	65.7	67.5	69.2
S.D.												
CV												
LOW												
HIGH												

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <H91582C2 SAS T55KJP>

Table 6. Percent of Total Area Under the Plasma Concentration-Time Curves (ng•h/mL)) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16
201												
202												
203												
205												
206												
207												
209												
210												
212												
301												
302												
303												
304												
305												
401												
402												
404												
405												
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY												
N	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	69.0	71.4	73.1	75.3	77.1	79.2	81.1	83.5	85.1	87.3	88.4	90.6
MEDIAN	70.5	72.8	74.2	75.6	77.4	78.6	80.7	83.0	84.7	87.0	88.4	90.6
S.D.												
CV												
LOW												
HIGH												
SUMMARY STATISTICS EXCLUDING PATIENT 212												
N	17	17	17	17	17	17	17	17	17	17	17	17
MEAN	70.2	72.5	74.1	76.2	78.0	80.0	81.8	84.2	85.7	87.9	88.9	91.1
MEDIAN	70.6	72.8	74.8	75.7	77.6	78.6	81.2	83.0	85.0	87.2	88.6	90.7
S.D.												
CV												
LOW												
HIGH												

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

23MAY94 <M91582C2 SAS TSSKIP>

Table 6. Percent of Total Area Under the Plasma Concentration-Time Curves (ng•h/mL) Following Intramuscular Injection of a 22.5 Mg Three Month Lupron Depot Formulation in Men (Cont.)

PATIENT NUMBER	WEEK 17	18	19	20
201				
202				
203				
205				
206				
207				
209				
210				
212				
301				
302				
303				
304				
305				
401				
402				
404				
405				
SUMMARY STATISTICS FOR ALL PATIENTS WHO COMPLETED THE STUDY				
N	18	18	18	18
MEAN	93.6	96.4	98.4	100.0
MEDIAN	93.9	96.4	98.5	100.0
S.D.				
CV				
LOW				
HIGH				
SUMMARY STATISTICS EXCLUDING PATIENT 212				
N	17	17	17	17
MEAN	93.8	96.5	98.5	100.0
MEDIAN	94.2	96.6	98.5	100.0
S.D.				
CV				
LOW				
HIGH				

AREAS WERE CALCULATED USING ACTUAL TIMES OF SAMPLE COLLECTION AS GIVEN IN TABLES 2 AND 3.

(No.)

8-29-95

New commodity #

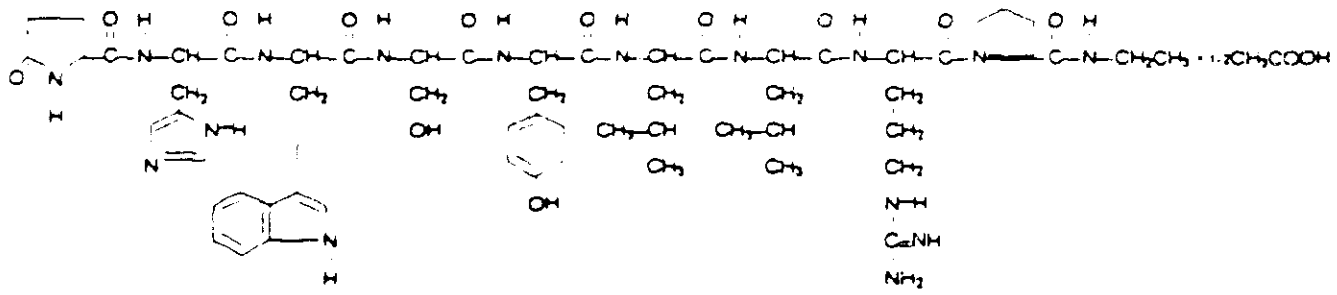
LUPRON DEPOT® - 3 Month 22.5 mg

(leuprolide acetate for depot suspension)

3-MONTH FORMULATION **(STATEMENT TO BE PRINTED IN COLOR)**

DESCRIPTION

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. The chemical name is 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt) with the following structural formula:



LUPRON DEPOT 22.5 mg is available in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS**.

The single-dose vial of LUPRON DEPOT 22.5 mg contains leuprolide acetate (22.5 mg), polylactic acid (198.6 mg), and D-mannitol (38.9 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (10 mg), D-mannitol (100 mg), polysorbate 80 (2 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 22.5 mg, acetic acid is lost leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon 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 the 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 patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

PHARMACOKINETICS

Absorption: Following a single injection of the three month formulation of LUPRON DEPOT 22.5 mg in patients, mean peak plasma leuprolide concentration of 48.9 ng/mL was observed at 4 hours and then declined to 0.67 ng/mL at 12 weeks. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing, providing steady plasma concentrations through the 12-week dosing interval. Detectable levels of leuprolide were present at all measurement points in all patients. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Metabolism: In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on two compartment model.

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, pentapeptide (Metabolite I), tripeptide (Metabolite II and III) and dipeptide (Metabolite IV). These fragments may be further catabolized.

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached mean maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of leuprolide concentrations.
Excretion: Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.
Special Populations: The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

INDICATIONS AND USAGE

LUPRON DEPOT 22.5 mg is indicated in the palliative treatment of advanced prostatic cancer. It offers an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient. In clinical trials, the safety and efficacy of LUPRON DEPOT 22.5 mg were similar to that of the original daily subcutaneous injection and the monthly depot formulation.

CONTRAINDICATIONS

A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

LUPRON DEPOT is contraindicated in women who are or may become pregnant while receiving the drug. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/600 to 1/6 the human dose) to rabbits, the monthly formulation of LUPRON DEPOT produced a dose-related increase in major fetal abnormalities. Similar studies in rats failed to demonstrate an increase in fetal malformations. There was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of LUPRON DEPOT in rabbits and with the highest dose in rats. The effects on fetal mortality are logical consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur if the drug is administered during pregnancy.

WARNINGS

Isolated cases of worsening of signs and symptoms during the first weeks of treatment have been reported with LH-RH analogs. Worsening of symptoms may contribute to paralysis with or without fatal complications. For patients at risk, the physician may consider initiating therapy with daily LUPRON® (leuprolide acetate) Injection for the first two weeks to facilitate withdrawal of treatment if that is considered necessary.

PRECAUTIONS

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy (see **WARNINGS** section).

Laboratory Tests: Response to LUPRON DEPOT 22.5 mg should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen and prostatic acid phosphatase. In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week. Castrate levels were reached within two to four weeks and once achieved were maintained for as long as the patients received their injections.

Drug Interactions: No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies were conducted in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice no pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems. These studies provided no evidence of a mutagenic potential.

Clinical and pharmacologic studies in adults (≥ 18 years) with leuprolide acetate and similar analogs have shown reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to 24 weeks.

Pregnancy Category X (See **CONTRAINDICATIONS** section.)

Pediatric Use: See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness of the monthly formulation in children with central precocious puberty.

ADVERSE REACTIONS

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment.

Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms (see **WARNINGS** section).

In two clinical trials of LUPRON DEPOT 22.5 mg, the following adverse reactions were reported to have a possible or probable relationship to drug as ascribed by the treating physician in 5% or more of the patients receiving the drug. **Often, causality is difficult to assess in patients with metastatic prostate cancer.** Reactions considered not drug related are excluded.

	LUPRON DEPOT	
	N=94	(Percent)
Body As A Whole		
Asthenia	7	(7.4%)
General Pain	25	(26.6%)
Headache	6	(6.4%)
Injection Site Reaction	13	(13.8%)
Cardiovascular System		
Hot flashes/Sweats*	55	(58.5%)
Digestive System		
GI Disorders	15	(16.0%)
Musculoskeletal System		
Joint Disorders	11	(11.7%)
Central/Peripheral Nervous System		
Dizziness/Vertigo	6	(6.4%)
Insomnia/Sleep Disorders	8	(8.5%)
Neuromuscular Disorders	9	(9.6%)
Respiratory System		
Respiratory Disorders	6	(6.4%)
Skin and Appendages		
Skin Reaction	8	(8.5%)
Urogenital System		
Testicular Atrophy*	19	(20.2%)
Urinary Disorders	14	(14.9%)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 22.5 mg.

Body As A Whole – Enlarged abdomen, Fever, *Cardiovascular System* – Arrhythmia, Bradycardia, Heart failure, Hypertension, Hypotension, Varicose vein; *Digestive System* – Anorexia, Duodenal ulcer, Increased appetite, Thirst/dry mouth; *Hemic and Lymphatic System* – Anemia, Lymphedema; *Metabolic and Nutritional Disorders* - Dehydration, Edema; *Central/Peripheral Nervous System* - Anxiety, Delusions, Depression, Hypesthesia, Libido decreased*, Nervousness, Paresthesia; *Respiratory System* - Epistaxis, Pharyngitis, Pleural effusion, Pneumonia; *Special Senses* - Abnormal vision, Amblyopia, Dry eyes, Tinnitus; *Urogenital System* - Gynecomastia, Impotence*, Penis disorders, Testis disorders

Laboratory: Abnormalities of certain parameters were observed, but are difficult to assess in this population. The following were recorded in ≥ 5% of patients: Increased BUN, Hyperglycemia, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Hyperphosphatemia, Abnormal liver function tests, Increased PT, Increased PTT. Additional laboratory abnormalities reported were: Decreased platelets, Decreased potassium and Increased WBC.

