CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-708/S-005

MEDICAL REVIEW(S)

C.Kish

Medical Review

JAN 29 1999

NDA:	20.708
Serial #:	167
Protocol #:	M96-506
Title:	Pharmacokinetic/Pharmacodynamic Study of Lupron Depot® 3.75 mg and Lupron Depot®-3 Month 11.25mg in Patients with Endometriosis
Sponsor:	Tap Holdings, Inc. Bannockburn Lake Office Plaza 2355 Waukegan Rd. Deerfield, IL 60015
Submission Date:	April 3, 1998
Date Review Completed:	January 21, 1999

General Information:

Name of drug:	Lupron Depot 3.75 mg and Lupron Depot 11.25 mg
Chemical name:	Leuprolide Acetate for depot suspension
Trade Names:	Lupron Depot ®
Pharmacologic category:	Gonadotropin releasing hormone agonist
Proposed indication:	Management of endometriosis
Dosage Form:	Lupron Depot 3.75 mg intramuscular formulation, Lupron Depot 11.25 mg intramuscular formulation
Route of administration :	Intramuscular injection
Approved indications:	Treatment of prostate cancer, endometriosis, anemia associated with leiomyomata and central precocious puberty.
Related Submissions:	NDA 20-011
Related Drugs:	Nafarelin Acetate (approved for precocious puberty and endometriosis), Goserelin Acetate (approved for the treatment of endometriosis and advanced breast cancer, and prostatic cancer), Histerelin Acetate (approved for precocious puberty).

Resume:

This application contains data from a single, phase IV pharmacokinetic and pharmacodynamic study comparing two depot formulations of leuprolide acetate in forty female patients with endometriosis. The goal of therapy with leuprolide acetate in the treatment of endometriosis is the creation of a hypoestrogenic state resulting in atrophic changes in ectopic endometrial tissue and subsequent symptomatic improvement.

The current study was a randomized, open label, two arm, eight site trial comparing the hormonal response during six months of treatment with Lupron Depot 3.75 mg every month (six injections) or with Lupron Depot 11.25 mg every three months (two injections) in patients with endometriosis. The objectives of the study were: (1) to characterize the pharmacokinetics of both Lupron Depot formulations as assessed by plasma concentrations of leuprolide acetate following intramuscular (IM) injections, and (2) to characterize the relationship between plasma leuprolide acetate concentration and pharmacodynamic response. The two Lupron formulations were assessed in terms of clinical efficacy (relief of pain and tenderness) and suppression of menses and serum estradiol levels.

Safety evaluations included assessment of clinical chemistry and hematology parameters prior to and during treatment as well as assessment of changes in vertebral and spinal bone mineral density as determined by dual energy x-ray absorptiometry (DEXA) scan.

Biometrics Review:

Statistical comments will be submitted as a separate report.

Regulatory Background:

Both Lupron Depot formulations were approved for the treatment of endometriosis, with the monthly formulation (containing 3.75 mg of leuprolide acetate) having been approved in October of 1980 and the 3-monthly formulation (containing 11.25 mg of leuprolide acetate) having been approved in March of 1997. Lupron Depot was also approved for the treatment of anemia associated with leiomyomata uteri. The monthly formulation was approved for this indication in March of 1995, and the 3-monthly formulation received approval for this indication in March of 1997. Subsequently, a commitment was made by the sponsor to conduct the current phase IV study comparing the pharmacokinetics and pharmacodynamics of the two formulations in the treatment of endometriosis.

Clinical Study:

The current study was conducted from November, 1996 to September, 1997. Forty patients, all of whom had endometriosis surgically diagnosed within eighteen months prior to study entry, were randomized to receive either six monthly IM injections of Lupron Depot 3.75 mg or two 3-monthly IM injections of Lupron Depot 11.25 mg.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were appropriate for the proposed study. Eligible patients were women aged 18 to 40 years with regular menstrual cycles and a history of symptomatic, surgically diagnosed endometriosis. At enrollment, all patients were noted to have pelvic pain or tenderness characteristic of endometriosis. A washout period for previous hormonal therapies was required prior to receipt of the first dose of study drug.

