

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 19-732/S-029

Name: Lupron Depot
leuprolide acetate (7.5 mg)

Sponsor: TAP Pharmaceuticals, Inc.

Approval Date: January 26, 1989

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**APPLICATION NUMBER:
NDA 19-732/S-029**

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APPLICATION NUMBER:

NDA 19-732/S-029

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

NDA's 19-732/S-027, S-029
20-708/S-020, S-021

20-517/S-018, S-019
19-943/S-022, S-024

19-010/S-031
20-011/S-029, S-031

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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 19-732/S-029

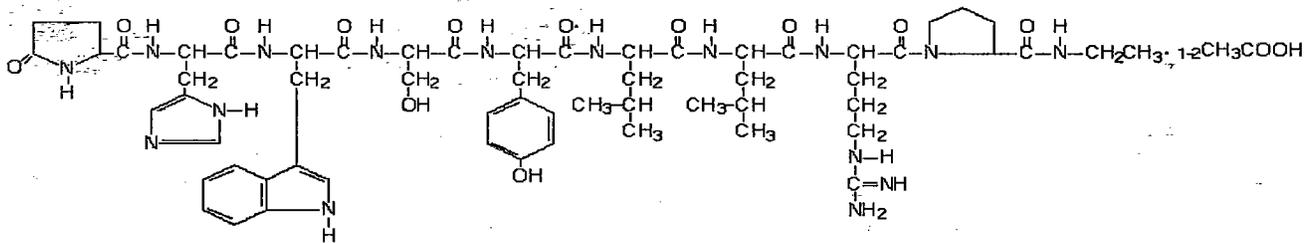
FINAL PRINTED LABELING

LUPRON DEPOT[®] 7.5 mg
(leuprolide acetate for depot suspension)

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 is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, becomes a suspension intended as a monthly intramuscular injection.

The front chamber of LUPRON DEPOT 7.5 mg prefilled dual-chamber syringe contains leuprolide acetate (7.5 mg), purified gelatin (1.3 mg), DL-lactic and glycolic acids copolymer (66.2 mg), and D-mannitol (13.2 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacture of LUPRON DEPOT 7.5 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. Castrate levels of testosterone in prostatic cancer patients have been demonstrated for up to 10 years.

Leuprolide acetate is not active when given orally.

Pharmacokinetics

Absorption Following a single injection of LUPRON DEPOT 7.5 mg to patients, mean plasma leuprolide concentration was almost 20 ng/mL at 4 hours and 0.36 ng/mL at 4 weeks. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study.

Nondetectable leuprolide plasma concentrations have been observed during chronic LUPRON DEPOT 7.5 mg administration, but testosterone levels appear to be maintained at castrate levels.

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 ¹⁴C-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.

