LABELING

This is combined labeling. Examples of different fonts appear below. 3-29-95

- General information
- Information on endometriosis
- Information on uterine fibroids

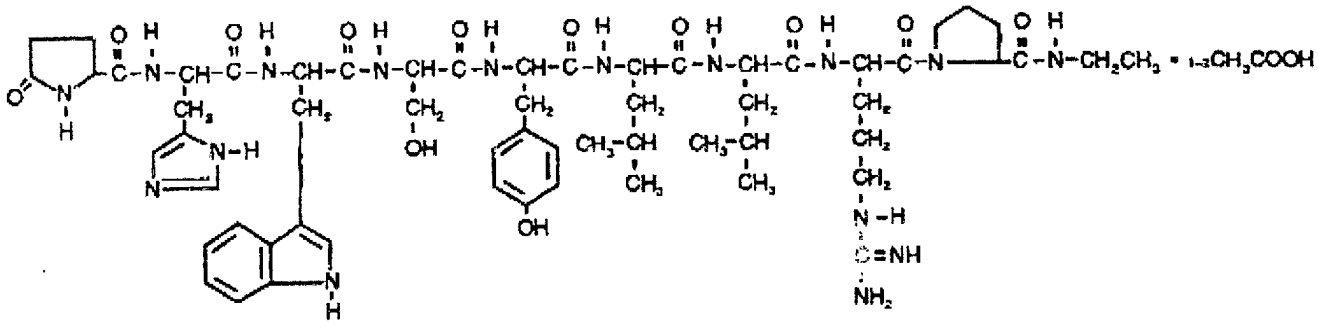
(No. 3639)
New

LUPRON DEPOT® 3.75 mg

(leuprolide acetate for depot suspension)

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 supplied in a vial containing sterile lyophilized microspheres, which when mixed with diluent, become a suspension, which is intended as a monthly intramuscular injection.

The single-dose vial of LUPRON DEPOT contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH.

During the manufacturing process of LUPRON DEPOT, acetic acid is lost, leaving the peptide.

CLINICAL PHARMACOLOGY

Leuprolide acetate is a long acting GnRH analog. A single monthly injection of LUPRON DEPOT results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Leuprolide acetate is not active when given orally. Intramuscular injection of the depot formulation provides plasma concentrations of leuprolide over a period of one month.

PHARMACOKINETICS

Absorption

A single dose of LUPRON DEPOT 3.75 mg was administered by intramuscular injection to healthy female volunteers. The absorption of leuprolide was characterized by an initial increase in plasma concentration, with peak concentration ranging from 4.6 to 10.2 ng/mL at four hours postdosing. However, intact leuprolide and an inactive metabolite could not be distinguished by the assay used in the study. Following the initial rise, leuprolide concentrations started to plateau within two days after dosing and remained relatively stable for about four to five weeks with plasma concentrations of about 0.30 ng/mL.

Distribution

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

Metabolism

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

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

The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached mean maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of leuprolide concentrations.

Excretion
Following administration of LUPRON DEPOT 3.75 mg, to 3 patients less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

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

CLINICAL STUDIES

Endometriosis

In controlled clinical studies, LUPRON DEPOT 3.75 mg monthly for six months was shown to be comparable to danazol, 800 mg/day in relieving the clinical symptoms of endometriosis (pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and in reducing the size of endometrial implants as evidenced by laparoscopy. The clinical significance of a decrease in endometriotic lesions is not known at this time and in addition, laparoscopic staging of endometriosis does not necessarily correlate with the severity of symptoms.

LUPRON DEPOT 3.75 mg monthly induced amenorrhea in 74% and 98% of the patients after the first and second treatment months respectively. Most of the remaining patients reported episodes of only light bleeding or spotting. In the first, second and third post-treatment months, normal menstrual cycles resumed in 7%, 71% and 95% respectively, of those patients who did not become pregnant.

FIGURE 1–PERCENT OF PATIENTS WITH SYMPTOMS AT BASELINE, FINAL TREATMENT VISIT, AND AFTER 6 AND 12 MONTHS OF FOLLOW-UP

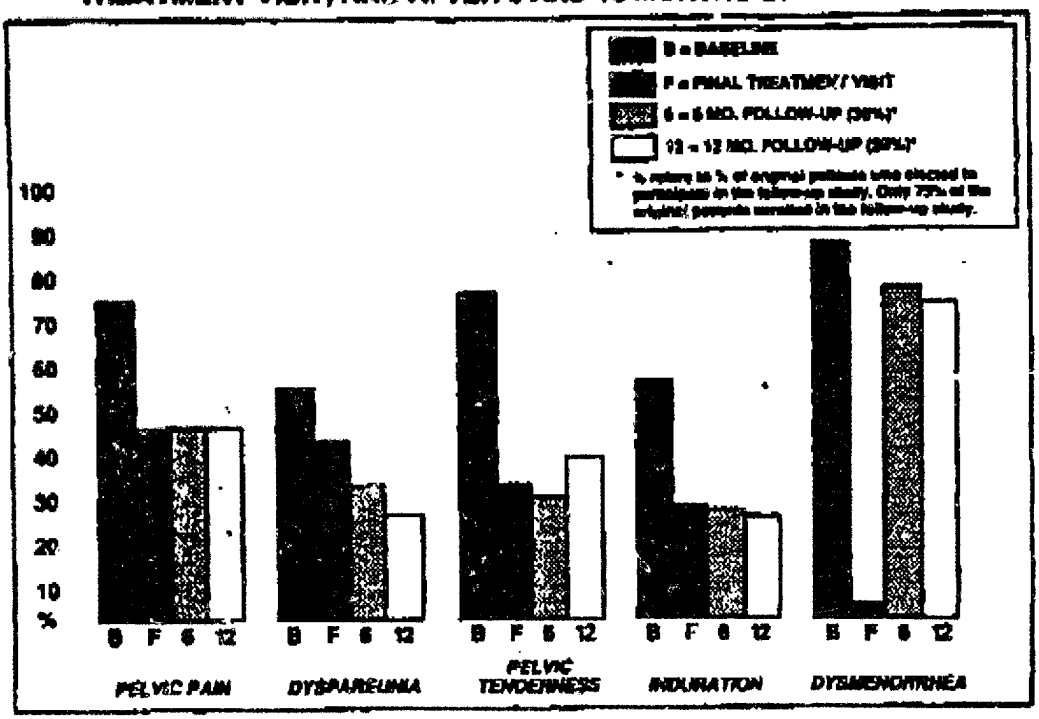


Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at six and 12 months following discontinuation of treatment for the various symptoms evaluated during the study. This included all patients at end of treatment and those who elected to participate at the follow-up periods. This might provide a slight bias in the results at follow-up as 75% of the original patients entered the follow-up study, and 36% were evaluated at six months and 26% at 12 months respectively.

Uterine Leiomyomata (Fibroids)

In controlled clinical trials, administration of LUPRON DEPOT 3.75 mg for a period of three or six months was shown to decrease uterine and fibroid volume, thus allowing for relief of clinical symptoms (abdominal bloating, pelvic pain, and pressure). Excessive vaginal bleeding (menorrhagia and menometrorrhagia) decreased, resulting in improvement in hematologic parameters.

In three clinical trials, enrollment was not based on hematologic status. Mean uterine volume decreased by 41% and myoma volume decreased by 37% at final visit as evidenced by ultrasound or MRI. These patients also experienced a decrease in symptoms including excessive vaginal bleeding and pelvic discomfort. Benefit occurred by three months of therapy, but additional gain was observed with an additional three months of LUPRON DEPOT 3.75 mg. Ninety-five percent of these patients became amenorrheic with 61%, 25%, and 4% experiencing amenorrhea during the first, second, and third treatment months respectively.

Post-treatment follow-up was carried out for a small percentage of LUPRON DEPOT 3.75 mg patients among the 77% who demonstrated a ≥ 25% decrease in uterine volume while on therapy. Menses usually returned within two months of cessation of therapy. Mean time to return to pretreatment uterine size was 8.3 months. Regrowth did not appear to be related to pretreatment uterine volume.

