CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-517/S-019

Name:	Lupron Depot-3 Month 22.5 mg & Lupron Depot-4 Month 30 mg (leuprolide acetate for depot suspension)
Sponsor:	TAP Pharmaceuticals, Inc.
Approval Date:	September 15, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-517/S-019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDAs 19-732/S-027, S-029
19-010/S-031
19-943/S-022, S-024
20-517/S-018, S-019
20-708/S-020, S-021
20-011/S-029, S-031

TAP Pharmaceutical Products Inc.
Attention: Tonya Haynes, M.P.H.
Regulatory Product Manager
675 North Field Drive
Lake Forest, IL 60045

Dear Ms. Haynes:

Please refer to your supplemental new drug applications as listed below, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

NDA	Supplement	Name of Drug	Letter Date	Receipt Date
19-732	SCS-027	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	May 6, 2005	May 9, 2005
19-732	SLR-029	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	August 18, 2005	August 19, 2005
20-517	SCS-018	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	May 6, 2005	May 9, 2005
20-517	SLR-019	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	August 18, 2005	August 19, 2005
19-010	SLR-031	Lupron Injection (leuprolide acetate	August 18, 2005	August 19, 2005
20-708	SCS-020	Lupron Depot (leuprolide acetate for depot suspension), 3-month	May 6, 2005	May 9, 2005
20-708	SLR-021	Lupron Depot (leuprolide acetate for depot suspension), 3-month	August 18, 2005	August 19, 2005
19-943	SCS-022	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	May 6, 2005	May 9, 2005
19-943	SLR-024	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	August 18, 2005	August 19, 2005
20-011	SCS-029	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	May 6, 2005	May 9, 2005
20-011	SLR-031	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	August 18, 2005	August 19, 2005

The Prior Approval supplemental new drug applications dated August 18, 2005, provide for changes in the package insert to include text regarding pituitary apoplexy.

The "Changes Being Effected" supplemental new drug applications dated May 6, 2005, provide for the addition of an appearance test, and changes in the package insert and mixing instructions regarding the LUPRON recall.

We completed our review of these applications, they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert, mixing instructions) on August 18, 2005.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA ##-###/S-YYY, S-ZZZ**", specific to the applications as listed above. Approval of these submissions by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of DIVISION NAME and two copies of both the promotional materials and the package insert(s) directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at (301) 827-7260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
9/15/2005 12:02:51 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-517/S-019

FINAL PRINTED LABELING

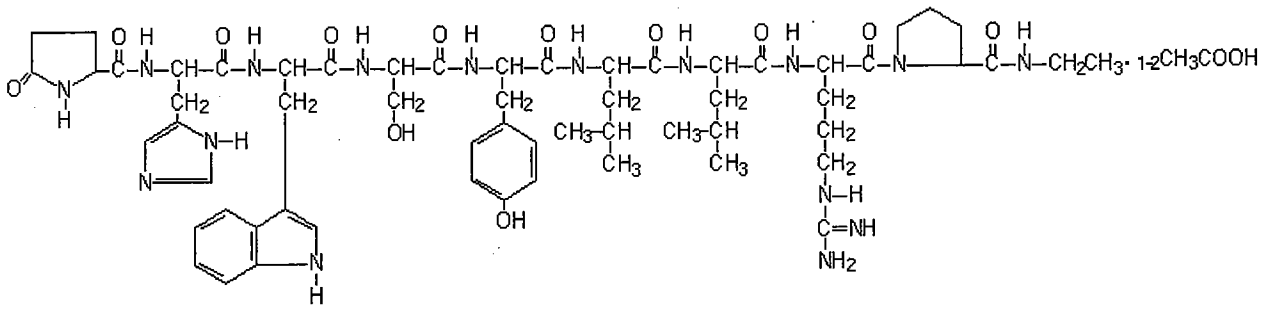
LUPRON DEPOT®–3 Month 22.5 mg
(leuprolide acetate for depot suspension)

3-MONTH FORMULATION

Rx only

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–3 Month 22.5 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given **ONCE EVERY THREE MONTHS (84 days).**

The front chamber of LUPRON DEPOT–3 Month 22.5 mg prefilled dual-chamber syringe contains leuprolide acetate (22.5 mg), polylactic acid (198.6 mg) and D-mannitol (38.9 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT–3 Month 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 premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal 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 more than five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption Following a single injection of the three month formulation of LUPRON DEPOT–3 Month 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 a two compartment model.

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

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached 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 mean 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.

