

<p>In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment</p> <p>is effective in reducing loss of bone mineral density that occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis.</p>	<p>In controlled clinical studies, patients with endometriosis (six months of therapy) or uterine fibroids (three months of therapy) were treated with LUPRON DEPOT 3.75 mg. In endometriosis patients, vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. Clinical studies demonstrate that concurrent hormonal replacement therapy (norethindrone acetate 5 mg daily) and calcium supplementation to LUPRON is effective significantly reducing loss of bone mineral density that occurs with LUPRON, without compromising the efficacy of LUPRON in relieving symptoms of endometriosis.</p>
<p>LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data from these two studies are presented in Table 6.</p>	<p>LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily was evaluated in two clinical trials. The results from this regimen were similar in both studies. LUPRON DEPOT 3.75 mg was used as a control group in one study. The bone mineral density data from these two studies are presented in Table 6.</p>

Table 5 Mean Percent Change from Baseline in Bone Mineral Density

	Lupron Depot 3.75mg		Lupron Depot 3.75 mg plus norethindrone acetate 5 mg daily		Open
	Controlled Study		Controlled Study		
	N	Change	N	Change	N
Week 24 ¹	41	-3.2%	42	-0.3%	115
Week 52 ²	29	-6.3%	32	-1.0%	84

¹ Includes on-treatment measurements that fell within 2-252 days after the first day of treatment.

² Includes on-treatment measurements >252 days after the first day of treatment.

<p>When LUPRON DEPOT 3.75 mg was administered for three months in uterine fibroid patients, vertebral trabecular bone mineral density as assessed by quantitative digital radiography (QDR) revealed a mean decrease of 2.7% compared with baseline. Six months after discontinuation of therapy, a trend toward recovery was observed. Use of LUPRON DEPOT for longer than three months (uterine fibroids) or six months (endometriosis) or in the presence of other known risk factors for decreased bone mineral content may cause additional bone loss and is not recommended.</p>	
<p>Changes in Laboratory Values During Treatment</p>	
<p>Plasma Enzymes</p>	
<p><i>Endometriosis:</i> During early clinical trials with LUPRON DEPOT 3.75 mg, regular laboratory monitoring revealed that AST levels were more than twice the upper limit of normal in only one patient. There was no clinical or other laboratory evidence of abnormal liver function.</p>	<p><i>Endometriosis:</i> During early clinical trials with LUPRON DEPOT 3.75 mg, regular laboratory monitoring revealed that AST levels were more than twice the upper limit of normal in only one patient. There was no clinical or other laboratory evidence of abnormal liver function.</p>
<p><u>In two other clinical trials, 5 of 191 patients receiving LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Four of the 5 increases were observed after 6 months of treatment. None were associated with an elevated bilirubin concentration.</u></p>	<p><u>In two other clinical trials, 5 of 191 patients receiving LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily for up to 12 months developed an elevated (at least twice the upper limit of normal) SGPT or GGT. Four of the 5 increases were observed beyond 6 months of treatment and 2 of the 4 were observed at least a month after treatment discontinuation. None were associated with an elevated bilirubin concentration.</u> [Sponsor to verify if statement is correct]</p>
<p><i>Uterine Leiomyomata (Fibroids):</i> In clinical trials with LUPRON DEPOT 3.75 mg, five (3%) patients had a post-treatment transaminase value that was at least twice the baseline value and above the upper limit of the normal range. None of the laboratory increases were associated with clinical symptoms.</p>	
<p>Lipids</p>	
<p><i>Endometriosis:</i> In earlier clinical studies, 4% of the LUPRON DEPOT 3.75 mg patients and 1% of the danazol patients had total cholesterol values above the normal range at enrollment. These patients also had cholesterol values above the normal range at the end of treatment.</p>	

<p>Of those patients whose pretreatment cholesterol values were in the normal range, 7% of the LUPRON DEPOT 3.75 mg patients and 9% of the danazol patients had post-treatment values above the normal range.</p>	
<p>The mean (\pmSEM) pretreatment values for total cholesterol from all patients were 178.8 (2.9) mg/dL in the LUPRON DEPOT 3.75 mg groups and 175.3 (3.0) mg/dL in the danazol group. At the end of treatment, the mean values for total cholesterol from all patients were 193.3 mg/dL in the LUPRON DEPOT 3.75 mg group and 194.4 mg/dL in the danazol group. These increases from the pretreatment values were statistically significant ($p < 0.03$) in both groups.</p>	
<p>Triglycerides were increased above the upper limit of normal in 12% of the patients who received LUPRON DEPOT 3.75 mg and in 6% of the patients who received danazol.</p>	
<p>At the end of treatment, HDL cholesterol fractions decreased below the lower limit of the normal range in 2% of the LUPRON DEPOT 3.75 mg patients compared with 54% of those receiving danazol. LDL cholesterol fractions increased above the upper limit of the normal range in 6% of the patients receiving LUPRON DEPOT 3.75 mg compared with 23% of those receiving danazol. There was no increase in the LDL/HDL ratio in patients receiving LUPRON DEPOT 3.75 mg but there was approximately a two-fold increase in the LDL/HDL ratio in patients receiving danazol.</p>	
<p><u>In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. LUPRON DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables below.</u></p>	<p>In two other clinical trials, LUPRON DEPOT 3.75 mg plus norethindrone acetate 5 mg daily were evaluated for 12 months of treatment. <u>LUPRON DEPOT 3.75 mg was used as a control group in one study. Percent changes from baseline for serum lipids and percentages of patients with serum lipid values outside of the normal range in the two studies are summarized in the tables below.</u></p>

Table 6 Serum Lipids: Mean Percent Changes from Baseline Values At Treatment Week 24

	Lupron		Lupron plus Norethindrone Acetate		
	Controlled Study (n = 39)		Controlled Study (n = 41)		Open Label
	Baseline Value *	Week 24 % Change	Baseline Value *	Week 24 % Change	Baseline Value *
Total Cholesterol	170.5	9.2%	179.3	0.2%	181.2
HDL Cholesterol	52.4	7.4%	51.8	-18.8%	51.0
LDL Cholesterol	96.6	10.9%	101.5	14.1%	109.1
LDL/HDL RATIO	2.0**	5.0%	2.1**	43.4%	2.3**
Triglycerides	107.8	17.5%	130.2	9.5%	105.4

* mg/dL
** ratio

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data returned to pretreatment values.

Changes from baseline tended to be greater at Week 52. After treatment, mean serum lipid levels from patients with follow up data returned to pretreatment values.

Table 7 Percentage of Patients With Serum Lipid Values Outside of the Normal Range

	Lupron		Lupron plus Norethindrone Acetate		
	Controlled Study (n = 39)		Controlled Study (n = 41)		Open Label
	Wk 0	Wk 24*	Wk 0	Wk 24	Wk 0
Total Cholesterol (>240 mg/dL)	15%	23%	15%	20%	6%
HDL Cholesterol (<40 mg/dL)	15%	10%	15%	44%	15%
LDL Cholesterol (>160 mg/dL)	0%	8%	5%	7%	9%
LDL/HDL RATIO >4.0**	0%	3%	2%	15%	7%

Triglycerides(>200 mg/dL)	13%	13%	12%	10%	5%
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* Includes all patients regardless of baseline value.

** NI range not defined

<p><u>Low HDL- cholesterol (<40 mg/dL) and elevated LDL- cholesterol (> 160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore assessment of cardiovascular risk factors should be considered prior to initiation of co-treatment with Lupron and norethindrone acetate.</u></p>	<p>Low HDL- cholesterol (<40 mg/dL) and elevated LDL- cholesterol (> 160 mg/dL) are recognized risk factors for cardiovascular disease. The long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown. Therefore assessment of cardiovascular risk factors should be considered prior to initiation of concurrent treatment with Lupron and norethindrone acetate.</p>
<p><i>Uterine Leiomyomata (Fibroids):</i> In patients receiving LUPRON DEPOT 3.75 mg, mean changes in cholesterol (+11 mg/dL to +29 mg/dL), LDL cholesterol (+8 mg/dL to +22 mg/dL), HDL cholesterol (0 to +6 mg/dL), and the LDL/HDL ratio (-0.1 to +0.5) were observed across studies. In the one study in which triglycerides were determined, the mean increase from baseline was 32 mg/dL.</p>	<p></p>
<p>Other Changes</p>	<p></p>
<p><i>Endometriosis:</i> In comparative studies, the following changes were seen in approximately 5% to 8% of patients. LUPRON DEPOT 3.75 mg was associated with elevations of LDH and phosphorus, and decreases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH.</p>	<p><i>Endometriosis:</i> In comparative studies, the following changes were seen in approximately 5% to 8% of patients. LUPRON DEPOT 3.75 mg was associated with elevations of LDH and phosphorus, and decreases in WBC counts. Danazol therapy was associated with increases in hematocrit, platelet count, and LDH. <u>Lupron plus Neta was associated with elevation of SGPT and/or GGT.</u></p>
<p><i>Uterine Leiomyomata (Fibroids):</i></p>	<p></p>

