CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-011/S-021

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

DEC - 7 2000

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW	
NDA:	**20-011 ref # 021 suppl. SE-1 and 20-708 ref # 011 suppl. SE-1**
To:	**HFD-580**
Place:	PKLN 17B43
Compound:	3.75 mg leuprolide acetate 1-month depot + 5 mg norethindrone acetate(NDA 20-011) 11.25 mg leuprolide acetate 3-month depot + 5 mg norethindrone acetate(NDA 20-708)
Sponsor:	Tap Pharmaceuticals Inc.
Date:	December 4, 2000, 8:30 a.m.
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background:
Intramuscular injections of LUPRON DEPOT® (3.75 mg leuprolide acetate suspension monthly; NDA 20-011) and LUPRON DEPOT®-3 Month (11.25 mg leuprolide acetate suspension every 3 months; NDA 20-708) are indicated for the management of endometriosis for up to 6 months. Bone mineral density reduction limits the use of both preparations to within 6 months. Sponsor submitted these 2 NDA supplements to seek approval of both LUPRON DEPOT® 3.75 mg with 5 mg norethindrone acetate daily and LUPRON DEPOT®-3 Month 11.25 mg with 5 mg norethindrone acetate daily to manage endometriosis for 12 months. Both LUPRON labels contain the statement "Hormonal replacement therapy: 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." Norethindrone acetate (5 mg oral tablet; Aygestin®) is a progestin.

Comments:

1. Sponsor conducted 2 Phase IV clinical studies (M92-878 and M97-777) to assess the safety and efficacy of LUPRON DEPOT® 3.75 mg with 5 mg norethindrone acetate daily to manage endometriosis for 12 months (see Attachment).
2. Sponsor used marketed LUPRON DEPOT® 3.75 mg and Aygestin® products in Studies M92-878 and M97-777.
3. Dose selection information for LUPRON DEPOT® 3.75 mg and Aygestin® was provided.
4. Sponsor did not measure biological leuprolide or norethindrone concentrations in both Studies M92-878 and M97-777. However, serum estradiol concentrations were measured as secondary endpoints in both studies.
5. Sponsor did not conduct clinical study to assess the safety and efficacy of LUPRON DEPOT®-3 Month 11.25 mg with 5 mg norethindrone acetate daily for 12-month management of endometriosis.
6. Sponsor conducted a Phase IV study (M96-506) to assess the PK/PD of LUPRON DEPOT® 3.75 mg and 11.25 mg in patients with endometriosis for 24 weeks. Sponsor used marketed LUPRON products in this study.
7. Per Study M96-506's results, these statements "In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular 11.25 mg LUPRON DEPOT® (n=19) every 12 weeks or intramuscular 3.75 mg LUPRON DEPOT® (n=15) every 4 weeks was administered

for 24 weeks. There was no statistically significant difference between the 2 treatment groups in trough plasma concentrations of leuprolide or M-I collected from weeks 4 through 24. No accumulation of plasma leuprolide or M-I concentrations was observed with multiple dosing of either treatment group. There was also no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups." were incorporated onto the LUPRON DEPOT®-3 Month 11.25 mg label.

8. Study M96-506 may be a safety and efficacy link between LUPRON DEPOT® 3.75 mg and LUPRON DEPOT®-3 Month 11.25 mg for the management of endometriosis for 12 months. However, Study M96-506 was only conducted for 24 weeks.
9. LUPRON DEPOT® 3.75 mg and LUPRON DEPOT®-3 Month 11.25 mg labels contain the addition of hormonal replacement therapy statements. Therefore, drug interaction study or combination drug rule for these 2 supplements is not an issue.
10. Sponsor provided both proposed LUPRON DEPOT® 3.75 mg and LUPRON DEPOT®-3 Month 11.25 mg labelings.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) finds that:

- NDA 20-011 ref # 021 suppl. SE-1 is fileable.
- NDA 20-708 ref # 011 suppl. SE-1 is fileable.

/S/ December 7, 2000

S.W. Johnny Lau, R.Ph., Ph.D.
(OCPB/DPEII)

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/ 12/7/00

cc: NDA 20-011 and NDA 20-708, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (S. Monroe, J. Best), CDR (B. Murphy for Drugs)

Attachment starts from here.

APPEARS THIS WAY
ON ORIGINAL

1.0 INTRODUCTION

Gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide acetate [Lupron ®]) are an accepted and widely used treatment modality for symptomatic endometriosis. Their efficacy has been established based on findings of significant reductions in the extent of disease (i.e., endometriotic implants) and associated pain, as well as hormonal suppression.[1-8] GnRH agonists are efficacious due to their ability to create a hypoestrogenic environment.

