CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-708/S-011

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-708 /SE1 - 011

Drug Lupron Depot®-3 Month 11.25 mg Applicant TAP Pharmaceutical Products, Inc.

RPM Jeanine Best, MSN, RN Phone (301) 827-4260

■505(b)(1)
☐505(b)(2) Reference listed drug

☐Fast Track ☐Rolling Review Review priority: ■ S ☐P

Pivotal IND(s) —

Application classifications:
Chem Class 3S
Other (e.g., orphan, OTC)

PDUFA Goal Dates:
Primary 22-Sep-2001
Secondary 22-Nov-2001

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☐ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ■ User Fee Exemption-No Clinical Data Submitted for Review

- Action Letter..... ■AP ☐ AE ☐NA

- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... NA
  Has DDMAC reviewed the labeling? ..... ☐ Yes (include review) ■ No
  Immediate container and carton labels ..... NA
  Nomenclature review ..... NA

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ■ is not on the AIP.
  Exception for review (Center Director's memo)..... NA
  OC Clearance for approval..... NA

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) NA ☐ Materials requested in AP letter

- Post-marketing Commitments — NA
  - Agency request for Phase 4 Commitments — NA
  - Copy of Applicant's commitments — NA

- Was Press Office notified of action (for approval action only)? — ☐ Yes ■ No
  - Copy of Press Release or Talk Paper — NA

- Patent
  - Information [505(b)(1)] — X
  - Patent Certification [505(b)(2)] — X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] — X

- Exclusivity Summary — X

- Debarment Statement — X

- Financial Disclosure
  - No disclosable information — X
  - Disclosable information – indicate where review is located — Financial Dis Review

- Correspondence/Memoranda/Faxes — X

- Minutes of Meetings — X
  - Date of EOP2 Meeting NA
  - Date of pre NDA Meeting 11-Jul-2000
  - Date of pre-AP Safety Conference NA

- Advisory Committee Meeting — NA
  - Date of Meeting — NA
  - Questions considered by the committee — NA
  - Minutes or 48-hour alert or pertinent section of transcript — NA

- Federal Register Notices, DESI documents — NA

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) — X

- Clinical review(s) and memoranda — X

Continued ⇨

- Safety Update review(s) X

- Pediatric Information
  ■ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... X
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... NA
  Recommendation for scheduling ..... NA

- Microbiology (efficacy) review(s) and memoranda ..... NA

- DSI Audits ..... NA
  ☐Clinical studies ☐ bioequivalence studies ..... _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda ..... NA

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... NA

- DMF review(s) ..... NA

- Environmental Assessment review/FONSI/Categorical exemption ..... NA

- Micro (validation of sterilization) review(s) and memoranda ..... NA

- Facilities Inspection (include EES report) NA
  Date completed _____ ..... ☐ Acceptable ☐ Not Acceptable

- Methods Validation ☐ Completed ☐ Not Completed
  .....NA.....

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda ..... NA

- Memo from DSI regarding GLP inspection (if any) ..... NA

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... NA
- CAC/ECAC report ..... NA

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

/s/

Jeanine Best
9/21/01 11:35:41 AM

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for injectable suspension)
TAP Pharmaceutical Products, Inc.

User Fees not submitted or required for this application; no clinical data submitted; all clinical data cross-referenced in NDA 20-011/S-021 .

/S/

8/9/01

REPUBLIC OF THE PHILIPPINES
DEPARTMENT OF HEALTH
BUREAU OF FOOD AND DRUGS
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City

March 29, 2001

MS. ASUNCION SAYSON
Bole Takeda
Makati City

Re: Leuprorelin acetate (Luprolex)

Dear Ms. Sayson:

May we inform you of the favorable review and approval of the submitted documents as per 13 February 2001. Based on studies done abroad (U.S.), the study M92-878 and study M97-777, the addition of norethindrone acetate, 5mg, daily has been shown to inhibit the loss of bone mineral density without compromising the efficacy of Luprolex depot, in the 1 year treatment of endometriosis. The addition of norethindrone acetate to Luprolex Depot is approved if treatment of endometriosis is not more than 6 months.

The Luprolex package insert modification as requested is approved.

Please be guided accordingly.

Very truly yours,

WILLIAM [illegible] TORRES, Ph.D.
Director

: #2839477
500.00
7-01

01-3-01
Bole
Takeda-Luprolex

LEUPRORELIN

LUPROLEX

3.75 mg Powder
For Injection - IM/SC

1-month Sustained Release

COMPOSITION
Each vial contains 3.75 mg leuprorelin acetate as lyophilized microspheres.

INDICATIONS
- Endometriosis
- Uterine myoma/fibroids
- Premenopausal breast cancer
- Prostate cancer

DOSAGE ADMINISTRATION
LUPROLEX Must Be Administered Under the Supervision of a Physician.

Luprolex 3.75 mg is to be given ONCE A MONTH.

Incorporated in a depot formulation, the lyophilized microspheres are to be reconstituted and administered as a single intramuscular/subcutaneous injection, in accordance with the following directions:

1. Using a syringe with a 23 gauge needle, withdraw 2 mL of diluent from the ampule, and inject it into the vial.
2. Shake well to thoroughly disperse particles to obtain a uniform suspension. The suspension will appear milky.
3. Withdraw the entire contents of the vial into the syringe and inject it at the time of reconstitution.

The suspension settles very quickly following reconstitution, therefore, it is preferable that Luprolex 3.75mg to be injected and used immediately. Reshake suspension if settling occurs.

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

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

CONTRAINDICATIONS
1. Hypersensitivity to GnRH, GnRH Agonist analogs or any of the excipients in LUPROLEX DEPOT.
2. Undiagnosed abnormal vaginal bleeding
3. Luprolex is contraindicated in women who are or may become pregnant while receiving the drug. The patient should be instructed to prevent conception with the use of a non-hormonal method.
4. Nursing mothers: It is not known whether Luprolex Depot is excreted in human milk. Because many drugs are excreted in human milk, and because of the effects of Luprolex on lactation and/or the breast-fed child have not been determined, Luprolex should not be used by nursing mothers.
6. Pediatric Use: Safety and effectiveness of Luprolex Depot have not been established in pediatric patients.

WARNINGS
1. As the effects of Luprolex Depot are present throughout the course of therapy, the drug should only be used in patients who require hormonal suppression for at least one month.
2. 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.
3. When used at the recommended dose and dosing interval, Luprolex Depot usually inhibits ovulation and stops menstruation. Contraception is not insured, however, by taking Luprolex Depot. Therefore, patients should use non-hormonal 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. (See Contraindications).
4. Since a decrease in bone mass may occur, the recommended duration of administration of this drug should be limited to 6 months. However, the treatment period can be extended to 12 months if norethindrone acetate 5mg daily is given concurrently with Luprolex Depot 3.75mg (for endometriosis).

PRECAUTIONS

1. Since menstruation should stop with effective doses of Luprolex Depot, the patient should notify her physician if regular menstruation persists. Patients missing successive doses of Luprolex Depot may experience breakthrough bleeding.
2. Patients should not use Luprolex Depot if they are pregnant, breastfeeding, have diagnosed abnormal vaginal bleeding, or are allergic to any of the ingredients in Luprolex Depot.
3. A decrease in bone mass may occur owing to estrogen-reducing effect of Luprolex. Therefore, when it is necessary to administer the drug for a long period or to resume its administration, the drug should be cautiously be administered after the bone mass is examined as far as possible.
4. Since a depressed state like climacteric disturbance may occur, the patient's condition should be closely observed.
5. It should be noted that the treatment of uterine myoma with Luprolex, is not a radical treatment. Therefore, as a rule, this drug should be used as a means of providing conservative treatment until operation on patients requiring operation or providing premenopausal conservative treatment.
6. The effectiveness and safety in using Luprolex for postoperative supplementary treatment has not been established. Therefore, it should not be used for prevention of relapse after curative operation (Premenopausal Breast Cancer).
7. Luprolex does not exhibit antitumor effect or when any progression of the tumor is observed, the administration should be discontinued (Premenopausal Breast Cancer).
8. Elevation of serum testosterone due to the stimulating effect of Luprolex as a highly active LH-RH derivative on the pituitary-gonad system may transiently aggravate bone pain in the early period after the first administration of the drug. If such a symptom occurs, pertinent symptomatic treatment should be given. Since urethral obstruction or spinal cord compression may occur, the drug should be cautiously administered, and close observation should be made during the first month after initiation of treatment and appropriate measures taken (Prostate Cancer).