<p>Hematology: (See CLINICAL STUDIES section.) In LUPRON DEPOT 3.75 mg treated patients, although there were statistically significant mean decreases in platelet counts from baseline to final visit, the last mean platelet counts were within the normal range. Decreases in total WBC count and neutrophils were observed, but were not clinically significant.</p> <p>Chemistry: Slight to moderate mean increases were noted for glucose, uric acid, BUN, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, LDH, calcium, and phosphorus. None of these increases were clinically significant.</p>	
<p>Postmarketing</p>	
<p>During postmarketing surveillance, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported</p> <p>There have been very rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of <u>development or worsening of depression during treatment with Lupron.</u></p>	<p>During postmarketing surveillance, the following adverse events were reported. Like other drugs in this class, mood swings, including depression, have been reported. There have been very rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of depression or other psychiatric illness. Patients should be counseled on the possibility of development or worsening of depression during treatment with Lupron.</p>
<p>Symptoms consistent with an anaphylactoid or asthmatic process have been rarely reported. Rash, urticaria, and photosensitivity reactions have also been reported.</p>	
<p>Localized reactions including induration and abscess have been reported at the site of injection.</p>	
<p><i>Cardiovascular System</i> - Hypotension; <i>Hemic and Lymphatic System</i> - Decreased WBC; <i>Central/Peripheral Nervous System</i> - Peripheral neuropathy, Spinal fracture/paralysis; <i>Musculoskeletal System</i> - Tenosynovitis-like symptoms; <i>Urogenital System</i> - Prostate pain.</p>	
<p>See other LUPRON DEPOT and LUPRON Injection package inserts for other events reported in different patient populations.</p>	
<p>OVERDOSAGE</p>	

<p>In rats subcutaneous administration of 250 to 500 times the recommended human dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. There is no evidence that there is a clinical counterpart of this phenomenon. In early clinical trials using daily subcutaneous leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.</p>	
<p>DOSAGE AND ADMINISTRATION</p>	
<p><i>LUPRON DEPOT Must Be Administered Under The Supervision Of A Physician.</i></p>	
<p>The recommended dose of LUPRON DEPOT is 3.75 mg, incorporated in a depot formulation. The lyophilized microspheres are to be reconstituted and administered monthly as a single intramuscular injection, in accord with the following directions:</p>	
<p>1. To prepare for injection, screw the white plunger into the end stopper until the stopper begins to turn.</p>	
<p>2. Remove and discard the tab around the base of the needle.</p>	
<p>3. Holding the syringe upright, release the diluent by SLOWLY PUSHING the plunger until the first stopper is at the blue line in the middle of the barrel.</p>	
<p>4. Gently shake the syringe to thoroughly mix the particles to form a uniform suspension. The suspension will appear milky.</p>	
<p>5. If the microspheres (particles) adhere to the stopper, tap the syringe against your finger.</p>	
<p>6. Then remove the needle guard and advance the plunger to expel the air from the syringe.</p>	

<p>7. At the time of reconstitution, inject the entire contents of the syringe intramuscularly as you would for a normal injection. The suspension settles very quickly following reconstitution; therefore, it is preferable that LUPRON DEPOT 3.75 mg be mixed and used immediately. Reshake suspension if settling occurs.</p>	
<p>Since the product does not contain a preservative, the suspension should be discarded if not used immediately.</p>	
<p><i>Endometriosis:</i> The recommended duration of <u>treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate</u> is six months.</p>	<p><i>Endometriosis:</i> The recommended duration of treatment with LUPRON DEPOT 3.75 mg alone or in combination with norethindrone acetate is six months.</p>
<p><u>The choice of Lupron alone or Lupron plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to Lupron alone.</u></p>	<p>The choice of Lupron alone or Lupron plus norethindrone acetate therapy for initial management of the symptoms and signs of endometriosis should be made by the health care professional in consultation with the patient and should take into consideration the risks and benefits of the addition of norethindrone to Lupron alone.</p>
<p><u>If the symptoms of endometriosis recur after _____ completion of therapy, _____ retreatment with a single six-month course of LUPRON DEPOT and norethindrone acetate 5 mg daily is may be considered. _____ it is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits.</u></p> <p><u>Lupron Depot alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.</u></p>	<p>If the symptoms of endometriosis recur after a course of therapy, retreatment with a _____ six-month course of LUPRON DEPOT <u>monthly</u> and norethindrone acetate 5 mg daily may be considered. It is recommended that bone density be assessed before retreatment begins to ensure that values are within normal limits. Lupron Depot alone is not recommended for retreatment. If norethindrone acetate is contraindicated for the individual patient, then retreatment is not recommended.</p> <p><u>[Sponsor to propose revised wording for paragraph]</u></p>
<p><u>An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with Lupron and norethindrone acetate.</u></p>	<p>An assessment of cardiovascular risk and management of risk factors such as cigarette smoking is recommended before beginning treatment with Lupron and norethindrone acetate.</p>

<p><i>Uterine Leiomyomata (Fibroids):</i> Recommended duration of therapy with LUPRON DEPOT 3.75 mg is up to 3 months. The symptoms associated with uterine leiomyomata will recur following discontinuation of therapy. If additional treatment with LUPRON DEPOT 3.75 mg is contemplated, bone density should be assessed prior to initiation of therapy to ensure that values are within normal limits.</p>	
<p>As with other drugs administered by injection, the injection site should be varied periodically.</p>	
<p>HOW SUPPLIED</p>	
<p>LUPRON DEPOT 3.75 mg is packaged as follows:</p>	
<p>Kit with prefilled dual chamber syringe NDC 0300-3641-01</p>	
<p>Each syringe contains sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable copolymer of lactic and glycolic acids. When mixed with diluent, LUPRON DEPOT 3.75 mg is administered as a single monthly IM injection.</p>	
<p>Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]</p>	
<p>Rx only</p>	
<p>REFERENCE</p>	
<p>1. MacLeod TL, et al. Anaphylactic reaction to synthetic luteinizing hormone-releasing hormone. <i>Fertil Steril</i> 1987 Sept; 48(3):500-502.</p>	<p>+</p>
<p>U.S. Patent Nos. 4,652,441; 4,677,191; 4,728,721; 4,849,228; 4,917,893; 4,954,298; 5,330,767; 5,476,663; 5,575,987; 5,631,020; 5,631,021; and 5,716,640.</p>	
	
<p>Manufactured for TAP Pharmaceuticals Inc. Lake Forest, IL 60045, U.S.A. by Takeda Chemical Industries, Ltd. Osaka, JAPAN 541</p>	
<p>® — Registered Trademark</p>	

(No. 3641)

OX-XXXX-RXX; Revised: Month, Year

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Inc.

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NDA's 20-011, 20-708
Meeting Minutes
Page 34

cc:
Original NDA
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Monroe
drafted: JAB/September 20, 2001/N20011S21Tcon091901.doc
concurrence: Hixon, 09.21.01/Monreo, 09.21.01
final: JAB/ September 21, 2001
MEETING MINUTES

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MEMORANDUM OF TELECON

DATE: August 30, 2001

APPLICATION NUMBER: 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: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Clinical Information Request: Please provide the following new analyses for Studies M92-878 and M97-777

1. Change in weight listing:

Please prepare separate listing for each of the 3 treatment groups for the change in each patient's weight for the intervals from (1) baseline to the Week 24 Visit and (2) baseline to the Final Treatment Visit. Each listing should include (a) patient number, (b) patient's baseline weight, and (c) the change in weight from baseline to either the Week 24 Visit or the Final Treatment Visit as appropriate. Please format each listing so that patients are listed by change in weight (decreasing order). Altogether, there should be 6 separate listings.

2. Change in weight at the Week 24 Visit:

Please provide the n, mean (SD), median, maximum, and minimum values for the changes in patient weight at the Week 24 Visit for each treatment group.

3. New cross tabulation tables for serum lipids:

Please prepare 6 new cross tabulation tables for serum lipids following the format previously used. These tables should be based on the patients represented in ISS Tables 1.40, 3.11, and 4.33. For each treatment group please prepare 2 tables representing (a) change from baseline to the Week 24 Visit and (b) change from baseline to the Final Treatment Visit. These Tables will differ from those previously provided in that some of the limits for the normal range will be based on recent guidelines for serum lipid levels as recommended by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults in JAMA 2001; 285(19): 2486-2497.

Please use the following values for the lower and upper limits of the normal range in the new tables.

Measurement	Lower Limit	Upper limit
Total cholesterol	Lab normal*	240
LDL-cholesterol	Lab normal	160
HDL-cholesterol	40	Lab normal
Triglycerides	Lab normal	200
LDL/HDL ratio No. 1	None	4.0
LDL/HDL ratio No. 2	None	5.0

* The limit provided by the reference laboratory

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Jeanine Best, MSN, RN
Senior Regulatory Associate

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/s/

Jeanine Best
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NDA 20-011 and 20-708
Page 3

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

Drafted by: JAB/August 30, 2001
Final: JAB/August 30, 2001

TELECON

**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: August 17, 2001

APPLICATION NUMBER: 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: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Clinical Information Request: Request for Additional Information

Please respond to the following questions.

1. Norethindrone acetate (NETA) is not approved for the prevention or treatment of osteoporosis. Please provide information that changes in bone mineral density (BMD) resulting from treatment with NETA correlate with changes in bone strength. Such evidence might consist of preclinical or clinical data or published scientific reports that treatment with NETA is associated with a reduced incidence of fractures (not merely changes in BMD) or that bone strength in ovariectomized rats is increased following treatment with NETA.
2. Do you have data that indicate that a lower dose of NETA (i.e., 2.5 mg per day) would not be efficacious in preventing the decrease in BMD observed during treatment with Lupron?
3. In your submission of November 2000, you included 3 labels – the “approved” label, the “current” label, and the proposed label. What is the difference between the approved and the current labels?
4. Is there any information included the Submission of March 21, 2001 (incomplete post-treatment Study Report for Study M97-777) that is not included in the complete post-treatment Study Report for Study M97-777 submitted in June 2001. If so, please identify or direct us to that information.
5. In you proposed label, you state the following: “In the hormonal add-back studies single occurrences of anemia, bilirubinemia, and a urine abnormality were noted.” What is the urine abnormality to which you are referring? Which patient experienced this abnormality?