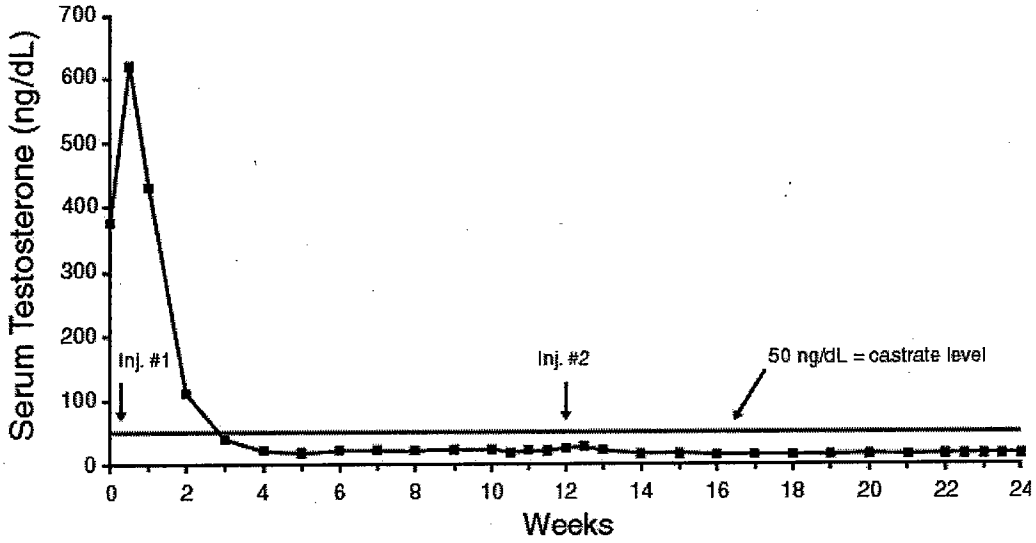
Special Populations The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.

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 stimulation of gonadotropin secretion.

Lupron Depot – 3 Month 22.5 mg
Mean Serum Testosterone Concentrations



Note: Measurements were taken in a subset of patients from one study at Weeks 10.5, 11.5, 12.5, 22.5 and 23.5.

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–3 Month 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–3 Month 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 of 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

General 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–3 Month 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.

Drug/Laboratory Test Interactions Administration of LUPRON DEPOT 3.75 mg in women results in suppression of the pituitary-gonadal system. Normal function is usually restored within one to three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to three months after discontinuation of LUPRON DEPOT 3.75 mg therapy may be misleading.

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, Teratogenic Effects 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.

Geriatric Use In the clinical trials for LUPRON DEPOT – 3 Month 22.5 mg, the majority (80%) of the subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON DEPOT in this population.

ADVERSE REACTIONS

Clinical Trials

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–3 Month 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-3 Month 22.5 mg	
	N=94	(%)
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–3 Month 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.

*Physiologic effect of decreased testosterone.

Postmarketing
During postmarketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (eg, joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System – Hypotension, Pulmonary embolism; *Hemic and Lymphatic System* - Decreased WBC; *Central/Peripheral Nervous System* - Peripheral neuropathy, Spinal fracture/paralysis; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Urogenital System* - Prostate pain.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in women and pediatric populations.

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–3 Month 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.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered every three months as a single intramuscular injection. *For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:*

1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc™ safety device.

AFTER INJECTION

8. Withdraw the needle. Immediately activate the LuproLoc™ safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

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.

HOW SUPPLIED

LUPRON DEPOT–3 Month 22.5 mg is packaged as follows:
Kit with prefilled dual-chamber syringe NDC 0300-3346-01

Each syringe contains 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–3 Month 22.5 mg is administered as a single IM injection **EVERY THREE MONTHS (84 days).**

An information pamphlet for patients is included with the kit.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

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. 4,728,721; 4,849,228; 5,330,767; 5,476,663; 5,480,656; 5,575,987; 5,631,020; 5,631,021; 5,643,607; 5,716,640; 5,814,342; 5,823,997; 5,980,488 and 6,036,976. Other patents pending.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, IL 60045, U.S.A.
by Takeda Pharmaceutical Company Limited
Osaka, JAPAN 540-8645

(No. 3346)
03-5450-R12; Revised: October, 2005

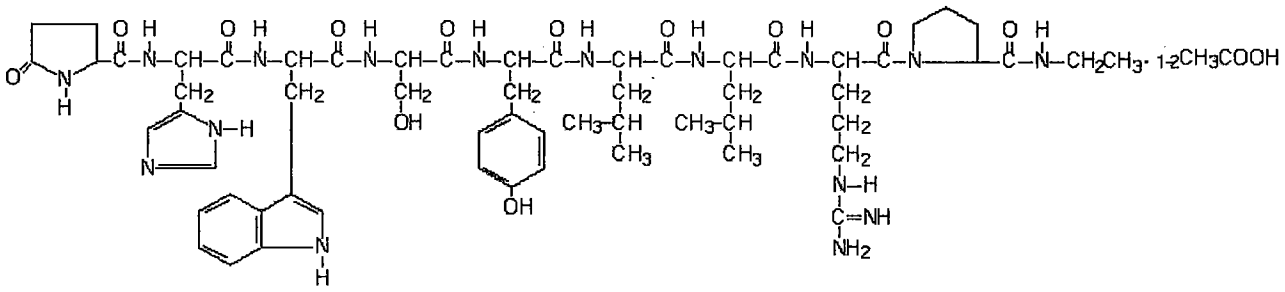
LUPRON DEPOT®– 4 Month 30 mg
(leuprolide acetate for depot suspension)