ADVERSE REACTIONS

Endometriosis, Uterine myoma, Premenopausal Breast Cancer -

1. Hypoestrogenism-related symptoms
   Skin & appendages disorder: Hair loss
   Muscullo-skeletal system disorder: Arthralgia, myalgia
   Central & peripheral nervous system disorders: Headache, Dizziness and Paresthesia
   Automonic nervous system disorder: Increased sweating
   Vision disorder: Visual disturbance
   Psychiatric disorders: Decreased libido, emotional lability, depression and sleep disorders
   Reproductive disorders, Female: Breast size decrease, dry vagina/vaginitis
   Body as a whole-General disorders: Hot flushes, edema and weight changes
2. Hypersensitivity: Anaphylactic reaction, rash and pruritus
3. Gastrointestinal: Nausea, Vomiting and Anorexia
4. Liver: Abnormal liver function test values, usually transient
5. Administration site: Injection site reactions

Prostate Cancer -

1. Flare phenomenon: Bone pain, urinary tract obstruction (as urinary symptoms), Weakness of lower extremity/ paresthesia (as neurologic symptoms).
2. Hypersensitivity: Anaphylactic reaction, rash and pruritus
3. Endocrine: Hot flushes, diaphoresis, decreased libido, impotence, orchiatrophy and gynecomastia
4. Gastrointestinal: Nausea, vomiting, anorexia and diarrhea
5. Liver: Abnormal liver function test values, usually transient
6. Administration site: Injection site reaction
7. Others: Headache, edema, dizziness and depression

STORAGE CONDITION

Store at a room temperature not exceeding 25°C and avoiding heat. Protect from freezing

AVAILABILITY

Box of 1 vial
One 2 mL ampule sterile diluent is included.

Manufactured by

TAKEDA CHEMICAL INDUSTRIES LTD
Osaka, Japan

Imported by

BOIE-TAKEDA CHEMICALS, INC.
Makati City

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Ireland Label .

/S/

9/2014

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for injectable suspension)
TAP Pharmaceutical Products, Inc.

Ireland Label

APPEARS THIS WAY
ON ORIGINAL

Intramuscular injection 5-6 weeks prior to surgery. Therapy should be initiated during days 3 to 5 of the menstrual cycle.

The Elderly: As for adults.

OVERDOSAGE

There is no clinical experience with the effects of an acute overdose of PROSTAP. In animal studies, doses of up to 500 times the recommended human dose resulted in dyspnoea, decreased activity and local irritation at the injection site. In cases of overdosage, the patients should be monitored closely and management should be symptomatic and supportive.

SIDE EFFECTS

Side effects seen with PROSTAP are due mainly to the specific pharmacological action, namely increases and decreases in certain hormone levels. Adverse events which have been reported infrequently include peripheral oedema, hypertension, palpitations, fatigue, muscle weakness, diarrhoea, nausea, vomiting, anorexia, fever/chills, headache (occasionally severe), arthralgia, myalgia, dizziness, insomnia, paraesthesia, visual disturbances, weight changes, increases in liver function test values and irritation at the injection site. Changes in blood lipids and alteration of glucose tolerance have also been reported which may affect diabetic control. Thrombocytopenia and leucopenia have been reported rarely. Hypersensitivity reactions including rash, pruritus, urticaria and, rarely, wheezing or interstitial pneumonitis have also been reported. Anaphylactic reactions are rare.

Infarction of pre-existing pituitary adenoma has been reported rarely after administration of both short- and long-acting GnRH agonists.

Men: In cases where a "tumour flare" occurs after PROSTAP therapy, an exacerbation may occur in any symptoms or signs due to disease, for example, bone pain, urinary obstruction etc. These symptoms subside on continuation of therapy.

Impotence and decreased libido will be expected with PROSTAP therapy.

The administration of PROSTAP is often associated with hot flushes and sometimes sweating. Gynaecomastia has been reported occasionally.

Women: Those adverse events occurring most frequently with PROSTAP are associated with hypo-oestrogenism; the most frequently reported are hot flushes, mood swings including depression (occasionally severe) and vaginal dryness. Oestrogen levels return to normal after treatment is discontinued. Breast tenderness or change in breast size may occur occasionally. Hair loss has also been reported occasionally.

The induced hypo-oestrogenic state results in a small loss in bone density over the course of treatment, some of which may not be reversible (refer to 'Precautions for Use').

PHARMACEUTICAL PRECAUTIONS

PROSTAP SR and PROSTAP Sterile Vehicle should not be used after the expiry date indicated on the labelling. Out of date product should be discarded.

PROSTAP SR should be stored below 25°C in the original container in order to protect from light.

LEGAL CATEGORY

POM

FURTHER INFORMATION

PROSTAP is inactive when given orally.

DATE OF PREPARATION

August 2000

Distributed by Wyeth Laboratories, 765 South Circular Road, Islandbridge, Dublin 8, Ireland.

Takeda

Under licence of Takeda Chemical Industries, Ltd., Japan.

* Registered Trademark of Takeda

P474335

055

USER LEAFLET

PROSTAP* SR 3.75mg

Leuprorelin Acetate
(Powder and vehicle for suspension for injection)

PRODUCT PRESENTATION

Each pack contains one vial of PROSTAP SR Powder and one syringe containing Sterile Vehicle. The Sterile Vehicle is used to reconstitute PROSTAP SR Powder for administration to the patient.

PROSTAP SR Powder

The sterile, lyophilised, white odourless powder comprises microcapsules of 3.75mg of the active ingredient, leuprorelin acetate, and a copolymer, Copoly (DL-lactic acid/glycolic acid) 75:25 mol%.

Sterile Vehicle

The prefilled syringe contains a clear, colourless, slightly viscous solution of sodium carboxymethylcellulose 5mg, mannitol 50mg, polysorbate 80 1mg in water for injection to 1ml.

PROSTAP SR is a single dose depot injection.

THERAPEUTIC ACTIVITY

Leuprorelin acetate (also referred to as PROSTAP) is a synthetic nonapeptide analogue of naturally occurring gonadotrophin releasing hormone (GnRH) possessing greater potency than the natural hormone. PROSTAP is a peptide and therefore unrelated to the steroids.
Administration of leuprorelin acetate results in an initial increase in circulating levels of gonadotrophins which leads to a transient increase in gonadal steroid levels in both men and women. Continued administration of leuprorelin acetate results in a decrease in gonadotrophin and sex steroid levels. Oestradiol and androgen levels will decrease to postmenopausal levels in premenopausal women. These hormonal changes occur within one month of initiating treatment and are reversible on discontinuation of therapy.

The depot formulation is designed to provide, in a single subcutaneous or intramuscular injection, 3.75mg leuprorelin acetate which is released at a constant rate over a period of one month. In males the constant release of drug provides for testosterone suppression equivalent to the daily subcutaneous injection of 1mg leuprorelin acetate.

MARKETING AUTHORISATION HOLDER / NUMBER

Cyanamid of Great Britain Ltd.
Fareham Road, Gosport, Hants. PO13 0AS, United Kingdom.

PA 37/59/5 (Packs containing 1ml Sterile Vehicle)

MANUFACTURER

Wyeth Laboratories, New Lane, Havant, Hants., PO9 2NG, United Kingdom.
The Sterile Vehicle is made by: Solvay Pharmaceuticals BV, Veerweg 12, 8121 AA OLST, The Netherlands.

THERAPEUTIC INDICATIONS

i) Management of prostatic carcinoma for which a suppression of testosterone is indicated.

ii) Management of oestrogen dependant gynaecological disorders including the management of pain and lesions associated with endometriosis.

iii) Preoperative management of uterine fibroids to reduce their size and associated bleeding.

iv) Endometrial preparation prior to intrauterine surgical procedures including endometrial ablation or resection.