6. Five patients in the Lupron plus NETA treatment groups and no patient in the Lupron alone group reported breast discharge or galactorrhea as an adverse event. The patients reporting these adverse events were Pts 1108 and 1158 in Study M92-878 and Pts 2204, 2208, and 3204 in Study M97-777. At least one of these patients was treated with Parlodel. Please provide any additional information, not already provided in the adverse event listings, that you have regarding these patients. Actual serum prolactin levels and any radiographic assessments of the pituitary gland (i.e., CT scans) would be particularly helpful. Please comment on each of these patients and the lack of balance between the treatment arms concerning the occurrence of these adverse events.

7. Three patients had a renal calculus – Pts 1905 and 1701 in the Study M97-777 and Pt 1233 in Study M92-878. Please comment on these patients and the possible association of these adverse events with Lupron treatment for one year (with or without NETA). The incidence of renal calculi appears to be higher than expected in a group of healthy young women.

{See appended electronic signature page}

Jeanine Best, MSN, RN
Regulatory Project Manager

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Jeanine Best
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Page 01

NDA's 20-011 and 20-708
Page 3

cc:

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

Drafted by: JAB/August 17, 2001
Final: JAB/August 17, 2001

TELECON

**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: July 27, 2001

APPLICATION NUMBER: 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: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Clinical Information Request: Request for New Efficacy Analyses and New Information

New Efficacy Analyses

1. Please analyze the post treatment clinical efficacy data from Studies M92-878 and M97-777 by the same analysis as was used for Figure 1 in the current label for Lupron.
2. Please perform the standard efficacy analyses for the subset of patients treated with Lupron plus norethindrone acetate stratified by prior treatment with a GnRH analog or no prior treatment with a GnRH analog. Based on Listing 16.2_7.5 (Study M92-878) and Listing 16.2_7.1.4 (Study M97-777), 39 women who were treated with Lupron plus norethindrone received prior GnRH treatment. Terms used in these listings to identify prior GnRH therapy are Lupron, Lupron Depot, Depo-Lupron, Lupron Injection, Synarel, and Synalar. (In Study M97-777, the term "Synalar" appears to have been incorrectly used to represent Synarel treatment for Patients 404, 2401, and 3003). Please conduct a separate analysis for the patients from each Study as well as a combined analysis. Please perform the analyses that were used in Statistical Tables 1.11 through 1.20 in the ISE (or modifications of these analyses that you believe would be appropriate considering the imbalance of sample sizes) and any additional analyses that you believe would be appropriate.

Regulatory Questions

1. Has a one-year Lupron treatment period for endometriosis received marketing approval in any country to date? If so, please provide copies of the approved label from the two countries with the largest sales.
2. Is a one-year Lupron treatment period for endometriosis under review for marketing in any other country or have any such applications not received approval?

NDA's 20-011 and 20-708

Page 2

3. Is retreatment (with or without add back therapy) approved in any country in which Lupron is currently marketed? If so, please provide the approved labeling from the two markets with the largest sales.

{See appended electronic signature page}

Jeanine Best, MSN, RN
Regulatory Project Manager

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NDA 20-011 and 20-708
Page 3

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

Drafted by: JAB/July 27, 2001
Final: JAB/July 27, 2001
Filename: _____

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Scott Monroe
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Teleconference Meeting Minutes

Date: July 27, 2001

Time: 11:00-11:30 AM

Location: Parklawn; 17B-43

NDA's 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: Clinical Information Request

Meeting Chair: Scott Monroe, M.D.

External Lead: Aruna Dabholkar, M.D.

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

FDA Attendees:

Scott Monroe, M.D., Medical Officer, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

TAP Pharmaceutical Products, Inc.

Karl Agre, M.D., Ph.D., Senior Medical Director

Robert Browneller, Assistant Director, Clinical Development

Linda Frederick, Statistician

Dennis Jennings, Ph.D., Director of Statistics

Aruna Dabholkar, Associate Director, Regulatory Affairs

Meeting Objective: To discuss the sponsor's proposal for labeling for 12 months treatment with Lupron plus NETA add-back versus six months of treatment with a provision for retreatment for return of symptoms.

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 as hormonal add-back therapy to reduce bone loss in Lupron-treated women with endometriosis.

Discussion:

- the Division referred to Figure 1 that is in the current and proposed Lupron labeling; this Figure shows good continuation of symptomatic relief for up to one year for 4 of 5 (except dysmenorrhea) symptoms in the majority of women after six months of treatment; the Division asked the sponsor to provide a rationale for treating all women for greater than six months if it is not necessary for many

women; the sponsor responded that their trials were designed for 12 months of treatment and there is no safety risk involved with this treatment; the sponsor was asked to provide the identical analysis concerning recurrence of symptoms that appears in Figure 1 for the data that forms the basis of these applications

- the Division is not aware of data that demonstrates that non-responders after six months of treatment will respond if further treatment is given; the efficacy response tends to occur early in treatment; the Division also does not believe that the relapse rate will be different after six or 12 months of treatment; the Agency's stance is to avoid use of therapies if not indicated or necessary
- the Division asked the sponsor to provide rationale for the selection of the 5 mg NETA dose for hormonal add-back; the lipid and androgenic effects associated with NETA are dose related, and possibly, a lower dose would be equally effective in protecting bone mineral density; the sponsor responded that the dose selection of 5 mg of NETA was mainly a logistical choice for clinical trial use (a scored 5 mg tablet is currently marketed), and not a scientific based choice
- both the Division and the sponsor suggested that possibly labeling could address the issue of length of treatment but that the studies did not directly address the issue of retreatment or the issue of hormonal add-back with retreatment

Decisions:

- the Division will continue its review of (1) the safety of 12 months of treatment with Lupron plus NETA and (2) the benefit of 12 months of treatment instead of 6 months of treatment

Action Items:

- S. Monroe will request additional clinical information via fax by close of business today
- 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.

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/s/

Scott Monroe
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NDA 20-011/S-021/20-708/S-011
Page 3

cc:
Original NDA
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Monroe

concurrency: Monroe, 07.27.01
final: JAB/August 7, 2001

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELECON

DATE: July 26, 2001

APPLICATION NUMBER: 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: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Clinical Information Request: Request for Modified and New Safety Analyses

Laboratory Safety Data

1. Please provide modified summary tables of the laboratory safety data for both treatment arms in Study M92-878, and the single treatment arm in Study M97-777. The tables should summarize the laboratory data using simple descriptive statistics and not model based statistics. For each visit represented in the tables, include (1) the number of patients (n), and the mean (SD), median, minimum, and maximum values, (2) the number of patients and the values for the mean (SD) and median changes from baseline, and (3) the significance (p-value) of the within group changes from baseline. The tables should include both on-treatment and post treatment visits, namely, Baseline, Week 24, Week 52, Final Treatment Visit, and Post-Treatment Visits. The analyses should be similar to those used to prepare Statistical Table 2.16 in the ISS with the additional descriptive statistics listed above.
2. The purpose of this analysis is to determine the changes in laboratory test values after the Week 24 measurement. Please provide new summary tables of the laboratory safety data for both treatment arms in Study M92-878 and the single treatment arm in Study M97-777 that will include data for all patients with Week 52 measurements and/or a final on-treatment measurement that is later than the Week 24 measurement. Visits to be represented in the table will be ~~Week 24~~, Week 52, and Final Treatment Visit. For each visit represented in the Table include (1) the number of patients (n), and the mean (SD), median, minimum, and maximum values, (2) the number of patients and the values for the mean (SD) and median changes from Week 24, and (3) the significance (p-value) of the within group changes from Week 24.
3. Please provide modified "cross-tabulation or shift tables" for Statistical Tables 1.40, 3.11, and 4.33 in the ISS. For the study/data represented in each table, please prepare separate tables for the following analyses (1) shift from baseline to Week 52, and (2) shift from Week

24 to Final Treatment Visit for patients having a Week 52 Visit or a Final Treatment Visit later than the Week 24 Visit.

4. Please provide a modified analysis of the data represented in Statistical Table 1.43 (vital signs and body weight) of the ISS. In the modified analysis, please do not use model based statistical procedures but rather, descriptive procedures for each treatment group similar to those used for Statistical Table 2.17.
5. Please document the basis for the normal range values for LDL-cholesterol, HDL-cholesterol, and triglycerides that were used in Study M92-878. The Laboratory Reports from the Reference Lab () lists the upper limit of normal of 200 ng/dL for triglycerides (not 499), the lower limit of the desirable range for HDL-cholesterol for women as 45 ng/dL (not 33), and no value for upper normal range for LDL-cholesterol. These limits were used to generate the "cross-tabulation tables" referred to in Item 3 above.

Adverse Event Data

1. The purpose of this analysis is to determine (1) the proportion of patients that experienced adverse events with an onset during the first 24 weeks of treatment and (2) the proportion of patients that experience adverse events with an onset after Week 24. Please prepare modified adverse event summary tables for (1) all adverse events, (2) treatment-related (definite, probable, possible, and unknown) adverse events, and (3) serious adverse events for both Study M92-878 and Study M97-777 similar in presentation to Tables 1.6-1.8 and 3.2-3.4 in the ISS. For each study and each of the 3 types of adverse event listings, please summarize the adverse events in terms of those with an onset date between Day 1 and Day 168 and those with an on-treatment onset date after Day 168. The tables should list (1) the number of patients experiencing adverse event using the same Costart terms as previously used in the ISS, (2) the percentage of patients experiencing the respective adverse event based on the number of at risk patients in each of the treatment periods, and (3) the number of patients experiencing the respective adverse event divided by the number of patient treatment months (28 day periods) represented in the respective treatment interval.