The following additional adverse reactions have been reported with other formulations of leuprolide acetate. Reactions considered by the treating physician as not related to drug are excluded.

Body As A Whole - Body odor, Infection/inflammation, Injection site abscess; *Cardiovascular System* – Angina, Congestive heart failure, ECG changes/ischemia, Myocardial infarction, Murmur, Palpitations, Phlebitis/thrombosis, Pulmonary emboli, Transient ischemic attack/stroke; *Digestive System* – Appetite changes, Constipation, Dysphagia, Gastrointestinal bleeding/disturbance, Gingivitis, Hard nodule in throat, Hepatic dysfunction, Peptic ulcer, Rectal polyps; *Endocrine System* – Accelerated sexual maturity, Androgen-like effects, Diabetes, Thyroid enlargement; *Hemic and Lymphatic System* - Lymphadenophathy; *Metabolic and Nutritional disorders* - Growth disorder, Hypoglycemia, Weight gain/loss; *Musculoskeletal System* – Ankylosing spondylosis, Myalgia, Pelvic fibrosis; *Central Peripheral Nervous System* – Emotional lability, Libido increase, Lethargy, Memory disorder, Numbness, Peripheral neuropathy, Personality disorder, Spinal fracture/paralysis, Syncope/blackouts; *Respiratory System* – Cough, Hemoptysis, Pleural rub, Pulmonary fibrosis, Pulmonary infiltrate, Sinus congestion; *Skin and Appendages* – Acne/Seborrhea, Carcinoma of skin/ear, Dermatitis, Dry skin, Ecchymosis, Erythema Multiforme, Hair loss/Growth/Disorders, Itching, Pigmentation, Skin lesions, Skin striae; *Special Senses* - Hearing disorders, Ophthalmologic disorders, Taste disorders; *Urogenital System* – Bladder spasms, Breast tenderness/pain, Cervix disorder, Lactation, Penile swelling, Prostate pain, Testicular pain, Urinary incontinence, Urinary obstruction, Vaginitis/bleeding/discharge; *Miscellaneous* - Swelling (temporal bone)

Laboratory – Hypoproteinemia, Increased creatinine, Increased calcium, Increased uric acid

*Physiologic effect of decreased testosterone

OVERDOSAGE

In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence at present that there is a clinical counterpart of this phenomenon. In early clinical trials with daily subcutaneous leuprolide acetate, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

DOSAGE AND ADMINISTRATION

LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.

The recommended dose of LUPRON DEPOT 22.5 mg to be administered is one injection every three months. Due to different release characteristics, a fractional dose of this 3-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given. **(THIS PARAGRAPH TO BE PRINTED IN COLOR)**

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every three months as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 23 gauge needle, withdraw 1.5 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)

2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.

3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, it is preferable that LUPRON DEPOT 22.5 mg be mixed and used immediately. Reshake suspension if settling occurs.

Although the potency of the reconstituted suspension has been shown to be stable for 24 hours, since the product does not contain a preservative, the suspension should be discarded if not used immediately.

As with other drugs administered by injection, the injection site should be varied periodically.

The vial of LUPRON DEPOT 22.5 mg and the ampule of diluent may be stored at room temperature.

HOW SUPPLIED

LUPRON DEPOT - 3 Month 22.5 mg (NDC 0300-xxxx-xx) is available in a single use kit. Each kit contains a vial of sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable polymer of polylactic acid. When mixed with 1.5 mL of accompanying diluent, LUPRON DEPOT 22.5 mg is administered as a single IM injection **EVERY THREE MONTHS**

NDA20517
S-001

APPROVED

DEC 3 1996

NDA 20-517/S-001

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

Dear Dr. Dabholkar:

Reference is made to your supplemental new drug application dated April 12, 1996, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot (leuprolide acetate for depot suspension) 3 month, 22.5 mg.

We also refer to your amendment dated May 21, 1996

This supplemental application provides for a dual chamber syringe as a new container closure system

We have completed the review of this supplemental application, as amended, and it is approved

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 Mr. Alvis Dunson at 310-827-5260

Sincerely yours,

MRhee 12/3/96

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

cc
Original NDA
HFD-580
HFD-580/MRhee/ADunson
HFD-80
HFD-232
DISTRICT OFFICE
HFD-222/YChiu
HFD-580/CKish/11-29-96/n20517ap s1
concurrences MRhee 12-3-96
SUPPLEMENT APPROVAL (S-001)

ORIGINAL

NOV 26 1996

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-580

2. NDA Number
20-517

3. Name amd Address of Appiicant
TAP Holdings Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Rd
Deerfield, Il 60015

4. Supplement
S-001 —
4-12-96

5. Name of Drug
Lupron Depot, 3-month, 22.5mg

6. Nonproprietary Name
Leuploride acetate for depot suspension

7. Supplement Provides For
A dual chamber syringe as a new container closure system.

8. Amendment
5-21-96 (Micro. Responses)

9. Pharmacological Category
Gonadorelin agonist

10. How Dispensed
Rx

11. Related
19-732 (S-009)

12. Dosage form
Lyophilized powder to be reconstituted for Injection (IM)

13. Potency
22.5mg

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 supplement dscribes a new container/closure system which is a

A similar dual chamber syringe (slightly smaller) was previously approved for NDA 19-732 (S-009). This supplement provides the following information I) CMC . information (vol. 6.1), III) Facilities and aseptic process validation (vol. 6.2), III) methods validation samples labels (vol.6.3). Consult for microbiology was sent on 5.28.96 and Microbiologist's review recommened approrval from sterility assurance point of view. EER was forwarded on 10.28.96 and returned with "Acceptable" rating (11.21.96)

16. Conclusion and Recommendation
This supplement can be approved from the chemistry point of view. Issue an approval letter.

17. Name
Moo-Jhong Rhee, Ph.D.

Reviewer's Signature
MJ Rhee

Date
11.21.96

Distribution
R/D initialed by
sl.260

Original Jacket — Reviewer — Division File

MJR 11/26/96

TAP HOLDINGS INC.

April 12, 1996

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot®-3 Month 22.5 mg
(leuprolide acetate for depot suspension)
NDA 20-517
Supplemental Application for Prior Approval

Dear Doctor Sobel:

The sponsor, TAP Holdings Inc., submits this Supplemental Application under the provisions of Section 505(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.70 (b) (2) (vi) and (vii).

This supplement requests for approval of an additional container closure system for Lupron Depot®-3 Month 22.5 mg approved under NDA 20-517.

This supplement consists of 3 volumes labeled as Volume 1-3. Volume 1 contains all chemistry, manufacturing and controls information. Volume 2 contains information on facilities and aseptic process validations for review by CDER's Sterile Products Group. This volume is labeled as "Sterile Process Validation Package." Volume 3 contains the Methods Validation Package. Four copies of all three volumes are submitted.

Attached is the information required for this supplement.

Sincerely,

REVIEWS COMPLETED

DATE

Aruna Dabholkar, M.D.
Regulatory Products Manager
(847) 317-4893

AD/pjp
Attachment

NDA SUPPL AMENDMENT ORIGINAL

TAP HOLDINGS INC.

May 21, 1996

Division of Metabolism and Endocrine Drug Products
Document Control Room 14B-19, HFD-510
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 3-Month, 22.5 mg (leuprolide acetate for depot suspension)
NDA 20-517
S-001, Amendment No. 001

Dear Doctor Sobel:

Pursuant to 21 CFR §314.60 (a), the Sponsor, TAP Holdings Inc., submits this amendment to the pending supplemental application 001 with the enclosed information.

This amendment is submitted as requested by Microbiology reviewer (Dr. Uratani) to clarify the sterile process validation documents and to respond to her questions regarding the validations.

The manufacturing process and the validation protocols submitted in this SNDA (001) are the same as the one submitted in our approved NDA 19-732, S-009 for Lupron Depot 7.5 mg The NDA 19-732, S-009 may be referred to for these documents. Please note that the current supplement (001) also contains the results of the validation studies performed on Lupron Depot 3 Month 22.5 mg, dual chamber prefilled syringe.

The responses to the reviewer's questions about sterilization validation of the diluent are attached.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

REVIEWS COMPLETED

MAY 22 1996
HFD-510
EVALUATION AND RES

AD/pjp

Attachment

NDA20-517
S-002

AP Ltr

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-517/S-002

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.