CONTRA-INDICATIONS

Men: Use in patients insensitive to endocrine therapy or in those patients post orchidectomy.

Women: PROSTAP is contra-indicated in women who are or may become pregnant while receiving the drug. PROSTAP should not be used in women who are breastfeeding or have undiagnosed abnormal vaginal bleeding.

PRECAUTIONS FOR USE

Diabetic patients may require more frequent monitoring of blood glucose during treatment with PROSTAP.

Men: In the initial stages of therapy, a transient rise in levels of testosterone, dihydrotestosterone and acid phosphatase may occur. In some cases, this may be associated with a "flare" or exacerbation of the tumour growth resulting in temporary deterioration of the patient's condition. These symptoms usually subside on continuation of therapy. "Flare" may manifest itself as systemic or neurological symptoms in some cases.

In order to reduce the risk of "flare", an anti-androgen may be administered beginning 3 days prior to leuprorelin therapy and continuing for the first two to three weeks of treatment. This has been reported to prevent the sequelae of an initial rise in serum testosterone. If an anti-androgen is used over a prolonged period, due attention should be paid to the contra-indications and precautions associated with its extended use.
Patients with urinary obstruction and patients with metastatic vertebral lesions should begin PROSTAP therapy under close supervision for the first few weeks of treatment.

Patients at risk of ureteric obstruction or spinal cord compression should be considered carefully and also be closely supervised in the first few weeks of treatment. These patients should be considered for prophylactic treatment with anti-androgens. Should urological/neurological complications occur, these should be treated by appropriate specific measures.

PROSTAP therapy should not be discontinued when remission or improvement occurs. Response to PROSTAP therapy may be monitored by clinical parameters and by measuring serum levels of testosterone and acid phosphatase. Clinical studies have shown that testosterone levels increased during the first 4 days of treatment in the majority of non-orchidectomised patients. They then decreased and reached castrate levels by 2-4 weeks. Once attained, castrate levels were maintained as long as drug therapy continued. Transient increases in acid phosphatase levels sometimes occur early in the treatment period but usually return to normal or near normal values by the 4th week of treatment.

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

Whilst the development of pituitary adenomas has been noted in chronic toxicity studies at high doses in some animal species, this has not been observed in long term clinical studies with PROSTAP.

Women: Treatment should be initiated during the first 5 days of the menstrual cycle. When used monthly at the recommended dose, PROSTAP usually inhibits ovulation and stops menstruation. Contraception is not ensured by taking PROSTAP however, and therefore patients should use non-hormonal methods of contraception during treatment. Patients should be advised that if they miss successive doses of PROSTAP, breakthrough bleeding or ovulation may occur with the potential for conception. Since menstruation should stop with successive doses of PROSTAP, the patient should notify her physician if regular menstruation persists.

During the early phase of therapy, sex steroids temporarily rise above baseline because of the physiological 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.

In the case of uterine fibroids, it is mandatory to confirm the diagnosis of fibroids and exclude an ovarian [illegible] either surgically by laparoscopy or by ultrasonography or other investigative technique as appropriate, before PROSTAP therapy is initiated.

PROSTAP may cause an increase in uterine cervical resistance, which may result in difficulty in dilating the cervix for intrauterine surgical procedures.

The induced hypo-oestrogenic state may result in a small loss in bone density over the course of treatment, some of which may not be reversible. The extent of bone demineralisation due to hypo-oestrogenaemia is proportional to time and, consequently, is the adverse event responsible for limiting the duration of therapy to 6 months. The generally accepted level of bone loss with LHRH analogues such as PROSTAP is 5%. In clinical studies the levels varied between 2.3% and 15.7% depending on the method of measurement. During one 6-month treatment period, this bone loss [illegible] patients with major risk factors for decreased bone mineral content such as perimenopausal women, 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, PROSTAP therapy may pose an additional risk. In these patients, the risks and benefits must be weighed carefully before therapy with PROSTAP is instituted.

In women receiving GnRH analogues for the treatment of endometriosis, the addition of HRT (an oestrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms.

Children: Safety and efficacy in children have not been established.

Elderly: As for adults.

Drug Interactions: None have been reported.

Pregnancy / Lactation: Safe use of leuprorelin acetate in pregnancy has not been established clinically. Before starting treatment with PROSTAP, pregnancy must be excluded. 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. No teratological effect has been demonstrated in rats and rabbits. The patient must be appraised of this evidence and the potential for an unknown risk to the foetus.

PROSTAP should not be used in women who are breastfeeding.

DOSAGE AND ADMINISTRATION

Dosage:
Prostatic Carcinoma: The usual recommended dose is 3.75mg administered as a single subcutaneous or intramuscular injection every month. The majority of patients will respond to a 3.75mg dose.

Endometriosis: The recommended dose is 3.75mg administered as a single subcutaneous or intramuscular injection every month for a period of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle.

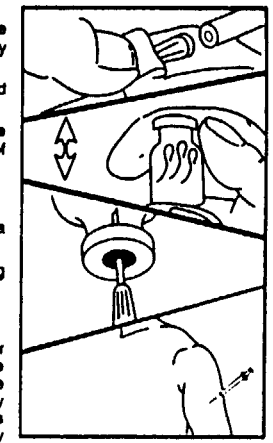
In women receiving GnRH analogues for the treatment of endometriosis, the addition of hormone replacement therapy (HRT - an oestrogen and progestogen) has been shown to reduce bone mineral density loss and vasomotor symptoms. Therefore if appropriate, HRT should be co-administered with PROSTAP taking into account the risks and benefits of each treatment. If PROSTAP is co-administered with HRT, treatment may be extended for up to 12 months in women with chronic symptomatic endometriosis.

Uterine Fibroids: The recommended dose is 3.75mg administered as a single subcutaneous or intramuscular injection every month usually for 3-4 months but for a maximum of 6 months. Treatment should be initiated during the first 5 days of the menstrual cycle.

Endometrial Preparation Prior to Intrauterine Surgery: A single 3.75mg subcutaneous or

Administration:
The vial of PROSTAP SR microcapsule powder should be reconstituted immediately prior to administration by subcutaneous or intramuscular injection.

1. Remove flip-cap from vial of PROSTAP SR Powder and cap from prefilled syringe of Sterile Vehicle.
2. [illegible] 23 gauge needle to syringe, twist to ensure needle is fully engaged and inject whole contents of syringe into vial of PROSTAP SR [illegible] aseptic technique. Re[illegible] keep aseptic.
3. Shake vial gently for 15-20 seconds to produce a uniform cloudy suspension of PROSTAP.
4. Immediately draw up suspension into syringe taking care to exclude air bubbles.
5. Change the needle on syringe using a 23 needle if the suspension is to be adminis[illegible] subcutaneously or alternatively a 21 gauge needle for intramuscular administration. Twist the needle to ensure it is fully engaged. Having cleaned an appropriate injection site, administer the suspension immediately by subcutaneous or intramuscular injection as appropriate, taking care not to enter a blood vessel. Apply sterile dressing to injection site if required.



The injection should be given as soon as possible after mixing. If any settling of suspension occurs in vial or syringe, re-suspend by gentle shaking and administer immediately.

No other fluid can be used for reconstitution of PROSTAP SR Powder.

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

OPDRA Tradename Review NA .

/S/

9/21/01

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Application Integrity Policy-NA .

/S/ - 9/2/04

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Advertising Information .

/S/ 9/21/01

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Postmarketing Commitments-NA .

/S/ 9/21/3

APPEARS THIS WAY
ON ORIGINAL

NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Press Office Information-NA .

/S/ 9/21/01

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-708 SUPPL # 011

Trade Name Lupron Depot-3 Month 11.25 mg

Generic Name leuprolide acetate for depot suspension

Applicant Name TAP Pharmaceutical products, Inc.