Bone Density Data

1. Please prepare modified summary tables for changes in bone mineral density (BMD) based on the data represented in Statistical Tables 1.30, 1.31, 1.32, and 1.34 in the ISS. In the modified tables the mean values, changes from baseline, and statistical significance of each of the intragroup changes from baseline should be calculated using procedures similar to those used to generate Statistical Table 2.7 in the ISS (i.e., non model based calculations).
2. For Study M97-777, please merge the BMD Statistical Tables from the Treatment and Post-Treatment Periods (Statistical Table 14.3.7_2 from the Treatment Period Report) and Statistical Table 14.3_7.2.1 from the Post-Treatment Report). The final table should resemble BMD Statistical Table 14.3.7_5 in the M92-878 Final Report.

3. We would like to compare baseline BMD values and changes from baseline BMD values in women who were previously treated with a GnRH analog to values in women who previously were not treated with a GnRH analog. Based on Listing 16.2_7.5 (Study M92-878) and Listing 16.2_7.1.4 (Study M97-777), approximately 40 women who were treated with Lupron plus norethindrone received prior GnRH treatment. Terms used in these listings to identify prior GnRH therapy are Lupron, Lupron Depot, Depo-Lupron, Lupron Injection, Synarel, and Synalar. (In Study M97-777, the term "Synalar" appears to have been incorrectly used to represent Synarel treatment for Patients 404, 2401, and 3003). Please perform the analyses represented in Statistical Tables 4.17, 4.18, 4.19, and 4.20, stratifying patients treated with Lupron plus norethindrone by those who did and those who did not have prior treatment with a GnRH analog instead of stratification by age. Also perform the same analyses represented in Statistical Tables 4.23, 4.24, and 4.25 comparing BMD changes in Lupron plus norethindrone-treated patients who did and who did not have prior GnRH treatment (instead of comparing LD/N to LD-Only).

{See appended electronic signature page}

Jeanine Best, MSN, RN
Regulatory Project Manager

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/s/

Jeanine Best
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**APPEARS THIS WAY
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MEMORANDUM OF TELECON

DATE: July 13, 2001

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

BETWEEN:

Name: Jessie Lee, Ph.D.
Phone: (847) 267-4924
Representing: TAP Pharmaceutical Products, Inc.

AND

Name: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products

SUBJECT: Clinical Information Request

1. Please provide all four volumes of the June 20, 2001, Safety Update. Only Volume 1 of 4 was received.
2. Please provide a marked-up proposed label that shows proposed revisions to the last approved label.

Please provide the following information as in Microsoft Word (Office 97 format). The information is to include both text and tables that were included in the narrative sections of the reports. The first 5 items refer to the November 21, 2000 submission. Item 6 refers to the second Safety Update submitted on June 21, 2001.

1. ISS. Vol. 16, pg. 1-120.
2. ISE. Vol. 22, pg. 1-81.
3. Overview of Clinical Studies. Vol. 3, pg. 1-148.
4. Final Report for Study M92-878, Vol. 5, pg. 1-181.
5. Final Report for the Treatment Phase of Study M97-777, Vol. 11, pg. 1-165.
6. Final Report for the Posttreatment Phase of Study M97-777, pg. 1-129.

Jeanine Best, MSN, RN
Regulatory Project Manager

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/s/

Jeanine Best
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cc:

Archival NDA 20-011/20-708

HFD-580/Division Files

HFD-580/Monroe

Drafted by: JAB/July 13, 2001

Final: JAB/July 13, 2001

TELECON

**APPEARS THIS WAY
ON ORIGINAL**

Teleconference Meeting Minutes

Date: July 11, 2000

Time: 1:00-1:30 PM

Location: Parklawn; 17B-43

IND — Drug: Lupron Depot 3.75 mg (leuprolide acetate for depot suspension) with Aygestin (norethindrone acetate) 5 mg

Indication: Endometriosis

Sponsor: TAP Pharmaceuticals Products, Inc.

Type of Meeting: Pre-SNDA

Meeting Chair: Dr. Susan Allen

External Lead: Dean Sundberg

Meeting Recorder: Jeanine Best

FDA Attendees:

Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Marianne Mann, M.D, Deputy Director, DRUDP (HFD-580)

Dan Shames, M.D., Team Leader, DRUDP (HFD-580)

Jerry Willett, M.D., Team Leader, DRUDP (HFD-580)

Scott Monroe, M.D., Medical Officer, DRUDP (HFD-580)

Kate Meaker, M.S., Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants:

TAP Pharmaceutical Products, Inc.

Dean Sundberg, Director, Regulatory Affairs

Aruna Dabholkar, Associate Director, regulatory Affairs

Robert Browneller, Associate Director, Clinical Development

Linda Frederick, Statistics

James Lancaster, Statistics

Sarah Khalil, Regulatory Affairs

Dennis Jennings, Director, Statistics and Data Management

Meeting Objective: To discuss the issues submitted for discussion in the Pre-SNDA Meeting Package

Background: The sponsor submitted an Efficacy Supplement (S-012) on February 12, 1997 to change the Lupron label to extend product usage to twelve months with the addition of norethindrone acetate as hormonal add-back therapy to reduce bone loss in Lupron-treated women with endometriosis. The sponsor conducted a Phase 4, double-blind, randomized, parallel-group, multicenter study lasting one year with a two-year, treatment-free, follow-up period, involving four treatment arms, three with hormonal add-back therapy; all add-back treatments demonstrated less BMD loss than the Lupron alone treatment. The Division sent a refuse to file (RTF) letter for this supplement on April 4, 1997 because there was no dose-ranging study performed by the sponsor for NET and the sample size was too small to adequately evaluate safety and efficacy of Lupron plus NET since NET had not previously been approved for prevention of loss of bone mineral density (BMD). The sponsor then conducted an open-label, single-arm, multi-center study to replicate the results from one of the treatment arms (5 mg norethindrone acetate + Lupron) in the previous study.

Discussion:

Questions:

1. We believe that the second add-back study (M97-777) meets the criteria set a priori. Do you concur?

Answer:

- the study appears acceptable; data appears to support fileability; however, this will be a review issue when NDA is received
 - sponsor to provide evidence of quality control program for BMD data and documentation that shows standards are acceptable today. The sponsor reported that all bone density measurements were measurements of the spine alone
2. If the final results are similar to the data submitted in the briefing document, are they adequate to support the proposed changes to the Package inserts?

Answer:

- the actual labeling will be a review issue
 - the present label shows that six months of treatment with Lupron for endometriosis demonstrates long-term benefit in many patients
 - sponsor should consider labeling to recommend retreatment in patients with recurrent symptoms following 6 months of treatment, rather than a priori recommendation of one year of treatment since 5 mg norethindrone acetate has negative effects on lipid profile
3. Appendix A describes comparisons to be made and statistical methods to be used in the individual study summaries and integrated reports. Are these adequate?

Answer:

- sponsor should provide separate study reports rather than combining data from different studies
 - how the data is presented in the label will be a review issue
 - compare six-month BMD results for completers and dropouts.
4. Are the content and format of the Electronic Submission as described in SNDA Content and Format section acceptable?

Answer:

- yes

5. Case Report forms will be submitted electronically only (no paper copy) as per electronic submission guidelines. Is this acceptable?

Answer:

- yes

6. As described in the section of SNDA Content and Format, datasets of efficacy, certain demographic variables and bone mineral density will be provided as individual SAS transport files. Is this adequate?

Answer:

- Yes, also submit safety data in this fashion, e.g., lipid data and vasomotor symptoms

7. Is it acceptable to submit only data listings (no Case Report Tabulations) in SAS transport data file format? The data listings will completely display all relevant data as would be displayed in the Case Report Tabulations.

Answer:

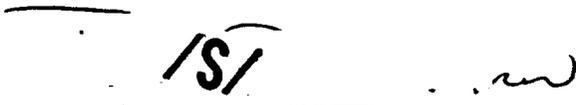
- yes

Decisions made:

- information presented in the Meeting Package would appear to support fileability of SNDA
- if sponsor is co-packaging the drug products, then a new NDA will be required instead of a supplement
- sponsor plans to submit SNDA in November 2000

Action Items:

- Meeting Minutes to sponsor within 30 days



Minutes Preparer



Concurrency, 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.

IND
Meeting Minutes
Page 4

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Allen/Mann/Shames/Willett/Monroe/Meaker/Rumble

concurrence: Meaker,07.11.00/Willett,07.11.00/Rumble,07.11.00/Mann,07.12.00/Monroe,07.12.00/
Allen,07.24.00
final: JAB/July 25, 2000

MEETING MINUTES

**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.**

Advisory Committee Meeting-NA .

✓ + /S/ 3/21/01

**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.

Federal Register Notice-NA .

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**APPEARS THIS WAY
ON ORIGINAL**

Group Leader Memorandum
NDA 20-011/S-021
NDA 20-708/S-011

Drug	Lupron Depot 3.75 mg Lupron Depot-3 Month 11.25 mg
Generic Drug Name	Leuprolide acetate for depot suspension
Dose	3.75 mg IM monthly (q 28 days) 11.25 mg IM q 3 months
Indication	Management of endometriosis
Applicant	TAP Pharmaceutical Products 675 North Field Drive Lake Forrest., IL 60045
Date of Submission	November 21, 2000
Date of Memorandum	September 21, 2001
Reviewer	Dena R. Hixon, M.D., FACOG Team Leader, DRUDP

Summary

Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are currently approved for 6 months of therapy for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Re-treatment or treatment for longer than 6 months is not recommended because of hypoestrogenic side effects, including reduction in bone mineral density (BMD), associated with Lupron therapy. The progestin norethindrone acetate (NETA) is also approved for the treatment of endometriosis in escalating doses from 5 to 15 mg/day for a duration up to 6 to 9 months. The data presented for these NDA efficacy supplements are sufficient to support treatment with 5 mg NETA daily during Lupron therapy to reduce the drug-induced loss of BMD and hot flashes without reducing the efficacy of Lupron for management of endometriosis. The data are not sufficient to demonstrate a meaningful additional benefit of extending therapy to 12 months compared to the approved 6 months duration of therapy. However, with concomitant NETA therapy, Lupron can be safely used for a single 6-month re-treatment following an initial 6-month treatment period in women who experience a return of symptoms after completion of treatment.

