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APPLICATION NUMBER:

203696Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203696
Priority or Standard	Standard
Submit Date(s)	February 15, 2012
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Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Ronald J. Orleans, M.D.
Review Completion Date	November 15, 2012
Established Name	Leuprolide acetate / Norethindrone acetate
(Proposed) Trade Name	
Therapeutic Class	Synthetic nonapeptide analogue/ Synthetic progestin
Applicant	Abbott Laboratories
Formulation(s)	Depot suspension/oral tablet
Dosing Regimen	Lupron Depot injection monthly (3.75 mg) or every 3 months (11.25 mg) with oral norethindrone acetate 5 mg daily
Indication(s)	Management of endometriosis with add-back therapy
Intended Population(s)	Women with endometriosis associated pain

Template Version: March 6, 2009

Table of Contents

Table of Tables

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Co-treatment consisting of Lupron Depot 3.75 mg and norethindrone acetate 5 mg daily (NDA 020011/S-011) and co-treatment consisting of Lupron Depot-3 month 11.75 mg and norethindrone acetate 5 mg daily (NDA 020708/S-021) were both found by the FDA to be safe and effective for the initial management of endometriosis and for the management of recurrence of symptoms. With either combination, the duration of initial treatment or retreatment should be no longer than 6 months. Co-treatment with these two drugs was approved for this indication on September 21, 2001 under NDAs 20-011 and 20-708; however, joint labeling was not implemented at that time.

The current application proposes to market a one-month and a 3-month co-packaged kit configuration for these two FDA-approved products. The proposed indication for the co-packaged products would be for the initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. The duration of initial treatment or retreatment should not be longer than 6 months.

Medical Reviewer's Comment

- *The availability of co-packaged Lupron Depot/norethindrone acetate tablets for the management of endometriosis-associated pain facilitates the concurrent use of these two dosage regimens of this FDA-approved endometriosis treatment. Therefore, I recommend approval of the co-packaged product contingent upon agreement upon labeling.*

1.2 Risk Benefit Assessment

It has been adequately demonstrated in two phase 3 clinical trials that co-treatment with monthly Lupron Depot 3.75 mg plus 5 mg of norethindrone acetate attenuates the decrease in bone mineral density that is associated with Lupron Depot treatment alone without reducing the efficacy of the Lupron treatment. Co-treatment with Lupron plus norethindrone acetate also reduced the frequency and severity of hot flashes compared to treatment with Lupron alone. Treatment with 5 mg of norethindrone acetate, however, has an adverse effect on serum lipid profiles as it decreases serum concentrations of HDL-cholesterol.

Medical Reviewer's Comment

- *The clinical significance of the decrease in HDL-cholesterol is uncertain.*

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The combination of Lupron Depot and norethindrone acetate 5 mg has been approved for the management of endometriosis since 2001. No new postmarket risk evaluation and mitigation strategies are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

The combination of Lupron Depot and norethindrone acetate 5 mg has been approved for the management of endometriosis since 2001. No new postmarketing requirements or commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Lupron Depot (leuprolide acetate for depot suspension) is a synthetic, long acting, analogue of naturally occurring gonadotropin-releasing hormone (GnRH) in which D-leucine has replaced glycine in position 6 of the natural peptide. Two depot formulations of Lupron have been approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Both formulations are also approved with concomitant iron therapy for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.

The 3.75 mg formulation is administered by intramuscular (IM) injection once a month and the 11.25 mg formulation is administered IM once every 3 months. Both Lupron Depot 3.75 mg and Lupron Depot-3 Month 11.25 mg are indicated for initial management of endometriosis and for management of recurrence of symptoms. The recommended duration of initial treatment or retreatment with the Lupron 1-month or 3-month formulation in combination with norethindrone acetate (NETA) is not to exceed six months.

NETA is a progestin in the class of 19-nortestosterone derivatives. NETA 5 mg is also currently FDA-approved as a monotherapy for the treatment of endometriosis. The initial daily dosage is 5 mg for two weeks. Dosage can be increased by 2.5 mg per day every two weeks until 15 mg per day is reached. Therapy may be held at this level for six to nine months or until breakthrough bleeding requires temporary termination. Other FDA-approved indications for NETA include the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

The Applicant, Abbott Endocrine Inc., has submitted a New Drug Application (NDA) to obtain marketing authorization for two co-packaged kit configurations of previously

approved drug products, leuprolide acetate for depot suspension and NETA tablets, for the treatment of endometriosis with addback therapy. The proposed kits will be for a one-month and three-month dosage regimen.