HFD- 580

Approval Date September 21, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /X_/ NO /___/

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

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

      YES /X_/ NO /___/

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

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

data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /X_/ NO /___/

If yes, NDA # 20-708 Drug Name Lupron Depot®-3 Month 11.25 mg

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

   YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

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

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

Investigation #1

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

_____

_____

Investigation #2

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

_____

_____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____ _____

Signature of Preparer Date

Title:_____

_____ _____

Signature of Office of Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
9/21/01 01:55:48 PM
For Susan Allen

APPEARS THIS WAY
ON ORIGINAL

TAP PHARMACEUTICAL PRODUCTS INC.

675 N. Field Drive
Lake Forest, IL 60045

October 30, 2000

Division of Reproductive and Urologic
Drug Products (HFD-580)
Attn: Central Document Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Debarment Certification
Lupron Depot 3.75 mg (leuprolide acetate for depot suspension)
Efficacy Supplement

TAP Pharmaceutical Products Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the *Federal Food, Drug, and Cosmetic Act* in connection with this application.

Harold Cohen
Director, Quality Assurance

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 4, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 20-011/S-021 and NDA 20-708/S-011

I have reviewed the financial disclosure information submitted by TAP Pharmaceuticals Products Inc. in support of their Supplemental NTAS 20-011/S-021 and 20-708/S-011.

Two pivotal studies were conducted to assess the safety and efficacy of Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension) with norethindrone acetate 5 mg and Lupron Depot® - 3 Month 11.25 mg (leuprolide acetate for depot suspension) with norethindrone acetate 5 mg for the indication of management of endometriosis for 12 months. The study numbers and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study M92-978/ "Combination Lupron Depot-Hormonal Add-Back in the Management of Endometriosis"	Completed December 1997 (one-year follow-up period-December 1998)	Appropriate documentation received, no financial disclosure submitted.
Study M97-777/ "Leuprolide Acetate for Depot Suspension (A-43818), Combination Lupron Depot and Aygestin Add-Back in the Management of Endometriosis"	Ongoing as of 2/2/99	Appropriate documentation received, no financial disclosure submitted.

Documents Reviewed:

- Financial Certification Information submitted November 21, 2000
- response to request for additional Financial Disclosure Information submitted November 27, 2000 (request for sites and addresses for sponsors)
- further response to request for additional Financial Disclosure Information submitted December 19, 2000 (request for financial disclosure information foe Study M92-978)
- further response to request for additional Financial Disclosure Information submitted May 22, 2001 (request for the sponsor to provide a table listing the site, the number of patients at each site, the investigators at each site, and financial disclosure information for each investigator)

Study M92-878
There were 157 principal and subinvestigators (investigators) at 27 sites in this trial. Study M92-878 including the "one year following the completion of the study" as required by the financial disclosure regulations, was completed on December 23, 1998, therefore, due diligence to obtain financial information from the individual investigators is not required. The sponsor has submitted certification for the requirements under 21 CFR 54.2, that none of the investigators participating in Study M92-878 had (a) "compensation affected by the outcome of clinical studies", (b) "any ownership interests", and (c) "proprietary interests in the tested product"

Study M97-777
There were 188 principal and subinvestigators (investigators) at 28 sites in this trial. Financial disclosure information was received for all the principal investigators, and for most of the subinvestigators with the exception of the following:

There was no disclosable information from the remaining investigators.

Conclusion:
Adequate documentation was submitted to comply with 21 CFR 54. While the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. There was no disclosure of financial interests that could bias the outcome of the trials.

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

/s/

Jeanine Best
6/4/01 02:20:04 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-011/S-021
NDA 20-708/S-011

DISCIPLINE REVIEW LETTER

TAP Pharmaceuticals Products, Inc.
Attention: Aruna Dabholkar, M.D.
Assistant Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Dabholkar:

Please refer to your November 21, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension) and Lupron Depot®-3 Month 11.25 mg (leuprolide acetate for depot suspension).

Our review of the Clinical Pharmacology and Biopharmaceutics section of your submission is complete, and we have identified the following deficiencies:

Please conduct *in vitro* studies to characterize:

1. The effect of leuprolide on cytochrome P450 metabolizing activities.
2. The effect of leuprolide on the binding of drugs to albumin and sex hormone binding globulin.
3. The effect of norethindrone on leuprolide pharmacokinetics.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jeanine Best, M.S.N., R.N., Senior Regulatory Associate, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble, B.S.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
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/

Jeanine Best
9/19/01 12:22:53 PM
Signing for Terri Rumble

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-011/S-021
NDA 20-708/S-011

PRIOR APPROVAL SUPPLEMENT

TAP Pharmaceuticals Products, Inc.
Attention: Aruna Dabholkar, M.D.
Assistant Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Dr. Dabholkar:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act in response to our refuse-to-file letter for the following:

NDA Number	Supplement Number	Drug Name
20-011	S-021	Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
20-708	S-011	Lupron Depot®-3 Month 11.25 mg (leuprolide acetate for depot suspension)

Date of Supplements: November 21, 2000

Date of Receipt: November 22, 2000

These supplements propose the following changes: use of Lupron Depot® 3.75 mg and Lupron Depot®-3 Month 11.25 mg with norethindrone acetate 5 mg daily for the management of endometriosis for 12 months.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on January 21, 2001 in accordance with 21 CFR 314.101(a). If the applications are filed, the primary user fee goal date will be September 21, 2001 and the secondary user fee goal date will be November 21, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Terri F. Rumble
12/5/00 03:19:57 PM

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 21, 2001

APPLICATION NUMBERS: NDA 20-011/S-021
NDA 20-708/S-011

BETWEEN:

Name: Aruna Dabholkar, M.D.
Phone: (847) 317-4893
Representing: TAP Pharmaceutical Products, Inc.

AND

Name: Dena Hixon, M.D.
Scott Monroe, M.D.
Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Additional Labeling Comments

Patient Package Inserts

- additional editorial revisions recommended throughout the labels for clarity

Package Inserts:

- additional editorial revisions recommended throughout the labels for clarity
- define abbreviations such as LD and LD/N used throughout the labels
- reorder Adverse Event Tables (**Table 3**) either by body system or the prevalence or incidence of the events
- reinsert inadvertent deleted statement with regard to no changes in bilirubin levels in original proposed labeling in **Changes in Laboratory Values During Treatment** section
- in the Lupron Depot-3 Month 11.25 mg label, note that the monthly Lupron Depot 3.75 was the formulation used in the clinical trials to support this new indication; this information should be accurately conveyed in the label
- the text in Lupron Depot-3 Month 11.25 mg label should be consistent with the Lupron Depot 3.75 label
- insert additional Adverse Events in the **POSTMARKETING** section of the Lupron Depot 3.75 label that appear in the Lupron Depot-3 Month 11.25 mg label

Action Items:

- Sponsor to e-mail final labeling by 12 Noon today.

{See appended electronic signature page}

Jeanine Best, MSN, RN
Senior Regulatory Associate

cc:
Archival NDA 20-011/20-708
HFD-580/Division Files
HFD-580/Monroe/Hixon

Drafted by: JAB/September 21, 2001
Final:JAB/September 21, 2001

TELECON

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

/s/

Jeanine Best
9/21/01 11:17:50 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 20, 2001

APPLICATION NUMBERS: NDA 20-011/S-021
NDA 20-708/S-011

BETWEEN:

Name: Aruna Dabholkar, M.D.
Phone: (847) 317-4893
Representing: TAP Pharmaceutical Products, Inc.

AND

Name: Scott Monroe, M.D.
Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Additional Labeling Comments

Patient Package Insert

- multiple editorial revision recommended throughout the label for clarity

What You Should Know If You Are Receiving Co-Treatment With Lupron Depot 3.75 mg And Norethindrone Acetate Hormonal Add-Back Treatment section:

- "If your symptoms return after treatment is finished and repeat treatment is desired, you will need co-treatment with Lupron Depot and norethindrone acetate."

Could You Get Pregnant section:

- "If you — think you may be pregnant...."