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 # 20-512/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(f) 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.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

4/21/07
Date

cc: Orig NDA
HFD-[illegible]/Div File
NDA Action Package

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

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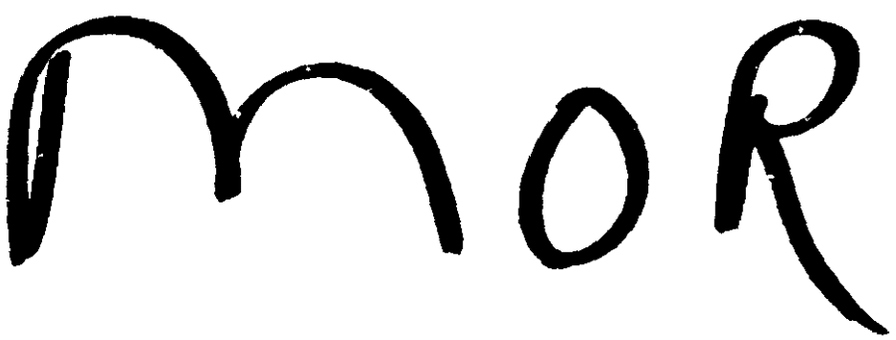

mOR

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 MD 5/28/97
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)

Duncan

MAY 19 1997

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

NDA #	20-517 (S-002)	Original Submission Date:	5/30/96
Sponsor:	TAP Holdings Inc.	Filing Date:	7/30/96
		Date Assigned to M.O.:	8/29/96
		User Fee Goal Date:	5/31/97
		Date Review Completed:	5/9/97

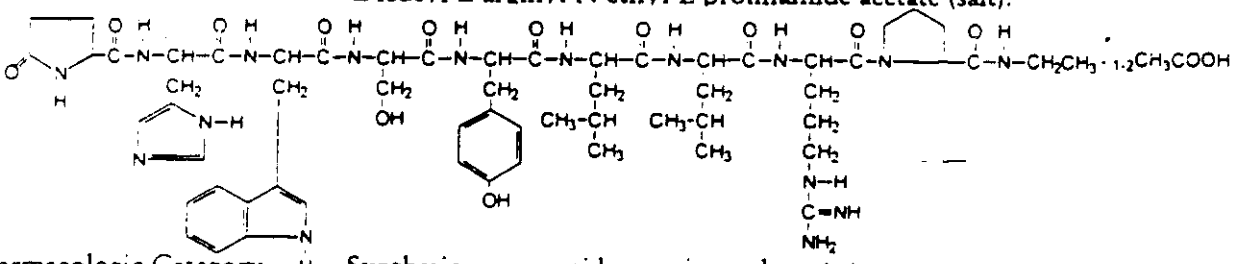
1.0 General Information

Name 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

2.0 Table of Contents — Page of MOR

3.0 Material Reviewed

Volume 8.1	Table of Contents and Application Summary, 5/30/96
Volume 8.6	Section IV. Human Pharmacokinetics and Pharmacodynamics Section: Table of Contents, Study Report of Clinical Pharmacokinetics Study M93-012
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 (E_1) and estradiol (E_2) 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 T 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 [redacted] 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 methods[1] by both

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

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 R.W.Johnson/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 (29,430 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-orchiectomy. 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 orchiectomized 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 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 UrologicWellness	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:

Pt #	Age/Sex/Race	#Days in Study	#Injections Rec'd	Reason for Dropout
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:

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

During the Long Term Treatment Phase:

Pt #	Age/Sex/Race	# Days in Study	Reason for Termination
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
65M	Oriental	450	Adverse Event: Fever, Thrombocytopenia; Death due to prostate cancer

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

Pt #	Age/Sex/Race	# Days in Study	Reason for Termination
	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:

Pt #	Age/Sex/Race	# Days in Study	# Injections Received	Reason for Exclusion from Efficacy Analysis
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:

REASON for Exclusion	Number of Patients
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:

Pt #	Rx Days (Weeks) Excluded	Specific Data Excluded	Reason for Exclusion
	246 (35) and 477 (68)	T, LH, PSA, PAP, DRE @ day 246 only	Procedures within 28 days after late injection
	821 (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):

Pt #	Rx Days (Weeks) Excluded	Specific Data Excluded	Reason for Exclusion
	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.

Pt #	Time Flutamide Treatment Initiated
	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).

Pt #	Age/Sex	Day of First Injection	Day of 2nd Injection (# Days Delayed)	Day of 3rd Injection (# Days Delayed)
	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 nephrovitamins. Baseline serum T level of 414 ng/dl rose to 742 ng/dl 4 days after the initial L ron 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):

Formulation Studied	Pivotal Trial	Sample Size (n)
Lupron Depot 7.5 mg	M85-097	56
Lupron Depot 3-Month 22.5 mg	M91-583	61
	M91-653	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 % "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):

Pt #	Age Sex	Rx Day of Onset	Days Since Last Injection at Onset	Reported Event/Action Taken or Treatment Given
	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):

Pt #	Age Sex	Rx Day of Onset	Days Since Last Injection at Onset	Reported Event/Action Taken or Treatment Given
	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):

Pt #	Age Sex	Rx Day of Onset	Days Since Last Injection at Onset	Reported Event/Action Taken or Treatment Given
	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

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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 h 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 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 due to non-compliance with visit schedule after 96 days; Pt 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 (2/20/97) 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 , anemia requiring blood transfusion (Pt , and bladder carcinoma with gross hematuria (Pt 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-orchiectomized and 24 orchiectomized 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 orchiectomized 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 > = 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-orchiectomized 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 The required revisions are briefly described below.

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 Precaut

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.

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

Concur that application is approvable Hfetz, 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 Reinjection 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 > = 5% incidence level in either M93-012 and M93-013, NDA Amendment #5, pg 73

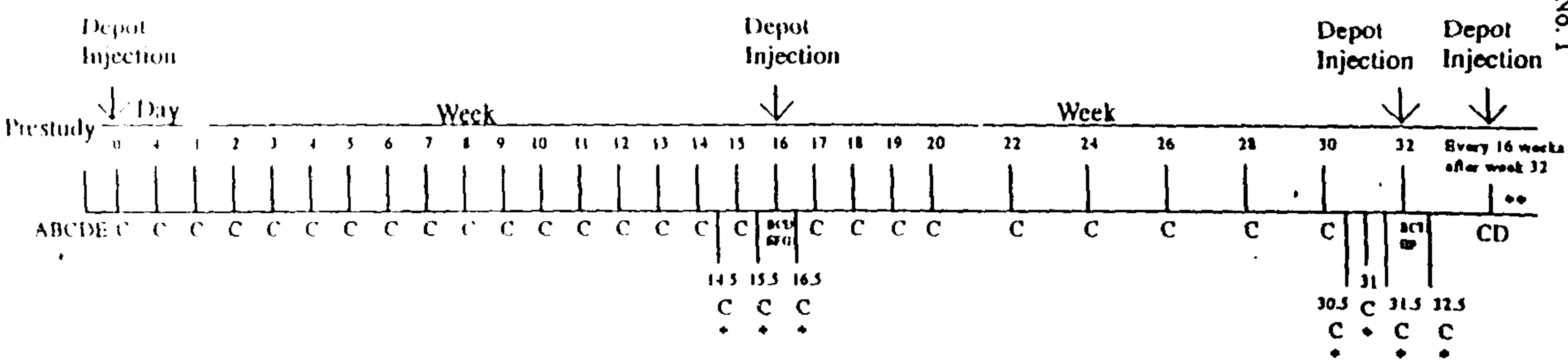
Drafted: 1.10.97 LGolden/n-20517s.mor
Revised: 4.30.97; 5.9.97 LGolden/n-20517s.mor

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

(MOR FIGURE 1)

Figure 1.