The one-month co-packaged kit includes:

- Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (for 1-month administration) syringe/needle/alcohol swabs (Abbott NDA 020011)
- Norethindrone acetate 5 mg tablets; 30 tablets/bottle (Glenmark ANDA 091090).

The three-month co-packaged kit includes:

- Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg (for 3-month administration) syringe/needle/alcohol swabs (Abbott NDA 020708)
- Norethindrone acetate 5 mg tablets; 90 tablets/bottle (Glenmark ANDA 091090).

Medical Reviewer's Comments

- *Lupron and NETA are not currently co-packaged. Each drug is obtained separately.*
- *The current application is for the endometriosis indication only.*

2.2 Tables of Currently Available Treatments for Proposed Indications

Medical therapy is the first line of treatment for endometriosis-associated pain. Non-steroidal anti-inflammatory drugs and combined oral contraceptive therapy are currently the most common initial treatments for this disorder. When these fail, FDA-approved options include oral norethindrone acetate, subcutaneous injectable depot medroxyprogesterone acetate, Danazol, and GnRH agonists.

Medical Reviewer's Comment

- *Danazol is an androgenic drug that has been used for the treatment of endometriosis-associated pain. Although highly effective, it is no longer available in the US.*

The concept of add-back therapy was proposed based on the theory that while suppression of estrogen can produce significant adverse effects, profound suppression is not needed to effectively treat endometriosis-associated pain. It was hypothesized that by adding a small amount of sex steroid hormone to the GnRH agonist treatment regimen, the efficacy of the treatment could be maintained while side effects could be minimized. The expected result would be improved compliance with the medication resulting in better outcomes. This theory has been proven correct in that a number of

add-back regimens maintain GnRH agonist efficacy while substantially reducing side effects. In a large, multicenter trial, GnRH agonist plus norethindrone acetate 5 mg/day was as effective for pain relief as the agonist alone, but side effects were substantially reduced: vasomotor symptoms were decreased by two-thirds and bone mineral density loss was eliminated.[1] This result led to the Agency approval of norethindrone acetate as appropriate add-back with GnRH agonist treatment.

Medical Reviewer's Comment

- *Add-back treatment does not decrease the efficacy of pain relief observed during 3 months or 6 months of GnRH agonist treatment. Therefore, the add-back regimen can be started immediately with the GnRH agonist.*

2.3 Availability of Proposed Active Ingredient in the United States

The following Abbott Lupron Depot sNDAs were approved on September 21, 2001 for the original endometriosis add-back indication:

- sNDA 020011/S-021: Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration
- sNDA 020708/S-011: Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration

Glenmark, the application holder for generic NETA 5 mg tablets (ANDA 91-090/S-002), received Agency approval for marketing on January 17, 2012.

2.4 Important Safety Issues with Consideration to Related Drugs

GnRH agonists produce a menopause-like state that often results in side effects such as vasomotor instability, vaginal dryness, mood alterations, and bone mineral density loss.

Medical Reviewer's Comment

- *The loss of bone mineral density is the most clinically significant and potentially the most serious adverse consequence of therapy with Lupron. Hot flushes are the most commonly reported adverse event.*

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As mentioned in Section 2.3, Lupron Depot was previously approved for use in combination with NETA for the endometriosis add-back indication in the following NDA applications:

[1] Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. Lupron Add-Back Study Group. *Obstet. Gynecol.* 91, 16–24 (1998).

- Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration; sNDA 020011/S-021; approved September 21, 2001
- Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration, sNDA 020708/S-011; approved September 21, 2001
- Glenmark ANDA 91-090: norethindrone acetate 5 mg tablets; 30 tablets/bottle and 90 tablets/bottle; Office of Generic Drugs approval letter dated January 17, 2012

The two clinical trials that supported the original endometriosis add-back indication in sNDA 20-011/S-021 and sNDA 20-708/S-011 are:

- Clinical Study M97-777 entitled: Combination Lupron Depot and Aygestin Add-Back in the Management of Endometriosis
- Clinical Study M92-878 entitled: Combination Lupron Depot – Hormonal Add-Back in the Management of Endometriosis

Medical Reviewer's Comment

- *In the FDA Meeting Minutes from a November 10, 2011 teleconference, the Division agreed that it was acceptable to cross-reference the historical Lupron NDAs that supported the approval of the Lupron endometriosis add-back indication and that no additional clinical trials were needed to support this application.*

Numerous presubmission agreements were made with the Applicant prior to the NDA submission.