What About Pregnancy After Therapy Is Finished section:

- the first sentence refers to treatment for fibroids/myomas; add wording to make meaning clear

Package Insert

CLINICAL STUDIES section:

- delete **Figure 2 (Treatment Period Mean Pain Scores)** or only present LD/N data with the deletion of the Figure footer; the study was not designed to provide comparative data
- move the following statement to the end of the *Hormonal add-back therapy* paragraph:

  "Suppression of menses was maintained throughout treatment in 76% of patients receiving LD/N, using data combined across the two studies. The median time for menses resumption after ——— of treatment with LD/N was 8 weeks."

PRECAUTIONS section:

- reformat statement #5 under **Information for Patients** and revise statement (recommended) to include daily calcium supplementation because all patients received NETA and calcium and, therefore, it is unknown if NETA alone will prevent bone mineral density loss:

  "...Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily and calcium supplementation daily is effective in reducing loss of bone mineral density that occurs with LUPRON. (See Changes In Bone Density section).

- revise statement #6 under **Information for Patients:**

  "If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered. Retreatment beyond this one six-month course cannot be recommended."

ADVERSE REACTIONS section:

- **Figure 3 (Adverse Events Reported During 6 Months Of Treatment With Lupron Depot 3.75 mg)**, revise footer:

  Possible Effect of Decreased Estrogen"

- **Table 2 (Treatment-Related Adverse Events Occurring in ≥ 5% Of Patients)**, delete all asterisks after individual adverse events

- delete the following text preceding **Table 3 (Vasomotor Symptoms During the 28 Days Prior to Week 24 of Treatment with LD/N and LD only)** and **Table 3;** vasomotor symptoms were not a studied endpoint

- Replace **Table 3** with the following text:

  "In the controlled clinical trial, 50 of 51 (98%) patients in the LD group and 55 (87%) patients in the LD/N group reported experiencing hot flashes on one or more occasions during treatment. During Month 6 of treatment, 32 of 39 (87%) patients in the LD group and 22 of 38 (58%) patents in the LD/N group reported having experienced hot flashes. The mean

  number of days on which hot flashes were reported during this month of treatment was 19 and 7 in the LD and LD/N treatment groups, respectively. The mean maximum number of hot

flashes in a day during this month of treatment was 5.8 and 1.9 in the LD and LD/N treatment groups."

- use means rather than medians to represent numbers in all tables
- **Table 4 (Adverse Events Observed in > 5% Of Patients And Thought To be Potentially Related To Drug)** footer, revise:

  "*=Possible ——— effect of ———)f decreased estrogen"

Changes in Bone Density section:

- revise the following statement as recommended in the **PRECAUTIONS** section:

  "...Clinical studies demonstrate that concurrent hormonal therapy (norethindrone acetate 5 mg daily and calcium supplementation daily is effective in significantly reducing loss of bone mineral density that occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. ———

- **Table 5**, revise the title:

  "Mean Percent Change From Baseline in Bone Mineral Density of the Lumbar Spine"

Changes in Laboratory Values During Treatment section:

- The following statement is unclear; delete the underlined portion of the statement or add the post days on which lab values were obtained:

  " Five of the 6 increases were observed beyond 6 months of treatment and 2 of the 5 were observed at least a month after treatment discontinuation. None were associated with an elevated bilirubin concentration."

DOSAGE AND ADMINISTRATION section:

- ***Endometriosis:*** revise the statement as done in the **PRECAUTIONS** section:

  "If the symptoms of endometriosis recur after a course of therapy, retreatment with a six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered ——— Retreatment beyond this one ——— six-month course cannot be recommended."

Action Items:

- sponsor to fax label revisions this afternoon

{See appended electronic signature page}

Jeanine Best, MSN, RN
Senior Regulatory Associate

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-011/20-708
HFD-580/Division Files
HFD-580/Monroe

Drafted by: JAB/September 20, 2001
Concurrence: Monroe,09.20.01
Final:JAB/September 20, 2001

TELECON

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

/s/

Jeanine Best
9/21/01 10:44:14 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Teleconference Minutes

Date: September 19, 2001 **Time:** 3:00-4:00 PM **Location:** Parklawn; 17B-43

NDAs 20-011/S-021 Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
20-708/S-011 Lupron Depot®-3 Month 11.25 mg (leuprolide acetate for depot suspension)
both with Aygestin® (norethindrone acetate) 5 mg/daily

Indication: Endometriosis

Sponsor: TAP Pharmaceuticals Products, Inc.

Type of Meeting: Labeling

Meeting Chair: Dena Hixon, M.D.

External Lead: Aruna Dabholkar, M.D.

Meeting Recorder: Jeanine Best, M.S.N., R.N.

FDA Attendees:
Dena Hixon, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Senior Regulatory Associate, DRUDP (HFD-580)

External Participants:
TAP Pharmaceutical Products, Inc.
Robert Browneller, Assistant Director, Clinical Development
C. B. (Katie) Clarke, Director, Medical Services
Aruna Dabholkar, M.D., Associate Director, Regulatory Affairs
Linda Fredrick, Statistician
Dennis Jennings, Ph.D., Director of Statistics
Dennis Snyder, Group Marketing Manager, GYN
Dean Sundberg, Vice President, Regulatory Affairs
Una Ortel, Assistant Director, Regulatory Affairs

Meeting Objective: To discuss labeling revisions for these pending Efficacy Supplements.

Background: The sponsor submitted these Efficacy Supplements (20-011/S-021 and 20-708/S011) on November 21, 2001 to change the Lupron label to extend product usage to twelve months and/or permit retreatment, both with the addition of norethindrone acetate 5 mg as hormonal add-back therapy to reduce bone loss in Lupron-treated women with endometriosis.

Discussion:
- see attached package insert (Lupron Depot® 3.75 mg) for agreed upon and proposed revisions

- the sponsor accepted the following revision to the Lupron Depot®-3 Month 11.25 mg package insert:

CLINICAL PHARMACOLOGY
Pharmacokinetics
Metabolism

"In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular 11.25 mg LUPRON DEPOT (n=19) every 12 weeks or intramuscular 3.75 mg LUPRON DEPOT (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups."

- the Division stated that comparative tables that present data that was not declared *a priory* and defined in the statistical analysis plan cannot be presented as such in the labeling; instead, absolute data may be given
- the issues outlined in the Clinical Pharmacology and Biopharmaceutics Discipline Review letter that was sent to the sponsor today will not affect approvability of these Efficacy Supplements, nor will they lead to requests for Phase 4 studies

Decisions:

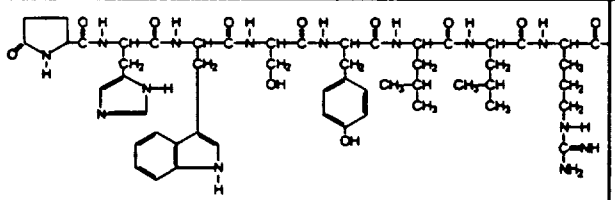
- sponsor to submit revised labeling for Division review and acceptability

Action Items:

- sponsor to provide revised labeling by start of business tomorrow; sponsor to provide final revised labeling in an electronic format by COB tomorrow, September 20, 2001
- Meeting Minutes to sponsor within 30 days

Minutes Preparer **Concurrence, Chair**

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

This is combined labeling. Examples of different fonts and colors appear below.	
• General information	
• Information on endometriosis	
• Information on uterine fibroids	
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 available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a monthly intramuscular injection.	
The front chamber of LUPRON DEPOT 3.75 mg prefilled dual-chamber syringe 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 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 3.75 mg, acetic acid is lost, leaving the peptide.	
CLINICAL PHARMACOLOGY	