In another controlled clinical study, enrollment was based on hematocrit ≤ 30% and/or hemoglobin ≤ 10.2 g/dL. Administration of LUPRON DEPOT 3.75 mg, concomitantly with iron, produced an increase of ≥ 6% hematocrit and ≥ 2 g/dL hemoglobin in 77% of patients at three months of therapy. The mean change in hematocrit was 10.1% and the mean change in hemoglobin was 4.2 g/dL. Clinical response was judged to be a hematocrit of ≥ 36% and/or hemoglobin of ≥ 12 g/dL, thus allowing for autologous blood donation prior to surgery. At three months, 75% of patients met this criterion.

At three months, 80% of patients experienced relief from either menorrhagia or menometrorrhagia. As with the previous studies, episodes of spotting and menstrual-like bleeding were noted in some patients.

In this same study, a decrease of ≥ 25% was seen in uterine and myoma volumes in 60% and 54% of patients respectively. LUPRON DEPOT 3.75 mg was found to relieve symptoms of bloating, pelvic pain, and pressure.

There is no evidence that pregnancy rates are enhanced or adversely affected by the use of LUPRON DEPOT.

INDICATIONS AND USAGE

Experience with LUPRON DEPOT in females has been limited to women 18 years of age and older.

Endometriosis

LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions.

Uterine Leiomyomata (Fibroids)

Lupron Depot 3.75 mg and iron therapy are indicated for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata. The clinician may wish to consider a one-month trial period on iron alone inasmuch as some of the patients will respond to iron alone (see clinical trial results below). Lupron may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with Lupron Depot is **up to** 3 months.

PERCENT OF PATIENTS ACHIEVING HEMOGLOBIN ≥ 12 GM/DL

Treatment Group	Week 4	Week 8	Week 12
Lupron Depot 3 75 mg with Iron	41*	71**	79*
Iron Alone	17	40	56

* P-Value < 0.01
** P-Value < 0.001

CONTRAINDICATIONS

1. Hypersensitivity to GnRH, GnRH agonist analogs or any of the excipients in LUPRON DEPOT.
2. Undiagnosed abnormal vaginal bleeding.
3. LUPRON DEPOT is 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 (see Pregnancy Section). The effects on fetal mortality are expected consequences of the alterations in hormonal levels brought about by the drug. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus.
4. Use in women who are breast feeding (see Nursing Mothers Section).
5. A report of an anaphylactic reaction to synthetic GnRH (Factrel) has been reported in the medical literature.[1]

WARNINGS

Safe use of leuprolide acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.

When used monthly at the recommended dose, LUPRON DEPOT usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking LUPRON DEPOT. Therefore, patients should use nonhormonal methods of contraception. Patients should be advised to see their physician if they believe they may be pregnant. If a patient becomes pregnant during treatment, the drug must be discontinued and the patient must be apprised of the potential risk to the fetus.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiologic effect of the drug. Therefore, an increase in clinical signs and symptoms may be observed during the initial days of therapy, but these will dissipate with continued therapy.

PRECAUTIONS

Information for Patients: An information pamphlet for patients is included with the product. Patients should be aware of the following information:

1. Since menstruation should stop with effective doses of LUPRON DEPOT, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of LUPRON DEPOT may experience breakthrough bleeding.

2. Patients should not use LUPRON DEPOT if they are pregnant, breast feeding, have undiagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in LUPRON DEPOT.

3. Safe use of the drug in pregnancy has not been established clinically. Therefore, a nonhormonal method of contraception should be used during treatment. Patients should be advised that if they miss successive doses of LUPRON DEPOT, breakthrough bleeding or ovulation may occur with the potential for conception. If a patient becomes pregnant during treatment, she should discontinue treatment and consult her physician.

4. Adverse events occurring in clinical studies with LUPRON DEPOT that are associated with hypoestrogenism include: hot flashes, headaches, emotional lability, decreased libido, acne, myalgia, reduction in breast size, and vaginal dryness. Estrogen levels returned to normal after treatment was discontinued.

5. The induced hypoestrogenic state also results in a small loss in bone density over the course of treatment, some of which may not be reversible. For a period up to six months, this bone loss should not be important. In patients with major risk factors for decreased bone mineral content such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids, LUPRON DEPOT therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT is instituted. Repeated courses of therapy with gonadotropin-releasing hormone analogs beyond six months are not advisable in patients with major risk factors for loss of bone mineral content.

6. Retreatment cannot be recommended since safety data beyond six months are not available.

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 43% bound to plasma proteins, drug interactions would not be expected to occur.

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 one to three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and up to one to two months after discontinuation of LUPRON DEPOT therapy may be misleading.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A two-year carcinogenicity study was 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 testes 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 with leuprolide acetate and similar analogs have shown full reversibility of fertility suppression when the drug is discontinued after continuous administration for periods of up to six months. Although no clinical studies have been completed in children to assess the full reversibility of fertility suppression, animal studies (prepubertal and adult rats and monkeys) with leuprolide acetate and other GnRH analogs have shown functional recovery.

Pregnancy, Teratogenic Effects: Pregnancy Category X. See "Contraindications" section. When administered on day 6 of pregnancy at test dosages of 0.00024, 0.0024, and 0.024 mg/kg (1/300 to 1/3 the human dose) to rabbits, 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 LUPRON DEPOT in rabbits and with the highest dose (0.024 mg/kg) in rats.

Nursing Mothers: It is not known whether LUPRON DEPOT is excreted in human milk. Because many drugs are excreted in human milk, and because the effects of LUPRON DEPOT on lactation and/or the breastfed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.

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

ADVERSE REACTIONS

Estradiol levels may increase during the first weeks following the initial injection, but then decline to menopausal levels. This transient increase in estradiol can be associated with a temporary worsening of signs and symptoms (See "Warnings" section).

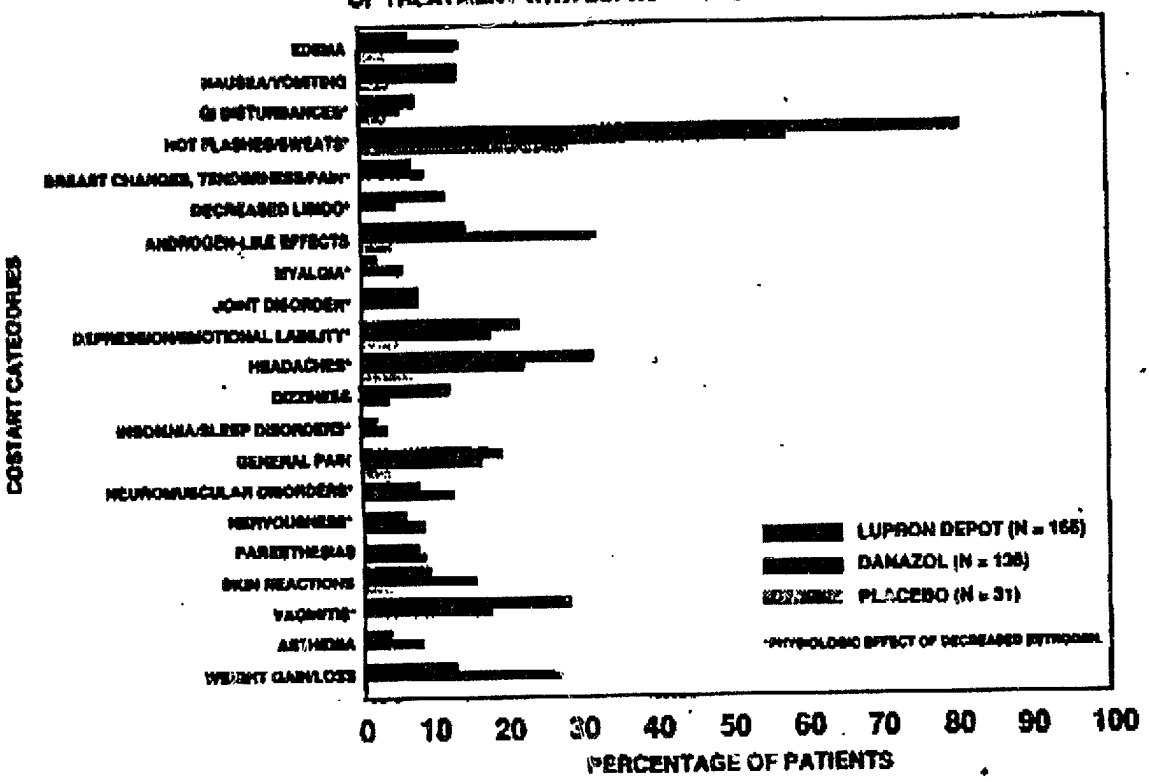
As would be expected with a drug that lowers serum estradiol levels, the most frequently reported adverse reactions were those related to hypoestrogenism.