March 23, 2011: Advice Request

1. The Applicant initially proposed that the co-packaged product have the following labeled indication:

(b) (4)

(b) (4)

, the Division suggested the proposed indication for the co-packaged product: be the following:

TRADENAME is indicated for initial management of the painful symptoms of

endometriosis and for management of recurrence of symptoms. Duration of initial treatment or retreatment should be limited to 6 months.

2. The Agency agreed that it was acceptable to cross-reference the historical Lupron NDAs that supported the approval of the Lupron add-back indication and that no additional phase 1 or phase 3 studies were necessary to support the NDA, provided that the proposed indication was amended.

November 10, 2011: Type B Pre-NDA Teleconference

1. The Applicant agreed to use the Division's March 23, 2011 suggested wording for the indication.
2. The Agency again agreed that it was acceptable to cross-reference the historical Lupron NDAs and that no documents need to be included in Modules 2, 4 and 5 with the exception that the PSUR will be included in Module 5.
3. The Applicant was asked to provide a 120-day safety update to include reviews of the current literature and a summary of postmarketing safety information.
4. Regarding the Applicant's proposed pediatric waiver request, the Division requested the Applicant to provide data supporting the rarity of endometriosis in women under age 18 in order to support a full waiver request in pediatric females. Alternatively, the Applicant could request a partial waiver of studies in premenarcheal females and extrapolation of data from adult women to address the need for data in postmenarcheal pediatric patients.

2.6 Other Relevant Background Information

The first marketing authorization (the international birth date) for Lupron was granted in Germany on July 31, 1984. Lupron has now been approved for marketing as an agent to treat prostate cancer, metastatic prostate cancer, locally advanced prostate cancer, endometriosis, uterine myomas, breast cancer, central precocious puberty, or infertility, in 87 countries.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA concluded that marketing this product under a unique proprietary name was a better option than marketing the product with the root name. The option of using a modifier in the root name, Lupron, carries the risk of omission of the modifier which could lead to drug errors.

The proposed name for this product, if approved, is Lupaneta Pack, which is found acceptable to DMEPA.

Office of Surveillance and Investigation (OSI)

Inspection of clinical sites was not performed as no clinical studies were submitted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the overall submission was acceptable.

3.2 Compliance with Good Clinical Practices

As mentioned above, the Division has previously agreed that no new phase 3 clinical trials were needed for the proposed Lupron Co-Pack NDA submission. Therefore, no issues regarding compliance with good clinical practice needed to be addressed.

3.3 Financial Disclosures

Financial Disclosure Certifications are not required in this NDA because there are no new clinical data that supports this indication in this NDA. The financial disclosure certifications were included at the time of study completion in NDA 20-011/S-021; submitted November 21, 2000 for clinical study M97-777.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone. Norethindrone acetate is a synthetic, orally active progestin. No significant new chemistry data were submitted with this application.

Medical Reviewer's Comment

- *The chemistry reviewer from the Division of New Drug Quality Assessment stated in his review dated October 2, 2012 that the applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.*

4.2 Clinical Microbiology

Clinical microbiology was not relevant to this submission.

4.3 Preclinical Pharmacology/Toxicology

No preclinical studies have been submitted and none were requested for these two approved drugs.

Medical Reviewer's Comment

- *Pharmacology/Toxicology recommends approval of NDA 203696 from the P/T perspective.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Administration of Lupron Depot in therapeutic doses results in an initial stimulation followed by a prolonged suppression of the pituitary-gonadal system. Repeated dosing at monthly (Lupron Depot 3.75 mg) or quarterly (Lupron Depot 11.25 mg) intervals results in decreased secretion of gonadal steroids; consequently, tissues that depend on these steroids become hormonally inactive. It has been confirmed that these effects of Lupron are reversible with discontinuation of treatment.

4.4.2 Pharmacodynamics

Leuprorelin is a synthetic GnRH derivative that was developed as a result of research on GnRH (or luteinizing hormone-releasing hormone; LHRH). It has stronger gonadotropin-releasing activity than natural gonadotropic hormone, and its continuous administration at a therapeutic dose inhibits gonadotropin production, resulting in suppression of sex hormone secretion from the ovaries and testes.