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



A MEDICAL AND SURGICAL HISTORIES
PROSTATE CANCER HISTORY

B DRE
BONE SCAN
PERFORMANCE STATUS
PHYSICAL EXAM

C BLOOD DRAW FOR SERUM LH AND TESTOSTERONE
RECORD ADVERSE EVENTS AND CONCOMITANT MEDICATIONS

D BLOOD DRAW FOR SERUM PSA, PAP, ALKALINE PHOSPHATASE

E ROUTINE LABS

F OBJECTIVE TUMOR RESPONSE

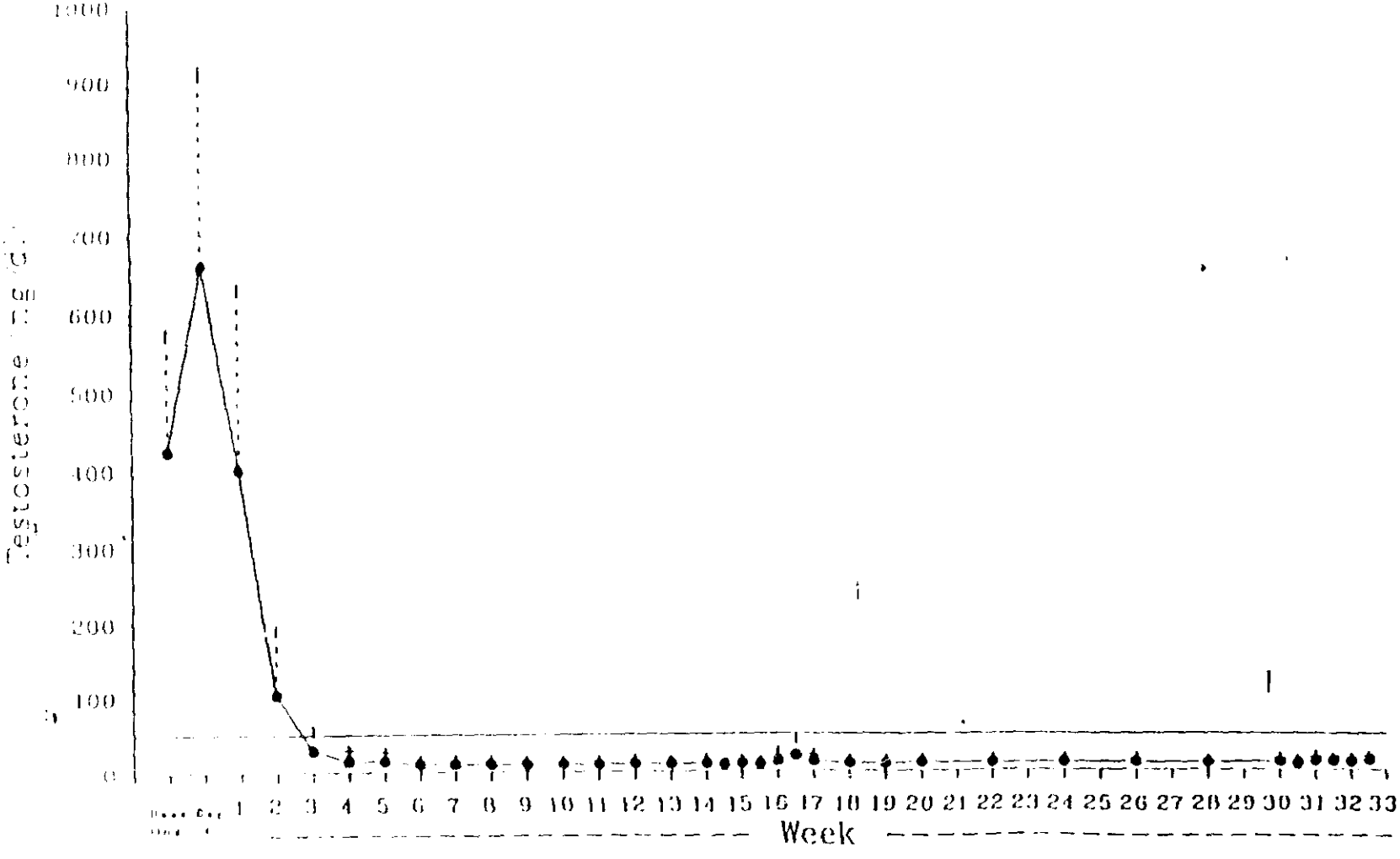
G BLOOD DRAWS FOR SERUM LH AND TESTOSTERONE 4, 8, AND 12 HOURS AFTER THE WEEK 16 DEPOT INJECTION

**<u>LONG-TERM PHASE (BEYOND WEEK 32)</u>
DOSING VISITS EVERY 16 WEEKS FOR
AS LONG AS CLINICAL BENEFIT CONTINUES
AT DISCRETION OF THE PHYSICIAN INVESTIGATOR

PROCEDURES: C,D EACH VISIT

* WITHIN 4 WEEKS OF DOSING
* SELECTED PATIENTS (N=15)

Figure 1
Mean (+ SD) Testosterone



MOR FIGURE 2

MOR FIGURE 3

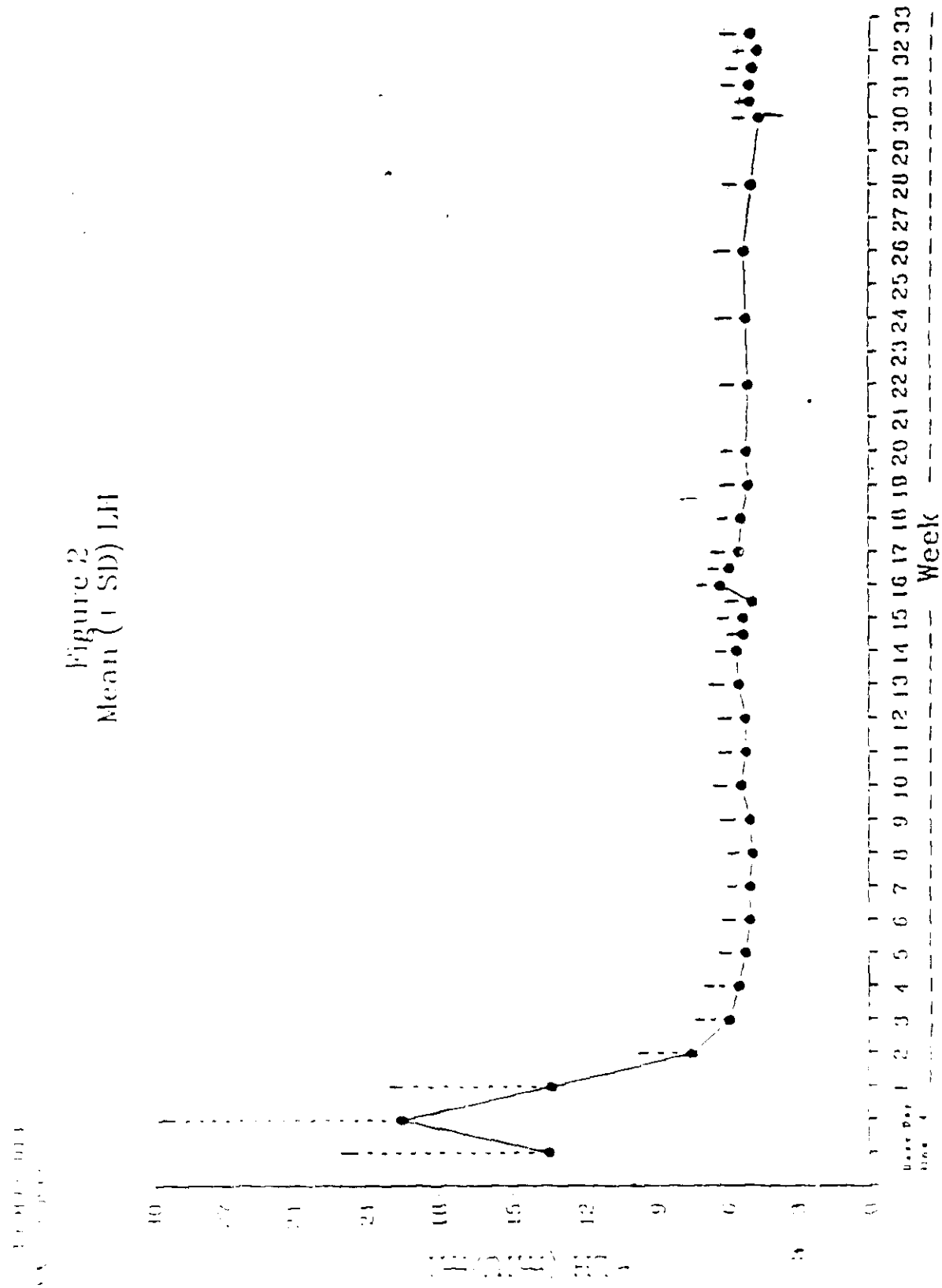


Figure 2
Mean (+ SD) LH

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	55	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) Pauents Suppressed By Week 3	By Week 4	By Week 8	Median Time (Day of Study) of Onset of Castrate Testosterone Levels (Range)
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 pauents by Weeks 15 and 28

* 1 pauent unable to reach suppression due to death on Day 6

• Onset of castrate testosterone levels for 1 pauent by Day 66 and 2 pauents unable to reach suppression due to not having data bevond 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

Testosterone (ng/dL) Injection #2*					LH (mIU/mL) Injection #2*				
Hrs Post-inj	Pre	4	8	12	Hrs Post-inj	Pre	4	8	12
M93-013					M93-013				
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
M91-583					M91-583				
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
M91-653					M91-653				
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
M85-097 (Inis 7-10 combined)									
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

MDR TABLE 6

Summary of Injection Delays

Study	Dosing Interval Length/No	No. of Days Between Injections Range	Median	Inj. Delayed by ≥ 3 days 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"

	Favorable			
Pretreatment Performance Status	Improved	No Change	Worsened	Total
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 15a-d

MOR TABLE 13

Adverse Events Occurring at ≥ 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.