Patients were excluded for any of the following conditions: pregnancy within 3 months prior to the first dose of study drug, currently lactating, experiencing undiagnosed vaginal bleeding, having a history of osteoporosis or a baseline bone mineral density of less than 80% of the age-matched control value, having a history of known or suspected cancer that had not been in

remission for five years prior to study entry, having a history of emotional disorder precluding treatment with GnRH analogs, or having a history of allergic reaction to GnRH analogs.

Prestudy Screening Examination

Potential volunteers were screened via medical history and physical examination. Endometriosis was assessed by grading dysmenorrhea, pelvic pain, pelvic tenderness and pelvic induration. Routine clinical laboratory tests were performed including pregnancy testing, hematology and blood chemistry analyses. Serum samples for estradiol and FSH were also obtained, and endometrial biopsies were performed if clinically indicated. Determination of spinal bone mineral density was measured by DEXA scan.

Treatment Period

Patients were randomized to one of the two treatment groups (Lupron Depot 3.75 mg or Lupron Depot 11.25 mg). Twenty patients were randomized to the 3.75 mg dose group, and twenty-one patients were randomized to the 11.25 mg dose group.

Injections of Lupron were begun during the first four days of the menstrual cycle. After receiving the initial injection of study drug, volunteers returned for follow-up visits every month during the six month treatment period and at months 3 and 6 of a post-treatment follow-up period.

Women in the 3.75 mg Lupron treatment group received injections of study drug every 4 weeks (for a total of six injections), while those in the 11.25 mg Lupron treatment group received injections every 3 months (for a total of two injections). Calcium supplements (calcium carbonate 500 mg plus vitamin D 125 mg, one tablet twice a day) were given to patients for self-administration for a proposed duration of two years (one year during the study and one year post-treatment).

Patients were seen every four weeks during the treatment period for monthly evaluations which included: a pelvic examination; clinical evaluation of endometriosis (using the Biberoglu and Behrman Scale); patient evaluation of pelvic pain and dysmenorrhea (using a scale of 0 to 10); serum estradiol, leuprolide acetate and M-I metabolite level determinations; review of menstrual records, patient diaries and concurrent medications; and review of adverse events. At week 24, a complete physical exam, clinical laboratory testing and DEXA bone scan were performed.

Post -Treatment Period

After completion of the 24-week treatment period, study volunteers were followed for six additional months. Volunteers were contacted by telephone at months 1,2,4 and 5 to determine if menses resumed and were seen in the clinic setting at months 3 and 6 during this follow-up period. Estradiol level was measured at the first follow-up visit after menses. A review of concurrent medications, adverse events and patient diary reports were conducted at both the 3- and 6-month follow-up visits. A DEXA bone scan was also performed at the 6-month follow-up visit.

Safety Considerations

During the course of this study, volunteers had a medical history, gynecologic examinations, and laboratory evaluations performed as described in the "Prestudy" and "Treatment" sections

above. Each volunteer was closely monitored for evidence of adverse events throughout both the treatment and follow-up periods. If a volunteer terminated her participation prior to completing the treatment and follow-up periods, a complete physical examination and DEXA scan were performed, blood was drawn for clinical chemistry and hematology assessments and for drug and estradiol levels, and a final interview was performed to assess adverse events and concomitant medication use and to review patient diaries.

Study Results

Patient Demographics:

Patients' ages ranged from 20-39 years. Their weights ranged from 108-165 pounds, and their heights ranged from 60-70 inches. There were 36 Caucasian women, 3 Hispanic women, and 2 African American women in this study. No statistically significant between-group differences were noted for any demographic parameter.