Endometriosis

In controlled studies comparing LUPRON DEPOT, 3.75 mg monthly and danazol (800 mg/day), or placebo, adverse reactions most frequently

reported and thought to be possibly or probably drug-related are shown in Figure 2.

FIGURE 2–ADVERSE EVENTS REPORTED DURING 6 MONTHS OF TREATMENT WITH LUPRON DEPOT 3.75 MG



Cardiovascular System - Palpitations, Syncope, Tachycardia; *Gastrointestinal System* - Dry mouth, Thirst, Appetite changes; *Central/Peripheral Nervous System* - Anxiety,* Personality disorder, Memory disorder, Delusions; *Integumentary System* - Ecchymosis, Alopecia, Hair disorder; *Urogenital System* - Dysuria,* Lactation; *Miscellaneous* - Ophthalmologic disorders,* Lymphadenopathy.

Uterine Leiomyomata (Fibroids)

In controlled clinical trials comparing LUPRON DEPOT 3.75 mg and placebo, adverse events reported in >5% of patients and thought to be potentially related to drug are noted in the following table.

	Lupron Depot N=166 (%)	Placebo N=163 (%)
Body as a Whole		
Asthenia	14 (8.4)	8 (4.9)
General pain	14 (8.4)	10 (6.1)
Headache*	43 (25.9)	29 (17.8)
Cardiovascular System		
Hot flashes/sweats*	121 (72.9)	29 (17.8)
Metabolic and Nutritional Disorders		
Edema	9 (5.4)	2 (1.2)
Musculoskeletal System		
Joint disorder*	13 (7.8)	5 (3.1)
Nervous System		
Depression/emotional lability*	18 (10.8)	7 (4.3)
Urogenital System		
Vaginitis*	19 (11.4)	3 (1.8)

Symptoms reported in < 5% of patients included. *Body as Whole* - Body odor, Flu syndrome, Injection site reactions; *Cardiovascular System* - Tachycardia; *Digestive System* - Appetite changes, Dry mouth, GI disturbances, Nausea/vomiting; *Metabolic and Nutritional Disorders* - Weight changes; *Musculoskeletal System* - Myalgia; *Nervous System* - Anxiety, Decreased libido,* Dizziness, Insomnia, Nervousness,* Neuromuscular disorders,* Paresthesias; *Respiratory System* - Rhinitis; *Integumentary System* - Androgen-like effects, Nail disorder, Skin reactions; *Special Senses* - Conjunctivitis, Taste perversion; *Urogenital System* - Breast changes,* Menstrual disorders.

* = Physiologic effect of the drug.

In one controlled clinical trial, patients received a higher dose (7.5 mg) of LUPRON DEPOT. Events seen with this dose that were thought to be potentially related to drug and were not seen at the lower dose included palpitations, syncope, glossitis, ecchymosis, hypesthesia, confusion, lactation, pyelonephritis, and urinary disorders. Generally, a higher incidence of hypoestrogenic effects was observed at the higher dose.

In other clinical trials involving patients with prostate cancer and during postmarketing surveillance, the following adverse reactions were reported to have a possible, probable, or unknown relationship to LUPRON as ascribed by the treating physician. Often, it is difficult to assess causality in patients with prostate cancer. Reactions considered not drug related have been excluded.

Cardiovascular System - Congestive heart failure, ECG changes/ischemia, High blood pressure, Murmur, Phlebitis/thrombosis, Angina, Cardiac arrhythmias, Myocardial infarction, Pulmonary emboli, Hypotension, Transient ischemic attack/stroke; *Gastrointestinal System* - Dysphagia, Gastrointestinal bleeding, Peptic ulcer, Rectal polyps, Hepatic dysfunction; *Endocrine System* - Decreased testicular size, gynecomastia, Impotence, Libido increase, Thyroid enlargement; *Hemic and Lymphatic System* - Anemia, Decreased WBC, Hemoptysis; *Musculoskeletal System* - Bone pain; *Central/Peripheral Nervous System* - Peripheral neuropathy, Syncope/blackouts, Hearing disorder, Spinal fracture/paralysis; *Respiratory System* - Dyspnea, Sinus congestion, Cough, Pleural rub, Pneumonia, Pulmonary fibrosis, Respiratory disorders; *Urogenital System* - Frequency/urgency, Hematuria, Urinary tract infection, Bladder spasm, Incontinence, Testicular pain, Urinary obstruction, Penile swelling, Prostate pain; *Miscellaneous* - Diabetes, Fever, Hypoglycemia, Increased BUN, Increased calcium, Increased creatinine, Inflammation.

Changes in Bone Density:

Endometriosis

A controlled study in endometriosis patients showed that vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.9% at six months compared with the pretreatment value. Earlier studies in endometriosis patients, utilizing quantitative computed tomography (QCT), demonstrated that in the few patients who were retested at six and 12 months, partial to complete recovery of bone density was recorded in the post-treatment period. Use of LUPRON DEPOT for longer than six months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss.

Uterine Leiomyomata (Fibroids)

In one study, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% at three months compared with the pretreatment value. It would be anticipated that this loss of bone mineral density would be complete to partially reversible following discontinuation of therapy. Use of LUPRON DEPOT 3.75 mg for uterine leiomyomata for longer than three

months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended.**

Changes in Laboratory Values During Treatment:

Plasma enzymes:

Endometriosis

During clinical trials with LUPRON DEPOT, regular laboratory monitoring revealed that SGOT levels were more than twice the upper limit of normal in only one patient. There was no other clinical or laboratory evidence of abnormal liver function.

Uterine Leiomyomata (Fibroids)

In clinical trials with LUPRON DEPOT 3.75 mg, five (3%) patients had a post-treatment transaminase value that was at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.

Lipids:

Endometriosis

At enrollment, 4% of the LUPRON DEPOT patients and 1% of the danazol patients had total cholesterol values above the normal range. These patients also had cholesterol values above the normal range at the end of treatment.

Of those patients whose pretreatment cholesterol values were in the normal range, 7% of the LUPRON DEPOT patients and 9% of the danazol patients had post-treatment values above the normal range.

The mean (±SEM) pretreatment values for total cholesterol from all patients were 178.8 (2.9) mg/dL in the LUPRON DEPOT groups and 175.3 (3.0) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 193.3 mg/dL in the LUPRON DEPOT group and 194.4 mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p<0.03$) in both groups.

Triglycerides were increased above the upper limit of normal in 12% of the patients who received LUPRON DEPOT and in 6% of the patients who received danazol.

At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT compared with 23%

of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.

Uterine Leiomyomata (Fibroids)

In patients receiving LUPRON DEPOT 3.75 mg, mean changes in cholesterol (+11 mg/dL to +29 mg/dL), LDL cholesterol (+8 mg/dL to +22 mg/dL), HDL cholesterol (0 to 6 g/dL), and the LDL/HDL ratio (-0.1 to +0.5) were observed across studies. In the one study in which triglyceride levels were determined, the mean increase from baseline was 32 mg/dL.

Other Changes:

Endometriosis

In comparative studies, the following changes were seen in approximately 5% to 8% of patients. LUPRON DEPOT was associated with elevations of LDH and phosphorus, and deceases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH.

Uterine Leiomyomata (Fibroids)

Hematology: See "Clinical Pharmacology, Clinical Studies" section. In LUPRON DEPOT treated patients, although there were statistically significant mean decreases in platelet counts from baseline to final visit, the last mean platelet counts were within the normal range. Decreases in total WBC count and neutrophils, were observed, but were not clinically significant.

Chemistry: Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant.