Clin. Pharm
& Bio

Duncan

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 Garv 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 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).**

TABLE OF CONTENTS:

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

(D-Leu^{6}, des-Gly-NH_2^{10}, Pro-ethylamide^{9})-GnRH

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

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

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:

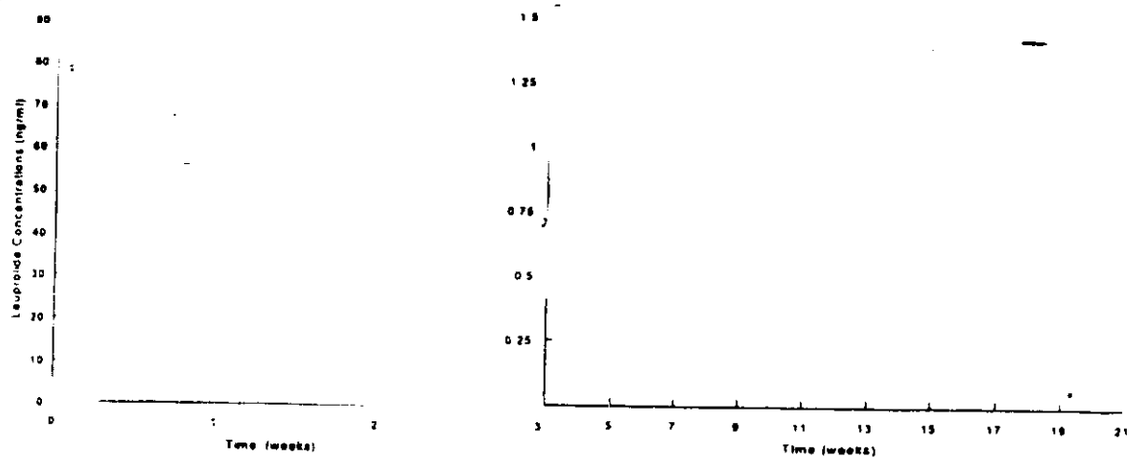
1 *The method and specifications proposed herein are the same as those used for the currently marketed Lupron Depot® 3-month 22.5 mg, indicated for the palliative treatment of advanced prostate cancer (NDA20-517) and Lupron Depot®-3 month 11.25 mg for treatment of endometriosis (NDA 20-708)*

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 Tmax 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 Cmax and Tmax 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 (± SD) $Cavg_{(3\text{-}16\ weeks)}$ 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 Cavg(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.

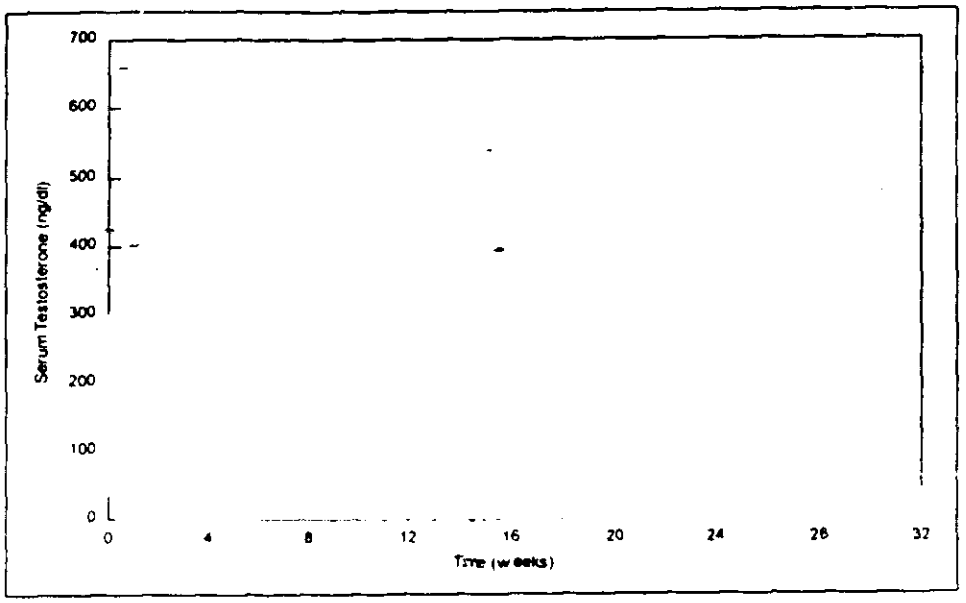
Table 6

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 thatlevels 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)
Deleted

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 ± SD age of the 24 patients enrolled in the study was 73.3 ± 7.2 years (range: yrs), the mean ± SD weight was 89.0 ± 14.9 kg (range: kg), and the mean ± 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 Cmax was not assessed (see Figure 3). Additionally, since 42% of the total measured AUC was during the first week and the valid Cmax 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:

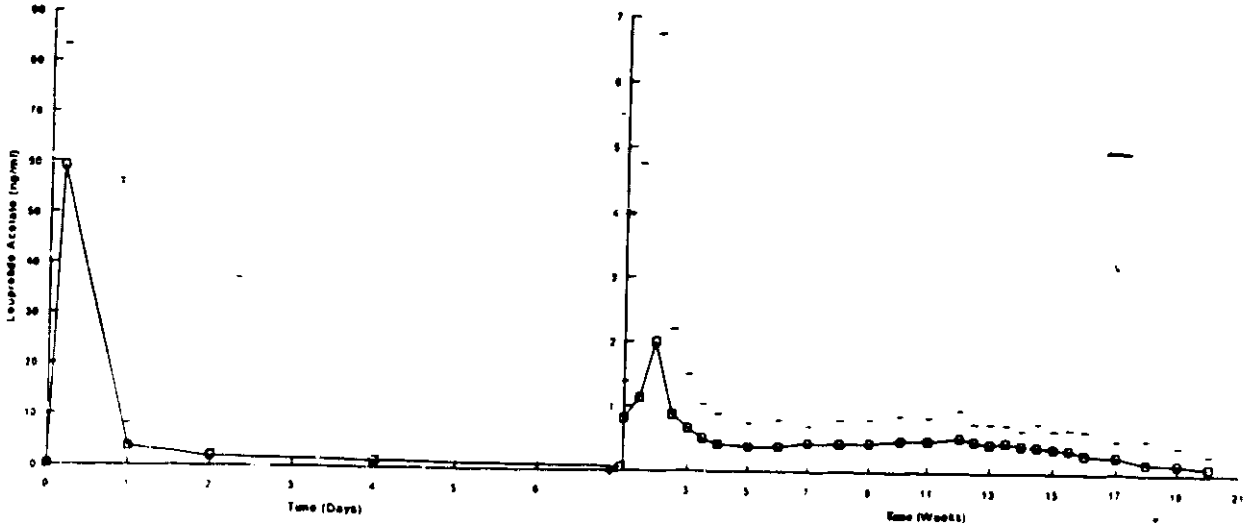
Mean ± SD Leuprolide Acetate Concentrations and AUC

	All Patients†	Patients with Complete Data‡	
Week	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	79 ± 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 Conclusion:

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:

1 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.

2 Sixteen missing or lost plasma concentrations were replaced using linear interpolation (Patient Da, 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.*

Pharm

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-trytpphyl-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 [TAP-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.

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

A. Jordan
6/18

Original NDA 20-517 S002
HFD-345
HFD-510
HFD-510/A.Jordan
HFD-510/K.Raheja, 6-18-1996, N20517.S-002

Chem

DAWSON

APR 25 1997

CHEMIST'S REVIEW

1. Organization
DMEDP HFD-580

2. NDA Number
20-517

3. Name amd 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
Leuploride 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

4/25/97

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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.

1-22-97

David Hussong, Ph.D.

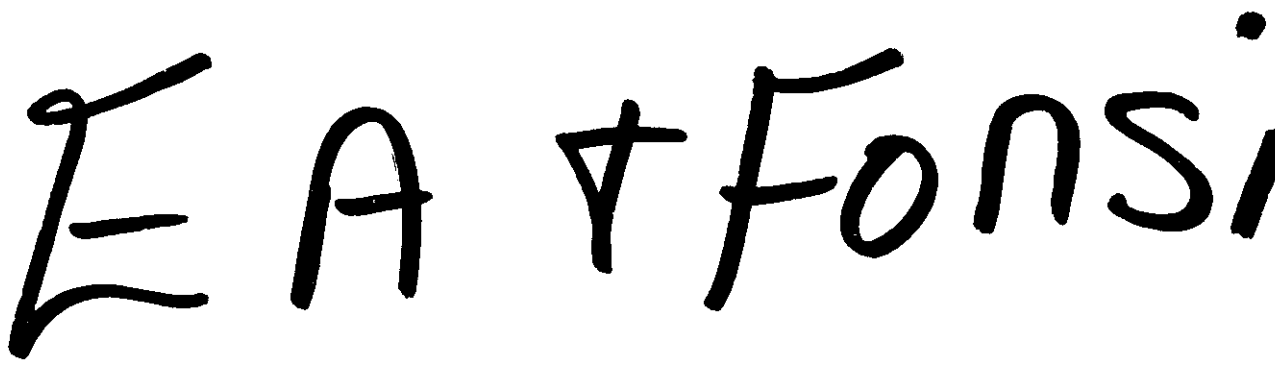
1/21/97

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:\d\nda\s\20-517r1.s02



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 25.3la (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
3 1/ HFD-~~004~~/FONSI File 20-517
3 1/ HFD-~~004~~/~~FONSI~~ File
2 1 HFD-~~019~~/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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Note: The page numbers in this Table of Contents refer to the document pagination, NOT the pagination found in the lower right hand corner.