Disease and Fertility History:

There were no statistically significant differences between treatment groups with respect to prior pregnancy, prior medical treatment for endometriosis or mean baseline American Fertility Society (AFS) scores for endometriosis. The Lupron 11.25 mg group had a statistically significantly greater mean number of years since diagnosis of endometriosis (average = 3.5 years) when compared to the Lupron 3.75 mg group (average = 1.3 years).

Clinical Results-Efficacy:

Primary efficacy analyses were performed on data obtained from all patients as an intent-to-treat analysis. Fifteen of the 20 patients randomized to the 3.75 mg treatment group and 19 of the 21 patients randomized to the 11.25 mg treatment group completed the study.

Efficacy parameters included: a) clinical pain evaluations; b) patient pain evaluation; c) menstrual suppression; and d) estradiol levels.

a) Clinical pain evaluations:

Clinical assessments of dysmenorrhea, non-menstrual pelvic pain, pelvic tenderness and induration were made at each visit during the treatment period and were graded as none, mild, moderate, or severe according to the Biberoglu and Behrman Scale. Each rating on this scale was assigned a score (none=1, mild=2, moderate=3, and severe=4), and the changes in scores from baseline were calculated for each treatment visit. While there was no statistically significant difference in mean baseline severity score between groups for any pain variable, there were statistically significant within-group decreases in mean severity score for each pain variable at every treatment visit.

Mean changes in pain severity scores from baseline to each treatment visit were analyzed by both Cochran-Mantel-Haenszel (CMH) and ANOCOVA analyses. Using CMH analysis, the only statistically significant difference between treatment groups in mean change from baseline pain severity score was in pelvic tenderness at 24 weeks. The Lupron 11.25 mg group had a significantly greater reduction in mean pain severity score for this pain variable than did the Lupron 3.75 mg group. Using ANOCOVA analysis, the only statistically significant difference between treatment groups in mean change from baseline severity scores for any of the clinical

or patient pain evaluations was for dysmenorrhea at week eight. The Lupron 3.75 mg group had a significantly greater reduction in mean pain severity score for this pain variable than did the Lupron 11.25 mg group.

b) Patient pain evaluation:

Patients assessed severity of pelvic pain using a scale containing scores ranging from 0 to 10. The within-group mean decrease from baseline in symptom score averaged over the entire treatment period was statistically significant for each treatment group. There were no statistically significant between-group differences in mean change from baseline severity scores averaged over the entire treatment period.

c) Menstrual suppression:

Menstrual suppression was defined in two ways; one, based upon bleeding criteria and the other, based upon a combination of estradiol level and bleeding criteria. In the former instance, menstrual suppression was defined as "no new occurrence of menses for at least 60 consecutive days, regardless of whether any bleeding occurred thereafter". In the latter instance, menstrual bleeding was defined as "the occurrence of an estradiol level $\leq$ 4.0 ng/dL with no menses within 28 days after that estradiol level."

Time to menstrual suppression was defined as "the number of days from the start of treatment to the first day of the last menstrual cycle prior to suppression". Maintenance of suppression was defined as "all subsequent estradiol values during treatment remaining at or below 4.0 ng/dL and no occurrence of menses during the treatment period."

Using the first definition, one hundred percent of patients who were in the study for 60 days had menstrual suppression within 60 days of starting treatment. The maximum number of days to suppression for those patients who suppressed was 24 days and 54 days for the Lupron 3.75 mg treatment group and the Lupron 11.25 mg treatment group, respectively. The median time to suppression was 0 days for both treatment groups. There was no statistically significant difference in the treatment groups in the percentage of patients achieving suppression or the percentage of patients maintaining suppression.

According to the estradiol level-bleeding criteria definition for menstrual suppression, 90% of the 3.75 mg treatment group and 100% of the 11.25 mg treatment group achieved menstrual suppression.