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 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 3.75 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:

1. Using a syringe with a 22 gauge needle, withdraw 1 mL of diluent from the ampule, and inject it into the vial. (Extra diluent is provided; any remaining should be discarded.)
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

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

Endometriosis

The recommended duration of administration is six months. Retreatment cannot be recommended since safety data for retreatment are not available. If the symptoms of endometriosis recur after a course of therapy, and further treatment with LUPRON DEPOT is contemplated, it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.

Uterine Leiomyomata (Fibroids)

Recommended duration of therapy with LUPRON DEPOT is **up to** 3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.

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

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

HOW SUPPLIED

LUPRON DEPOT is available in a vial containing sterile lyophilized microspheres which is leuprolide acetate incorporated in a biodegradable copolymer of lactic and glycolic acids.

The single-dose vial of LUPRON DEPOT contains leuprolide acetate (3.75 mg), purified gelatin (0.65 mg), DL-lactic and glycolic acids copolymer (33.1 mg), and D-mannitol (6.6 mg). The accompanying ampule of diluent contains carboxymethylcellulose sodium (7.5 mg), D-mannitol (75 mg), polysorbate 80 (1.5 mg), water for injection, USP, and glacial acetic acid, USP to control pH. When mixed with 1 mL of diluent, LUPRON DEPOT (leuprolide acetate for depot suspension) is administered as a single monthly IM injection.

LUPRON DEPOT 3.75 mg is available in a single use kit (NDC 0300-3639-01) and in a six pack of drug only (NDC 0300-3639-06).

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

No refrigeration necessary. Protect from freezing.

New

REFERENCE:

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

U.S. Patent Nos. 4,005,063; 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; and 4,954,298.

TAP Pharmaceuticals Inc.
Deerfield, Illinois 60015-1595, U.S.A.

LUPRON DEPOT manufactured by Takeda Chemical Industries, Ltd. Osaka, JAPAN 541

®—Registered Trademark

b) Vial Label

02-7453-R3

c) Vial Carton

09-6760-R3

LUPRON
DEPOT 3.75 mg
leuprolide acetate
for depot suspension

Protect from freezing

See bottom of carton for expiration date and lot number

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

09-6760-R3

leuprolide acetate 3.75 mg

For intramuscular injection after mixing

LUPRON DEPOT® 3.75 mg

leuprolide acetate
for depot suspension

Each vial contains:
leuprolide acetate, 3.75 mg,
purified gelatin, 0.65 mg,
DL-lactic & glycolic acids
copolymer, 33.1 mg,
D-mannitol, 6.6 mg

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

TAP

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

Exp.

Lot

d) Diluent Ampule Label

02-7378-R3

Sterile Diluent for
LUPRON
DEPOT®

TAP Pharmaceuticals Inc.
Deerfield, IL 60015, U.S.A. (27378-R3

e) Diluent Ampule Carton Label

09-6781-R5

NDC 0300 3625-01 1.5 mL sterile diluent

Sterile Diluent
LUPRON
DEPOT®

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

Exp

Lot

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

09-6781-R5

1 2

Sterile Diluent

LUPRON DEPOT®

Each ampule contains: D mannitol, 75 mg, carboxymethylcellulose sodium, 7.5 mg, polysorbate 80, 1.5 mg; water for injection, USP, and acetic acid, NF to control pH

Usual Dose: For use with Lupron Depot. See enclosure for full mixing directions

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

f) Single Dose Administration Kit Label

02-7506-R2

Single Dose
Administration Kit
NDC 0300-3639-01

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

Includes:
- *One Vial Lupron Depot® NDC 0300-3623-01 (Leuprolide Acetate 3.75 mg)*
- *One 1.5 mL Ampule Sterile Diluent NDC 0300-3625-01*
- *One Syringe with 22 Gauge Needle*
- *One 22 Gauge Needle*

LUPRON DEPOT®

02-7506-R2

EXP.

LOT

3.75mg

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

h) Six Dose Package Carton Label

09-6763-R1

0300363906

No refrigeration necessary. Protect from freezing

Exp

Lot

NDC 0300-3639-06

LUPRON DEPOT® 3.75 mg
leuprolide acetate
for depot suspension

Contains: Six Vials Lupron Depot® 3.75 mg NDC 0300-3623-01
Six 1.5 mL Ampules Sterile Diluent NDC 0300-3625-01
For Intramuscular injection after mixing

h) Six Dose Package Carton Label

09-6763-R1

LUPRON
DEPOT® 3.75 mg
leuprolide acetate
for depot suspension

NDC 0300-3639-06

NDC 0300-3639-06

LUPRON
DEPOT® 3.75 mg
leuprolide acetate
for depot suspension

Each single-dose vial contains:
leuprolide acetate, 3.75 mg, purified gelatin, 0.65 mg, DL-lactic & glycolic acids copolymer, 33.1 mg, D-mannitol, 6.6 mg
Each ampule of diluent contains:
D-mannitol, 75 mg, carboxymethylcellulose sodium, 7.5 mg, polysorbate 80, 1.5 mg; water for injection, USP, and acetic acid, NF to control pH

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

09-6763-R1

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

i) Instruction on How to Mix and Administer

01-2582-R2

INSTRUCTIONS ON HOW TO MIX AND ADMINISTER

NOTE: LUPRON DEPOT must be administered under the supervision of a physician

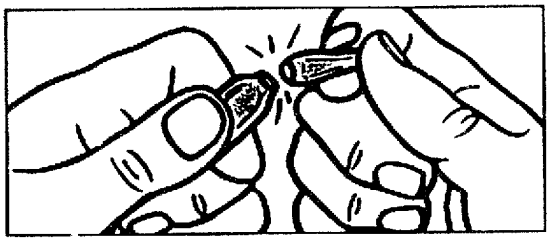
LUPRON DEPOT®

LEUPROLIDE ACETATE FOR DEPOT SUSPENSION

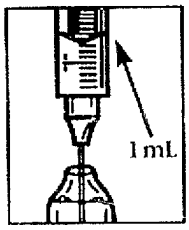
i) Instruction on How to Mix and Administer

01-2582-R2

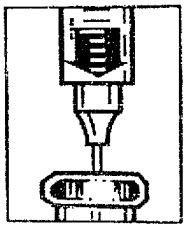
1. Use aseptic technique throughout. Assure that all liquid is in the bottom section of the ampule of diluent by lightly flicking the top with your finger.



2. The top of this ampule is designed to break off in any direction. To open, simply snap the tip. Only moderate pressure is required.

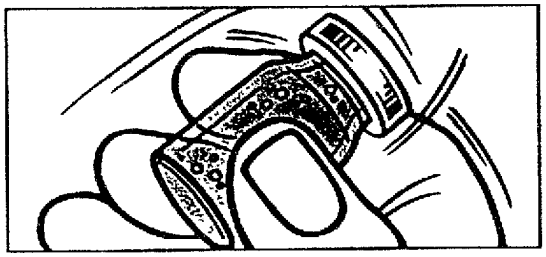


3. Use the syringe included in the kit or any syringe with at least a 22 gauge needle. **Remember to tighten the luer lock mechanism by twisting the needle until it does not move.** Withdraw 1 mL of diluent.

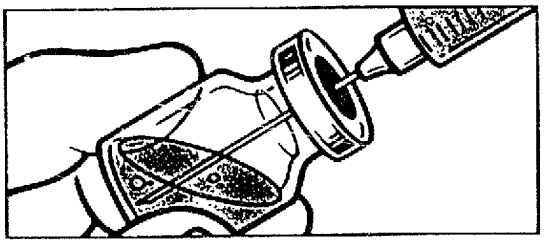


4. Remove the plastic cap from the vial and inject the diluent into the vial.

5. Shake the vial thoroughly to mix the particles to form a uniform suspension. The liquid will be milky.



6. Withdraw the entire contents of the vial into the syringe used in step 3.



7. Immediately after reconstitution, inject the medication into any site usable for an intramuscular injection.

8. Discard the remainder of the diluent, the ampule, and the vial. None of the components is hazardous. No special handling or disposal procedures are needed.

i) Instruction on How to Mix and Administer

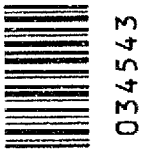
01-2582-R2

SPECIAL INFORMATION

If you have any questions regarding the drug or this procedure, call 1-800-622-2011.