Background

Endometriosis is a common gynecologic disorder, occurring in up to 10% of women of reproductive age. It is defined by functioning endometrial tissue outside of the uterus, and the most common symptoms are dysmenorrhea, chronic pelvic pain unrelated to menses, and/or dyspareunia. It may also be associated with infertility. A definitive diagnosis can be made only by surgical visualization of the pelvic and abdominal organs, usually with laparoscopy. Although the clinical presentation of the disease may to some degree be related to the anatomic location and extent of the disease, the severity of symptoms is often disproportionate to the extent of visible lesions. Endometriosis is usually estrogen-dependent and is rarely present after menopause. Current therapies include surgical ablation, analgesics, hormonal therapies such as combination hormonal contraceptives, progestins (including NETA), or danazol, and gonadotropin releasing hormone (GnRH) agonists such as leuprolide acetate.

The goal of therapy with GnRH agonists in the treatment of endometriosis is to create a hypoestrogenic state similar to menopause, resulting in atrophic changes in the ectopic endometrial tissue and subsequent relief of symptoms. Suppression of menses and relief of pain symptoms are usually seen during the first month of treatment and may continue for many months after completion of 6 months of treatment. The

hypoestrogenic environment produced by GnRH agonists results in significant side effects including vasomotor symptoms and a loss of bone mineral density (BMD). Although clinically significant events are not known to occur with therapy of 6 months duration or less, there is concern that a longer courses of therapy could lead to clinically significant effects. Therefore, the approved duration of treatment with GnRH agonists for endometriosis is currently limited to 6 months, and re-treatment is generally not recommended. There are some patients who experience recurrence of symptoms after completion of therapy and may benefit from re-treatment. Previous studies have suggested that the hypoestrogenic side effects may be prevented or reduced by the co-administration of "add-back" hormonal therapy with estrogens and/or progestins.

Regulatory History

Lupron Depot 3.75 mg (NDA 20-011) was approved in October 1990 for the treatment of endometriosis (for 6 months) and in March 1995 for the pre-operative treatment of anemia associated with leiomyomata uteri (for up to 3 months). Lupron Depot-3 Month 11.25 mg (NDA 20-708) was approved for both indications in March 1997 based upon a single open-label uncontrolled pharmacokinetic/pharmacodynamic study of a single administration of the 3-month depot formulation in 20 healthy female subjects and historical comparisons to the marketed 1-month depot formulation regarding reduction of estradiol concentrations and menstrual suppression.

TAP submitted an efficacy supplement to NDA 20-011 in 1996 to allow for treatment of endometriosis with Lupron for up to 1 year, and for re-treatment, with the addition of norethindrone acetate (NETA) 5 mg daily. The Division of Reproductive and Urologic Drug Products refused to file the application because it was based upon a single study (M92-878) and adequate dose ranging data were not provided for the add-back hormone therapies for either a progestin alone or progestin plus estrogen.

DRUDP requested that the sponsor conduct a second study to confirm that add-back therapy reduced the degree of BMD loss during 1 year of treatment with Lupron. Study protocol M97-777 was submitted in December 1997, and a successful outcome for reducing or preventing bone loss was set as a decrease in BMD from baseline at one year of treatment of no greater than -2.2% for the lower bound of a 2-sided 95% CI. The sponsor selected the 5 mg marketed dose of NETA, which is the lowest recommended dose for treatment of endometriosis and the smallest marketed dosage unit. As noted in the minutes of a September 22, 1997 teleconference with the sponsor, the agency did not require dose-ranging studies for norethindrone acetate as add-back therapy.

The sponsor also submitted another NDA supplement in 1997 that was approved in 1998, adding the following information to the labeling as a safety consideration:

"A controlled study in endometriosis patients showed that vertebral bone density as measured by dual energy x-ray absorptiometry (DEXA) decreased by an average of 3.2% at six months compared with the pretreatment value. In this same study, Lupron Depot 3.75 mg alone and Lupron Depot 3.75 mg plus three different hormonal add-back regimens were compared for one year. All add-back groups demonstrated mean changes in bone mineral density of $\leq 1\%$ from baseline and showed statistically significantly (P-value <0.001) less loss of bone density than the group treated with Lupron Depot 3.75 mg alone, at all time points. 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."

Efficacy

The sponsor presents results of the two U.S. clinical trials discussed below, in which women with painful symptoms of endometriosis were treated with Lupron Depot 3.75 mg either alone or in combination with hormonal add-back therapy. Calcium supplementation was administered to participants in all study groups. Whereas Lupron Depot-3 Month 11.25 mg was approved on the basis of bioequivalence to Lupron Depot 3.75 mg, no clinical studies were performed with the 3 Month formulation for the current efficacy supplement.

Reviewer's comment

Although bioequivalence has been shown between the two formulations in a single, open-label uncontrolled pharmacokinetic/pharmacodynamic study of a single administration of the 3-month depot formulation, it is likely that the hypoestrogenic effects may continue longer after each 3-month injection than after 3 monthly injections of Lupron Depot. In a Phase IV study comparing the two depot formulations of Lupron, 5 patients treated with the 3-month formulation and one patient treated with the 1-month formulation had BMD measurements after 6 months of follow-up that were lower than the final measurements at the end of 6 months of treatment. The differences were small and could be consistent with the range of error in the method of detection or could be due to a prolonged hypoestrogenic effect of the 3-month formulation. The findings of the Phase IV study and the demonstrated bioequivalence of the two formulations, along with the data presented in the current efficacy supplement, are adequate to support 6 months of co-treatment with either formulation of Lupron and NETA. However, additional clinical trials with both formulations would be needed before consideration could be given to extending treatment beyond 6 months.

In each of the 2 studies, the primary efficacy assessments were based on the patient's and/or investigator's assessment of each of 5 symptoms or signs of endometriosis, dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration. Each symptom or sign was assigned a numeric score of 1 (not present), 2 (mild), 3 (moderate), or 4 (severe). The total numeric score was referred to as the symptom severity score. The primary efficacy endpoints were the improvement from baseline for each of the 5 symptoms or signs of endometriosis.

Study M92-878

This was a double-blind, randomized, 4-arm, parallel group, multi-center study conducted from November 1993 to December 1997 to determine the safety and efficacy of 1 year of treatment of women with endometriosis with 1) Lupron Depot 3.75 mg alone, 2) Lupron plus NETA 5 mg daily 3) Lupron plus NETA plus 0.625 mg conjugated estrogens, or 4)) Lupron plus NETA plus 1.25mg conjugated estrogens. Total enrollment was 201 women, randomized 1:1:1:1 to the 4 treatment arms. This review focuses on the Lupron alone and Lupron/NETA arms because the current efficacy supplements do not address the safety or effectiveness of estrogen therapy.

The mean AFS total endometriosis score was 15.7 for the Lupron-only group, and 9.8 for the Lupron/NETA arm. However, it is commonly recognized that AFS scores do not correlate well with severity of endometriosis symptoms and signs. The proportions of women in the two groups experiencing each of the 5 symptoms and signs of endometriosis was similar at baseline. The mean baseline scores for each sign and symptom were also similar in both groups except for a statistically higher score for pelvic induration for the Lupron alone group (1.9) compared to the Lupron/NETA group (1.6). Of the 51 women in the Lupron-alone arm, 32 (63%) completed 1 year of treatment, and 14 (27%) completed 1 year of follow-up. Only 4 women completed the entire 24 months of follow-up. Of the 55 women in the Lupron/NETA arm, 31 (56%) completed 1 year of treatment, and 10 (20%) completed 1 year of follow-up. Six women completed 24 months of follow-up.

The proportion of patients with each of the 5 symptoms or signs of endometriosis decreased significantly from baseline to week 24 and from baseline to week 52 in both the Lupron alone and Lupron/NETA group with no significant difference between treatments. There were smaller declines in the proportion of patients with each of the symptoms from week 24 to week 52. The decline in mean scores for each of the 5 symptoms and signs from baseline to week 24 and from baseline to week 52 was also statistically and clinically significant with no significant difference between treatments. The change from week 24 to week 52 was small and of doubtful clinical significance (0 and -0.04 for dysmenorrhea, -0.1 and -0.3 for pelvic pain, -0.29 and -0.22 for dyspareunia, -0.23 and +0.08 for pelvic tenderness, and 0 and 0 for pelvic induration in the Lupron alone group and Lupron/NETA group, respectively.) The percent of patients with each symptom at baseline who had improved clinical pain scores at their final treatment visit in the Lupron and Lupron/NETA groups respectively was 96 and 100% for dysmenorrhea, 66 and 73% for pelvic pain, 71% in both groups for dyspareunia, 75 and 83% for pelvic tenderness, and 88 and 79% for pelvic induration. The difference between treatments was not significant.