APPEARS THIS WAY
ON ORIGINAL

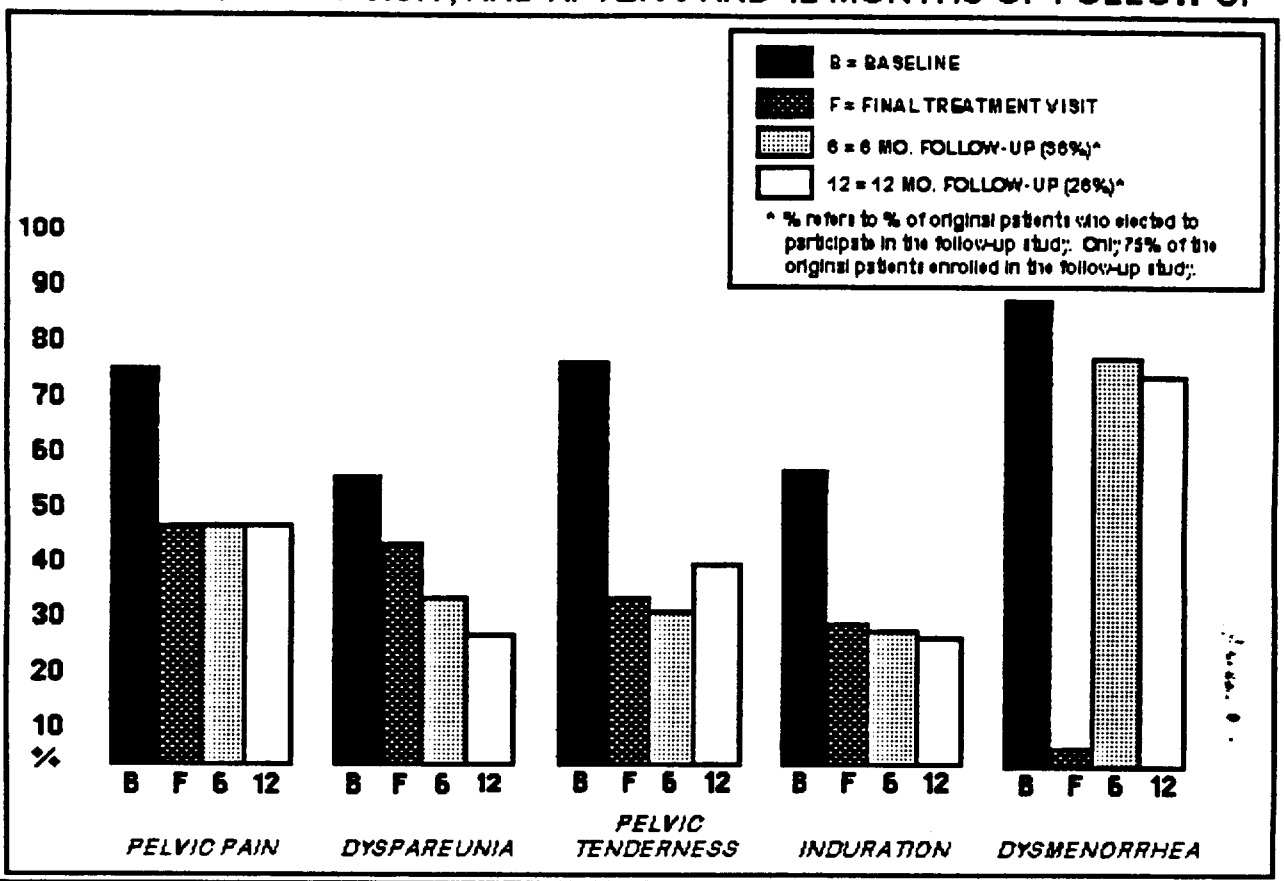
Leuprolide acetate is a long-acting GnRH analog. A single monthly injection of LUPRON DEPOT 3.75 mg results in an initial stimulation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at monthly intervals results in decreased secretion of gonadal steroids; consequently, 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 a two compartment model.	

In rats and dogs, administration of ^{14}C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.	
The major metabolite (M-I) plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.	
Excretion Following administration of LUPRON DEPOT 3.75 mg to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.	
Special Populations The pharmacokinetics of the drug in hepatically and renally impaired patients have not been determined.	
CLINICAL STUDIES	
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 sign/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.	

APPEARS THIS WAY
ON ORIGINAL

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% of patients respectively excluding those who became pregnant.	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% of patients respectively, excluding those who became pregnant.
Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 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 in 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 6 months and 26% at 12 months	Figure 1 illustrates the percent of patients with symptoms at baseline, final treatment visit and sustained relief at 6 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 in 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 6 months and 26% at 12 months.

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

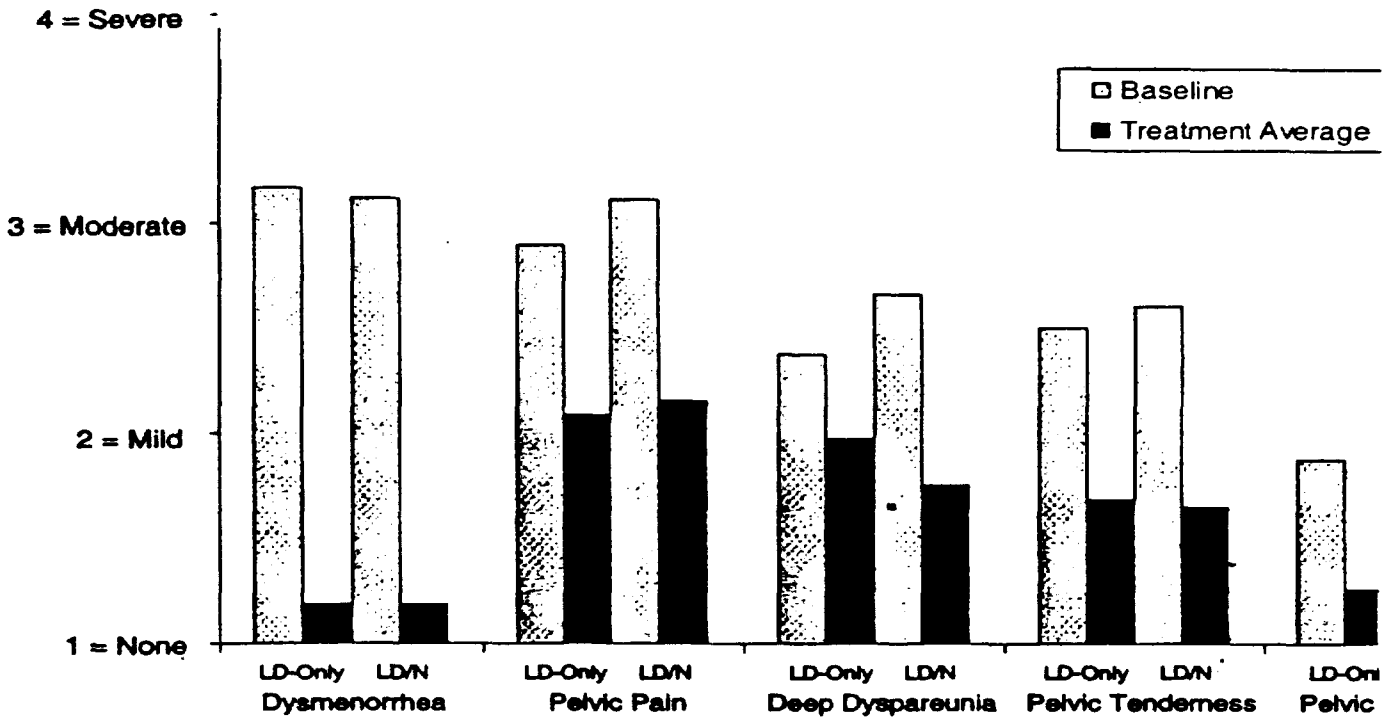


APPEARS THIS WAY
ON ORIGINAL

[redacted] *Hormonal add-back therapy*: Two clinical studies with a treatment duration of 12 months [redacted] showed that concurrent hormonal [redacted] therapy (norethindrone acetate 5 mg daily) and calcium supplementation with 1000mg elemental calcium is effective in reducing loss of bone mineral density that occurs with LUPRON alone, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. One study (M92-878) was controlled, randomized and double blinded and included 51 women treated with Luporn alone and 55 women reated with Lupron plus norethindrone acetate 5 mg daily. The second study (M97-777) was an open label study in which 136 women were treated with Lupron plus norethindrone acetate 5mg. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled trial.	*Hormonal add-back therapy*: Two clinical studies with a treatment duration of 12 months indicate that concurrent hormonal therapy (norethindrone acetate 5 mg daily) is effective in [redacted] significantly reducing the loss of bone mineral density [redacted] associated with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. (All patients in these studies received calcium supplementation with 1000 mg elemental calcium. One randomized and double-blind study included 51 women treated with Lupron Depot alone and 55 women treated with Lupron plus norethindrone acetate 5 mg daily. The second study was an open label study in which 136 women were treated with Lupron plus norethindrone acetate 5 mg daily. This study confirmed the reduction in loss of bone mineral density that was observed in the controlled study.
[redacted]	Figure 2 illustrates the mean pain scores from the [redacted] -LD/N treated patients.