The goal of therapy with Lupron Depot® in women with endometriosis is to create a hypoestrogenic environment resulting in atrophic changes in ectopic endometrial tissue, thus allowing for symptomatic improvement.

Various formulations of Lupron (leuprolide acetate, A-43818) are marketed by TAP Pharmaceuticals Inc. (TAP) for the following indications:

Date Introduced	Formulation	Indication
April 1985	Lupron Injection	Advanced Prostate Cancer
January 1989	Lupron Depot 7.5 mg	Advanced Prostate Cancer
October 1990	Lupron Depot 3.75 mg	Endometriosis
April 1993	Lupron Depot-PED 7.5, 11.25, and 15 mg and Lupron Injection	Central Precocious Puberty
March 1995	Lupron Depot 3.75 mg	Anemia Associated with Leiomyoma Uteri
December 1995	Lupron Depot-3 Month 22.5 mg	Advanced Prostate Cancer
March 1997	Lupron Depot 11.25 mg	Endometriosis and Anemia Associated with Leiomyoma Uteri
May 1997	Lupron Depot-4 Month 30 mg	Advanced Prostate Cancer

The occurrence of side effects attributable to this hypoestrogenic environment (e.g., vasomotor symptoms and loss of bone mineral density [BMD]) has limited the recommended duration of treatment to six months. While symptomatic relief is usually

noted within the first month of treatment with GnRH agonists, and relief may continue for several months after treatment is concluded, there are some patients for whom the current restrictions on duration of therapy are problematic. These patients have an unmet medical need due to the chronic nature of the disease, which may result in persistent pain or rapid recurrence of pain. A six-month treatment duration may be insufficient for patients with refractory or more severe disease, and they may benefit from extended treatment.

Approaches to increasing the duration of GnRH agonist treatment have addressed ways to limit the hypoestrogenic side effects, most importantly the loss of BMD. Supplementation with sex-steroid hormones, referred to as "add-back" therapy, has been evaluated for its ability to minimize bone loss and ameliorate vasomotor symptoms while preserving efficacy.[9-18] Treatment protocols have included the addition of progestins alone,[10-13], progestins plus estrogen,[9,14,15] and progestins plus organic bisphosphonates.[16]

In order to reduce the loss in BMD seen in women treated with Lupron Depot, investigations into hormone replacement (add-back) have been made. An optimal add-back regimen should prevent or reduce the bone loss without sacrificing efficacy of Lupron Depot. It has been postulated that combining estrogen with GnRH agonist therapy can suppress disease and reduce the level of side effects, including decreases in BMD.[19] The initial clinical study (Study M92-878) was designed in collaboration with investigators who, based on clinical experience with various add-back therapies, advised that norethindrone acetate 5 mg (Aygestin®) might be the preferred treatment option. Norethindrone acetate (Aygestin®), a 19-nortestosterone derivative, is one of the progestins that have been studied as add-back therapy. It has been shown to maintain efficacy while providing relief from vasomotor symptoms and greatly minimizing BMD loss when administered in combination with GnRH agonists.

1.1 Study M92-878

This Phase IV, double-blind, randomized, parallel-group, multi-center study was conducted with 26 sites enrolling a total of 201 patients. There were four treatment groups in the study as described in Section 2.1. Only the results for two of the treatment groups, Lupron Depot 3.75 mg-Only (LD-Only) and Lupron Depot and norethindrone acetate 5 mg (Aygestin®) (LD/N), are presented in this integrated summary since this add-back regimen was selected as the optimal regimen and evaluated in Study M92-878 as well as in a subsequent study (M97-777).

Statistically significant mean decreases from baseline for the clinical evaluation of pain variables were noted at nearly all Treatment Period visits in both the LD-Only and LD/N treatment groups. Improvement in all clinical evaluation variables, averaged over the Treatment Period, was similar between the two treatment groups. Results of patients' self-assessments of pain were generally similar to the investigators' assessments of pain. Menstrual suppression was attained in 100% of LD-Only and LD/N patients who were in the Treatment Period for at least 60 days.

The most commonly reported adverse event during the Treatment Period was hot flashes, which was reported by 98% of LD-Only patients and 89% of LD/N patients.

The hormonal add-back regimen was associated with only a very slight change in bone mineral density (BMD). Mean changes in BMD from baseline to the Final Treatment Visit were -5.3% and -0.9% for the LD-Only and LD/N groups, respectively, and were statistically significant.