During the follow-up period, the mean and median number of months until the return to baseline pain severity was consistently longer for successful completers than for the group of all patients treated. In the Lupron alone group, the median for successful completers was 8 months for return of dysmenorrhea, pelvic pain, and pelvic tenderness, 12 months for deep dyspareunia, and 16 months for pelvic induration. For the group of all patients treated, the median was 1 month for deep dyspareunia, 2 months for pelvic tenderness, 3 months for pelvic pain, 4 months for dysmenorrhea, and 12 months for pelvic induration. For successful completers in the Lupron/NETA group, the median time for return to baseline pain severity was 4 months for dysmenorrhea, 8 months for pelvic induration, and 12 months for pelvic pain, deep dyspareunia, and pelvic tenderness. For the group of all patients treated, the medians were 2 months for deep dyspareunia, 4 months for dysmenorrhea, and 8 months for pelvic pain, pelvic tenderness, and pelvic induration.

Clinical pain scores were significantly lower at month 12 of follow-up than at baseline for all 5 signs and symptoms with no consistent differences between treatment groups.

Study M97-777

This was an open-label, single-arm multi-center study conducted from February 1998 to March 2000 to evaluate the safety and efficacy of Lupron Depot 3.75 mg in combination with norethindrone acetate 5 mg daily for one year for the management of endometriosis and to increase the number of women who were studied with this treatment regimen. Enrollment was 136 women, with 82 (60%) completing 1 year of treatment and 64 (47%) completing 1 year of follow-up. The baseline mean AFS total endometriosis score was 18.4.

The proportion of patients with each of the 5 symptoms or signs of endometriosis decreased significantly from baseline to week 24 and from baseline to week 48. There was a smaller decline in the proportion of patients with each of the symptoms from week 24 to week 48. The decline in mean scores for each of the 5 symptoms and signs from baseline to week 24 and from baseline to week 48 was also statistically and clinically significant. The change from week 24 to week 48 was small and of doubtful clinical significance (0 for dysmenorrhea and pelvic tenderness, -0.1 for deep dyspareunia and pelvic induration, and -0.3 for pelvic pain).

During the follow-up period, the mean and median number of months until the return to baseline pain severity was consistently longer for successful completers than for the group of all patients treated. For successful completers the median was 8 months for dysmenorrhea, 12 months for pelvic pain, and 16 months for deep dyspareunia, pelvic tenderness, and pelvic induration (The sponsor projected 16 months based on no return to baseline by the end of the 12-month follow-up period). For the group of all patients treated, the time for return to baseline severity was 4 months for dysmenorrhea and pelvic pain, 8 months for pelvic tenderness, 12 months for deep dyspareunia, and 16 months for pelvic induration.

The mean clinical pain scores were significantly lower at month 12 of follow-up than at baseline for all 5 signs and symptoms.

At the medical officer's request, the sponsor provided a subset analysis of patients in both studies who received Lupron/NETA and were previously treated with a GnRH agonist compared to those who received Lupron/NETA and were not previously treated, and there were no consistent differences in the proportion of patients with painful symptoms or in the mean changes from baseline at weeks 24, 48 or final treatment visit between the groups with and without prior GnRH agonist therapy.

Reviewer's comment

The above information supports the efficacy of a single course of re-treatment with Lupron combined with NETA in women who have received previous treatment with Lupron.

Secondary efficacy endpoints were serum estradiol concentrations, menstrual bleeding pattern, and patient's assessment of pain (on a 10-point analogue scale).

In Study M92-878, the mean serum estradiol concentrations averaged over the treatment period were within the menopausal range (≤ 20 pg/ml) for both treatment groups. The suppression of total serum estradiol

concentrations was statistically greater with Lupron/NETA treatment than with Lupron alone. The medical officer observed that the difference could be related to the reduction of sex hormone binding globulin (SHBG) that is known to occur with norethindrone acetate and other androgenic progestins. The concentrations of unbound estradiol were not measured, but the difference between groups is likely to be less.

The proportion of women who ceased to have menstrual bleeding was 87% with Lupron alone and 84% with Lupron/NETA treatment in Study M922-878, and 73% with Lupron/NETA treatment in M97-777.

Reviewer's comment

- *These data demonstrate that treatment with Lupron/NETA is as effective as treatment with Lupron alone in relieving the symptoms of endometriosis.*
- *Although there was a continued decline in the proportion of women having all of the symptoms of endometriosis from week 24 to week 48 or 52, this can be explained in part by the probability that women experiencing no improvement would be more likely to discontinue therapy. (In Study M92-878, 9 (18%) of the 51 patients receiving Lupron alone discontinued by week 24, and 19 (37%) by week 52. Of the 55 patients receiving Lupron/NETA, 13 (24%) discontinued the study by week 24, and 24 (44%) by week 52. In Study 97-777, 33 (24%) of the 136 patients treated with Lupron/NETA discontinued by week 24, and 54 (40%) by week 52.) The mean changes in scores from week 24 to week 48 or 52 was small and of doubtful clinical significance. The data are not adequate to demonstrate a clinically meaningful benefit of treatment with either Lupron alone or Lupron/NETA beyond 6 months*
- *Of those patients who entered the follow-up period in Study M92-878, only 14 (36%) of the 39 women treated with Lupron and 10 (26%) of the 39 women treated with Lupron/NETA completed one year of follow-up. Only 4 Lupron patients and 6 Lupron/NETA patients completed 2 years of follow-up. The studies presented with these efficacy supplements were not designed to compare the duration of symptomatic improvement following the completion of 6 months vs. 12 months of therapy, and the sponsor was unable to provide adequate information to allow any such comparison.*

Safety and Tolerance

In the combined studies, a total of 191 women were treated with the combination of Lupron and norethindrone acetate 5 mg daily and 113 received all 13 injections (one year of therapy). Both individual drugs are currently approved for treatment of endometriosis

Bone Mineral Density

Of the 51 patients enrolled into the Lupron alone treatment arm of study M92-878, 41 had on-treatment BMD measurements at week 24 and 29 at week 52 visits. The mean percent change from baseline was -3.3% at week 24 and -6.3% at week 52. During post-treatment follow-up, the mean percent change from baseline was -3.3% at month 8, -2.2% at month 12, and -1.9% at the final visit (at discontinuation or end of the study). The largest individual change from baseline at post-treatment month 8 was -11.7%, at month 12, -4.8%, and at final visit -5.5%.

In the Lupron/NETA treatment arm of study M92-878, 55 patients were enrolled, 42 had BMD measurements at week 24, and 32 at week 52. The mean change from baseline was -0.3% at week 24 and -1.0% at week 52. During follow-up, the mean change from baseline was -0.9% at month 8, -0.7% at month 12, and -0.4% at the final visit. The largest individual change from baseline at post-treatment Month 8 was -7.3%, at month 12 -4.3%, and at the final visit -7.3%.

In Study M97-777, of the 136 women treated with Lupron/NETA, 115 had BMD measurements on treatment at week 24, and 84 at week 52. The mean change from baseline was -0.3 at week 24 and -1.1% (range: -) at week 52. During follow-up, the mean change from baseline was -0.6% at month 8, 0.1% at month 12, and 0.0% at the final visit. The largest individual change from baseline was -7.5% at post-treatment month 8, -4.9% at post-treatment month 12, and -7.5% at the final visit.

The lower bound of the 95% CI for the change in BMD from baseline to week 24, week 52, and the final visit was above -2.2% for the Lupron/NETA treatment groups in both studies, and the lower bound of the

95% CI for the change from baseline for the Lupron alone group was below -2.2% at each assessment time.

A consultation from Division of Metabolic and Endocrine Drug Products (DMEDP) revealed that the data provided would not be adequate for labeling NETA with an indication for prevention of postmenopausal osteoporosis. No preclinical studies have been presented to show that NETA increases or maintains bone strength in ovariectomized animals, and no dose-ranging studies have been performed for such an indication. However, the data do support the use of NETA to counteract the adverse effect (BMD loss) of the approved drug Lupron. Some individuals will experience more than the observed BMD losses during a 6 month treatment period and may not replace those losses after discontinuation of treatment; therefore, it may be helpful to co-administer NETA with Lupron for the initial 6 months of treatment in certain individuals at high risk of bone loss.

Reviewer's comment:

- *As noted by the primary reviewer, the results of both studies demonstrate that co-administration of NETA 5 mg daily and elemental calcium 1000 mg daily with Lupron therapy significantly reduced the loss of BMD at weeks 24 and 52, compared to treatment with Lupron alone and calcium supplementation. In a subset of 40 women who had been previously treated with GnRH agonist therapy, NETA appeared to be as effective in preventing BMD loss as in women not previously treated.*
- *Although the mean change in BMD was reduced with co-administration of NETA, the loss of BMD was still greater at 12 months with Lupron/NETA (approximately 1%) than at 6 months of therapy (approximately 0.3%). Some individuals had considerably greater than the mean loss of BMD, and some had not returned to their baseline values after 12 months of follow-up. The greatest individual decrease in BMD from baseline to 12 months of follow-up was similar in the Lupron alone and Lupron/NETA arms in Study M92-878. Therefore, even with the addition of NETA, Lupron therapy should not be continued beyond 6 months without a clear demonstration of additional benefit, either further clinically meaningful reduction of symptoms from 6 to 12 months or a significantly longer duration of symptom relief after completion of therapy.*
- *Given the continued loss of BMD with Lupron alone, re-treatment with Lupron alone is not recommended.*
- *As noted above, it is likely that the hypoestrogenic effects may continue longer after each 3-month injection than after 3 monthly injections of Lupron Depot. Concerns about persistent loss of BMD were previously raised in the Medical Officer review of the Phase IV study comparing the two depot formulations of Lupron. In that study 5 patients treated with the 3-month formulation and one patient treated with the 1-month formulation had BMD measurements after 6 months of follow-up that were lower than the final measurements at the end of 6 months of treatment. The differences were small and could be consistent with the range of error in the method of detection or could be due to a prolonged hypoestrogenic effect of the 3-month formulation. Additional clinical trials with both formulations would be needed before consideration could be given to extending treatment beyond 6 months.*
- *In light of the fact that the 1-month and 3-month formulations are currently approved for the treatment of endometriosis, the addition of norethindrone acetate to treatment with either formulation alone will be an important safety measure for reduction of bone mineral density loss with treatment.*

Vasomotor symptoms

In Study M92-878, 98% of patients treated with Lupron alone and 96% of patients treated with Lupron/NETA reported hot flashes as an adverse event that was considered treatment-related at some time during the study. Detailed data were collected regarding hot flashes in this study, and at week 24, 87% of Lupron-alone patients and 58% of Lupron/NETA patients experienced hot flashes. The mean number of days with hot flashes reported by all patients at 24 weeks was 19 days for the Lupron alone group and 7 days for the Lupron/NETA group. The mean of the maximum number of hot flashes in 24 hours at 24 weeks was 5.8 for the Lupron alone group and 1.9 for the Lupron/NETA group. In Study M97-777, 95% of patients reported hot flashes as an adverse event that was considered treatment related. However, no additional data regarding hot flashes was collected.