4.4.3 Pharmacokinetics

No new pharmacokinetic data were submitted with this application.

Medical Reviewer's Comment

- *Prior PK/PD studies in healthy female subjects, have demonstrated that the onset of estradiol suppression occurs between Day 4 and Week 4 after dosing.*

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The original NDA holder (TAP Pharmaceutical Products) conducted 2 clinical trials in the United States in which women with painful symptoms of endometriosis were treated with Lupron 3.75 mg plus “hormone add-back therapy” for up to one year.

The first clinical trial (Study M92-878) was a randomized, blinded, 4-arm multicenter study in which a total of 201 women with endometriosis were enrolled and treated with either Lupron alone, Lupron plus 5 mg NETA per day, or Lupron plus 5 mg NETA plus either 0.625 mg or 1.25 mg of conjugated equine estrogen daily. Women were randomly assigned to one of the treatment groups in a 1:1:1:1 ratio.

The second trial (M97-777) was an open-label, single-arm, multicenter study in which 136 women with endometriosis were enrolled. All patients were treated with once monthly Lupron and 5 mg NETA per day.

Across the two studies, a total of 337 women with a diagnosis of endometriosis confirmed by laparoscopy or laparotomy, were enrolled. A total of 242 subjects were treated with Lupron alone or Lupron plus NETA. The remaining 95 subjects were treated with Lupron plus NETA plus conjugated estrogens. In both studies, Lupron Depot 3.75 mg was administered by intramuscular injection once every 4 weeks (a total of 13 injections) during the treatment period and oral NETA or placebo was administered daily. Calcium supplementation was supplied throughout the treatment and follow-up periods.

Although both clinical trials differed significantly in overall design, the efficacy and safety assessments and endpoints of these trials were very similar.

Medical Reviewer's Comment

- *All the clinical data submitted to support the original application for co-treatment were obtained with the 3.75 mg formulation of Lupron. A study conducted by TAP Pharmaceutical Products as part of a phase 4 commitment for the approval of the 11.25 mg formulation did not reveal any clinically significant differences between the 3.75 mg and the 11.25 mg formulations in terms of either efficacy (reduction of painful symptoms of endometriosis) or magnitude of the decrease in bone mineral density (BMD). Based on these findings, it was concluded that co-treatment with NETA would have the same protective effect on BMD in women treated with the 11.25.mg formulation of Lupron, so only clinical trials using the 3.75 mg formulation were cross-referenced to this NDA.*

5.2 Review Strategy

No new clinical trial data were submitted with this application.

5.3 Discussion of Individual Studies/Clinical Trials

No new clinical trial data were submitted with this application.

6 Review of Efficacy

Efficacy Summary

There were two clinical trials that supported the original endometriosis add-back indication in sNDA 20-011/S-021 and sNDA 20-708/S-011. Assessment of changes in BMD was the primary objective of both clinical trials. In Study M92-878, 51 subjects were enrolled into the Lupron alone group and 55 were enrolled in the Lupron plus NETA group. In Study M97-777, 136 subjects were enrolled and all were treated with Lupron plus NETA.

Clinical data obtained from both trials demonstrated that co-treatment with monthly LD 3.75 (or LD 11.25) plus NETA 5 mg daily attenuates the decrease in BMD observed when Lupron is used alone. Women with symptomatic endometriosis co-treated with Lupron Depot plus NETA for up to one year had mean changes in BMD from baseline to Week 24 and Week 52 of treatment of -0.2% and -1.0%, respectively. Women treated with Lupron alone had mean changes in BMD at Week 24 and Week 52 of -3.2% and -6.3%, respectively.

Evaluation of efficacy was a secondary objective. At the final treatment visit in each treatment group (LD, LD/NETA in Study M92-878 and LD/NETA in Study M97-977), there was a statistically significant decrease in each of the efficacy variables (dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness and pelvic induration)

evaluated by (1) the proportion of subjects with these respective signs or symptoms and (2) the mean clinical pain severity score. The response to treatment in subjects in both the LD alone group and in the LD/NETA group was similar, so efficacy was demonstrated.

In the one comparative trial, Study M92-878, there was no significant difference between the clinical responses in the LD and LD/NETA treatment groups. Therefore, co-treatment with LD/NETA did not decrease the efficacy of Lupron treatment alone when used to treat women with symptomatic endometriosis.