TABLE OF CONTENTS (Continued)

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 prostrate 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-solicate 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 CO_2, 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 prostrate 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 sewered 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 sewered 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 sewered 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 : 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 facility are served by the City of North Chicago municipal water supply. The source of the municipal water supply is Lake Michigan. The 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 Wisconsonian 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 Ironton-Galesville and Glenwood-St. Peter (Ancell 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

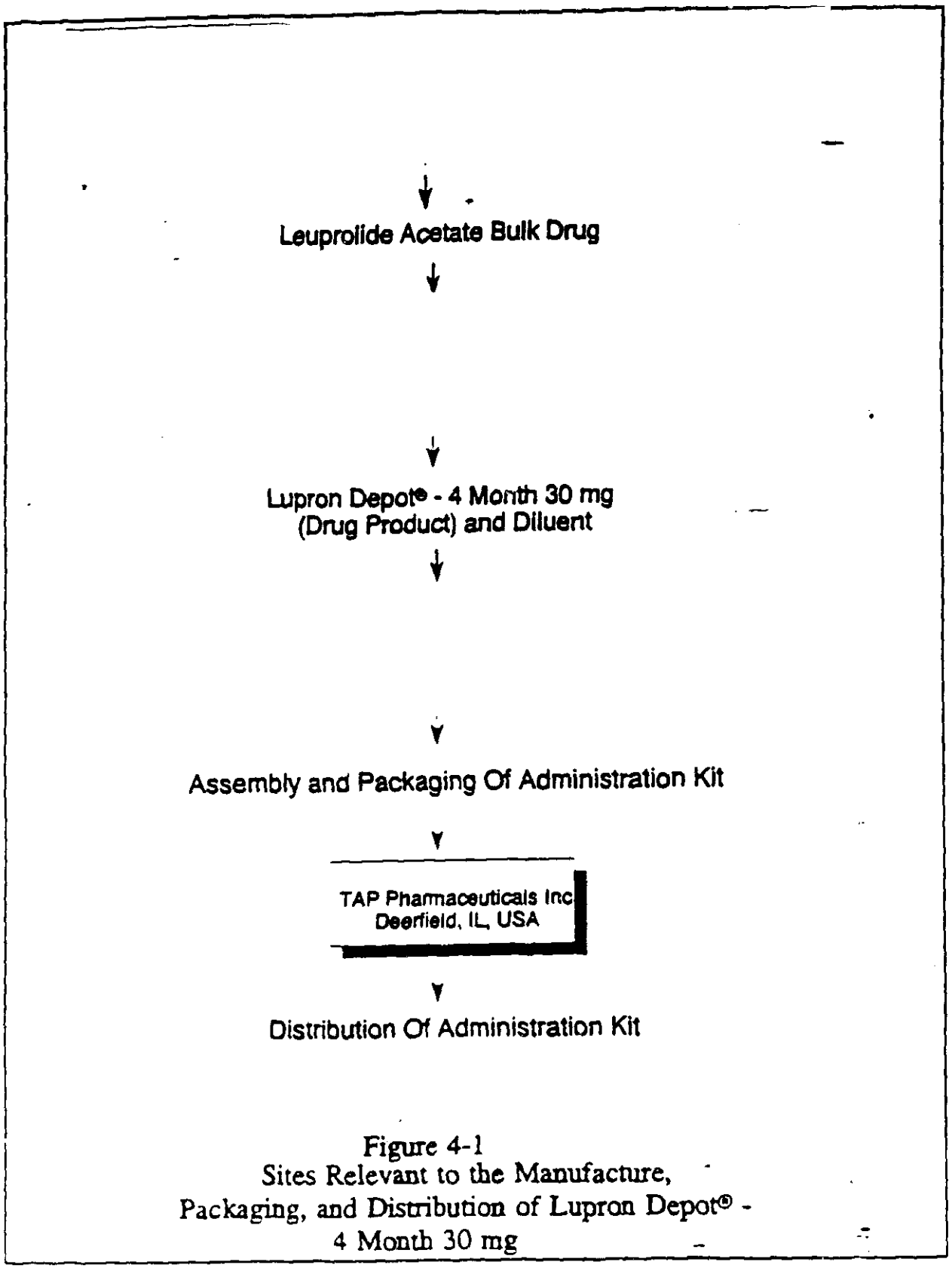


Figure 4-1
Sites Relevant to the Manufacture,
Packaging, and Distribution of Lupron Depot® -
4 Month 30 mg

5.1.2 Brand or Proprietary Name

Lupron Depot®-4 Month 30 mg

5.1.3 Chemical Abstracts Name

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide

5.1.4 CAS Registry Number

74381-53-6

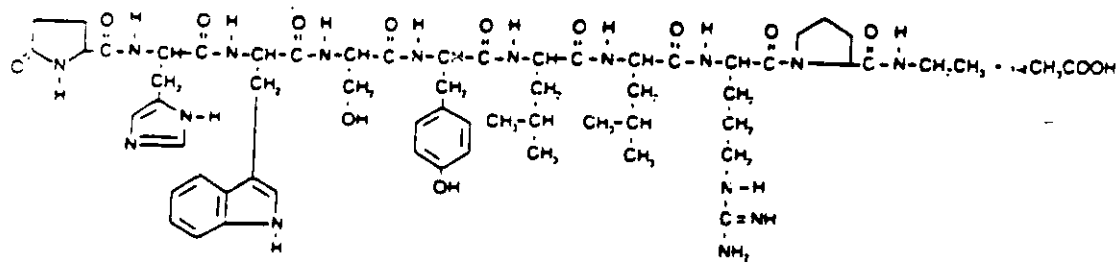
5.1.5 Laboratory Codes

Abbott-43818/Takeda-TAP-144

5.1.6 Molecular Formula and Weight

Formula - $C_{59}H_{84}N_{16}O_{12}.CH_3COOH$; Weight - 1269.47

5.1.7 Structural (Graphic) Formula



5.1.8 Dissociation Constant and K_{ow}

Three ionization sites are present: imidazolyl nitrogen of histidine, pKa 6.0; the phenolic hydroxyl of tyrosine pKa 10.0; and the guanidine nitrogen of arginine pKa 13.0; log K_{ow} is 0.52 to 0.98

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 sewered. 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 sewered. 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*

Contractor	USEPA ID#	Function
	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 Perfectural 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 CO_2. 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 $^{14}CO_2$, 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 $^{14}CO_2$. 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 ($^{14}CO_2$), 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 $^{14}CO_2$, 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 poylactic 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:

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

Total leuprolide acetate produced [peak year (1998) production estimate] = ***** ******** (**) = or ***** x 10^9 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:

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

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 (x 10^6 = ppb)

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

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) x 1/1.115 x 10^{11} (B) x 1/365 (C) x 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.