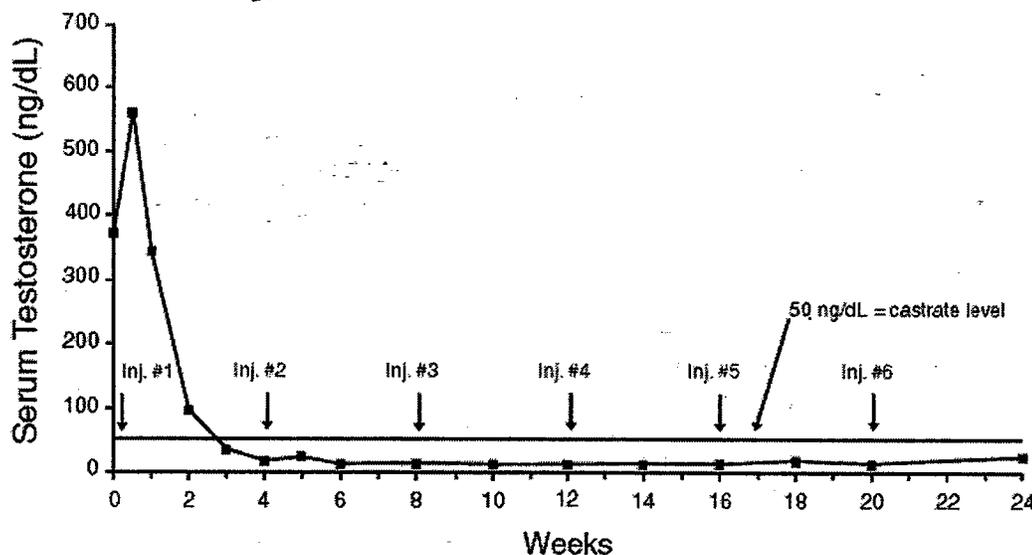
CLINICAL STUDIES

In an open-label, non-comparative, multicenter clinical study of LUPRON DEPOT 7.5 mg, 56 patients with stage D₂ prostatic adenocarcinoma and no prior systemic treatment were enrolled. The objectives were to determine if a 7.5 mg depot formulation of leuprolide injected once every 4 weeks would reduce and maintain serum testosterone to castrate range (≤ 50 ng/dL), to evaluate objective clinical response, and to assess the safety of the formulation. During the initial 24 weeks, serum testosterone was measured weekly, biweekly, or every four weeks and objective tumor response assessments were performed at Weeks 12 and 24. Once the patient completed the initial 24-week treatment phase, treatment continued at the investigator's discretion. Data from the initial 24-week treatment phase are summarized in this section.

In the majority of patients, serum testosterone increased by 50% or more above baseline during the first week of treatment. Serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54) of patients for whom testosterone suppression was achieved (2 patients withdrew prior to onset of suppression) and within 66 days in all 54 patients. Mean serum testosterone suppressed to

castrate level by Week 3. The median dosing interval between injections was 28 days. One escape from suppression (2 consecutive testosterone values >50 ng/dL after achieving castrate level) was noted at Week 18, associated with a substantial dosing delay. In this patient, serum testosterone returned to the castrate range at the next monthly measurement. Serum testosterone was minimally above the castrate range on a single occasion for 4 other patients. No clinical significance was attributed to these rises in testosterone.

**Lupron Depot 7.5 mg
Mean Serum Testosterone Concentrations**



Secondary efficacy endpoints evaluated included objective tumor response, assessed by clinical evaluations of tumor burden (complete response, partial response, objectively stable, and progression), as well as changes in local disease status, assessed by digital rectal examination, and changes in prostatic acid phosphatase (PAP). These evaluations were performed at Weeks 12 and 24. The objective tumor response analysis showed a “no progression” (ie. complete or partial response, or stable disease) in 77% (40/52) of patients at Week 12, and in 84% (42/50) of patients at Week 24. Local disease improved or remained stable in all (42) patients evaluated at Week 12 and in 98% (41/42) of patients elevated at Week 24. PAP normalized or decreased at Week 12 and/or 24 in the majority of patients with elevated baseline PAP.

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 7.5 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.¹

2. 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 administered 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 7.5 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 for the duration of treatment in all 54 patients. Minimal and transient increases to above the castrate level occurred in eight patients (see **CLINICAL STUDIES** section).

Drug Interactions (See **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 leuprolide acetate-induced tumors or 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.

Geriatric Use In the clinical trials for LUPRON DEPOT, the majority (68%) 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 a clinical trial of LUPRON DEPOT 7.5 mg, the following adverse reactions were reported in 5% or more of the patients during the initial 24-week treatment period regardless of causality.

| LUPRON DEPOT 7.5 mg (N=56) | | |
|-------------------------------------|----|--------|
| | N | (%) |
| Body as a Whole | | |
| General pain | 13 | (23.2) |
| Infection | 3 | (5.4) |
| Cardiovascular System | | |
| Hot flashes/sweats* | 32 | (57.1) |
| Digestive System | | |
| GI disorders | 8 | (14.3) |
| Metabolic and Nutritional Disorders | | |
| Edema | 8 | (14.3) |
| Nervous System | | |
| Libido decreased* | 3 | (5.4) |
| Respiratory System | | |
| Respiratory disorder | 6 | (10.7) |
| Urogenital System | | |
| Urinary disorder | 7 | (12.5) |
| Impotence* | 3 | (5.4) |
| Testicular atrophy* | 3 | (5.4) |

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

In this same study, the following adverse reactions were reported in less than 5% of the patients on LUPRON DEPOT 7.5 mg.