APPEARS THIS WAY
ON ORIGINAL

Figure 2
Treatment Period Mean Pain Scores



Note: LD-ONLY = LUPRON DEPOT 3.75 mg; LD/N = LUPRON DEPOT 3.75 mg plus norethindrone acetate
All of the within-group decreases from baseline were statistically significant (p<0.001). No statistically differences between groups in mean change from baseline were noted.

[redacted]

{Sponsor: Delete above Note and LD-only data}

[redacted]

- Suppression of menses was maintained throughout treatment in [redacted] 84% of patients in the controlled study receiving [redacted] LD/N [redacted] The median time for menses resumption after 12 months of treatment [redacted] , LD/N was [redacted] d 8 weeks, [redacted] ; using the data combined across the two studies.

[redacted]

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 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 3.75 mg.	
INDICATIONS AND USAGE	
Endometriosis:	
LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT with (norethindrone acetate 5 mg daily) is also indicated for initial management of endometriosis and for management of recurrence of symptoms (Refer also to norethindrone acetate prescribing information for WARNINGS, PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of treatment with Lupron alone or in combination with norethindrone acetate should be limited to 6 months	LUPRON DEPOT 3.75 mg is indicated for management of endometriosis, including pain relief and reduction of endometriotic lesions. LUPRON DEPOT monthly with norethindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms (Refer also to norethindrone acetate prescribing information for WARNINGS, PRECAUTIONS, CONTRAINDICATIONS and ADVERSE REACTIONS associated with norethindrone acetate). Duration of initial treatment or retreatment
Uterine Leiomyomata (Fibroids):	
LUPRON DEPOT 3.75 mg concomitantly with iron therapy is 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 Table 3 LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to** three months.	LUPRON DEPOT 3.75 mg concomitantly with iron therapy is 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 Table 1.) LUPRON may be added if the response to iron alone is considered inadequate. Recommended duration of therapy with LUPRON DEPOT 3.75 mg is **up to** three months.

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

TABLE 1

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, the patient should be apprised of the potential hazard to the fetus.	
4. Use in women who are breast-feeding. (See **Nursing Mothers** section.)	
[redacted]	
5. Norethindrone acetate is contraindicated in women with the following conditions:	5. Norethindrone acetate is contraindicated in women with the following conditions:
- Thromophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions	- Thromophlebitis, thromboembolic disorders, cerebral apoplexy, or a past history of these conditions

- Markedly impaired liver function or liver disease	- Markedly impaired liver function or liver disease
- Known or suspected carcinona of the breast	- Known or suspected carcinona of the breast
WARNINGS	
Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with LUPRON DEPOT, pregnancy must be excluded.	Safe use of leuprolide acetate or norethindrone 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 non-hormonal 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.	
Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.	Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported post-marketing.
The following applies to co-treatment with Lupron and norethindrone acetate:	The following applies to co-treatment with Lupron and norethindrone acetate:
Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of protosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.	Norethindrone acetate treatment should be discontinued if there is a sudden partial or complete loss of vision or if there is sudden onset of protosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn.
Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.	Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking progestogens, the physician should be alert to the earliest manifestations of the disease in women taking norethindrone acetate.
Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caustion in women with risk factors, including lipid abnormalities or cigarette smoking.	Assessment and management of risk factors for cardiovascular disease is recommended prior to initiation of add-back therapy with norethindrone acetate. Norethindrone acetate should be used with caustion in women with risk factors, including lipid abnormalities or cigarette smoking.
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 non-hormonal 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.	
ced hypoestrogenic state **also** results in a — loss in over the course of treatment, some of which may not be For a period up to six months, this bone loss should not hormonal therapy with norethindrone acetate 5 mg daily supplementation (1000 mg elemental calcium daily) is reducing loss of bone mineral density that occurs with	5. The induced hypoestrogenic state **also** results in a 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 clinically significant. Clinical studies show that concurrent hormonal therapy with norethindrone acetate 5 mg daily s effective in reducing loss of bone mineral density that occurs with LUPRON. (All patients received 1000 mg elementalcalcium supplementation daily.) See **Changes In Bone Density section.**

6 [redacted] If the symptoms of endometriosis recur after completion of therapy [redacted] retreatment with a single six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily ~~is~~ may be considered. [redacted] It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Concurrent hormonal add-back should be considered if retreatment or extended therapy is contemplated. Retreatment with Lupron Depot alone is not recommended [redacted]	6. If the symptoms of endometriosis recur after a course of therapy, retreatment with a ~~single~~ six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily may be considered [redacted] It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Retreatment with Lupron Depot alone is not recommended. **[Sponsor to propose revised wording for paragraph]**