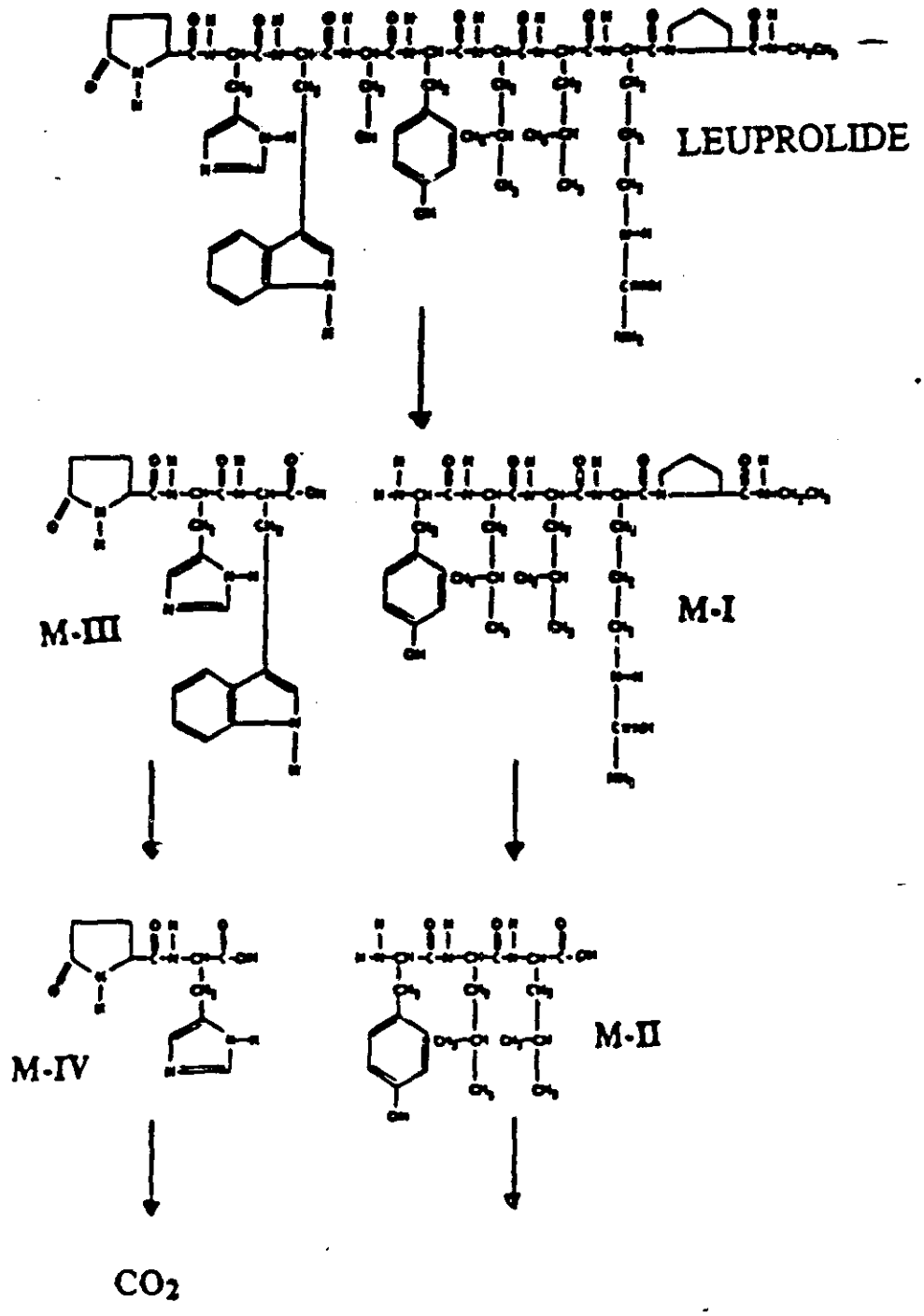


Figure 6-1
Proposed Pathway of Leuprolide Metabolism

10 MITIGATION MEASURES

See Sections 4.1 and 7.

11 ALTERNATIVES TO THE PROPOSED ACTION

See Sections 4.1 and 7

12 PREPARER

Ranga Velagaleti, Ph.D
Director
Pharmaceutical Manufacturing Support & Environmental Compliance Division
Analytical Biochemistry Laboratories, Inc.
7200 East ABC Lane
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 Dog: 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 Perfectural 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 governors.

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 1960s, 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 1987). 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" (*Kankyo Nenpo*, 1988, 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 [illegible]ating 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 1978 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 on the preparation of regional pollution control programs; (4) the planning, formulation, and promotion of basic policies for environmental impact assessments; (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 assessment, the *Planning and Coordination Bureau* formulates and promotes the basic policy for assessment, 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 aris-

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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 Toroku 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 1,288,774 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 court of 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 30 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 minis-

ter 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 *Seto Inland Sea Environmental Conservation Council*, which has a maximum of 36 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 Seto 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 environmental-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 (*kankyo eikyo hyoka*) 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 28, 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 rewrites 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 1988, 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 Organs," 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 Agen-

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 actions 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, noxious 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, noxious 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, cadmium, chlorine, hydrogen fluoride, lead, particulate matter, carbon monoxide, and hydrocarbons produced by combustion, synthesis, mechanical processes, or residuals. However, the law is not applicable to air pollution caused by radioactive materials.

Emission standards for facilities emitting soot and smoke 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*

Controlled Laws. Substances covered by the law are the eight substances listed in the Cabinet Order, including ammonia, carbonyl sulfide, hydrogen sulfide, and styrene.

Prefectural governors are required, after consultation with the mayors of local governments, to designate areas in which odors are to be regulated, as well as the regulation standards. Maximum concentrations in the air are set for substances 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 5 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-Health Damage Compensation Grievance Board (see "Environmental 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, 1988 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 consequent 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 SO_x-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 13,200 at the beginning of the program to 107,323 as of January, 1987. Paid benefits for FY 1986 totaled approximately ¥100 billion (US$800 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 transferral, and in general prohibits the handling or sale of contaminated, unripe, unclean, 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 prevention 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 these 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 plans, as well as private waste disposal trak 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 recommendations 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 acton.

Nature Protection

The Nature Conservation Law states the obligations of the national government, local governments, business and industry, and the citizen 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 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 national 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 governors 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 fauna 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 fauna 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 provisions 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 compensation when the landfill operation prevents effective use of the concerned area of water, and for the procedure 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 (Kankyo-cho)

No. 5 Joint Government Building (19th to 22nd Floors)
1-2-2 Kasumigaseki, Chiyoda-ku, Tokyo 100
Telephone: (03) 581-3351

Ministry of International Trade and Industry (Tsusansangyo-sho or Tsusan-sho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 501-1511
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 (Kosei-sho)

2-2 Kasumigaseki 1-chome
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 (Norinsuisan-sho)

2-1 Kasumigaseki 1-chome
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 (Kensetsu-sho)

1-3 Kasumigaseki 2-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 580-4311
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-cho)

2-2 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-2311
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 (Sorifu)

1-6-1 Nagata-cho
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-2361

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

1-2 Kasumigaseki 2-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-0141
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 (Kogai-to Chosei Iinkai)

1-6-1 Nagata-cho
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-2361
General Affairs Division, Investigations.

Forestry Agency (Rinya-cho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111
Planning Division, Private Forest Department, Silviculture Division, Forest Road Division, Forest Protection Division.

Fisheries Agency (Suisan-cho)

2-1 Kasumigaseki 1-chome
Chiyoda-ku, Tokyo 100
Telephone: (03) 502-8111
Fishing Port Planning Division, Fishing Port Department, Fishing Ground
Preservation Division.

Science and Technology Agency (Kagaku-gijutsu-cho)

2-2-1 Kasumigaseki
Chiyoda-ku, Tokyo 100
Telephone: (03) 581-5271
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. 78 of 1972).

Law for the Punishment of Crimes Relating to the Environmental Pollution which Adversely Affects the Health of Persons (Law No. 142 of 1970).

Air Pollution and Odors

Air Pollution Control Law (Law No. 97 of 1968; last amended by Law No. 65 of 1974; 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. 329 of 1968; last amended by Cabinet Order No. 162 of 1972).

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 1977).

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. 287 of 1972; amended by Ordinance of Prime Minister's Office No. 43 of 1976).

Environmental Quality Standards Regarding Air Pollution (Environment Agency Notification No. 25, May 8, 1973; amended by Notification No. 47 of 1981).

Environmental Quality Standard for Nitrogen Dioxide (Environment Agency Notification No. 38, 1978).

Noise and Vibration

Regulatory Standards for Noise Emitted from Specified Factories (Notification No. 1 of November 27, 1968, 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 1998).

Standards for Noise from Special Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 27, 1968; amended by Environment Agency Notification No. 12 of 1987).

Environmental Quality Standards for Noise (Cabinet Decision of May 23, 1981).

Environmental Quality Standards for Shinkansen Superexpress Railway Noise (Environment Agency Notification No. 46 of July 23, 1975).

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

Noise Regulation Law (Law No. 98 of 1968; last amended by Law No. 88 of 1971; Environment Agency, National Police Agency, Ministry of Transport).

Cabinet Order for Implementation of the Noise Regulation Law (Cabinet Order No. 324 of 1968; last amended by Cabinet Order No. 22 of 1998).

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. 280 of 1976; amended by Cabinet Order No. 23 of 1998).

Regulatory Standards for Vibration Emitted from Specified Factories (Environment Agency Notification No. 90 of November 10, 1976; amended by Environment Agency Notification No. 13 of 1998).

Standards for Vibration Emitted from Specified Construction Works (Ministry of Health and Welfare, and Ministry of Construction Notification No. 1 of November 27, 1968; amended by Environment Agency Notification No. 1 of 1998).

Water Pollution

Water Pollution Control Law (Law No. 138 of 1970; last amended by Law No. 86 of 1982; Environment Agency, Ministry of Transport).

Cabinet Order for Implementation of the Water Pollution Control Law (Cabinet Order No. 188 of 1971; last amended by Cabinet Order No. 89 of 1987).