During the treatment period, total serum estradiol levels were also determined at each scheduled visit. Statistically significant within-group mean decreases from baseline were noted in all treatment groups at each visit during the treatment period. Mean total serum estradiol levels during the treatment period were lower in the LD/NETA treatment groups (8.6 pg/mL and 8.4 pg/mL) compared to the LD treatment group (14.5 pg/mL).

Medical Reviewer's Comment

- *NETA is known to reduce serum concentrations of SHBG. Since approximately 50% of total estradiol in serum is bound to SHBG (and hence not biologically active), this would account for the greater reduction of total estradiol in the LD/NETA group. It is not known if biologically active levels of estradiol differed in each group.*

7 Review of Safety

Safety Summary

The proportion of subjects experiencing any adverse event, treatment-related adverse events and treatment-related serious adverse events as well as premature withdrawals due to adverse events were similar across the LD treatment group and the two LD/NETA treatment groups in the two studies described above. A lower proportion of subjects treated with LD/NETA reported adverse events that were rated as severe in intensity. This difference was thought to be due to a reduction in the severity and frequency of severe hot flashes in the LD/NETA treated subjects.

Co-treatment with 5 mg of NETA did not raise any new safety concerns with the exception of an adverse effect on serum concentrations of HDL-cholesterol thought to be due to NETA's androgenic properties.

7.6 Additional Safety Evaluations

No additional safety evaluations were requested or provided for review.

7.6.1 Human Carcinogenicity

No new pharmacology/toxicology studies were submitted with this application.

7.6.2 Human Reproduction and Pregnancy Data

Safe use of leuprolide acetate or norethindrone acetate in pregnancy has not been established clinically. Before starting treatment with Lupron, pregnancy should be excluded.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant requested a full waiver for pediatric studies in patients aged 0-17 and listed the following reasons:

- Time from onset of symptoms to diagnosis of endometriosis takes approximately 7 years; this time delay means that even in women with early menarche would likely be at least age 18 years before specific therapeutic interventions like GnRH agonist treatment are started. Therefore, treatment with the proposed leuprolide acetate for depot suspension and norethindrone acetate tablets kits would not generally be considered for the use in patients before the age of 18 years.
- A controlled clinical study in the few potential patients below 18 years is considered not feasible due to the very low number of cases.
- Neither drug component within the proposed kit, leuprolide acetate for depot suspension and norethindrone acetate tablets is currently approved for use in children.

Medical Reviewer's Comments:

- *At a teleconference held on November 11, 2011, the FDA told the Applicant the following:*

  "The Sponsor should provide data supporting the rarity of endometriosis in women under age 18 in order to support a full waiver request in pediatric females. Alternatively, the Sponsor could request a partial waiver of studies in premenarcheal females and extrapolation of data from adult women to address the need for data in postmenarcheal pediatric patients."

- *Evidence was provided in the submission that the overall time from onset of symptoms to a diagnosis of endometriosis is approximately 7.0 years as observed in Brazilian women (Arruda et al, 2003) and is similar to that reported earlier by The National Endometriosis Society of Great Britain and the Australian Endometriosis Association and as also reported for the diagnosis of endometriosis in the US (Hadfield 1996, Schindler 2007).*

8 Postmarket Experience

Periodic Safety Update Reports (PSURs)

1. The 27th PSUR covers the period from February 1, 2011 to July 31, 2011.

This PSUR was submitted in the original submission (S-0001).

Lupron has been approved as an agent to treat patients with prostate cancer, metastatic prostate cancer, locally advanced prostate cancer, endometriosis, uterine myoma/fibroids, breast cancer, central precocious puberty, and infertility, in 87 countries as of the data-lock point (31 January 2011). The indications for use of leuprorelin vary in different countries.

The number of patients receiving Lupron in the 6-month period covered by this PSUR was estimated at 583,599. A total of 424 safety reports that met the criteria for inclusion were received globally during the period under review. Cumulatively, 3,531 serious unlisted cases have been received, of which 142 were received during the current reporting period.