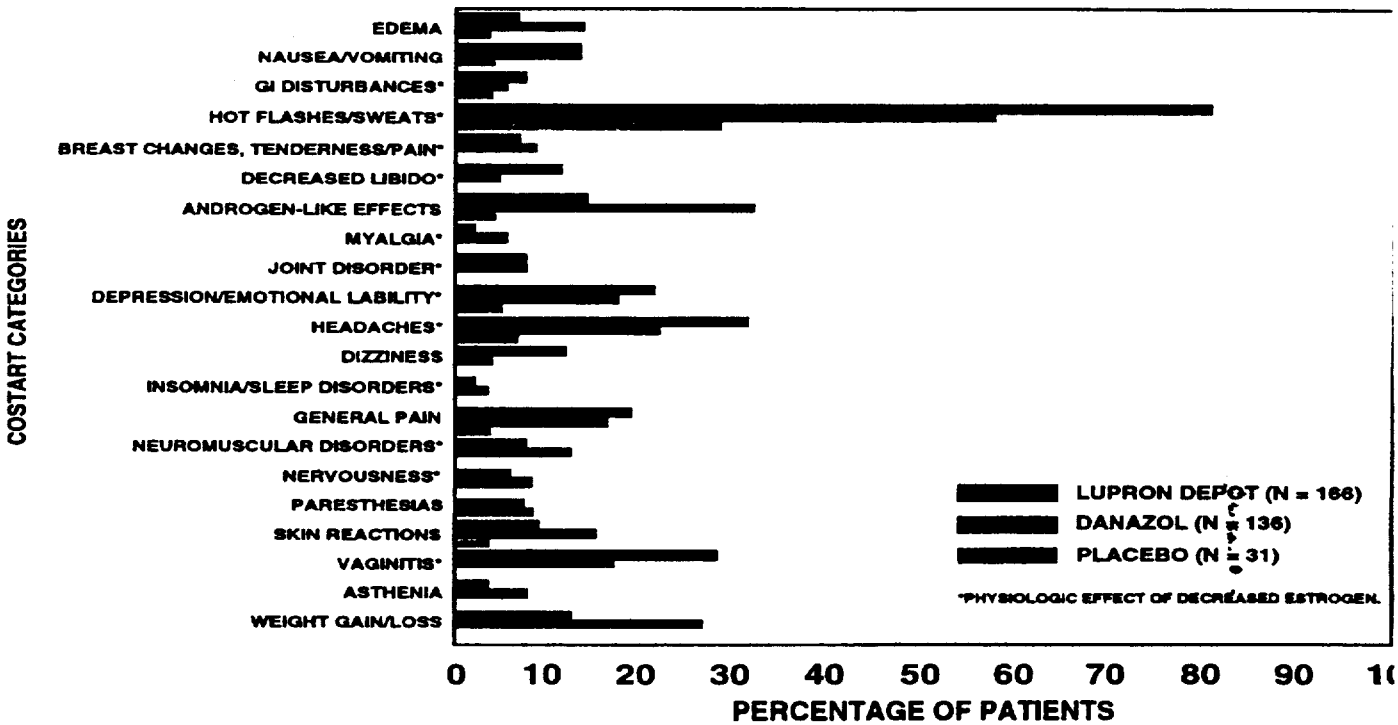
APPEARS THIS WAY ON ORIGINAL

7. 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, therapy with patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with LUPRON is not advisable in patients with major risk factors for loss of bone mineral content. Clinical studies suggest that the addition of hormonal replacement therapy (estrogen and/or progestin) to LUPRON is effective in reducing loss of bone mineral density which occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis. The optimal drug/dose is not established.	7. 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, therapy with Lupron Depot may pose an additional risk in these patients, the risks and benefits must be weighed carefully before therapy with LUPRON DEPOT alone is instituted, and concomitant treatment with norethindrone acetate 5 mg daily should be considered. Retreatment with gonadotropin releasing hormone analogs including LUPRON is not advisable in patients with major risk factors for loss of bone mineral content.
8. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.	8. Because norethindrone acetate may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunctions require careful observation during norethindrone acetate add-back therapy.
9. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.	9. Patients who have a history of depression should be carefully observed during treatment with norethindrone acetate and norethindrone acetate should be discontinued if severe depression occurs.
Laboratory Tests See **ADVERSE REACTIONS** section.	
Drug Interactions No pharmacokinetic-based drug-drug interaction studies have been conducted with LUPRON DEPOT. However, because leuprolide acetate is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.	

Drug/Laboratory Test Interactions Administration of LUPRON DEPOT in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of LUPRON DEPOT 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 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. 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 of 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 breast-fed child have not been determined, LUPRON DEPOT should not be used by nursing mothers.	
Pediatric Use Experience with LUPRON DEPOT 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older.	**Pediatric Use** Experience with LUPRON DEPOT 3.75 mg for treatment of endometriosis has been limited to women 18 years of age and older.
See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.	See LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) labeling for the safety and effectiveness in children with central precocious puberty.
Geriatric Use This product has not been studied in women over 65 years of age and is not indicated in this population.	**Geriatric Use** This product has not been studied in women over 65 years of age and is not indicated in this population.
ADVERSE REACTIONS	**ADVERSE REACTIONS**
Clinical Trials	**Clinical Trials**
Estradiol levels may increase during the first weeks following the initial injection of Lupron, 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.)	Estradiol levels may increase during the first weeks following the initial injection of LUPRON, 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.	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~~3.	*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~~3.

FIGURE 3–ADVERSE EVENTS REPORTED DURING 6 MONTHS OF TREATMENT WITH LUPRON DEPOT 3.75 MG



[Sponsor: Delete * after certain Adverse Events and delete the word "Physiologic" from the table footnote]

In these same studies, other symptoms reported included: *Cardiovascular System* - Palpitations, Syncope, Tachycardia; *Gastrointestinal System* - Appetite changes, Dry mouth, Thirst; *Central/Peripheral Nervous System* - Anxiety, Delusions, Memory disorder,* Personality disorder; *Integumentary System* - Alopecia, Ecchymosis, Hair disorder; *Urogenital System* - Dysuria,* Lactation; *Miscellaneous* – *Lymphadenopathy, Ophthalmologic disorders.	In these same studies, other symptoms reported included: *Cardiovascular System* - Palpitations, Syncope, Tachycardia; *Gastrointestinal System* - Appetite changes, Dry mouth, Thirst; *Central/Peripheral Nervous System* - Anxiety, Delusions, Memory disorder,* Personality disorder; *Integumentary System* - Alopecia, Ecchymosis, Hair disorder; *Urogenital System* - Dysuria,* Lactation; *Miscellaneous* – *Lymphadenopathy, Ophthalmologic disorders.

Table 2 lists the potentially drug-related adverse events observed in at least 5 % of patients during the first 6 months of treatment in the clinical studies.	Table 2 lists the potentially drug-related adverse events observed in at least 5 % of patients in any treatment group during the first 6 months of treatment in the add-back clinical studies.

Table 2: Treatment-Related Adverse Events Occurring in ≥ 5% Of Patients

[Sponsor: Delete * from the Table]

Adverse Events *	Controlled Study				Open Label Study	
	LD- Only N= 51		LD/N N=55		LD/N N=136	
	N	(%)	N	(%)	N	(%)
Any Adverse Event	50	(98)	53	(96)	126	(93)
Hot flashes/Sweats*	50	(98)	48	(87)	78	(57)
Headache/Migraine	33	(65)	28	(51)	63	(46)
Insomnia/Sleep Disorders	16	(31)	7	(13)	20	(15)
Nausea/Vomiting	13	(25)	16	(29)	17	(13)
Depression/Emotional Lability	16	(31)	15	(27)	46	(34)
Vaginitis	10	(20)	8	(15)	11	(8)
Asthenia	9	(18)	10	(18)	15	(11)
Dizziness/Vertigo	8	(16)	6	(11)	10	(7)
	6		6			
Pain	12	(24)	16	(29)	29	(21)
	6		4			
Libido — Changes	5	(10)	2	(4)	10	(7)
Weight — Changes	6	(12)	7	(13)	6	(4)
	4					
Nervousness	4	(8)	2	(4)	15	(11)
Anxiety	3	(6)	0	(0)	11	(8)
	3					
	3					
Breast Changes/ Pain/ Tenderness	3	(6)	7	(13)	11	(8)
Memory Disorders	3	(6)	1	(2)	6	(4)
Androgen-Like Effects	2	(4)	3	(5)	24	(18)
	2					
			4			
			4			
			4			
			5			
			4			

Changes in Appetite	[redacted]	(4)	0	(0)	8	(6)
Injection Site eaction	1	(2)	[redacted]	(9)	4	(3)
			4			
Alopecia	0	(0)	5	(9)	4	(3)
dema	0	(0)	[redacted]	(9)	[redacted]	(7)
Menstrual Disorders	[redacted]	(2)	[redacted]	(0)	[redacted]	(5)
Altered Bowel Function	[redacted]	(14)	[redacted]	(15)	[redacted]	(10)
GI Disturbance	[redacted]	(4)	[redacted]	(7)	[redacted]	(4)
Neuromuscular Disorder	[redacted]	(2)	[redacted]	(9)	[redacted]	(3)
Skin/Mucous Membrane Reaction	[redacted]	(4)	[redacted]	(9)	[redacted]	(11)

The frequency of hot flashes in patients treated with the combination of Lupron and norethindrone acetate in a controlled clinical trial is shown in the following table (Table 3);	The frequency of hot flashes in patients treated with Lupron alone and with the combination of Lupron and norethindrone acetate in a controlled clinical trial is shown in the following table (Table 3);

[Division will discuss the sponsor's proposed revision to the text and Table with regard to presentation of Vasomotor Symptoms]

Table 3 Vasomotor Symptoms During the 28 Days Prior to Week 24 of Treatment with LD/N and LD only

	Number of Patients	Number Reporting Hot Flashes (%)	Days with Hot Flashes (Median)	Maximum Number Hot Flashes in 24 Hours (Median)
LD-Only	37#	87%	25.0	4.0
LD/N	38	58%**	2.0***	1.0***

N=36 for maximum number in 24 hours.

** Statistically significant difference between groups at the 0.01 and 0.001 levels, respectively.

*** Statistically significant difference between groups at the 0.01 and 0.001 levels, respectively.

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 [redacted] Table 5 4.	*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 Table 4.

TABLE 4
ADVERSE EVENTS OBSERVED IN > 5% OF PATIENTS AND THOUGHT TO BE POTENTIALLY RELATED TO DRUG

	Lupron Depot 3.75 mg 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.

Changes in Bone Density