Based upon both definitions, there was no statistically significant difference in the treatment groups in the percentage of patients achieving suppression or the percentage of patients maintaining suppression.

d) Estradiol evaluation:

Serum estradiol samples were obtained at each visit during the treatment period. The mean estradiol level for patients in the Lupron 3.75 mg group ranged from 1.4 to 1.9 ng/dL during the Treatment Period. The mean estradiol level for patients in the Lupron 11.25 mg group ranged from 1.1 to 2.0 ng/dL during the Treatment Period. There were no statistically significant differences in changes from baseline in estradiol levels between the Lupron 3.75 mg and Lupron 11.25 mg groups at any visit. There were statistically significant within-group decreases in estradiol levels from baseline for the Lupron 3.75 mg and Lupron 11.25 mg groups at every visit.

Clinical Results-Safety

a) Adverse Events:

Ninety-eight percent of all patients enrolled in the study (n = 41) had one or more adverse events during the treatment period. Hot flushes and headaches were the most common adverse events, with 80% of patients in the 3.75 mg treatment group and 86% in the 11.25 mg treatment group experiencing hot flushes and 75% of patients in the 3.75 mg treatment group and 62% of patients in the 11.25 mg treatment group experiencing headaches.

Four patients experienced serious adverse events during the treatment period as follows:

- One patient in the 11.25 mg treatment group (patient experienced fluid retention of the lower pelvis requiring hospitalization. This event was not thought to be related to study drug, in the opinion of the investigator.
- Dehydration requiring hospitalization was noted in one patient (patient) in the Lupron 3.75 mg group. Review of CRFs for this patient revealed that hospitalization for dehydration occurred secondary to a viral flu syndrome which was not thought to be related to study drug.
- One patient in the Lupron 3.75 group (patient) experienced increased heart rate and shakiness that did not require hospitalization and, in the investigator's opinion, was not thought to be related to study drug.
- Pelvic pain requiring hospitalization was experienced by one patient in the Lupron 3.75 mg group (patient). The pelvic pain was thought to be related to endometriosis and incisional pain from a hysterectomy performed on 5/12/97.

Reviewer's comments:

1) CRFs for patient were reviewed and it was noted that she was first hospitalized for fluid retention in the lower pelvis on 2/7/97. On 3/26/97 she underwent a CT scan of the abdomen for continuing symptoms. The results of this scan showed no abdominal or pelvic masses or adenopathy. On 6/4/97 she was again admitted to the hospital for increasing pelvic pain and continued fluid retention of the lower pelvis. As stated in the admission history, the fluid retention was noted to have been aggravated by Lupron Depot therapy during the trial. The volunteer underwent a total abdominal hysterectomy during the latter hospitalization and was subsequently discontinued from the study. The pathology report showed subserosal leiomyoma, superficial adenomyosis and multiple serosal fibrous adhesions with no identifiable endometriosis.
2) CRFs and MedWatch report forms for patient were reviewed and revealed that the patient was admitted to the hospital on 4/27/97 with a diagnosis of dehydration secondary to viral flu syndrome. She received intravenous fluids and antibiotics and was released from the hospital on 4/28/97. This adverse event does not appear to be related to study drug.

Two patients (patient) discontinued their participation in the trial early due to adverse events or disease progression. In both instances, the adverse events resulting in early discontinuation were thought to be related to study drug. A summary of their trial experience is as follows:

- Patient was admitted to the trial on 11/22/96 and was randomized to the 11.25 mg treatment group. On 3/22/97 the patient requested early termination from the study for continued adverse events (including mood swings, decreased libido, headaches, hot flushes) and increased family stress. All adverse events were noted to have resolved as of May 16, 1997.

- Patient was admitted to the trial on 10/28/96 and was randomized to the 3.75 mg treatment group. On 4/2/97 she underwent an emergency laparoscopy for pelvic pain and metrorrhagia. Stage II endometriosis was noted at laparoscopy, and a D&C procedure was performed. The patient was discontinued from the study on 4/15/97 but continued to have pelvic pain and subsequently underwent a hysterectomy on 7/7/97. At a post-operative follow-up visit on 10/28/97, her pelvic pain was noted to have resolved.