Body as a Whole - Asthenia, Cellulitis, Fever, Headache, Injection site reaction, Neoplasm; *Cardiovascular System* - Angina, Congestive heart failure; *Digestive System* - Anorexia, Dysphagia, Eructation, Peptic ulcer; *Hemic and Lymphatic System* - Ecchymosis; *Musculoskeletal System* - Myalgia; *Nervous System* - Agitation, Insomnia/sleep disorders, Neuromuscular disorders; *Respiratory System* - Emphysema, Hemoptysis, Lung edema, Sputum increased; *Skin and Appendages* - Hair disorder, Skin reaction; *Urogenital System* - Balanitis, Breast enlargement, Urinary tract infection.

Laboratory: Abnormalities of certain parameters were observed, but their relationship to drug treatment are difficult to assess in this population. The following were recorded in $\geq 5\%$ of patients at final visit: Decreased albumin, decreased hemoglobin/hematocrit, decreased prostatic acid phosphatase, decreased total protein, decreased urine specific gravity, hyperglycemia, hyperuricemia, increased BUN, increased creatinine, increased liver function tests (AST, LDH), increased phosphorus, increased platelets, increased prostatic acid phosphatase, increased total cholesterol, increased urine specific gravity, leukopenia.

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 is 7.5 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly 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 7.5 mg is packaged as follows:

Kit with prefilled dual-chamber syringe NDC 0300-3642-01

Each syringe contains sterile lyophilized microspheres which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT 7.5 mg is administered as a single monthly IM injection.

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. 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; 5,330,767; 5,476,663; 5,575,987; 5,631,020; 5,631,021; 5,716,640; 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

TM—Trademark

®—Registered Trademark

(No. 3642)

03-5451-R17; Revised: October, 2005

©1988-2005, TAP Pharmaceutical Products Inc.

ADDITIONAL INFORMATION

- None of the components is hazardous; therefore, no special handling or disposal procedures are needed.
- Dispose of the syringe according to local regulations/procedures.

LuproLoc™

U.S. Patent Nos. 5,823,997 and 5,980,488.

Other patents pending.



TAP Pharmaceuticals Inc.
Lake Forest, IL 60045

INSTRUCTIONS ON HOW TO MIX AND ADMINISTER

If you have any questions regarding the drug or the mixing/administration procedure, please call
1-800-622-2011
for further assistance.



**REVIEW REVISED
MIXING INSTRUCTIONS**



035410

**NOTE: LUPRON DEPOT® and
LUPRON DEPOT-PED®**

must be administered under the supervision of a physician.

**LUPRON DEPOT®
LUPRON DEPOT-PED®**

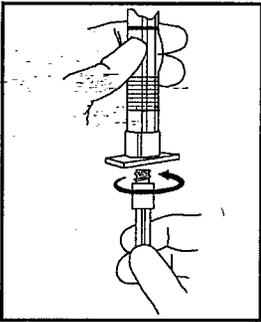
PREFILLED DUAL-CHAMBER SYRINGE

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

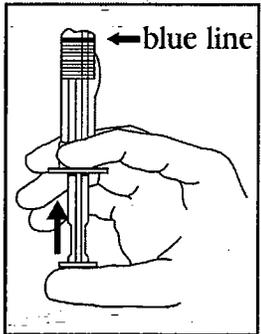
(Nos. 2108, 2282, 2440, 3346, 3641, 3642, 3663, 3683)
03-5410-R7; Revised: January, 2005
TM-Trademark
®-Registered Trademark
©2002-2005 TAP Pharmaceutical Products Inc.
Printed in U.S.A.

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

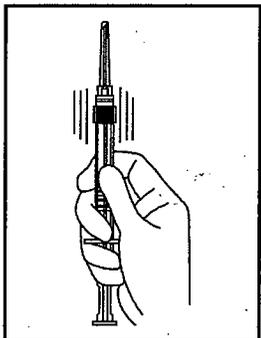
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2. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.



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.