4-MONTH FORMULATION

Rx only

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-4 Month 30 mg is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as an intramuscular injection to be given **ONCE EVERY FOUR MONTHS (16 weeks).**

The front chamber of LUPRON DEPOT-4 Month 30 mg prefilled dual-chamber syringe contains leuprolide acetate (30 mg), polylactic acid (264.8 mg) and D-mannitol (51.9 mg). The second chamber of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75.0 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT-4 Month 30 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 premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal levels. These decreases occur within two to four weeks after initiation of treatment. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption Following a single injection of LUPRON DEPOT-4 Month 30 mg in sixteen orchiectomized prostate cancer patients, mean plasma leuprolide concentration of 59.3 ng/mL was observed at 4 hours and the mean concentration then declined to 0.30 ng/mL at 16 weeks. The mean plasma concentration of leuprolide from weeks 3.5 to 16 was 0.44 ± 0.20 ng/mL (range: 0.20-1.06). Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the fourth week after dosing, providing steady plasma concentrations throughout the 16-week dosing interval. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the other depot formulations.

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 a two compartment model.

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

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached 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 mean 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.

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 the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

CLINICAL STUDIES

In an open-label, noncomparative, multicenter clinical study of LUPRON DEPOT-4 Month 30 mg, 49 patients with stage D2 prostatic adenocarcinoma (with no prior treatment) were enrolled. The objectives were to determine whether a 30 mg depot formulation of leuprolide injected once every 16 weeks would reduce and maintain serum testosterone levels at castrate levels (≤ 50 ng/dL), and to assess the safety of the formulation. The study was divided into an

initial 32-week treatment phase and a long-term treatment phase. Serum testosterone levels were determined biweekly or weekly during the first 32 weeks of treatment. Once the patient completed the initial 32-week treatment period, treatment continued at the investigator's discretion with serum testosterone levels being done every 4 months prior to the injection.

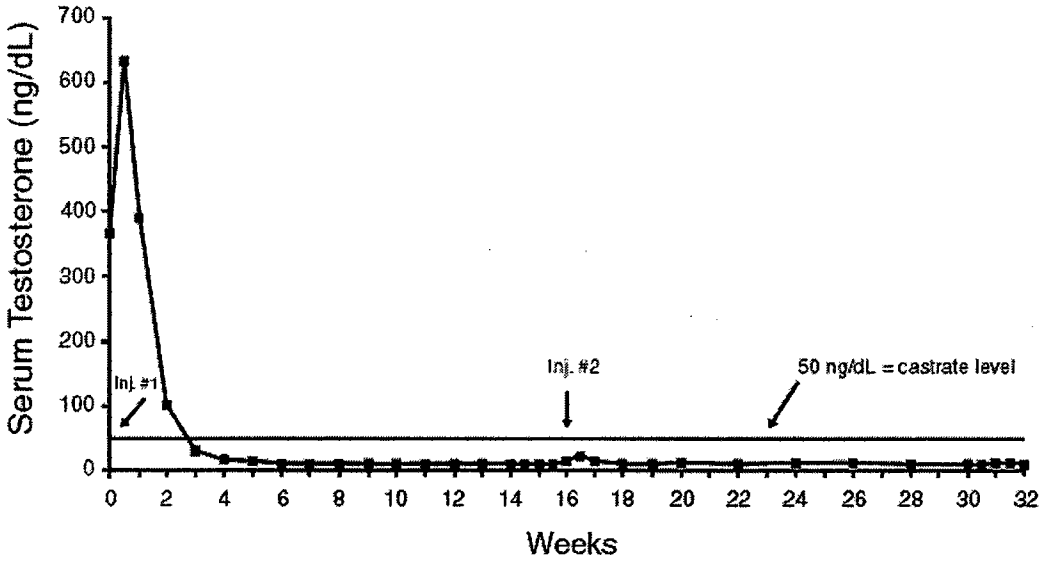
In the majority of patients, testosterone levels increased 50% or more above the baseline during the first week of treatment. Mean serum testosterone subsequently suppressed to castrate levels within 30 days of the first injection in 94% of patients and within 43 days in all 49 patients during the initial 32-week treatment period. The median dosing interval between injections was 112 days. One escape from suppression (two consecutive testosterone values > 50 ng/dL after castrate levels achieved) was noted at Week 16. In this patient, serum testosterone increased to above the castrate range following the second depot injection (Week 16) but returned to the castrate level by Week 18. No adverse events were associated with this rise in serum testosterone. A second patient had a rise in testosterone at Week 17, then returned to the castrate level by Week 18 and remained there through Week 32. In the long-term treatment phase two patients experienced testosterone elevations, both at Week 48. Testosterone for one patient returned to the castrate range at Week 52, and one patient discontinued the study at Week 48 due to disease progression.

