CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-708/S-011

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-011 S-021 and 20-708 S-011**
Compound:	3.75 mg leuprolide acetate + 5 mg norethindrone acetate; 11.25 mg leuprolide acetate + 5 mg norethindrone acetate
Sponsor:	TAP Pharmaceutical Products Inc.
Type of Submission:	Efficacy Supplement
Submission Dates:	November 21, 2000.
Reviewer:	S.W. Johnny Lau, R.Ph., Ph.D.

Synopsis:

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 approved for the management of endometriosis for up to 6 months. Bone mineral density reduction limits the use of both products 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 DEPOT® and LUPRON DEPOT®-3 Month 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.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-011 S-021 and 20-708 S-011 dated November 22, 2000. Based on the available pharmacokinetic data for the approved products plus sponsor's submitted 2 clinical studies that support the safety and efficacy of concomitant leuprolide acetate and norethindrone acetate use, OCPB finds that this is acceptable (i.e. 21CFR 320.24 (b)(4)) even though sponsor did not submit the Human Pharmacokinetics and Bioavailability sections for NDA 20-011 S-021 and 20-708 S-011. However, the following general comments should be conveyed to the sponsor:

- See Review Question 7 for labeling comments.
- Sponsor is encouraged to conduct in vitro studies to characterize:
  The effect of leuprolide on cytochrome P450 metabolizing activities.
  The effect of leuprolide on the binding of drugs to albumin and sex hormone binding globulin.
  Effect of norethindrone on leuprolide pharmacokinetics.

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

An Optional Intra-Division Clinical Pharmacology and Biopharmaceutics Briefing for NDA 20-011 S-021 and 20-708 S-011 was conducted on August 31, 2001; participants included S. Monroe, H. Malinowski, J. Hunt, A. Parekh, S. Al-Habet, and J. Lau.

FT signed by Ameeta Parekh, Ph.D., Team Leader 9/ /01

cc: NDA 20-011 S-021 and 20-708 S-011, HFD-870 (H. Malinowski, A. Parekh, J. Lau), HFD-580 (J. Best), CDR (B. Murphy for Drugs)

APPEARS THIS WAY
ON ORIGINAL

Background:
These 2 efficacy supplements concern the "Add-Back" therapy to manage endometriosis. In many cases it is difficult to determine the individual dose of gonadotropin hormone releasing hormone (GnRH) agonist (such as leuprolide) needed to reach the therapeutic window. In these cases, the depot formulations are suitable to completely inactivate the ovaries and then an estrogen or a progestin is given as add-back orally to avoid the hypoestrogenic adverse effects. See synopsis above for other background information.

The following questions, based on the content of NDA 20-011 S-021 and 20-708 S-011, guided this review.

1. What study results are submitted to support NDA 20-011 S-021 and 20-708 S-011?
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. However, 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.

2. What were the bioanalytical methods used for leuprolide and norethindrone in NDA 20-011 S-021 and 20-708 S-011?
Sponsor did not collect any blood samples in Studies M92-878 and M97-777 for the determination of leuprolide and norethindrone.

3. What are the PK of the leuprolide and norethindrone upon administration of leuprolide acetate (as monthly or every 3 months intramuscular injections) and norethindrone acetate daily oral administration?
Sponsor did not submit the Human Pharmacokinetics and Bioavailability section for NDA 20-011 S-021 and 20-708 S-011.

General leuprolide clinical pharmacology information is in the LUPRON® labelings and in reviews (P. Chriap and E.M. Sorkin. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic disorders. *Drugs & Aging* 1:487-509 1991 and G.L. Plosker and R.N. Brogden. Leuprorelin: a review of its pharmacology and therapeutic use in prostatic cancer, endometriosis and other sex hormone-related disorders *Drugs* **48**:930-967 1994). General norethindrone acetate clinical pharmacology information is in a monograph (Therapeutic Drugs. Edited by Sir Collin Dollery. Page N117 to N118, Churchill Livingstone, Volume 1991 edition).

4. What is the drug interaction potential between leuprolide and norethindrone as well as between other coadministered medications upon administration of leuprolide acetate (as monthly or every 3 months intramuscular injections) and norethindrone acetate daily oral administration?
Per Ms. Nichelle Cherry's (FDA medical librarian) literature search, no drug interactions were reported in Drug Facts and Comparisons, and PDR. No PK interaction study exists between leuprolide and norethindrone in the literature based on IPA, MEDLINE, EMBASE, Derwent Drug File, and Pharm-line databases, per Ms. Cherry's search on July 17, 2001.

Leuprolide acetate is intramuscularly administered and norethindrone acetate is orally administered.