If the ampule of diluent should break or become unusable for any reason, do not substitute saline or sterile water. Contact TAP Pharmaceuticals for a replacement. Call 1-800-622-2011.

TAP Pharmaceuticals Inc.
2355 Waukegan Road
Deerfield, IL 60015



Pauls

JUTG01N6

facsimile
TRANSMITTAL

to: Dean Sundberg / MARLEY HEGGIN
fax #: 708-317-5795
re: Final labeling revisions for NDA 19-943
date: March 28, 1995
pages: 2, including cover sheet.

MAR 28 1995

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Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane (HFD-510)
Rockville, MD 20857-1706

From the desk of...

Lana L. Pauls, M.P.H.
Consumer Safety Officer
DMEDP, ODE II, CDER, FDA
5600 Fishers Lane, Room 14B-19
Rockville, MD 20857

301-443-3510
Fax: 301 827-0878

The following labeling revisions are required for approval:

INDICATIONS AND USAGE section:

The phrase "up to" should be added after the word is in the last sentence. Therefore, this sentence should now read:

"Recommended duration of therapy with Lupron is **up to** (emphasis added) 3 months."

PRECAUTIONS section:

1. Under number 4, the first sentence should be revised to read:

   "Adverse events occurring in clinical studies with Lupron Depot THAT are associated with hypoestrogenism include: hot flashes, headaches, ..."

2. Under number 5, the word "also" should be added after the word "state" in the first sentence. Therefore, this first sentence should now read:

   "The induced hypoestrogenic state **also** (emphasis added) results in a small . . ."

ADVERSE REACTIONS section:

1. Under the heading **Changes in Bone Density**, the number "6" should be revised to the number "3", and the phrase "and is not recommended" should be added to the last sentence of the **Uterine Leiomyomata (Fibroids)** subheading. This sentence should now read as follows:

   "Use of Lupron Depot 3.75 mg for longer than 3 months or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss **and is not recommended** (emphasis added).

2. Under the heading **Changes in Laboratory Values During Treatment**, the phrase "or evidence of abnormal liver function" should be deleted from the last sentence of the **Uterine Leiomyomata (Fibroids)** subheading. This sentence should now read as follows:

   "None of the laboratory increases were associated with clinical symptoms."

DOSAGE AND ADMINISTRATION section:

Under the subheading **Uterine Leiomyomata (Fibroids)**, the phrase "up to" should be added to the first sentence (see comment above under INDICATIONS AND USAGE)

These labeling revisions are required for approval. They are to be faxed to TAP Pharmaceuticals.

Solomon Sobel, M.D.

NDA 19-943

TELEFAX

TO: DEAN SUNDBERG
TAP PHARMACEUTICALS

FAX: 708-317-5795

PHONE: -4893

FROM: LANA PAULS

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products
5600 Fishers Lane--HFD-510
Rockville, Maryland 20857-1706

FAX: 301/443-9282

PHONE: 301/443-3510
301/443-3490

DATE: 3/22/95

PAGES: 3 [inclusive]

The revisions below are to be faxed to TAP Pharmaceutical regarding the approval of NDA 19-943, Lupron Depot for the treatment of anemia associated with uterine fibroids.

Solomon Sobel 5/22/95

Solomon Sobel, M.D.
Division Director, DMEDP (HFD-510)

The following revisions to the labeling and a commitment to perform the Phase 4 study listed below are required for approval.

Labeling

Package Insert

1. The **Pharmacokinetic** subsection of the **CLINICAL PHARMACOLOGY** section should be revised as follows:

   a. Under the heading **Absorption**, the first two sentences of the first paragraph should be revised to read as follows:

      "A single dose of Lupron® Depot 3.75 mg was administered by intramuscular injection to healthy female volunteers. The absorption of leuprolide was characterized by an initial burst in plasma concentration, with peak concentrations ranging from 4.6 to 10.2 ng/ml at four hours post dosing. However, intact leuprolide and an inactive metabolite could not be distinguished by the assay which was employed in the study."

   b. Under the same heading, the second paragraph that currently begins "The absolute bioavailability for the . . ." should be deleted.

   c. Under the heading **Metabolism**, the first sentence of the second paragraph that begins "In rats and dogs . . ." should be revised to read:

      "In rats and dogs, administration of ^{14}C-labelled leuprolide was shown to be metabolized to smaller inactive peptides."

d. Under the same heading, the phrase "prostate cancer" should be added to first sentence of the third paragraph that begins "The major metabolite . . ." Therefore, this sentence should now read:

> "The major metabolite (M-I) plasma concentrations measured in 5 **prostate cancer** (emphasis added) patients reached mean maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration."

2. The heading **Uterine Leiomyomata (Fibroids)** of the **INDICATIONS AND USAGE** section of the package insert should be revised to read:

> "Iron therapy alone for the first one month should be considered as first line preoperative treatment of patients with anemia caused by uterine leiomyomata. Lupron® Depot 3.75 mg plus iron should be considered only for women who fail to improve on iron alone. This treatment should not be administered for longer than three months."

Patient Package Insert

A patient package insert should be developed to be distributed with this product. A commitment to submit this for review within 4 weeks from the date of approval must be made.

A commitment to conduct the following Phase 4 pharmacokinetic study must be made:

A multiple dose design in which 3 monthly doses of Lupron Depot plus iron are given to atleast 10 patients with uterine fibroids. A reasonable number of blood samples should be collected over 4 weeks following the first dose to characterize the plasma profiles of leuprolide and estradiol . In addition, trough levels of leuprolide and estradiol should be determined. Leuprolide plasma samples should be analyzed with a HPLC-RIA technique that can identify intact leuprolide and a metabolite.

Barnett

NDA 19-943

APR 8 1994

TAP Pharmaceuticals, Inc.
Attention: S. Albert Edwards, Pharm.D.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Edwards:

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

Name of Drug Product:	Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg
Therapeutic Classification:	S
Date of Application:	March 30, 1994
Date of Receipt:	March 31, 1994
Our Reference Number:	NDA 19-943

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 30, 1994, in accordance with 21 CFR 314.101(a).

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

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

Sincerely yours,

4/8/94

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

cc
Orig.
HFC-130/JAllen
HFD-510
HFD-510/LRarick/PCorfman/CNiu/YYChiu/KRaheja/AJordan
HFD-510/LBraithwaite/04.05.94/N19943.ACK