Lupron is available in five dose forms:

1. Daily injection
2. 1-month (1M) sustained release injection (Leuprorelin acetate-1M) used for the treatment of endometriosis-associated pain and the preoperative treatment of anemia with iron therapy in patients undergoing surgery for uterine fibroids.
3. 3-month (3M) sustained release injection (Leuprorelin acetate-3M) used for the treatment of endometriosis-associated pain and the preoperative treatment of anemia with iron therapy in patients undergoing surgery for uterine fibroids.
4. 4-month (4M) sustained release injection (Leuprorelin acetate-4M) used for the palliative treatment of advanced prostatic cancer.
5. 6-month (6M) sustained release injection (Leuprorelin acetate-6M) used for the palliative treatment of advanced prostatic cancer.

According to the Applicant, the following safety issues are being closely monitored:

- Interstitial lung disease
- Diabetes
- Cerebrovascular accident
- Coronary heart disease (including myocardial infarction)
- Embolism/Thrombosis
- Injection site reaction

- Loss of bone density
- Hypertension
- Severe depression
- Convulsion

A total of 424 cases (230 adult male cases, 172 adult female cases and 22 child cases) were reported worldwide during the reporting period and met the criteria for inclusion i.e., any event judged not to be related to Lupron by both the reporter and the company was not included in these line listings or tabulations. However, if either the reporter or the company judged an event to be anything other than not related, the event is included as suspected ADR in the line listings and/or summary tabulations.

For the 424 cases received, 149 included at least one suspected serious adverse drug reaction (ADR), of which 71 were received from clinical trials, 6 from the literature, and the remaining 72 were received through spontaneous reporting sources including reports from regulatory authorities.

During the reporting period, there were a total of 172 case reports worldwide dealing with females. A total of 40 of these reports were classified as serious. In the US, there were a total of 87 case reports, of which 19 were serious.

For Lupron, the profile of ADR reports is similar to that seen in the previous PSURs and reported in clinical trials conducted with Lupron. The greatest number of suspected ADRs were reported from the SOC “General disorders and administration site conditions” with a high number of injection site reactions reported in the covered period. Injection site reactions are known to occur with leuprorelin treatment (See Table 1 below).

The most commonly reported serious unlisted ADRs in females included abdominal pain, syncope, dyspnea, pulmonary embolism, vasodilatation, hypertension, chest pain and fatigue.

Table 1 ADRs Reported in the Female Population by SOC

Adverse Drug Reactions	Total
Blood and lymphatic system disorders	2
Cardiac disorders	3
Congenital, familial and genetic disorders	1
Ear and labyrinth disorders	1
Endocrine disorders	2
Eye disorders	5
Gastrointestinal disorders	20
General disorders and administration site conditions	66
Immune system disorders	5
Infections and infestations	7
Injury, poisoning and procedural complications	8
Investigations	19
Metabolism and nutrition disorders	2
Musculoskeletal and connective tissue disorders	40
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5
Nervous system disorders	43
Pregnancy, puerperium and perinatal conditions	8
Psychiatric disorders	24
Renal and urinary disorders	2
Reproductive system and breast disorders	34
Respiratory, thoracic and mediastinal disorders	14
Skin and subcutaneous tissue disorders	30
Surgical and medical procedures	3
Vascular disorders	17
Total	**361**

Source: 27th PSUR, Adapted from Table 6e, Page 9 (One subject may have more than1 event.)

The nature and frequency of the reported adverse drug reactions ADRs did not differ from those described in previous PSURs.

In the PSUR, there were 37 new reports of ADRs with a fatal outcome in which Lupron were considered a suspect medication. Four of these deaths occurred in women.

- An obese 40-year-old woman with a history of coagulopathy, epilepsy, polycystic ovaries, and endotracheal intubation who received leuprorelin 11.25 mg for uterine fibroids and endometriosis. She died of a cardiac arrest four days post sinus surgery.

- A 31-year-old woman had been receiving leuprorelin for 1½ months for the treatment of endometriosis experienced a fatal stroke.
- A 56-year-old woman with a history of deep vein thrombosis who was taking leuprorelin 3.75 mg for uterine fibroids for an unknown period of time. The patient started leuprorelin prior to pre-planned surgery for a hysterectomy and hernia repair. Two days after surgery, she experienced a pulmonary embolism and died.
- A 40-year-old woman with a history of migraines was receiving leuprorelin 3.75 mg depot for the treatment of uterine fibroids. The patient received treatment for 3 months. On an unknown date, she experienced a ruptured cerebral aneurysm, and died.