Water Pollution Control Law Enforcement Regulations (Order No. 9 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. 47 of 1988).

Law Concerning Special Measures for the Preservation of Lake Water Quality (Law No. 61 of 1984; amended by Law No. 69 of 1984; commonly known as the "Class 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, 1985; last amended by Cabinet Order No. 314 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, 1985; 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, 1973; last amended by Law No. 68 of June 12, 1978; Environment Agency, Ministry of Transport).

Soil Contamination, Agricultural Chemicals

Agricultural Land Soil Pollution Prevention Law (Law No. 139 of 1970; last amended by Law No. 87 of 1970; Environment Agency, Ministry of Agriculture, Forestry, and Fisheries).

Cabinet Order for Implementation of the Agricultural Land Soil Pollution Prevention Law (Cabinet Order No. 294 of 1971; last amended by Cabinet Order No. 163 of 1975)

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 Underground Water for Use in Buildings (Cabinet Order No. 335 of 1962; last amended by Cabinet Order No. 362 of 1976).

Industrial Water Law (Law No. 146 of 1956; 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. 162 of 1957; last amended by Cabinet Order No. 54 of 1967).

Wastes and Marine Pollution

Waste Disposal and Refuse Collection Law (Law No. 137 of 1970; last amended by Law No. 87 of 1987; 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 25, 1971; last amended by Cabinet Order No. 292 of 1987).

Law Relating to the Prevention of Marine Pollution and Maritime Disaster (Law No. 136 of 1970; last amended by Law No. 40 of 1987; 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. 301 of June 22, 1971; last amended by Cabinet Order No. 115 of 1987).

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 1986; 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. 202 of June 7, 1973; last amended by Cabinet Order No. 43 of 1987).

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 5, 1972; last amended by Cabinet Order No. 363 of November 6, 1987; Environment Agency, Ministry of International Trade and Industry).

Enforcement Order of the Pollution-Related Health Damage Compensation Law (Cabinet Order No. 295 of August 29, 1974; last amended by Cabinet Order No. 368 of 1987).

Pollution Disputes Settlement Law (Law No. 108 of June 1, 1970; last amended by Law No. 90 of 1983; Environmental Disputes Coordination Commission).

Costs and Assistance

Pollution Control Public Works Cost Allocation Law (Law No. 133 of December 25, 1970; amended by Law No. 43 of 1982; 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. 196 of May 8, 1971; last amended by Cabinet Order No. 214 of 1986).

Nature Conservation

Nature Conservation Law (Law No. 85 of 1972; last amended by Law No. 88 of 1987; Environment Agency).

Natural Parks Law (Law No. 161 of 1957; last amended by Law No. 87 of 1972; Environment Agency).

Wildlife Protection and Hunting Law (Law No. 33 of April 6, 1918; last amended by Law No. 63 of 1963; Environment Agency).

Cabinet Order for the Implementation of the Wildlife Protection and Hunting Law (Cabinet Order No. 254 of August 31, 1953; last amended by Cabinet Order No. 166 of April 14, 1978).

Enforcement Regulation for the Wildlife Protection and Hunting Law (Ordinance of the Ministry of Agriculture and Forestry No. 108 of September 30, 1950; last amended by Ordinance of the Prime Minister's Office No. 45 of 1983).

Law Relating to the Regulation of Transfer of Special Birds (Law No. 45 of 1972; amended by Law No. 65 of 1972; Environment Agency).

Order for the Implementation of the Law Relating to the Regulation of Transfer of Special Birds (Cabinet Order No. 405).

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. 42 of 1983).

Law for the Regulation, etc., of the Transfer of Endangered Species of Wild Fauna and Flora (Law No. 58 of June 2, 1987; 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. 375 of November 6, 1987).

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. 55 of December 1, 1987).

Basic Policy on Conservation of the Natural Environment (Prime Minister's Office Notification No. 30 of November 6, 1973).

Land Use and Urban Planning

Urban Planning Law (Law No. 100 of June 15, 1968; last amended by Law No. 66 of 1987; National Land Agency, Ministry of Transport, Ministry of Construction).

Public Waters Landfill Law (Law No. 57 of 1921; last amended by Law No. 5 of 1979).

Harbor Law (Law No. 218 of May 31, 1950; amended by Law No. 87 of 1987)

APPENDIX A

Material Safety Data Sheets

MATERIAL SAFETY DATA SHEET

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

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

LIST/CODE:3375,3508,3626/41450, 41558,41559

PRODUCT NAME: Leuprolide Acetate

CHEMICAL NAME: 6-D-Leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamidelutenizing hormone-releasing factor monoacetate; C61H88N16O14

DOT CLASSIFICATION: Not Regulated

HAZARDOUS INGREDIENTS/IDENTITY INFORMATION

NAME (CAS NO.)	OSHA PEL	ACGIH TLV	ABBOTT LIMIT	%
Leuprolide Acetate*(74381-53-6)	NL	NL	**	

**Hazardous per OSHA criteria

** = 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
Melting Point: N/D
pH: N/A
Vapor Pressure: N/A
Vapor Density: N/A
Density: N/A
Viscosity: 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 0.36 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 noncomparable effect has been found in man at doses up to 30 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; Later 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

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.

FDA Corresp.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-517/S-002

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).

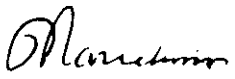
5. A summary and evaluation of all available clinical data (whether or not considered "related" to treatment) that may be used to estimate the incidence of severe adverse reactions associated with initiation of Lupron treatment (i.e., "flare" reactions of onset within the first 3-4 weeks of Lupron treatment). 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

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 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

FORM FDA 3217g (11/95)

PREVIOUS EDITION IS OBSOLETE

Co. Corresp.

TAP HOLDINGS INC.

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.

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

TAP HOLDINGS INC.

ORIGINAL

ORIG AMENDMENT

May 9, 1997

SE2-002
BC

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

rcvd 5-19-97

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I. ☐ MEMO
AD 5/27/97
CSO INITIALS DATE

NDA 20-517, S-002
(Lupron Depot®- 4 Month 30 mg)
(leuprolide acetate for depot suspension)
Amendment No. 008

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. MMiller 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.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 12 1997
HFD-580

Sincerely,

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

AD/pjp

Attachment

TAP HOLDINGS INC.

noted refer to minutes of interna meeting held 5/22/97 for comments on this draft labeling 5/23/97

ORIGINAL

ORIG AMENDMENT
SE2-002 BL

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 pamplet. The same attachment also contains the printed information pamplets 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

REC'D
MAY 0 9 1997
HFD-580
EVALUATION AND RESEARCH

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

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

NDA 20-517, S-002 (Lupron Depot® - 4Month 30 mg)
Amendment No. 006

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

CENTER FOR DRUG
RECD
APR [illegible] 1997
HFD-580
EVALUATION AND RESEARCH

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Lake Office Plaza

ORIGINAL

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

NDA 20-517, S-002 (Lupron Depot® - 4Month 30 mg)
Amendment No. 005

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 21 1997
HFD-580

TAP HOLDINGS INC.
parent of TAP Pharmaceuticals Inc

Lake Forest Office Park
Waukegan Rd
Deerfield IL 60015

ORIGINAL

SE2-002

SUPPL NEW CORRESP

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

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, M.D.
Regulatory Products Manager
(847) 317-4893

AD/pjp

Attachment

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

AD 3/20/97
CSO INITIALS DATE

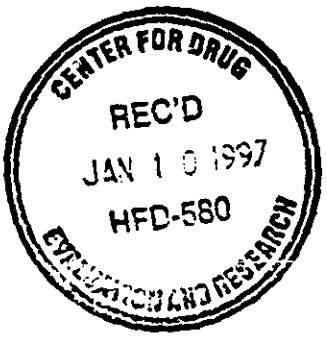
CENTER FOR DRUG EVALUATION
RECD
MAR 05 1997
HFD-580

TAP HOLDINGS INC.

Orig

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(I) 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

Patient Nos.	Reasons for Discontinuation
	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.

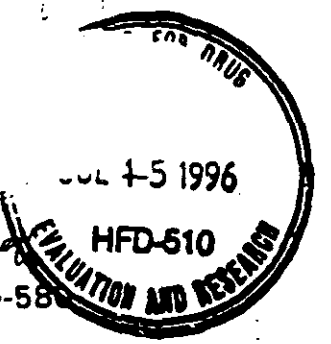
Sincerely,

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

TAP HOLDINGS INC.

ORIGINAL

NDA SUPPL AMENDMENT



July 12, 1996

Division of Reproductive and Urologic Drug Products, HFD-58
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ R.A.I. ☐ MEMO
4/6/97

CSO INITIALS DATE

NDA 20-517, S-002 (Lupron Depot-4Month 30 mg)
Amendment No. 1

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 debarrment 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