Secondary efficacy endpoints evaluated in the study were the objective tumor response as assessed by clinical evaluations of tumor burden (complete response, partial response, objectively stable and progression) and evaluations of changes in prostatic involvement and prostate-specific antigen (PSA). These evaluations were performed at Weeks 16 and 32 of the treatment phase. The long-term treatment phase monitored PSA at each visit (every 16 weeks). The objective tumor response analysis showed "no progression" (i.e. complete or partial response, or stable disease) in 86% (37/43) of patients at Week 16, and in 77% (37/48) of patients at Week 32. Local disease improved or remained stable in all patients evaluated at Week 16 and/or 32. For patients with elevated baseline PSA, 50% (23/46) had a normal PSA (< 4.0 ng/mL) at Week 16, and 51% (19/37) had a normal PSA at Week 32.

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.

Using historical comparisons, the safety and efficacy of LUPRON DEPOT-4 Month 30 mg appear similar to the other LUPRON DEPOT formulations.

Lupron Depot – 4 Month 30 mg
Mean Serum Testosterone Concentrations



Note: Measurements were taken in a subset of patients at Weeks 14.5, 15.5, 16.5, 30.5, 31 and 31.5.

INDICATIONS AND USAGE

LUPRON DEPOT-4 Month 30 mg is indicated in the palliative treatment of advanced prostatic cancer.

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT. Reports of anaphylactic reactions to synthetic GnRH (Factrel) or GnRH agonist analogs have been reported in the medical literature.
2. This formulation is not indicated for use in women. (See LUPRON DEPOT 3.75 mg and LUPRON DEPOT®–3 Month 11.25 mg package inserts.)
3. All formulations of LUPRON DEPOT are contraindicated in women who are or may become pregnant while receiving the drug. LUPRON DEPOT may cause fetal harm when administered to a pregnant woman. Major fetal abnormalities were observed in rabbits but not in rats after administration of LUPRON DEPOT throughout gestation. There was increased fetal mortality and decreased fetal weights in rats and rabbits. The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. Therefore, the possibility exists that spontaneous abortion may occur. If this drug is used during pregnancy, or if the patient becomes pregnant while taking any formulation of LUPRON DEPOT, the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Initially, LUPRON DEPOT, like other LH-RH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first week of treatment. Transient worsening of symptoms, or the occurrence of additional signs and symptoms of

prostate cancer, may occasionally develop during the first few weeks of LUPRON DEPOT treatment. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically. As with other LH-RH agonists, isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications.

For patients at risk, initiation of therapy with daily LUPRON® (leuprolide acetate) Injection (See **DOSAGE AND ADMINISTRATION** section in the LUPRON Injection labeling.) for the first two weeks to facilitate withdrawal of treatment may be considered. If spinal cord compression or renal impairment develops, standard treatment of these complications should be instituted.

PRECAUTIONS

Information for Patients An information pamphlet for patients is included with the product.

General 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-4 Month 30 mg should be monitored by measuring serum levels of testosterone, as well as prostate-specific antigen. 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 in most (45/49) patients for as long as the patients received their injections. (See **CLINICAL STUDIES** and **ADVERSE REACTIONS.)**

Drug Interactions See **CLINICAL PHARMACOLOGY, Pharmacokinetics**.

Drug/Laboratory Test Interactions Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Due to the suppression of the pituitary-gonadal system by LUPRON DEPOT, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT may be affected.

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, Teratogenic Effects. Pregnancy Category X. (See **CONTRAINDICATIONS** section.)

Pediatric Use Safety and effectiveness of LUPRON DEPOT-4 Month 30 mg have not been established in pediatric patients. 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.

Geriatric Use In the clinical trials for LUPRON DEPOT – 4 Month 30 mg, the majority (79%) of the subjects studied were at least 65 years of age. Therefore, the labeling reflects the pharmacokinetics, efficacy and safety of LUPRON DEPOT in this population.

ADVERSE REACTIONS

Clinical Trials

The 4-month formulation of LUPRON DEPOT 30 mg was utilized in clinical trials that studied the drug in 49 nonorchiectomized prostate cancer patients for 32 weeks or longer and in 24 orchiectomized prostate cancer patients for 20 weeks.

In the majority of nonorchiectomized patients, testosterone levels increased 50% or more above baseline during the first week of treatment with LUPRON DEPOT, declining thereafter to baseline levels or below by the end of the second week of treatment. Therefore, potential exacerbations of signs and symptoms during the first few weeks of treatment are of 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 the above described clinical trials, the following adverse reactions were reported in ≥ 5% of the patients during the treatment period regardless of causality.