With the possible exception of lipid changes, there were no clinically significant adverse trends in laboratory values associated with add-back therapy. A statistically significant decrease from baseline in HDL-cholesterol and a statistically significant increase from baseline in LDL-cholesterol were noted for the LD/N group.

At the time of its inception, this was the largest add-back study conducted with Lupron Depot. This study demonstrated that, in the treatment of endometriosis, hormonal add-back prevents bone loss without diminishing efficacy. Addition of norethindrone acetate 5 mg (Aygestin®) to Lupron Depot, administered over a one-year period, was demonstrated to be sufficient to minimize the loss of BMD without compromising the efficacy of Lupron Depot.

A supplemental application was submitted to change the treatment period for endometriosis patients to 12 months when Lupron Depot is administered with norethindrone acetate 5 mg (Aygestin®). The Division (DRUDP) refused to file (RTF) the application and a second study was requested. The Division agreed to add general wording to the labeling regarding considering hormonal add-back with six months of GnRH therapy. This was approved in April 1998.

During the meetings following the RTF decision, the sponsor, in conjunction with the Division, developed the protocol for an open-label, single-arm, multi-center study (M97-777) to replicate the results of the Lupron Depot 3.75 mg + norethindrone acetate 5 mg (Aygestin®) arm from Study M92-878.

1.2 Study M97-777

The objective of this study was to evaluate the efficacy and safety of Lupron Depot 3.75 mg in combination with norethindrone acetate 5 mg (Aygestin®), administered for one year, for the management of endometriosis and to increase the number of women studied who have received this regimen. The study was also intended to investigate if the bone mineral density changes and the efficacy from the above regimen in the previous study (M92-878) could be duplicated to support a change in Lupron Depot labeling.

Efficacy was evaluated based on improvement in symptoms. Safety evaluations included analyses of bone loss. Criteria for evaluating the bone loss were developed a priori in discussions with the FDA and were specified in the protocol. The treatment-free follow-up period is one year in duration.

In this open-label, single-arm, multi-center study, endometriosis patients received an intramuscular (IM) injection of Lupron Depot 3.75 mg monthly in combination with norethindrone acetate 5 mg (Aygestin®) daily for 12 months. Bone mineral density was evaluated pretreatment, at 24 weeks, and at 52 weeks. Pain evaluations were performed at every visit (4-week intervals).

Study M97-777 successfully replicated the results of the LD/N arm from Study M92-878 with regards to bone loss and efficacy. The primary end point (BMD loss) analysis results are well within the criteria stipulated by the Division. A change of -1.0% in bone density was seen at the final treatment visit and the two-sided 95% confidence interval for the mean percent change (-1.4% to -0.5%) was well above the -2.2% lower limit for change set by the FDA.

In addition to the analyses performed in the context of the individual studies, findings for all LD/N patients (i.e., integrated LD/N group) were compared to those for the LD-only patients in Study M92-878. The results of these analyses were consistent with those already described for the individual studies.

In conclusion, the results of both studies strongly indicate that norethindrone acetate 5 mg (Aygestin®), when administered with Lupron Depot for 12 months, does inhibit the loss of bone mineral density seen with LD-Only without compromising the efficacy of Lupron Depot. The safety and efficacy of this therapeutic regimen for a period of 12 months has been demonstrated in two adequate clinical studies, thus supporting the proposed labeling change to extend the treatment period to 12 months in endometriosis patients.

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 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Abuse Liability Review-NA.

/S/

9/21/01

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NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Micro Efficacy Review-NA.

/S/ 9/12/03

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

DSI Audits-NA.

/S/

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Chemistry Reviews-NA.

/S/ 9/2/05

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Statistical Review of Dissolution/Stability-NA.

/S/

5/10/04

NDA 20-011/S-021
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TAP Pharmaceutical Products, Inc.

DMF Reviews -NA.

/S/ 9/21/04

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NDA 20-011/S-021
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TAP Pharmaceutical Products, Inc.

EA Reviews/FONSI/CAT. Exemption -NA.

/S/ 9/2/04

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NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Micro Sterility Review -NA.

/S/

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Facilities Inspections -NA.

/S/

9/2.14

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Methods Validation-NA.

/S/

9/31/01

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Pharmacology/Toxicology Review -NA.

/S/ 9/2/04

APPEARS THIS WAY
ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

DSI memo/GLP Inspection-NA.

/S/

9/2/04

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ON ORIGINAL

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Statistical Review of Carci Studies-NA.

/S/

9/21/04

APPEARS THIS WAY
ON ORIGINAL