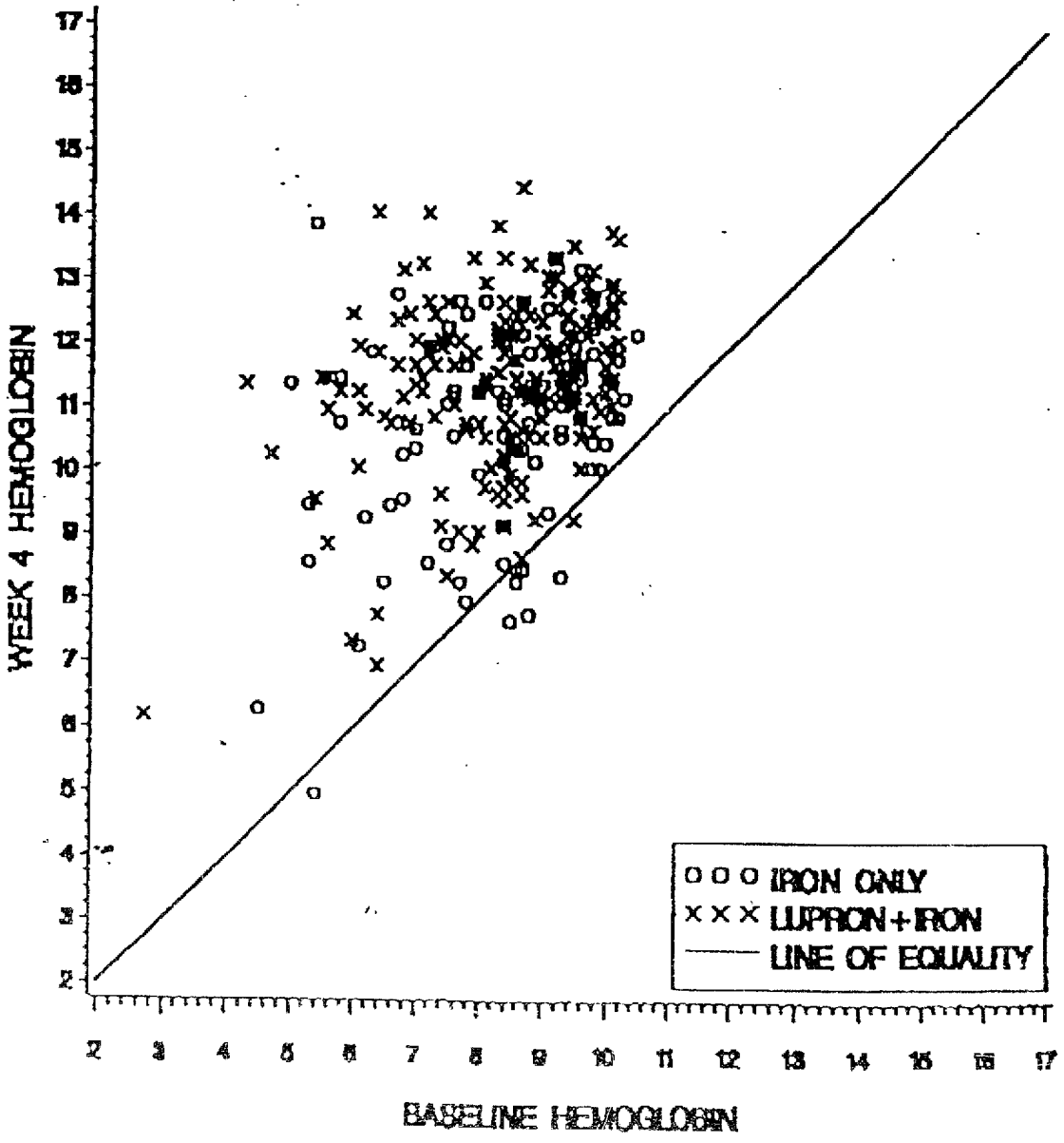
ACKNOWLEDGEMENT

4/5/94

<F411_HGZ SAS TEEKIP>

FIGURE 17

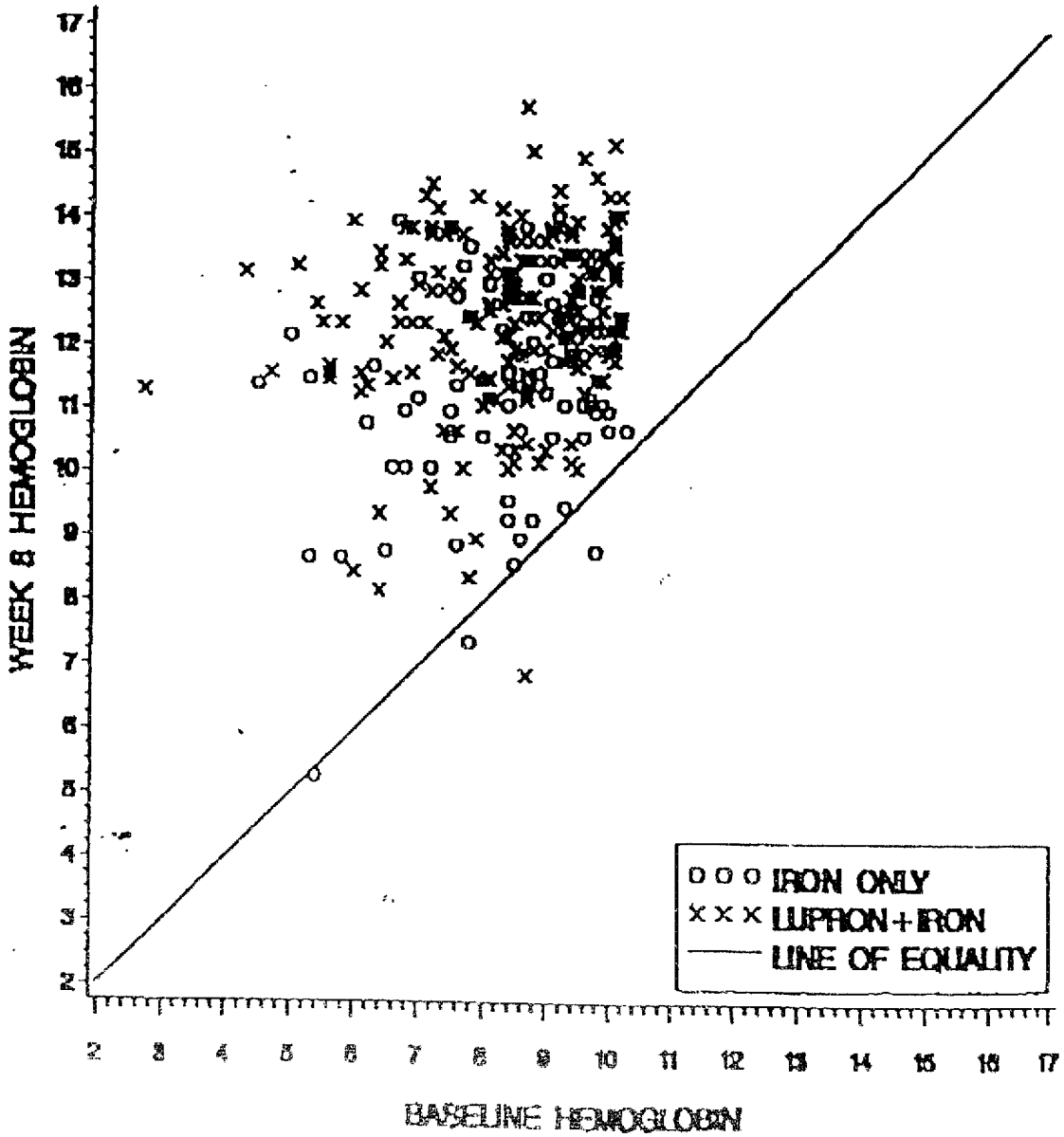
4—WEEK HEMOGLOBIN VERSUS BASELINE HEMOGLOBIN FOR ALL PATIENTS
WITH HEMOGLOBIN MEASURED AT BOTH BASELINE AND 4 WEEKS