Plasma protein binding of leuprolide is only 46% (Therapeutic Drugs. Edited by Sir Collin Dollery. Page N118, Churchill Livingstone, Volume 1991 edition). Norethindrone is about 60% bound to albumin and 35% bound to sex hormone binding globulin (SHBG) (Therapeutic Drugs. Edited by Sir Collin Dollery. Page N118, Churchill Livingstone, Volume 1991 edition). A decrease of SHBG concentration was observed in women on norethindrone only. Norethindrone alone has no effect on SHBG-binding capacity, but is capable of blocking the SHBG-binding capacity increase induced by ethinyl estradiol (S.M. Petak and E. Steinberger. The Adrenal Gland. Chapter 13, page 238 of Pharmacology of the Contraceptive Steroids. Edited by J.W. Goldzieher. Raven Press 1994 edition). The effect of leuprolide on albumin and SHBG concentrations and their binding characteristics is unknown. The effect of norethindrone on leuprolide plasma protein binding is unknown.

Leuprolide is metabolized via peptidase (P. Chriap and E.M. Sorkin. *Drugs & Aging* **1**:487-509 1991 and G.L. Plosker and R.N. Brogden. *Drugs* **48**:930-967 1994). Norethindrone acetate is a prodrug for norethindrone. The enzymes that metabolize norethindrone are unknown, however, cytochrome P450 (CYP) 3A may be involved (W. Kuhnz and H. Gleschen. Predicting the oral bioavailability of 19-nortestosterone progestins in vivo from their metabolic stability in human liver microsomal preparations in vitro. *Drug Metab. Dispos.* **26**:1120-1127 1998). The major metabolic pathway of norethindrone is reduction of the α,β-unsaturated oxo group in the A ring to produce tetrahydronorethindrone with the 5β,-3α-hydroxy configuration being predominant. This is then conjugated with glucuronic acid and excreted in the urine. Formation of the 4,5-epoxide is claimed as the active metabolite (Therapeutic Drugs. Edited by Sir Collin Dollery. Page N117 to N118, Churchill Livingstone, Volume 1991 edition). The effect of leuprolide on CYPs is unknown. The effect of norethindrone on peptidases' metabolizing activities is unknown.

The interaction potential between leuprolide and norethindrone cannot be assessed with the available information. However, the coadministration of leuprolide and norethindrone did not cause safety or efficacy concerns in sponsor's clinical studies M92-878 and M97-777. Moreover, other safety and efficacy studies exist in the published literature for the coadministration of leuprolide acetate and norethindrone acetate (M.D. Hornstein et al. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Lupron Add-back Study Group. *Obstet. Gynecol.* **91**:16-24 1998; A. Berqvist. Current drug therapy recommendations for the treatment of endometriosis. *Drugs.* **58**:39-50 1999).

The interaction potential between other medications and leuprolide plus norethindrone combination cannot be assessed. However, coadministering CYP inducing agents such as carbamazepine, griseofulvin, phenobarbital, phenytoin, and rifampin (M. Lebel et al. Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone. *J. Clin. Pharmacol.* **38**:1042-1050 1998) may increase the norethindrone clearance and thereby decrease norethindrone efficacy.

5. What are the formulations used in the clinical studies for NDA 20-011 S-021 and 20-708 S-011?

Sponsor used marketed LUPRON DEPOT® 3.75 mg and Aygestin® products in clinical Studies M92-878 and M97-777. 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.

Sponsor used gelatin capsule for Aygestin® blinding in Study M92-878 (see Attachment). Aygestin® is commercially available as a tablet. Generally, in vitro dissolution Aygestin® data should be provided to justify the lack of difference between the encapsulated Aygestin® and unencapsulated Aygestin®. Sponsor used unencapsulated Aygestin® in Study M97-777 (see Attachment). Since the effect on bone mineral density between these 2 treatment groups in Studies M92-878 and M97-777 are similar per Dr. Scott Monroe (medical reviewer), the absence of in vitro dissolution Aygestin® data to justify the lack of difference between encapsulated Aygestin® and unencapsulated Aygestin® is acceptable.

6. What are the proposed in vitro dissolution method and specifications for the Lupron 3.75 mg and Lupron 11.25 mg as well as 5 mg norethindrone tablets?

The in vitro dissolution methods and specifications for Lupron 3.75 mg and Lupron 11.25 mg as well as 5 mg norethindrone tablets (Aygestin®) are the same as those in the respective NDAs.

7. What are sponsor's proposed labeling for product's Clinical pharmacology section?

In the Clinical Pharmacology section of the 11.5 mg LUPRON labeling under Metabolism 2 statements "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." should be removed. Thanks to medical officer, Dr. Scott Monroe, who pointed out that the serum leuprolide and M-I concentrations were all under quantitation limit. These 2 statements were based on Study M96-506 submitted under [redacted] Amendment no. 167, April 2, 1998. The word "also" in the statement "There was also no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups." should be removed. This statement was based on the conclusion drawn on estradiol evaluation in the medical officer's review dated Jan 29 1999 (NDA 20-708 serial # 167, protocol # M96-506; see Attachment).

Labelings for the 3.75 mg LUPRON and 11.5 mg LUPRON follow.

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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.