Adverse Events Reported in ≥ 5% of Patients
Regardless of Causality
LUPRON DEPOT-4 Month 30 mg

	Nonorchiectomized, N = 49 Study 013		Orchiectomized, N = 24 Study 012	
	N	(%)	N	(%)
Body As a Whole				
Asthenia	6	(12.2)	1	(4.2)
Flu Syndrome	6	(12.2)	0	(0.0)
General Pain	16	(32.7)	1	(4.2)
Headache	5	(10.2)	1	(4.2)
Injection Site Reaction	4	(8.2)	9	(37.5)
Cardiovascular System				
Hot flashes/Sweats*	23	(46.9)	2	(8.3)
Digestive System				
GI Disorders	5	(10.2)	3	(12.5)
Metabolic and Nutritional Disorders				
Dehydration	4	(8.2)	0	(0.0)
Edema	4	(8.2)	5	(20.8)
Musculoskeletal System				
Joint Disorder	8	(16.3)	1	(4.2)
Myalgia	4	(8.2)	0	(0.0)
Nervous System				
Dizziness/Vertigo	3	(6.1)	2	(8.3)
Neuromuscular Disorders	3	(6.1)	1	(4.2)
Paresthesia	4	(8.2)	1	(4.2)
Respiratory System				
Respiratory Disorder	4	(8.2)	1	(4.2)
Skin and Appendages				
Skin Reaction	6	(12.2)	0	(0.0)
Urogenital System				
Urinary Disorders	5	(10.2)	4	(16.7)

In these same studies, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT-4 Month 30 mg.

Body As a Whole - Abscess, Accidental injury, Allergic reaction, Cyst, Fever, Generalized edema, Hernia, Neck pain, Neoplasm; *Cardiovascular System* - Atrial fibrillation, Deep thrombophlebitis, Hypertension; *Digestive System* - Anorexia, Eructation, Gastrointestinal hemorrhage, Gingivitis, Gum hemorrhage, Hepatomegaly, Increased appetite, Intestinal obstruction, Peridontal abscess; *Hemic and Lymphatic System* - Lymphadenopathy; *Metabolic and Nutritional Disorders* - Healing abnormal, Hypoxia, Weight loss; *Musculoskeletal System* - Leg cramps, Pathological fracture, Ptosis; *Nervous System* - Abnormal thinking, Amnesia, Confusion, Convulsion, Dementia, Depression, Insomnia/sleep disorders, Libido decreased*,

Neuropathy, Paralysis; *Respiratory System* - Asthma, Bronchitis, Hiccup, Lung disorder, Sinusitis, Voice alteration; *Skin and Appendages* - Herpes zoster, Melanosis; *Urogenital System* - Bladder carcinoma, Epididymitis, Impotence*, Prostate disorder, Testicular atrophy*, Urinary incontinence, Urinary tract infection.

* Due to the expected physiologic effects of decreased testosterone levels.

Laboratory: Abnormalities of certain parameters were observed, but their relationship to drug treatment is difficult to assess in this population. The following were recorded in ≥ 5% of patients: Decreased bicarbonate, Decreased hemoglobin/hematocrit/RBC, Hyperlipidemia (total cholesterol, LDL-cholesterol, triglycerides), Decreased HDL-cholesterol, Eosinophilia, Increased glucose, Increased liver function tests (ALT, AST, GGTP, LDH), Increased phosphorus. Additional laboratory abnormalities were reported: Increased BUN and PT, Leukopenia, Thrombocytopenia, Uricaciduria.

Postmarketing

During postmarketing surveillance, which includes other dosage forms and other patient populations, the following adverse events were reported.

Symptoms consistent with an anaphylactoid or asthmatic process have been rarely (incidence rate of about 0.002%) reported. Rash, urticaria, and photosensitivity reactions have also been reported.

Localized reactions including induration and abscess have been reported at the site of injection.

Symptoms consistent with fibromyalgia (eg, joint and muscle pain, headaches, sleep disorders, gastrointestinal distress, and shortness of breath) have been reported individually and collectively.

Cardiovascular System - Hypotension, Pulmonary embolism; *Hemic and Lymphatic System* - Decreased WBC; *Central/Peripheral Nervous System* - Peripheral neuropathy, Spinal fracture/paralysis; *Musculoskeletal System* - Tenosynovitis-like symptoms; *Urogenital System* - Prostate pain.

Changes in Bone Density: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with an LH-RH agonist analog. In a clinical trial, 25 men with prostate cancer, 12 of whom had been treated previously with leuprolide acetate for at least six months, underwent bone density studies as a result of pain. The leuprolide-treated group had lower bone density scores than the nontreated control group. It can be anticipated that long periods of medical castration in men will have effects on bone density.

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in women and pediatric populations.

OVERDOSAGE

In clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, 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-4 Month 30 mg to be administered is one injection **EVERY FOUR MONTHS (16 weeks).** Due to different release characteristics, a fractional dose of this 4-month depot formulation is not equivalent to the same dose of the monthly formulation and should not be given.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered **EVERY FOUR MONTHS (16 weeks)** as a single intramuscular injection.