<F411_HGZ 8A8 T56KJP>

FIGURE 18

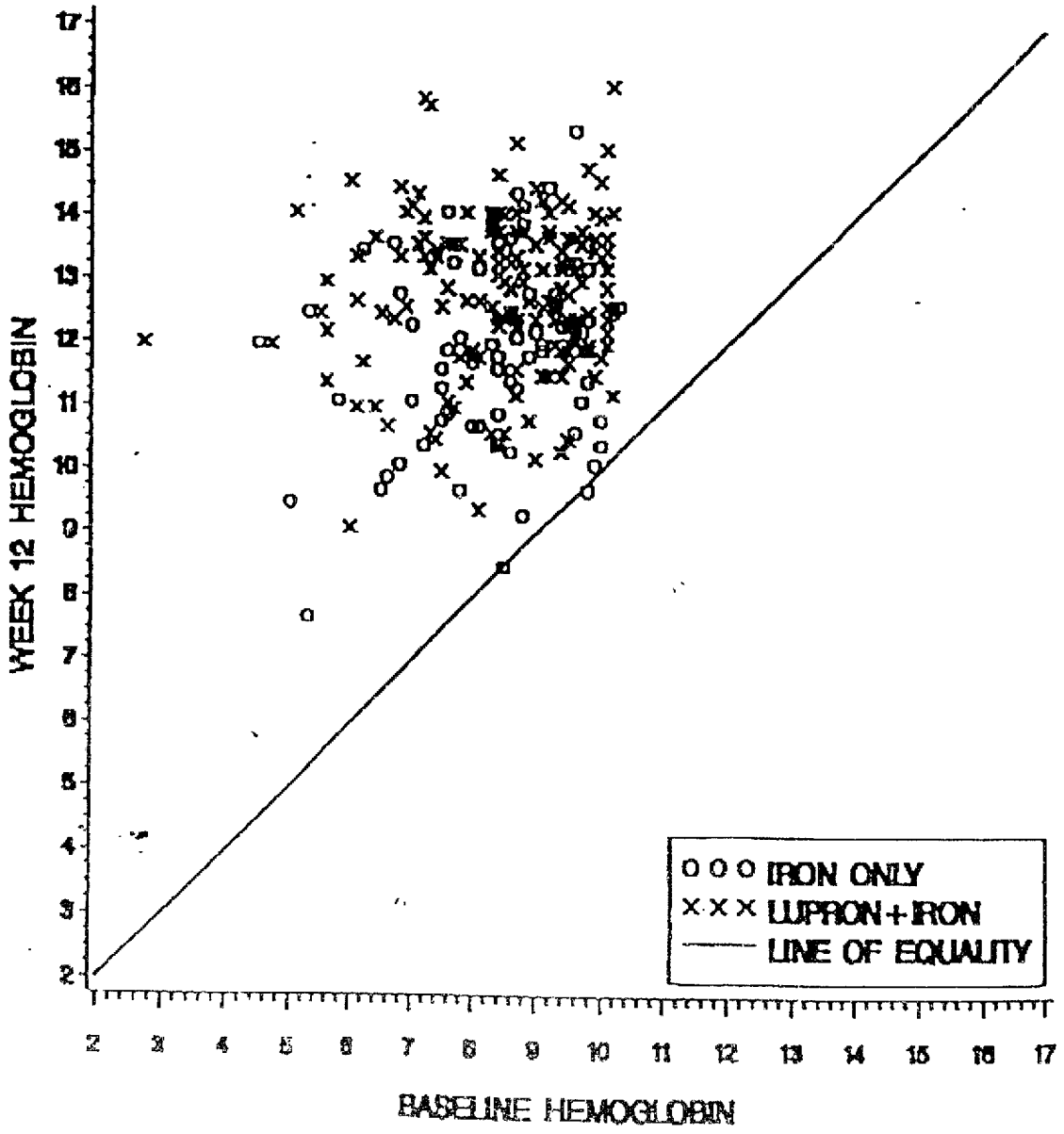
8–WEEK HEMOGLOBIN VERSUS BASELINE HEMOGLOBIN FOR ALL PATIENTS
WITH HEMOGLOBIN MEASURED AT BOTH BASELINE AND 8 WEEKS



<F471_HGX SAS T55KJP>

FIGURE 19

12–WEEK HEMOGLOBIN VERSUS BASELINE HEMOGLOBIN FOR ALL PATIENTS
WITH HEMOGLOBIN MEASURED AT BOTH BASELINE AND 12 WEEKS



<F411_HG2 BAS T5GKJP>

FIGURE 20

FINAL TREATMENT HEMOGLOBIN VERSUS BASELINE HEMOGLOBIN FOR ALL PATIENTS WITH LINE OF EQUAL TREATMENT AND BASELINE HEMOGLOBIN

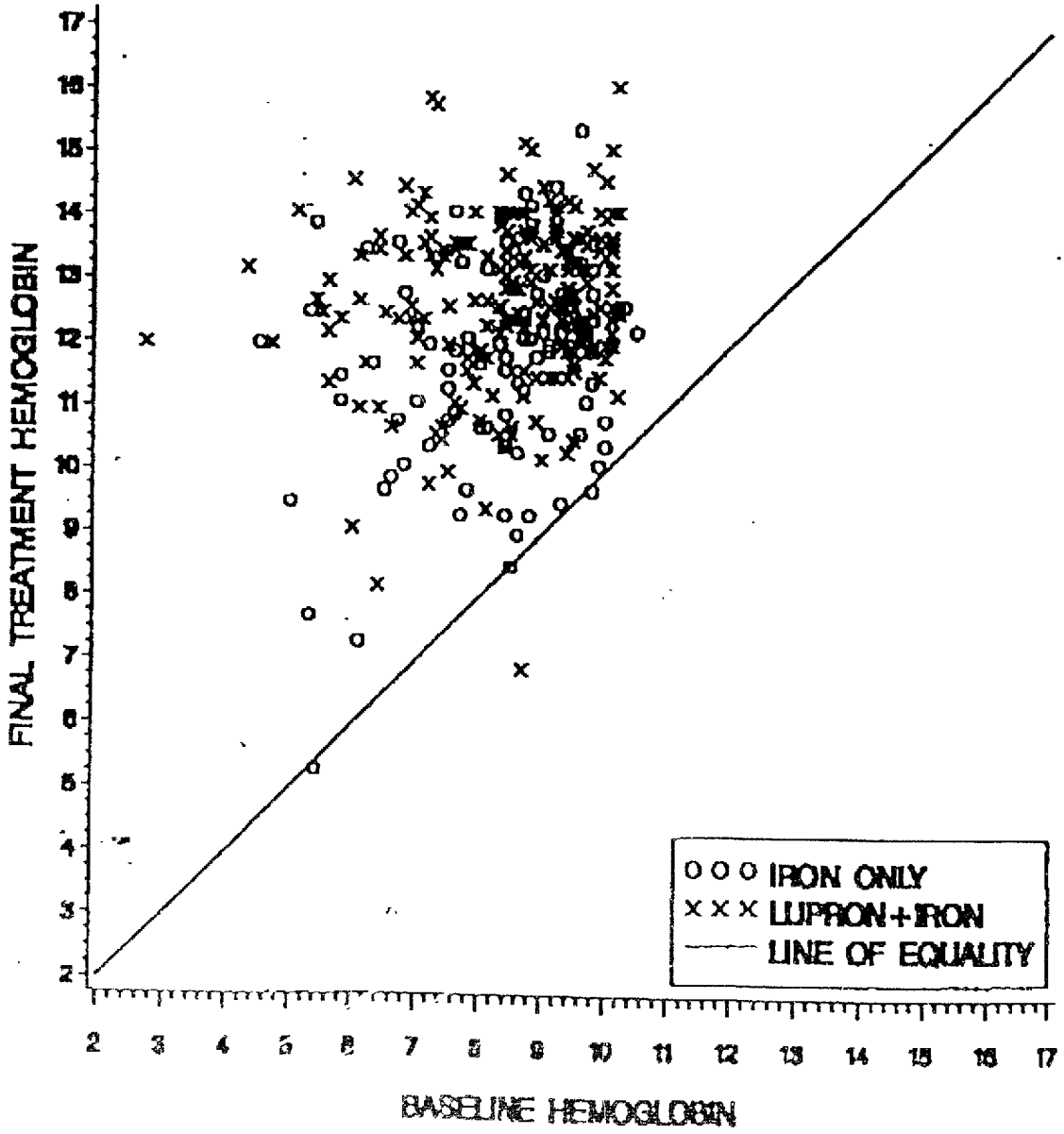


Figure 1
Percent of Patients Versus 4-Week Hemoglobin for All Patients
with Hemoglobin Measured at Both Baseline and 4 Weeks
(Iron Only Patients)