No patients were found to be pregnant and no endometrial biopsies were performed during the study.

b) Clinical laboratory parameters:

There were statistically significant differences between the treatment groups in mean changes from baseline for several chemistry parameters. These parameters were:

1) MCH (lower in the 3.75 mg treatment group)
2) Platelet count (lower in the 11.25 mg treatment group)
3) Alkaline phosphatase (higher in the 3.75 mg treatment group)
4) Total cholesterol (higher in the 3.75 mg treatment group)
5) LDL cholesterol (higher in the 3.75 mg treatment group)

Statistically significant <u>within-group</u> mean changes from baseline were noted for these five specific chemistry parameters as follows:

1) MCH (decrease from baseline levels for the 3.75 mg treatment group)
2) Platelet count (decrease from baseline levels for the 11.25 mg treatment group)
3) Alkaline phosphatase (increase from baseline levels for the 3.75 mg group)
4) Total cholesterol (increase from baseline levels for the 3.75 mg treatment group)
5) LDL cholesterol (increase from baseline levels for the 3.75 mg group)

Individual data for changes in total cholesterol and LDL cholesterol levels were examined further. Because the total cholesterol/HDL cholesterol level is a ratio which provides a more accurate assessment of cardiovascular disease risk than any single cholesterol measure alone, this ratio was calculated for study participants. Ratio values and their associated level of risk for cardiovascular disease are as follows:

<u>Chol/HDL Chol Ratio</u>	<u>Cardiovascular Risk Level</u>
< 3.2	very low
3.3-3.8	low
3.9-4.8	moderate
4.9-5.9	high
➢ 5.9	very high

Eleven patients had chol/HDL chol ratios above 3.9 following their last injection of either formulation of Lupron (serum samples were taken at the end of the last injection interval, just prior to the end of the treatment period), with the result that some of these individuals were shifted into a higher risk category for cardiovascular disease. Data for these individual patients are listed in Table #1 below.

Table #1: Baseline and Post-Initial Treatment Total Chol/HDL Chol Ratios for Study Participants Having Post-Treatment Ratios Above 3.8

Patient Number	Post-Treatment Ratio	Baseline Ratio	Change in cardiovascular risk category (new category)
	3.9	3.7	yes (moderate)
	4.4	4.2	no
	4.1	4.0	no
	3.9	4.0	no
	4.9	3.7	yes (high)
	5.7	3.7	yes (high)
	7.3	5.1	yes (very high)
	4.5*	4.8	no
	4.4	4.2	no
	4.7	4.1	no
	4.5	4.0	no

*Non-fasting blood sample

Reviewer's comments:

1) After review of the individual data related to changes in MCH, the within-group changes were not thought to be clinically significant.
2) The change in alkaline phosphatase levels post-treatment could be related to an associated decrease in bone mineral density following treatment with Lupron.
3) Of the eleven patients noted to have a post-initial-treatment cholesterol/HDL ratio above 3.8 (thereby placing them in the moderate risk category for cardiovascular disease), four had post-treatment ratios that shifted them from a lower to a higher cardiovascular disease risk category. Of these four volunteers, three were shifted to either a "high"or "very high" risk category following Lupron treatment. The change in chol/HDL chol ratio would be expected due to the decrease in estradiol levels which occurs following treatment; however, the duration of the change in risk category and the associated increased risk for cardiovascular disease following treatment with Lupron cannot be ascertained from the current study since serum chemistry measurements were not made at the end of the follow-up period.
4) While the changes in clinical chemistry parameters noted above were not determined to be clinically significant, no follow-up assessments of clinical chemistry or hematology parameters were performed at the end of the 6-month follow-up period. Thus, it is not possible to ascertain whether these parameter changes approach or return to baseline values following discontinuation of treatment.

c) Bone mineral density (BMD):

Bone mineral density of the vertebral body was measured at baseline and at the end of week 24 of the treatment period. There was a statistically significant mean percent change in BMD from baseline to the end of treatment noted for both the Lupron 3.75 mg and the Lupron 11.25 mg groups as shown in Table 1 below, but there was not a statistically significant difference between the two treatment groups in the mean percent change in BMD from baseline values.