Medical Reviewer's Comments

- *Most of the deaths that occurred with Lupron were in men being treated for prostate cancer.*

During the period under review, none of the following safety actions have been taken:

- Marketing authorization withdrawal, revocation or suspension
- Failure to obtain a marketing authorization renewal
- Restriction on distribution
- Clinical trial suspension

Medical Reviewer's Comments

- *There was no evidence of a change in characteristics of the reported listed adverse reactions during this PSUR period, i.e., in terms of severity, outcome, or target population.*
- *These reports do not suggest a trend or new safety signal.*
- *Based on the review of the information presented in this PSUR, there is no change to the benefit/risk evaluation for Lupron.*

2. The 28th PSUR covers the period from August 1, 2011 to January 31, 2012.

This PSUR was submitted to the NDA on June 14, 2102 (S-0005).

The number of patients receiving leuprorelin in the 6-month period was estimated at 799,096. A total of 508 cases that met the criteria for inclusion were received globally during the period under review. Cumulatively, 3,682 serious unlisted cases have been received, of which 151 were received during the current reporting period.

The Applicant continues to monitor the same case reports as outlined in the 27th PSUR.

A total of 508 cases (303 adult male cases, 166 adult female cases and 39 child cases) were reported globally during the reporting period and met the criteria for inclusion.

Of the 166 total case reports and 24 serious case reports received during the reporting period, 86 total reports and 24 serious case reports were received from the US.

For Lupron, the profile of ADR reports is similar to that seen in the previous PSURs and clinical trials conducted with Lupron. The greatest number of suspected ADRs were reported from the SOC "General disorders and administration site conditions" with a high number of injection site reactions reported in the covered period.

Table 2 ADRs Reported in the Female Population by SOC

Adverse Drug Reactions	Total
Blood and lymphatic system disorders	2
Cardiac disorders	1
Congenital, familial and genetic disorders	0
Ear and labyrinth disorders	1
Endocrine disorders	2
Eye disorders	5
Gastrointestinal disorders	19
General disorders and administration site conditions	57
Hepatobiliary disorders	2
Immune system disorders	2
Infections and infestations	9
Injury, poisoning and procedural complications	8
Investigations	25
Metabolism and nutrition disorders	9
Musculoskeletal and connective tissue disorders	26
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3
Nervous system disorders	28
Pregnancy, puerperium and perinatal conditions	2
Psychiatric disorders	13
Renal and urinary disorders	2
Reproductive system and breast disorders	22
Respiratory, thoracic and mediastinal disorders	5
Skin and subcutaneous tissue disorders	22
Surgical and medical procedures	1
Vascular disorders	15
Total	**281**

Source: 28th PSUR, Adapted from Table 6e, Page 9 (One subject may have more than1 event.)

In the PSUR, there were 38 new reports of ADRs with a fatal outcome in which leuprorelin were considered a suspect medication. Two of these deaths occurred in women.

- A 33 year old female patient received Leuprorelin acetate 3.75 mg for breast cancer. The patient experienced widespread metastatic breast cancer and died due to cardiopulmonary collapse.
- Solicited report of a 42 year old female patient who died on (b) (6) of an unknown cause. The patient started on Lupron therapy on September 2, 2010 for control of excessive bleeding. The last Lupron injection was on September 27, 2011.

Medical Reviewer's Comments

- *Most of the deaths that occurred with Lupron were in men with prostate cancer.*
- *The safety profiles of Lupron Depot and NETA are consistent with the known effects of these two drugs.*

During the period under review, none of the following safety actions have been taken:

- Marketing authorization withdrawal, revocation or suspension
- Failure to obtain a marketing authorization renewal
- Restriction on distribution
- Clinical trial suspension

Based on the review of the information presented in this PSUR, there is no change to the benefit/risk evaluation for leuprorelin. No new information affecting the known safety profile of leuprorelin was noted, and the benefit/risk profile of leuprorelin remained unchanged.

3. The 120-day Safety Update Report covers the period from February 1, 2012 through April 15, 2012.

The 120-day Safety Update Report was submitted to the NDA on June 14, 2012 (S-0005). This report supplements the 28th PSUR. The Applicant received 26 ADRs from February 1, 2012 through April 15, 2012. Of the 26 reports, 22 were nonserious. Four reports were submitted to the FDA as 15-day alerts. The four reports contained five serious unexpected events all of which occurred in female adult women. These were:

- Bundle branch block (n=2)
- Cough, dyspnea (n=2)
- Anaphylactic shock (n=1)

No reports described a fatal event.