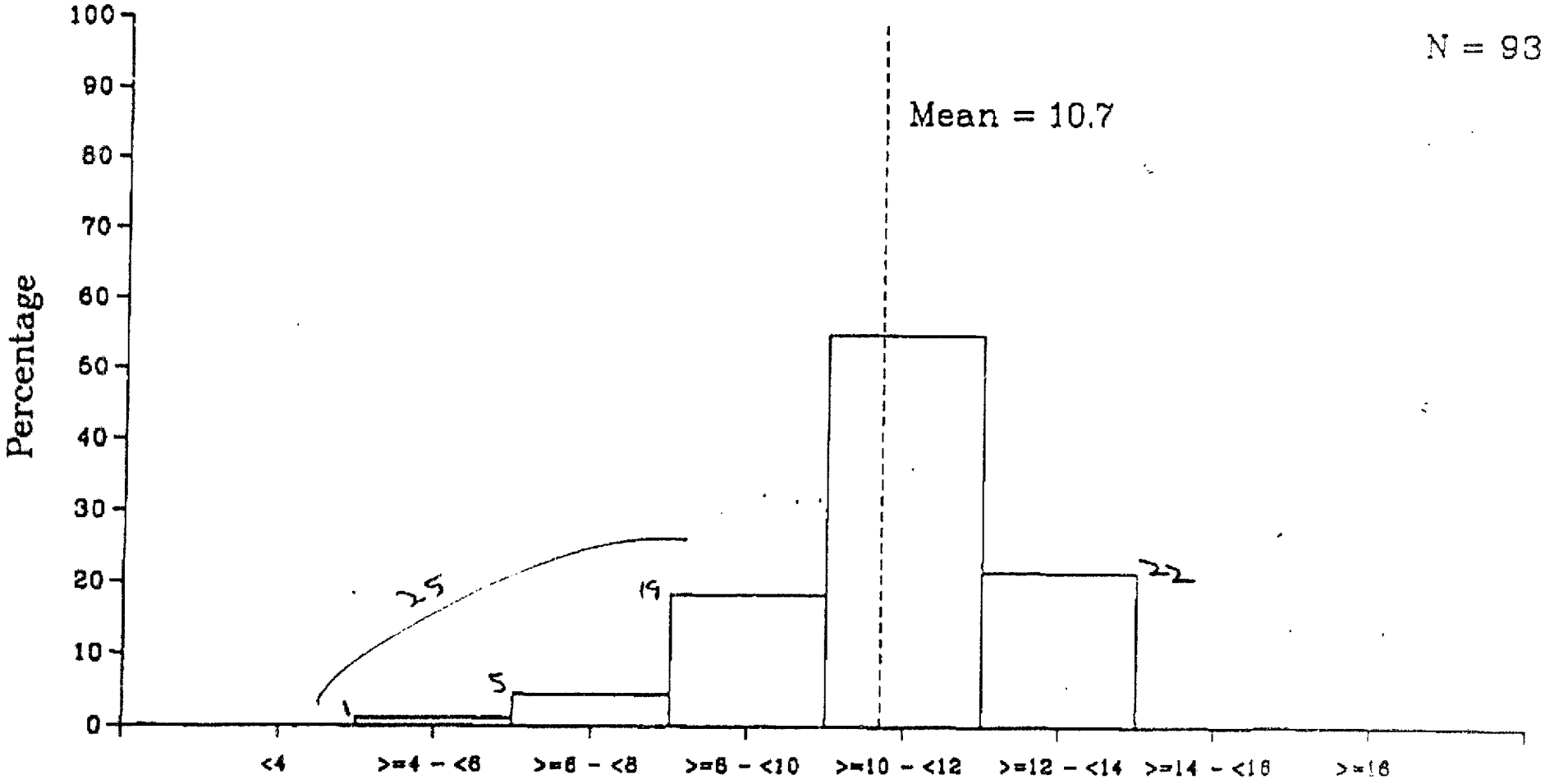
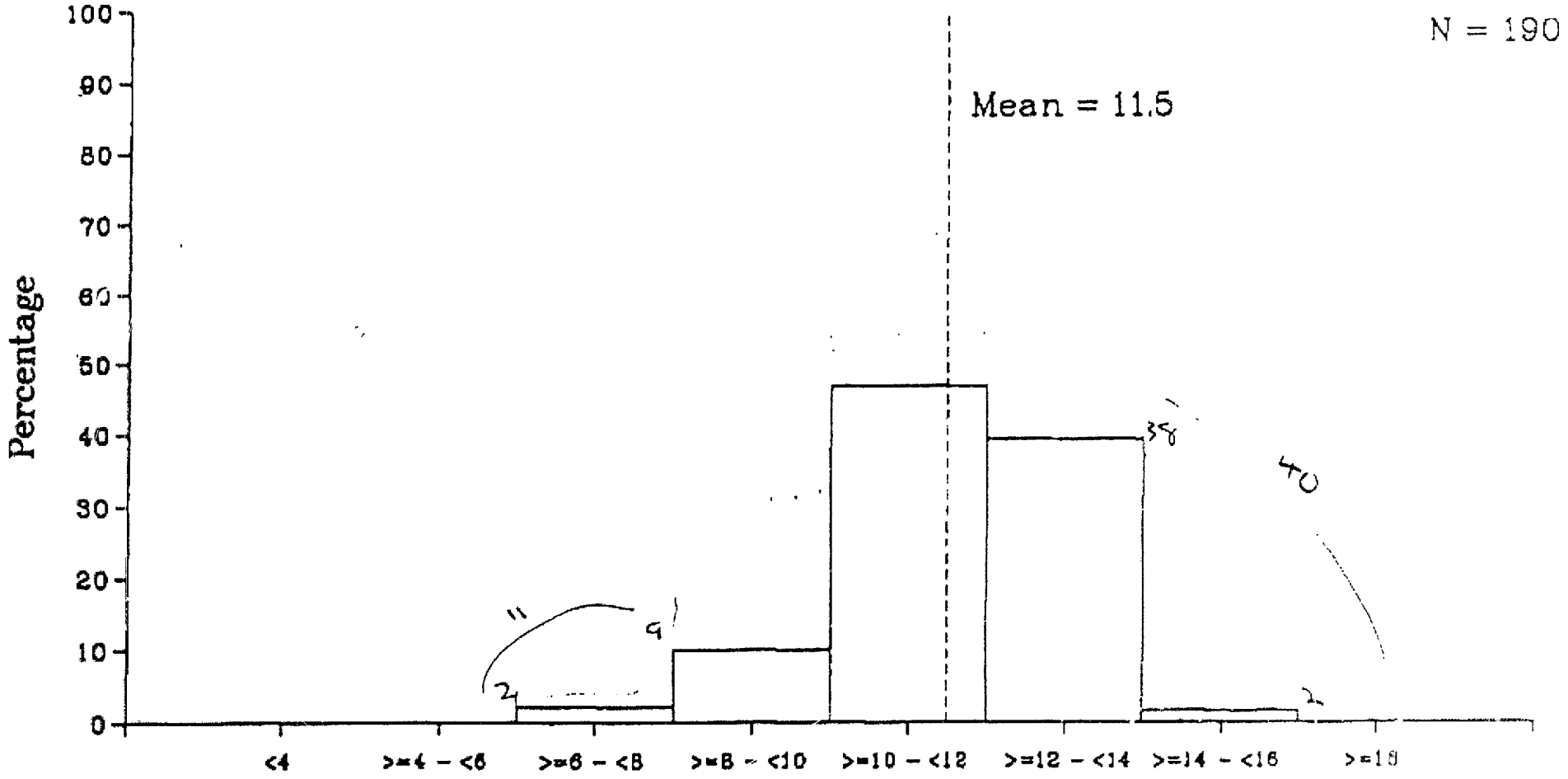


Figure 9
Percent of Patients Versus 4-Week Hemoglobin for All Patients
with Hemoglobin Measured at Both Baseline and 4 Weeks
(Lupron + Iron Patients)



March 24, 1995

Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, Illinois 60015

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

RE: Lupron Depot 3.75 mg for Management of Uterine Fibroids
NDA 19-943
Amendment No. 007

Dear Dr. Sobel:

Attached is a draft copy of the revised labeling for NDA 19-943. This revision incorporates all the changes requested in your letter dated March 22, 1995, and agreed to by the sponsor and the Division on March 24, 1995. The revised labeling also incorporates changes (under subsection of Metabolism) recommended by Biopharmaceutics reviewer on March 24, 1995. All revisions are underlined for ease of review.

The Sponsor, TAP Pharmaceuticals Inc., commits to develop and submit a draft copy of Patient Package Insert within four weeks from the date of approval.

The Sponsor also commits to conduct the Phase 4 pharmacokinetic study as recommended in the letter dated March 22, 1995.

All the adverse events from Study M90-411 were submitted in the 4 Month Safety Update (Submission dated July 29, 1994).

The required information for this amendment is attached.

Sincerely,

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

AD/pjp

NDA 19-943
Lupron® Depot (leuprolide acetate)
TAP Pharmaceuticals, Inc.

Safety Update Review

Included in the medical review dated March 13, 1995.