Table 1: Mean Percent Change and Range of Percentage Change in BMD from Baseline to End-of-Treatment for Lupron 3.75 mg and Lupron 11.25 mg Treatment Groups

Treatment Group (Lupron dose)	Mean Percent Change in BMD from Baseline to End-of-Treatment	Range of Percentage Change in BMD from Baseline to End-of-Treatment
3.75 mg	-3.0%	+2.5% to -7.3%
11.25 mg	-2.8%	+0.9% to -7.3%

Reviewer's comments:

1. Although the mean percent changes in BMD following 24 weeks of treatment with either dose of Lupron was 3.0% or less, percentage loss of BMD for some individual volunteers was significantly higher than the mean percentage loss. As described below in the "6-Month-Follow-Up" Section of this review, BMD measurements for several patients in this trial did not demonstrate a trend of returning to baseline values after treatment discontinuation. These results could indicate clinically significant safety risks for certain patients receiving Lupron for the treatment of endometriosis.
2. Patient had a baseline BMD measurement less than 80% of the age-matched control value and should not have been enrolled in the study.

d) Concurrent medication use:

The majority of study participants (95% of those in the 3.75 mg treatment group and 100% of those in the 11.25 mg treatment group) took concurrent medications during the treatment period, with the most commonly used medications being analgesics, antipyretics and anti-inflammatory agents. Eighty percent of volunteers in the 3.75 mg group and 86% of volunteers in the 11.25 mg group used these specific concomitant medications.

Reviewer's comments:

Patient assessment of pain was one of the primary efficacy endpoints for this study. Although patients were asked on a monthly basis to retrospectively grade their level of pain prior to concurrent medication administration, the fact that a high percentage of patients in both treatment arms self-administered analgesics for pain control could have confounded results for this primary efficacy endpoint variable. In addition, retrospective reporting of pain experienced by volunteers is subject to recall bias.

6-Month Follow-Up

a) Patient Accountability:

Of the 41 total patients who were randomized in the treatment period of the study, 37 entered the 6-month follow-up period, seventeen of the 20 patients in the 3.75 mg treatment group and 20 of the 21 patients in the 11.25 mg treatment group. For these patients, the number of days in the post-treatment period ranged from 62 to 201 days. Completion of the follow-up period was defined as having had a 6-month post-treatment bone scan performed.

Eleven of the 37 patients who entered the follow-up period terminated this phase of the study early. An additional 3 patients prematurely terminated their trial participation during the treatment period and did not complete the 6-month follow-up period.

During the 6-month follow-up period, pregnancy was the most common reason for study termination in both treatment groups (n = 4 patients, 2 in each treatment group). Patient request to leave the study was the next most common reason sited, with 1 patient from each treatment group terminating for this reason.

Of the 4 patients who were found to be pregnant during the follow-up period, 3 of the pregnancies proceeded normally, with the patients delivering healthy newborn infants. One patient) experienced intrauterine fetal demise at 16 weeks gestation and underwent a dilation and evacuation procedure.

b) Safety Results:

i) Menses return:

Of the thirty-nine patients in the treatment period for at least 60 days (all of whom achieved suppression of menses within 60 days of starting treatment), 33 reported return to menses during the follow-up period.