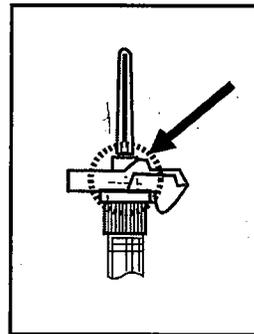


4. Keep the syringe UPRIGHT. Gently mix the microspheres (powder) thoroughly to form a uniform suspension. The suspension will appear milky. If the powder adheres to the stopper or caking/ clumping is present, tap the syringe with your finger to disperse. DO NOT USE if any of the powder has not gone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

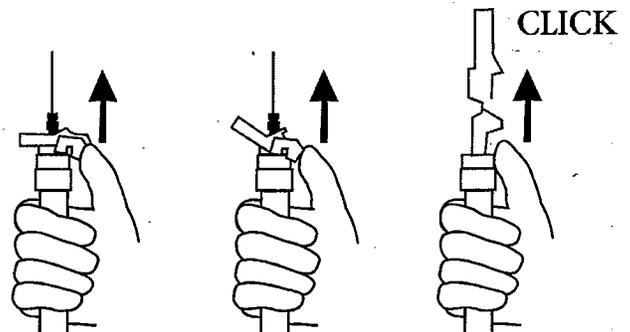
7. Inject the entire contents of the syringe intramuscularly at the time of reconstitution. The suspension settles very quickly following reconstitution; therefore, LUPRON DEPOT should be mixed and used immediately.



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, as illustrated, until the device is fully extended and a CLICK is heard or felt.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-732/S-029

ADMINISTRATIVE

PROJECT MANAGER REVIEW OF LABELING

NDA 19-732/S-027 and S-029

Drug: Lupron Depot 7.5 mg (leuprolide acetate for depot suspension)

Applicant: TAP Pharmaceutical Products, Inc.

Submission Date(s): October 28, 2005 **Receipt Date(s):** October 31, 2005

BACKGROUND:

The submission provides for FPL in accordance with the FDA September 15, 2005 letter.

DOCUMENTS REVIEWED:

The October 28, 2005 submitted package insert is compared with the package insert submitted August 18, 2005 and approved in the FDA September 15, 2005, letter.

REVIEW:

No differences are identified in the compared package inserts.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The FPL is acceptable and the supplement (FA) should be acknowledged and accepted.

Paul Zimmerman R.Ph., Project Manager/date 12-2-05

Dotti Pease, Chief, PMS/date 12-2-05

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/s/

Paul Zimmerman
12/2/2005 01:42:36 PM
CSO

Dotti Pease
12/5/2005-09:23:32 AM
CSO

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.

| | | | |
|-----------------|-----------------------|---|---|
| 20-517, 4 mo | SCS-018 Acceptable | SLR-019 Acceptable | <ol style="list-style-type: none"> The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN294-V2</u>; Revised: <u>Month, Year</u> Copyright year changed from <input type="checkbox"/> to <u>1997</u> - Year |
| 20-011 | SCS-029 Acceptable | SLR-031 Acceptable | <p>NDA 20-11 & 19-943 share the same label, therefore this portion of the review applies to both applications:</p> <ol style="list-style-type: none"> <u>Rx only</u> is moved from the end of the label to the beginning—before DESCRIPTION section. The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN296-V2</u>; Revised: <u>Month, Year</u> Copyright year changed from <input type="checkbox"/> to <u>1990</u> - Year |
| 19-943 | SCS-022 Acceptable | SLR-024 Acceptable | |
| 19-010 | | SLR 031, Adult & Pediatric Use sections are Acceptable. | <ol style="list-style-type: none"> The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN299-V2, Rev. Month, Year</u> Copyright year changed from <input type="checkbox"/> to <u>© 1993</u> - Year |
| 20-708 | SCS-020 Acceptable | SLR-021 Acceptable | <ol style="list-style-type: none"> "Rx only" is moved from the end of the label to the beginning The labeling revision code and date changed from <input type="checkbox"/> to <u>TAPDN297-V2, Revised: MONTH, YEAR</u> Copyright year changed from <input type="checkbox"/> to <u>© 1993</u> - 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 | <p>The following changes are in addition to the changes regarding Lupron Recall and are acceptable:</p> <ol style="list-style-type: none"> The Sponsor inserted the exact verbiage of the agreed-upon text in all of these supplements on the Mixing Instructions leaflet, as indicated above. In addition, the Sponsor added the following: <div style="text-align: center;">  <p>REVIEW REVISED -- MIXING INSTRUCTIONS</p> </div> |
| 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