For optimal performance of the prefilled dual chamber syringe (PDS), read and follow the following instructions:

1. The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.
2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.
3. Hold the syringe UPRIGHT. Release the diluent by SLOWLY PUSHING (6 to 8 seconds) the plunger until the first stopper is at the blue line in the middle of the barrel.
4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.
5. Hold the syringe UPRIGHT. With the opposite hand pull the needle cap upward without twisting.
6. Keep the syringe UPRIGHT. Advance the plunger to expel the air from the syringe.
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.

NOTE: Aspirated blood would be visible just below the luer lock connection if a blood vessel is accidentally penetrated. If present, blood can be seen through the transparent LuproLoc™ safety device.

AFTER INJECTION

8. Withdraw the needle. Immediately activate the LuproLoc™ safety device by pushing the arrow forward with the thumb or finger until the device is fully extended and a CLICK is heard or felt.

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.

HOW SUPPLIED
LUPRON DEPOT-4 Month 30 mg is packaged as follows:
Kit with prefilled dual-chamber syringe NDC 0300-3683-01

Each syringe contains 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-4 Month 30 mg is administered as a single IM injection **EVERY FOUR MONTHS (16 weeks).**

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]

U.S. Patent Nos. 4,728,721; 4,849,228; 5,330,767; 5,476,663; 5,480,656; 5,575,987; 5,631,020; 5,631,021; 5,643,607; 5,716,640; 5,814,342; 5,823,997; 5,980,488; and 6,036,976. Other patents pending.

Manufactured for
TAP Pharmaceuticals Inc.
Lake Forest, IL 60045, U.S.A.
by Takeda Pharmaceutical Company Limited
Osaka, JAPAN 540-8645

(No. 3683)
03-5449-R10; Revised: October, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-517/S-019

ADMINISTRATIVE

Division of Reproductive and Urologic Drug Products

REGULATORY PROJECT MANAGER REVIEW

Applicant: TAP Pharmaceutical Products, Inc.

Materials Reviewed:

NDA	Supplement	Name of Drug	Letter Date	Receipt Date
19-732	SCS-027	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	May 6, 2005	May 9, 2005
19-732	SLR-029	Lupron Depot (leuprolide acetate for depot suspension), 7.5mg	August 18, 2005	August 19, 2005
20-517	SCS-018	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	May 6, 2005	May 9, 2005
20-517	SLR-019	Lupron Depot (leuprolide acetate for depot suspension), 4-month, 30mg	August 18, 2005	August 19, 2005
19-010	SLR-031	Lupron Injection (leuprolide acetate	August 18, 2005	August 19, 2005
20-708	SCS-020	Lupron Depot (leuprolide acetate for depot suspension), 3-month	May 6, 2005	May 9, 2005
20-708	SLR-021	Lupron Depot (leuprolide acetate for depot suspension), 3-month	August 18, 2005	August 19, 2005
19-943	SCS-022	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	May 6, 2005	May 9, 2005
19-943	SLR-024	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	August 18, 2005	August 19, 2005
20-011	SCS-029	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	May 6, 2005	May 9, 2005
20-011	SLR-031	Lupron Depot (leuprolide acetate for depot suspension), 3.75mg	August 18, 2005	August 19, 2005

Background and Summary

In January 5, 2005, TAP issued a Dear Healthcare Professional letter and a Voluntary Recall of two particular lots from NDAs 20-517 and 20-708 where complaints of clumping were reported by healthcare professionals to TAP. In addition to TAP's initiation on investigating on the issue, they proposed changes to the labeling as a corrective action to the reported issue. Furthermore, the Sponsor proposes to revise the "Appearance" section of their drug product specification---as a chemistry supplement. These changes affects all of the Lupron Depot drug products with pre-filled syringes and therefore, the changes are being proposed for all of the NDAs listed above, except for NDA 19-010 (does not have a pre-filled syringe).

In addition, on October 18, 2004, the Office of Drug Safety reviewed the MedWatch reports with significant adverse events of pituitary apoplexy following the administration of GnRH agonists. This review was followed by a Prior Approval supplement request letter dated May 11, 2005, issued by the Division of Reproductive and Urologic Drug Products to all of the sponsors of GnRH agonists, including all of the listed NDAs above, containing the following verbiage:

The above paragraph was further revised by the Division, concluding the final version which was conveyed to the Sponsor on July 15, 2005 prior to submitting the supplement, as follows:

> *Pituitary apoplexy:* During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

REVIEW

Of the Lupron Recall changes, the labeling portion of the chemistry supplement was reviewed. See Chemistry review for the changes in the Appearance section of the specification. Listed below are the Sponsor's proposed changes containing the verbiage to the labels:

A. LUPRON RECALL:

1) In the Package Insert, under the DOSAGE AND ADMINISTRATION section, and in the INSTRUCTIONS ON HOW TO MIX AND ADMINISTER pamphlet:

   a. The sponsor proposed to add the following statement as item #1:

      The LUPRON DEPOT powder should be visually inspected and the syringe should NOT BE USED if clumping or caking is evident. A thin layer of powder on the wall of the syringe is considered normal. The diluent should appear clear.

   b. The sponsor proposed to add the following statement to add onto item #4:

      Keep the syringe UPRIGHT. Gently mix the microspheres (powder)

thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone into suspension.