Time to first post-treatment menses was defined as the number of days from the end of treatment to the start day of the first post-treatment menses. The median time to first post-treatment menses was 52 and 94 days for the 3.75 mg and 11.25 mg treatment groups, respectively.

ii) Estradiol levels:

For patients entering the follow-up period (n = 37), a single estradiol level was obtained during the 6-month follow-up period following the first post-treatment menstrual cycle in 31 patients. The mean estradiol levels in follow-up were 8.2 (+/-6.79) and 12.7 (+/-9.29) ng/dL for the 3.75 mg and 11.25 mg treatment groups, respectively.

iii) Bone mineral density:

Only BMD data that were collected 33 or more days after the end of treatment were included in the analyses of Follow-Up BMD data. A total of 23 patients had BMD scans performed at the end of 6-months of follow-up, 9 in the 3.75 mg treatment group and 14 in the 11.25 mg group.

Of the 23 patients with BMD scans performed at the end of the 6-month follow-up period, 17 (74%) had BMD measurements that were still below baseline 6-months after discontinuation of treatment. Of these 17 patients, 6 (36%) had BMD measurements that were below those obtained at the end of the treatment period (e.g., BMD at the end of the 6-month follow-up period was lower than BMD at treatment discontinuation). Five of these 6 patients were in the 11.25 mg treatment group and 1 was in the 3.75 mg treatment group. The range of percent change in BMD from end-of-treatment to end-of-follow-up was –0.1% to –1.0%. Data for these patients are summarized in Table 2 below.

Table 2: BMD Changes for Study Participants whose BMD at the end of the 6-Month Follow-Up Period was lower than that at Treatment Discontinuation

Patient Number	Treatment Group	Baseline BMD Measurement	End of Treatment BMD Measurement (% change from baseline)	6-Month Post-Treatment Measurement (% change from baseline)
	3.75 mg	1.009	1.008 (-0.1%)	1.004 (-0.5%)
	11.25 mg	1.023	1.032 (0.9%)	1.022 (-0.1%)
	11.25 mg	0.968	0.949 (-2.0%)	0.945 (-2.4%)
	11.25 mg	0.920	0.917 (-0.3%)	0.916 (-0.4%)
	11.25 mg	0.959	0.931 (-2.9%)	0.939 (-3.0%)
	11.25 mg	0.992	0.956 (-3.6%)	0.955 (-3.7%)

An assessment of underlying osteoporosis risk in these six women was performed and data are presented in Table 3 below. As seen from this data, none of these six patients would have been classified as being at increased risk for osteoporosis at enrollment.

Table 3: Summary Information on Osteoporosis Risk Factors for those Study Participants whose BMD at the end of the 6-Month Follow-Up Period was lower than that at Treatment Discontinuation

Patient Number	Race	Alcohol Use	Tobacco Use	Use of concomitant medication/s that increased osteoporosis risk	BMI
	Black	Non-drinker	Non-smoker	-	25.4
	Caucasian	Non-drinker	Non-smoker	-	22.3
	Caucasian	< 6 oz wine/day	Non-smoker	-	19.9
	Caucasian	Non-drinker	Ex-smoker	-	23.8
	Caucasian	Non-drinker	1-2 packs of cigarettes/day	-	20.7
	Caucasian	Non-drinker	Non-smoker	-	19.1

As described in the "Clinical Results-Safety" Section above, two patients (from the 3.75 mg treatment group and from the 11.25 mg treatment group) were noted to have a 7.3% loss of BMD at the end of treatment. Patient completed 6 months of follow-up and had an end-of-follow-up BMD measurement that was 3.6% below baseline, representing a trend toward returning to her baseline BMD. Patient prematurely terminated the follow-up period but had a BMD scan at 88 days post-treatment-discontinuation that was 9.5% below her baseline BMD measurement, representing a continued loss of BMD during this period.

Reviewer's comments:

1) Although the sample sizes in the follow-up period of this study are small and the changes in BMD measurements at the 6-month follow-up visit compared to baseline were not statistically significant for either treatment group, the fact that 74% of patients completing 6 months of post-treatment follow-up still had BMD measurements below baseline is of concern.
2) The fact that over one-third of patients with 6-month follow-up BMD measurements below baseline did not demonstrate either partial reversibility of BMD loss or a trend toward return to baseline BMD during the follow-up period is also of concern.