Reviewer's comment

These data demonstrate that co-treatment with NETA 5 mg daily is effective in reducing the vasomotor symptoms that result from the hypoestrogenic effect of Lupron.

Serum lipid profiles

In Study M92-878, patients treated with Lupron alone showed a mean increase in total serum cholesterol of 8.6% at 24 weeks and 9.6% at 52 weeks, and those treated with Lupron/NETA showed no significant change from baseline. However, mean serum HDL-Cholesterol decreased by 19.9% at 24 weeks, and 18.8% at 52 weeks while the Lupron alone group showed only small increases. This resulted in LDL/HDL ratios that increased by 38.8% for the Lupron/NETA treatment group at 24 weeks and 34.8% at 52 weeks, compared to small non-significant changes of 5.6% at 24 weeks and 14.1% at 52 weeks in the Lupron alone group. These changes were not evaluated during follow-up. Changes in serum triglycerides in both groups were small and generally not significant.

In Study M97-777, HDL-Cholesterol decreased by 16.5% in the Lupron/NETA treated patients at week 24 and 17.8% at week 52. The LDL/HDL ratios increased by 32.3% at week 24 and 40.0% at week 52. These changes resolved during follow-up.

A consultation from the Division of Metabolic and Endocrine Drug Products (DMEDP) noted that the HDL-C changes resulted in an HDL-C < 40 mg/dL in about 45% of patients in the Lupron/NETA exposed groups. Although a decreased HDL-C has been established as a risk factor for cardiovascular disease, the significance of short-term drug-induced reductions in HDL-C in premenopausal women at low risk for cardiovascular disease has not been determined. The consultant recommended that the effects seen on the lipid profile with Lupron/NETA treatment be included in the labeling and that labeling also include a statement regarding increased cardiovascular (CV) risk with low HDL-C and the unknown effect of treatment-induced low HDL-C levels on CV risk in endometriosis patients. Baseline assessment of CV risk factors and management of other risk factors during treatment with Lupron/NETA is also recommended. It was noted that the weight gain observed in the studies may also play a role in the decreased HDL-C, and that consideration should be given to investigating other add-back regimens with less androgenic progestins that may produce less effect on HDL-C.

Reviewer's comments

- *I agree with the consultant's recommendation that the decrease in HDL-C should be addressed in the label, including a statement regarding the increased CV risk of low HDL-C and the unknown long-term effects of this treatment-induced effect in endometriosis patients.*
- *Although the reductions in HDL-C observed in Lupron/NETA patients could be related to some extent to weight gain, further study of this relationship would be of limited clinical usefulness.*
- *To investigate other add-back regimens with less androgenic progestins may identify an alternative with less effect on HDL-C; however, use of the proposed regimen has been demonstrated to be safe and effective for 6 months of therapy with the possibility of a single 6-month course of retreatment if needed for recurrence of symptoms.*

Weight change and vital signs

In study M92-878, women treated with Lupron/NETA gained a mean of 6.37 pounds. The range of weight change for Lupron/NETA patients was 36 pounds gained to 22 pounds lost. Of 42 patients taking Lupron/NETA, 14 (33.3%) experienced a gain of 10 pounds or more, and 2 (4.8%) experienced a loss of 10 pounds or more. Patients treated with Lupron alone gained a mean of 3.19 pounds, a change from baseline that was not statistically significant. The range of weight change to the final visit was 58.0 pounds gained to 23.5 pounds lost in the Lupron-alone group, with 9 (20%) of 45 subjects gaining 10 pounds or more, and 6 (1.3%) subjects losing 10 pounds or more.

Patients in Study M97-777 gained a mean of 4.85 pounds with a range of weight change from 48 pounds gained to 22 pounds lost. . Of 120 patients taking Lupron/NETA, 36 (30%) and 8 (6.7%), respectively experienced a gain or loss of at least 10 pounds.

In the Lupron alone group in Study M92-878, the mean sitting pulse rate decreased by 5.14 beats per minute, a change that was statistically but not clinically meaningful. The pulse rate did not change significantly in the Lupron/NETA group. The mean changes from baseline in systolic blood pressure were not clinically significant in either group. Hypertension was reported as an adverse event for 1 of 55 (1.8%) patients in the Lupron/NETA group and none of the Lupron alone group.

In Study M97-777, mean systolic and diastolic blood pressure and pulse rate showed no statistically or clinically significant change from baseline. Hypertension was reported as an adverse event for 7 of 136 (5.1%) patients. Of these 7 reports, 5 were rated as mild and 2 as moderate in severity. Five of these 7 cases of hypertension were assessed as not related to treatment. The maximum blood pressure recorded was 160/100 mmHg in a patient with a baseline blood pressure of 132/90. One other patient had a single diastolic recording of 95 mmHg, and several others had diastolic recordings of 90 mmHg. Hypertension was not listed as an adverse event leading to discontinuation.

Reviewer's comment

- *As noted by the primary reviewer, the degree of weight gain reported with Lupron/NETA therapy is not unusual for women taking this dose of an androgenic progestin.*
- *The sporadic cases of elevated blood pressure do not present a significant safety concern.*

Adverse events

Adverse events were the most common reason for discontinuation in both studies, with 18% of Lupron alone patients and 20% of Lupron/NETA patients in M92-878 and 13% of Lupron/NETA patients in M97-777 discontinuing for an adverse event.

The two most commonly reported adverse events in all treatment groups were hot flashes (in 98.0% of Lupron alone and 89.1% of Lupron/NETA patients in M92-878 and 59.6% of Lupron/NETA patients in M97-777) and headaches (in 72.5%, 61.8%, and 58.8%, respectively). Adverse events reported in the treatment groups were similar, except that patients treated with Lupron alone reported pain, insomnia, and anxiety more often, and patients treated with Lupron/NETA more often reported urinary tract infection, myalgia, and sweating. Breast discharge or galactorrhea (both symptoms known to occur with progestin therapy) was reported for 5 patients in the Lupron/NETA treatment groups and none in the Lupron alone group.

Treatment-related adverse events that occurred in 10% or more of patients in both treatment groups in M92-878 were hot flashes, headache, insomnia, nausea, emotional lability, vaginitis, asthenia, pain, depression, and weight gain. Emotional lability was reported by 24% of patients treated with Lupron alone and 25% of those treated with Lupron/NETA, and depression was reported by 14% of patients treated with Lupron alone and 13% of those treated with Lupron/NETA. More patients treated with Lupron/NETA than with Lupron alone reported acne (9% vs. 4%) and sweating (15% vs. 2%).

In Study M97-777, 21% of patients treated with Lupron/NETA reported depression and 17% reported acne, 13% nervousness and 10% anxiety, proportions that are higher than in either treatment group in M92-878.

Serious adverse events were reported by 12 patients in M92-878. Only one in each treatment group was reported by the investigator to be study related. They were a renal calculus in one Lupron-treated patient and a urinary tract infection in a Lupron/NETA treated patient. Of the 4 serious adverse events reported in M97-777, none was considered treatment related by the investigator.

Reviewer's comments:

- *As noted by the primary reviewer, the adverse events noted above are primarily those commonly associated with the hypoestrogenic effects of GnRH agonists in all treatment groups, especially the Lupron alone group. Lupron/NETA treated patients reported fewer hypoestrogenic effects (hot flashes, insomnia, vaginitis, amnesia, and decreased libido) and more effects associated with an androgenic progestin (acne, breast discharge, galactorrhea). Weight gain and depression, both commonly seen with progestin therapy, were reported with both treatments. Weight gain was reported by 12% of Lupron treated patients and 18% of Lupron/NETA patients in M92-878 and 10% of*

Lupron/NETA patients in M97-777. Depression was reported by 14 and 13%, respectively of Lupron and Lupron/NETA patients in M92-878 and in 21% of Lupron/NETA patients in M97-777. The reasons for different reporting rates for these adverse events in Study M97-777 vs. the Lupron/NETA arm of Study M92-878 is unknown.

- The primary reviewer observed that depression rated as severe was reported by 1 (2%) of 55 Lupron/NETA treated patients (vs. none of the 51 patients treated with Lupron alone) in M92-878 and in 4 (3%) of the 136 patients receiving Lupron/NETA in Study 97-777. These reports included one suicide attempt which the investigator assessed as unrelated to the treatment.
- Although the adverse events reported are not unusual for treatment with GnRH agonists or androgenic progestins, they could result in significant discomfort for the women undergoing these treatments. Furthermore, as noted above, treatment with NETA results in lipid changes associated with potential cardiovascular risks, and treatment with Lupron alone results in significant loss of bone density. Therefore, therapy with either Lupron alone or Lupron with NETA should not be extended beyond 6 months without clear demonstration of additional benefit such as a further clinically meaningful reduction of symptoms after 6 months or a longer duration of symptom relief after completion of therapy.