B. PITUITARY APOPLEXY: The following text was inserted under the Postmarketing subsection of the Adverse Events section of the Package Insert:

Pituitary apoplexy: During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed, with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

A. PACKAGE INSERT: In addition to the changes listed below, all of the NDAs listed proposed the following change:

The manufacturing company changed from Takeda Chemical Industries, Ltd. Osaka, Japan 541 to Takeda Pharmaceutical Company Limited Osaka, Japan 540-8645.

NDA	Lupron Recall	Pituitary Apoplexy	Other Changes
	Text inserted is as proposed and requested for all of the supplements listed below.		
19-732	SCS-027: Acceptable	SLR-029: Acceptable	1. The labeling revision code and date changed from [ ] to TAPDN295-V2; Revised: Month,Year 2. Copyright year changed from [ ] to 1988- Year
20-517, 3 mo	SCS-018: Acceptable	SLR-019: Acceptable	1. The labeling revision code and date changed from [ ] to TAPDN293-V2; Revised: Month,Year 2. Copyright year changed from [ ] to 1995 – Year

20-517, 4 mo	SCS-018 Acceptable	SLR-019 Acceptable	1. The labeling revision code and date changed from ⊏ ⊐ to TAPDN294-V2; Revised: Month,Year 2. Copyright year changed from ⊏ ⊐ to 1997 – Year
20-011	SCS-029 Acceptable	SLR-031 Acceptable	NDA 20-11 & 19-943 share the same label, therefore this portion of the review applies to both applications: 1. Rx only is moved from the end of the label to the beginning—before DESCRIPTION section. 2. The labeling revision code and date changed from ⊏ ⊐ to TAPDN296-V2; Revised: Month,Year 3. Copyright year changed from ⊏ ⊐ to 1990 - Year
19-943	SCS-022 Acceptable	SLR-024 Acceptable	
19-010		SLR 031, Adult & Pediatric Use sections are Acceptable.	1. The labeling revision code and date changed from ⊏ ⊐ to TAPDN299-V2, Rev. Month, Year 2. Copyright year changed from ⊏ ⊐ ⊏ ⊐ to © 1993 – Year
20-708	SCS-020 Acceptable	SLR-021 Acceptable	1. "Rx only" is moved from the end of the label to the beginning 2. The labeling revision code and date changed from ⊏ ⊐ to TAPDN297-V2, Revised: MONTH, YEAR 3. Copyright year changed from ⊏ ⊐ ⊏ ⊐ to © 1993 – YEAR

B. MIXING INSTRUCTIONS: Text inserted in items #1 & #4 are as proposed for all the supplements listed below and are acceptable.

20-708	SCS-020	The following changes are in addition to the changes regarding Lupron Recall and are acceptable: 1. The Sponsor inserted the exact verbiage of the agreed-upon text in all of these supplements on the Mixing Instructions leaflet, as indicated above. 2. In addition, the Sponsor added the following:  REVIEW REVISED MIXING INSTRUCTIONS
19-943	SCS-022	
20-011	SCS-029	
20-517, 3mo & 4mo	SCS-018	
19-732	SCS-027	

Conclusions

Based on this labeling review, these supplemental applications are recommended for approval, as concurred by Chemistry and Clinical.

Nenita Crisostomo, R.N.
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

{see appended electronic signature}

Jennifer Mercier
Chief, Project Management Staff

Drafted: NIC/9.5.05
Revised/Initialed: AGassman9.9.05, MHirsch9.9.05, SDe9.9.05, JMercier/9.19.05
Finalized: DFS/NCrisostomo/9.9.05
Filename: review.SLR.apoplexy.Recall

CSO LABELING REVIEW

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nenita Crisostomo
9/20/2005 10:51:24 AM
CSO

Jennifer L. Mercier
9/21/2005 02:04:33 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-517/S-019

CORRESPONDENCE

Electronic Regulatory Submission for Archive

October 28, 2005

Dr. Daniel Shames, MD, Division Director
Division of Reproductive and Urologic Drug Products, HFD-580
Center for Drug Evaluation and Research
Electronic Document Room
5901-B Ammendale Road
Beltsville, MD 20705

Attn: Nenita Crisostomo, RN, Regulatory Project Manager

RE: Lupron Depot® 3 M 22.5 mg/ 4 M 30 mg (leuprolide acetate for depot suspension)
Prostate Cancer
NDA 20-517

FPL for Approved Supplements NDA 20-517/ S-018, S-019

Dear Dr. Shames:

TAP Pharmaceutical Products Inc. hereby submits the Final Printed Labeling (FPL) per the approval letter dated September 15, 2005 for the above-referenced supplemental New Drug Applications. The FPL is identical to the submitted labeling on August 18, 2005.