Because the changes in BMD seen in these patients from end-of-treatment to end-of-follow-up are small, the clinical significance of these findings is unclear. A more complete assessment of the effects of Lupron on BMD can only be made with longer term follow-up of these patients.

3) Of the six patients whose BMD measurements at the end of the 6-month follow-up period were lower than those at treatment discontinuation, five were in the 11.25 mg treatment group. The lack of return to baseline BMD measurements in these patients could be associated with the prolonged duration of action of this formulation as compared to that of the 3.75 mg formulation.
4) Adjustments to the text in the "PRECAUTIONS" section of the proposed labeling should be made to reflect the fact that the loss in BMD which occurs with use of Lupron may not be reversible (either partially or fully) after cessation of treatment.

Pharmacokinetic Results:

See Biopharmaceutics review.

Suggested Revisions in Proposed Labeling:

The sponsor submitted proposed "combined labeling" for both formulations of Lupron Depot® (3.75 mg and 11.25 mg doses).

Reviewers' comments:

The following revisions to the proposed labeling should be made:

1. The first sentence under the heading entitled "Endometriosis" on page 6 should have the phrase ' added to the end of the sentence.
2. Line 11 on page 6 states,

   The sponsor should change this statement to include their definition of based upon bleeding criteria only.
3. Line 10 on page 8 states,

   In order to convey clinically meaningful information to the prescribing clinician, the label should state the mean diameter of uterine fibroids before and after treatment with Lupron Depot®.
4. Item #5 on page 11 should be revised to accurately reflect changes in BMD post-treatment as follows: The term should be deleted from the first sentence, and the last phrase in the first sentence should delete the term
5. Item #6 on page 11 of the proposed should be deleted. In addition, item #6 of the "PRECAUTIONS" section of the 11.25 mg label should have the phrase ' deleted.
6. Table 3 on page 16 may be deleted.
7. On page 17, the section entitled "Changes in Bone Density" should be revised as follows:

8. On page 18, the section entitled ' ' should replace the currently listed LDL/HDL ratios with total cholesterol/HDL cholesterol ratios as these are more commonly used in clinical practice. Information in this section should include data obtained from the current phase IV study.
9. As found in the currently approved 3.75 mg label, a sub-section entitled "chemistry" should be added to both the proposed "combined label" and the 11.25 mg label under the section "Changes in Laboratory Values during Treatment", incorporating the text in the current 3.75 mg label.

Summary of Efficacy and Safety:

No statistically significant differences were noted between the Lupron 3.75 mg and the Lupron 11.25 mg groups for suppression of menses, suppression of estradiol levels and leuprolide and M-1 metabolite concentrations. There were several statistically significant differences between the two groups for clinical and patient evaluations of pain. These differences were infrequent and were not consistent over time.

The safety data presented in this submission supports the premise that the two treatment groups (Lupron 3.75 mg and Lupron 11.25 mg) were comparable with respect to the incidence of adverse events. However, detailed analysis of BMD data contained in this submission raises concerns regarding the lack of reversibility (either partial or full) of BMD loss for some patients receiving Lupron Depot for the treatment of endometriosis. The patients noted to have BMD measurements at the end of the follow-up period which were lower than those at treatment discontinuation were not at increased risk for osteoporosis at study entry based upon personal history. Thus, adjustments to the text in sections of the proposed label related to BMD changes should be made as described above in this review. The sponsor is encouraged to more fully assess the effects of Lupron therapy on BMD over time in a trial which is designed specifically with this objective in mind, rather than having changes in BMD measurements as a secondary endpoint.

/S/

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CKish
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MChen

NDA 20-708/S-005
Lupron Depot
TAP Holdings, Inc.

Safety Update Review

The Safety Update Review is included in the Medical Officers review.