Drug Interactions

No drug interaction studies were conducted for this efficacy supplement. However, the data show no decrease in the efficacy of Lupron with the addition of norethindrone acetate 5 mg daily, and interactions with other drugs are not expected to be different with the combined therapy than with the individual drugs alone.

Clinical Assessment and Recommendations

I agree with the primary medical reviewer's conclusions that the data presented in this NDA efficacy supplement are sufficient to support adding the benefits and potential risks of co-treatment with Lupron plus NETA 5 mg daily to the approved Lupron labeling. The data presented are not adequate to support extending treatment of endometriosis with Lupron from 6 months to 12 months. However, for patients with recurrence of symptoms, a single 6-month course of re-treatment with Lupron plus NETA 5 mg daily is supported.

Labeling should be revised to include the effects of NETA on serum lipids, and the unknown effect of those changes on cardiovascular risk for women with endometriosis. Baseline cardiovascular risk assessment is recommended. Significant contraindications, warnings, and precautions from the approved labeling for NETA should be included in the label.

Non-Clinical Assessments

The biopharmaceutics reviewer found the data related to suppression of serum estradiol concentrations acceptable to support approval of this efficacy supplement. A labeling recommendation regarding NDA 20-708 was accepted by the sponsor in a teleconference on September 19, 2001 and included in the final labeling received September 21, 2001. Recommendations regarding further characterization of the drug product were sent to the sponsor in a Discipline Review letter dated September 19, 2001. No preclinical toxicology data or new CMC information was submitted with this efficacy supplement. There were no DSI audits or facilities inspections, and no tradename review was needed for this approved product.

Labeling

The clinical review team recommends extensive revisions to the sponsor's proposed labeling to reflect the following:

- There is inadequate evidence for a benefit of extending initial treatment beyond 6 months.
- Re-treatment of women with recurrence of symptoms by co-administering norethindrone acetate 5 mg daily with Lupron for 6 months is safe and effective. However, there is inadequate evidence to support more than a single 6-month course of re-treatment
- The major Contraindications, Warnings, and Precautions for norethindrone acetate therapy should be added to the label.

- The effects of NETA on serum lipids should be included in the label along with a recommendation for assessment and management of other cardiovascular risk factors.

Recommended label revisions were communicated to the sponsor on September 14, 2001 and further discussed in a teleconference on September 19, 2001. Final agreement regarding acceptable labeling was reached on September 21, 2001.

Conclusions and Recommendations

The data submitted for these NDA efficacy supplements is not adequate to support extending primary therapy with Lupron alone or Lupron with NETA from 6 to 12 months. However, the data do support the safety and efficacy of co-administering NETA 5 mg with Lupron to reduce the loss of bone mineral density that is associated with Lupron therapy alone. The choice of treatment with Lupron alone vs. Lupron with NETA for initial management of the symptoms and signs of endometriosis should be made by the health care provider and the patient, taking into consideration both the risks and benefits of the addition of NETA to Lupron alone. For patients with recurrence of symptoms, a single 6-month re-treatment with Lupron combined with NETA 5 mg is shown to be safe and effective. These efficacy supplements can be approved with the final labeling received from the sponsor on September 21, 2001.

Dena R. Hixon, M.D., FACOG
Team Leader/DRUDP

Susan S. Allen, M.D., MPH
Director/DRUDP

**APPEARS THIS WAY
ON ORIGINAL**

Cc: HFD-580/ S. Allen /D. Shames/D. Hixon/S. Monroe

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

/s/

Dena Hixon
9/21/01 12:10:26 PM
MEDICAL OFFICER

Susan Allen
9/21/01 12:14:45 PM
MEDICAL OFFICER
I concur.

**APPEARS THIS WAY
ON ORIGINAL**

**Screening of New NDA
Division of Biometrics II**

Date: December 12, 2000

NDA #: 20-011 / SE001 and 20-708 / SE007

Priority Classification: 3S

Trade Name: Lupron Depot® 3.75 mg

Applicant: TAP Pharmaceutical

Generic Name: leuprolide acetate for depot suspension

Date of Submission: 11/22/00

Indication: Management of endometriosis for 12 months

No. of Controlled Studies: 2

User Fee Goal Date: 9/22/01

Date of 45-Day Meeting: 1/10/01

Medical Officer: Gerry Willett, M.D.

Project Manager: Jeanine Best

Screened by: Kate Meaker, M.S.

Volume numbers in statistical section: Vols. 38.1 – 38.26 for NDA 20-011;
Vol. 26.1 for NDA 20-708 (revised label)

Anticipated Review Completion Date: 8/15/01

Comments:

1. The primary endpoint in study M97-777 was bone mineral density, the safety endpoint. Efficacy variables were measured as secondary endpoints.
2. The index lists files for electronic submission, but does not specifically list the data files for statistical review. Please confirm with the applicant that the statistical data files are included.
3. This is fileable.

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Yes
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	N/A
Appropriate references included for novel statistical methodology (if present)	N/A
Sufficient data listings and intermediate analysis tables to permit statistical review	Yes
Data from primary studies on diskettes and/or CANDAs submitted	PM will confirm
Intent-to-treat analysis	Yes
Effects of dropouts on primary analyses investigated	Yes
Safety and efficacy for _____ racial, and _____ subgroups investigated	No

BRIEF SUMMARY OF CONTROLLED CLINICAL TRIALS
 (or attach relevant table from summary volume of NDA)

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
M92-878 (11/93 – 12/97)	26 (all U.S.)	Lupron Depot Only (n=51) Lupron Depot + norethindrone acetate 5 mg/day (n=55)	Active	Phase IV Double-blind Randomized Parallel group	12 months
M97-777 (2/98 – 3/00)	24 (all U.S.)	Lupron Depot + norethindrone acetate 5 mg/day (n=136)	Historical: Lupron Depot Only group from M92-878	Open-label Single-arm	12 months

Statistical Reviewer

Concur: Dr. Welch

cc:
 Archival NDA #20-011
 Archival NDA #20-708
 HFD-580
 HFD-580/GWillett, JBest, SAllen
 HFD-715/ENevius, MWelch, KMeaker, Chron

**APPEARS THIS WAY
 ON ORIGINAL**

/s/

Katherine Meaker
12/18/00 11:31:05 AM
BIOMETRICS

APPEARS THIS WAY
ON ORIGINAL

**Lupron Depot-3 Month 11.25 mg (NDA 20-708)
Regulatory History**

Description of Submission	Submission	Approval
NDA Submission (with a pK study)	March 1996	March 1997
S-001(Labeling change) to add safety data Based on post-marketing experience of Lupron Depot 3.75 mg	April 1997	Sept. 1997
S-003 Labeling supplement(Add-back data Addition based on study M92-878)	October 1997	April 1998
S-005 Efficacy & safety of two formulations	April 1998	February 1999

The three-month formulation of leuprolide differs from the one-month formulation only from the standpoint of the period over which the drug is released.

The initial NDA 20-708 for Lupron Depot-3Month 11.25 mg was submitted with one pharmacokinetic study and referred to the NDA 20-011(Endometriosis) and NDA 19-943(Hematologic improvement of patients with anemia due to Uterine Fibroids) for all the efficacy and most of the safety information from Lupron Depot 3.75 mg clinical studies for these indications. The NDA was approved in March 1997.

Since the approval of NDA 20-708, two supplemental applications were approved to include the information from the experiences (S-001 based on postmarketing data & S-003 based on study M92-878) with the one- month formulation.

A phase IV pharmacokinetic/pharmacodynamic study (M96-506) was performed to evaluate the two formulations (Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg) in endometriosis patients. The study report was submitted as an Efficacy supplement (S-005) in April 1998. This study demonstrated that the two formulations have comparable safety and efficacy and this information was added to Lupron Depot-3 Month 11.25 mg labeling upon approval of S-005 in February 1999.

In summary, the two formulations have been demonstrated to be equivalent for safety and efficacy and have been historically considered as such by the Division. All the data from the two hormonal Add-back studies (M92-878 and M97-777) that are being submitted as a supplemental application are also applicable to Lupron Depot-3 Month 11.25 mg (NDA 20-708).

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Abuse Liability Review-NA .

C /S/ 9/21/27

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Micro Efficacy Review-NA .

Handwritten initials: T, C, and S.

8/21/01

Vertical handwritten mark.

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

DSI Audit-NA .

CT/SI
9/21/01

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Chemistry Review-NA .

✓
S/

9/12/18

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NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Statistical Review Dissolution/Stability-NA .

/S/

9/2/04

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

DMF Reviews-NA .

C /S/ 9/21/04

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Micro (Sterility) Review-NA .

/S/

9/24/04

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NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Facilities Inspections-NA .

C /S/

9/21/16

1

NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

Methods Validation-NA .

C

/S/

9/12/16

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

Pharmacology/Toxicology Review-NA .

C /S/

9/21/01

NDA 20-708/S-011 .

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

DSI Memo (GLP Inspection)-NA .

C

/S/

9/21/11
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NDA 20-708/S-011
Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Statistical Review (Carci Studies)-NA .

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9/21/14

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NDA 20-708/S-011

Lupron Depot®-3 Month 11.25 (leuprolide acetate for depot suspension)

TAP Pharmaceutical Products, Inc.

CAC/ECAC Report-NA .

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9/26/21

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