The following information is included in this submission:

- Module 1.14.2.2: Final Printed Labeling for 3 Month 22.5 mg in PDF format (Commodity Number: 03-5450-R12; Revision Date: October 2005)
- Module 1.14.2.2: Final Printed Labeling for 4 Month 30 mg in PDF format (Commodity Number: 03-5449-R10; Revision Date: October 2005)
- Module 1.14.2.3: Final Labeling Text for 3 Month 22.5 mg in MS Word format
- Module 1.14.2.3: Final Labeling Text for 4 Month 30 mg in MS Word format

This submission is provided in an electronic Common Technical Document (eCTD) format. The only exception from electronic format is signatures, originals of which are provided on paper. Electronic documents are provided in Adobe PDF 1.3 (Adobe 4.05b) format. This submission is approximately 1 megabyte and is provided on one CD-ROM. This submission has been checked for viruses using McAfee Virus Scan Enterprise 7.1.0, and is virus free.

The printed contents of the index-md5.txt file are appended to this letter.

Should you have any questions or comments, please contact me at the information provided below.

Sincerely,

Tonya Haynes
Regulatory Product Manager
TAP Pharmaceutical Products Inc.
675 N. Field Drive
Lake Forest, IL 60045
Tel: (847) 582-2633
Fax: (847) 582-2880

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-517/S-019 NDA 20-011/S-031
NDA 20-708/S-021 NDA 19-732/S-029
NDA 19-010/S-031 NDA 19-943/S-024

PRIOR APPROVAL SUPPLEMENT

TAP Pharmaceutical Products Inc.
Attention: Tonya Haynes, M.P.H.
Regulatory Product Manager
675 North Field Drive
Lake Forest, IL 60045

Dear Ms. Hayes:

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

Name of Drug Product	**NDA#**	**Supplement number**	**Date of Supplement**	**Date of Receipt**
Lupron Depot (leuprolide acetate for depot suspension), 3-Month, 22.5 mg, *and,* Lupron Depot (leuprolide acetate for depot suspension), 4-Month, 30 mg	20-517	S-019	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	20-011	S-031	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 7.5 mg	19-732	S-029	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3-Month, 11.25 mg	20-708	S-021	August 18, 2005	August 19, 2005
Lupron Injection (leuprolide acetate)	19-010	S-031	August 18, 2005	August 19, 2005
Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg	19-943	S-024	August 18, 2005	August 19, 2005

These supplemental applications propose the revision to the Postmarketing subsection of the Adverse Reaction section in the package insert to add information regarding pituitary apoplexy.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 18, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 17, 2006.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, please call me, at (301) 827-7260.

Sincerely,

{See appended electronic signature page}

Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Reproductive and Urologic Drusg Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nenita Crisostomo
9/1/2005 07:14:45 PM

Electronic Regulatory Submission for Archive

August 18, 2005

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD#580
Attention: CENTRAL DOCUMENT ROOM
5901-B Ammendale Road
Beltsville, Maryland 20715-1266

ATTENTION: Daniel Shames, M.D.
Director

RE: NDA 20-517 Lupron Depot-3 Month 22.5 mg (leuprolide acetate for depot suspension)
Lupron Depot-4 Month 30 mg (leuprolide acetate for depot suspension)
Sequence No.: 0001

Prior Approval Labeling Supplement

TAP Pharmaceutical Products Inc. hereby supplements the above-referenced NDA to provide for the labeling revision to the package insert of Lupron to include the serious post-marketing adverse event, pituitary apoplexy, which may occur in all gonadotropin-releasing hormone (GnRH) agonists, including LUPRON.

This is in response to an FDA letter dated May 11, 2005 (received on July 11, 2005) requesting the labeling revision within 30 days of receipt of the letter. The suggested labeling change was further clarified by the Agency and the revised wording was received on August 5, 2005. TAP's request to postpone the labeling submission from the original committed date of August 10, 2005 to August 24, 2005 was granted.

As requested, the package insert has been revised to add pituitary apoplexy, a serious adverse event, in the Postmarketing subsection of the Adverse Reaction section. Provided are electronic files (both PDF and MS Word) for the annotated and draft labeling per eCTD format.

The original signatures are provided on paper for the cover letter and FDA Form 356h. The PDF documents are provided in Adobe PDF 1.3 (Abobe 4.05) format. This submission is approximately 2 MB and is provided in one CD-ROM. The electronic files have been scanned for computer viruses using Virus Scan Enterprise version 7.0 and are virus free. The printed contents of the index-md5.txt are appended to this letter.

If there are any further questions, please feel free to contact Donna Helms, Director of TAP Regulatory Affairs, at (847) 582-4922.

Sincerely,

TAP Pharmaceutical Products Inc.

Jessie Y. Lee, Ph.D. RAC
Principal Regulatory Advisor
Phone: (847) 582-4924
Fax: (847) 582-2880
E-mail:Jessie.Lee@TAP.com

JYL/jl

Attachment

C:08-2005FDA.JYL/16