PM Labeling Review: Lupron Recall & Apoplexy
Page 6 of 6

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

CSO LABELING REVIEW --

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/s/

Nenita Crisostomo
9/9/2005 04:11:28 PM
CSO

Jennifer L. Mercier
9/19/2005 04:48:47 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-732/S-029

CORRESPONDENCE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-732/S-027 and S-029

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

Dear Ms. Haynes:

We acknowledge receipt of your October 28, 2005 submission containing final printed labeling in response to our September 15, 2005 letter approving your supplemental new drug applications for Lupron Depot 7.5 mg (leuprolide acetate for depot suspension).

We have reviewed the labeling that you submitted in accordance with our September 15, 2005 letter and we find it acceptable.

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 796-1489.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Dotti Pease

12/5/2005 09:26:04 AM

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[®] 7.5 mg (leuprolide acetate for depot suspension)
Prostate cancer
NDA 19-732**

FPL for Approved Supplements NDA 19-732/ S-027, S-029

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 in PDF format (Commodity Number: 03-5451-R17; Revision Date: October 2005)
- Module 1.14.2.3: Final Labeling Text 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.

NDA 19-732

Lupron Depot[®] 7.5 mg (leuprolide acetate for depot suspension)

October 28, 2005

Page 2 of 2

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, <i>and</i> , 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 |

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
Page 2

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 Drug
Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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



"Crisostomo, Nenita"
<CrisostomoN@cder.fda.gov
v>

08/05/2005 05:26 PM

To "jessie.lee@TAP.com" <jessie.lee@TAP.com>

cc

bcc

Subject Pituitary Apoplexy—new wording

History:

This message has been replied to and forwarded.

Hi Jessie,

As we discussed this morning, here is the revised wording for the class labeling:

"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."

Please call me if you have any further questions. Have a nice weekend!

Thanks,
nita

301-827-7260



Food and Drug Administration
Rockville, MD 20857

NDA 19-010 NDA 19-732 NDA 19-943
NDA 20-011 NDA 20-517 NDA 20-708

RECEIVED

JUL 11 2005

REGULATORY

TAP Pharmaceutical Products Inc.
Attention: Jessie Y. Lee, Ph.D., R.A.C.
Principal Regulatory Advisor
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Lee:

Please refer to your new drug applications (NDAs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for:

| APPLICATION NUMBER | DRUG NAME | DOSAGE |
|--------------------|--|----------|
| NDA 19-010 | LUPRON [®] (leuprolide acetate) Injection | 5 mg/ml |
| NDA 19-732 | LUPRON DEPOT [®] (leuprolide acetate for depot suspension) | 7.5 mg |
| NDA 19-943 | LUPRON DEPOT [®] (leuprolide acetate for depot suspension) | 3.75 mg |
| NDA 20-011 | LUPRON DEPOT [®] (leuprolide acetate for depot suspension) | 3.75 mg |
| NDA 20-517 | LUPRON DEPOT [®] -3 Month (leuprolide acetate for depot suspension) | 22.5 mg |
| NDA 20-517 | LUPRON DEPOT [®] -4 Month (leuprolide acetate for depot suspension) | 30 mg |
| NDA 20-708 | LUPRON DEPOT [®] -3 Month (leuprolide acetate for depot suspension) | 11.25 mg |

We have conducted a review of post-marketing safety data for all gonadotropin-hormone agonists after a recent case report of pituitary apoplexy following gonadotropin releasing hormone agonist treatment. It is important that clinicians are informed of the risk of pituitary apoplexy through labeling.

Given the serious consequences of pituitary apoplexy, we recommend that you add this serious post-marketing adverse event to the LUPRON[®] labels. In addition, we encourage you to report cases of pituitary apoplexy to the FDA.

To assure that adequate safety information is available in your product label, these changes to your label must be submitted within 30 days of the receipt of this letter.

In the Postmarketing subsection of the Adverse Reactions section, the following text should be included:



Submit draft labeling electronically as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made. This change is not appropriate for reporting in an annual report.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-827-4260.

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

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/s/

Daniel A. Shames
5/11/05 06:03:44 PM