Medical Reviewer's Comments

- *These reports do not suggest a trend or a new safety signal.*

4. Literature review in the 120-day Safety Update Report

A review of the available literature published from February 1, 2012 through April 15, 2012 was conducted by the Applicant. No articles were found that focused on the use of GnRH agonists combined with add-back therapy during this time period.

9 Appendices

9.2 Labeling Recommendations

Labeling negotiations are currently ongoing. Issues involve PLR conversion, as well as integrating and updating the NETA and Lupron labeling for the co-packaged products. In addition, a Patient Package Insert needs to be developed by the Applicant.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not requested for this application because both drug products are already approved.

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

/s/

RONALD J ORLEANS
11/15/2012

LISA M SOULE
11/15/2012
I concur with Dr. Orleans' conclusions and recommendation that NDA 203-696 be approved contingent upon agreement upon labeling.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203696 | **Applicant: Abbott Laboratories** | **Stamp Date: February 15, 2012**

Drug Name: Leuprolide acetate depot and norethindrone acetate tablets | **NDA Type: 505(b)(1) Standard Review** | **PDUFA Date: December 15, 2012**

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			electronic CTD with Global Summit Review enabled
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?			X	Submission contains no new clinical trial data
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?			X	
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?			X	
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	X			PLR labeling submitted in Module 1.14
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?			X	No Module 2 summaries were required or submitted
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	No ISS was required or submitted
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	No ISE was required or submitted
11.	Has the applicant submitted a benefit-risk analysis for the product?			X	
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Application filed as a 505(b)(1)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	Dosages of Lupron and norethindrone acetate have previously been approved for the indication sought
EFFICACY					

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study: Indication:			X	Submission contains no new clinical trial data
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			PSURs for the last 4.5 years were submitted in Module 5
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Not needed for this application
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			PSURs were submitted in Module 5
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission			X	No new studies were requested or submitted

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	discussions with the sponsor?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant requested a full waiver for pediatric studies in patients aged 0-17 years inclusive
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Not needed for this application
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	Not needed for this application
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?			X	Not required since no new clinical trial data were submitted
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			X	Not required since no new clinical trial data were submitted
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	X			

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA 203696 seeks approval for two proposed co-packaged kits each combining Lupron Depot suspension and norethindrone acetate tablets.

One-month co-packaged kit that contains:

- Lupron Depot 3.75 mg (for 1-month administration) syringe/needle/alcohol swabs (Abbott NDA 20-011) and
- Norethindrone acetate (NETA) 5 mg; 30 tablets/bottle (Glenmark ANDA 91-090)

A second co-packaged kit contains:

- Lupron Depot 11.25 mg (for 3-month administration) syringe/needle/alcohol swabs (Abbott NDA 20-708) and
- NETA 5 mg; 90 tablets/bottle (Glenmark ANDA 91-090)

Abbott intends to provide the proposed co-packaged kits with an outer carton container that will contain the Lupron Depot syringe kit and NETA bottle components within one carton, which is secured with an adhesive seal.

Both Lupron Depot 3.75 mg and Lupron Depot 11.25 mg are FDA-approved for the management of endometriosis, including pain relief and reduction of endometriotic lesions.

NETA alone is approved for the treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer (Glenmark ANDA 91-090: norethindrone acetate 5 mg tablets; 30 tablets/bottle and 90 tablets/bottle; Office of Generic Drugs approval letter dated January 17, 2012.

The following Abbott Lupron Depot (leuprolide acetate for depot suspension) sNDAs have been approved for the use in endometriosis patients with add-back therapy (NETA 5 mg):

- sNDAs 20-011/S-021: Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration; approval letter dated September 21, 2001.
- sNDA 20-708/S-011: Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration; approval letter dated September 21, 2001.

The clinical studies that supported the original endometriosis add-back indication in sNDA 20-011/S-021 and sNDA 20-708/S-011 are:

- Clinical Study M97-777 entitled: Combination Lupron Depot and Aygestin Add-Back in the Management of Endometriosis
- Clinical Study M92-878 entitled: Combination Lupron Depot – Hormonal Add-Back in the Management of Endometriosis

Abbott is seeking an indication for the “initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. Duration of initial treatment or retreatment should be limited to 6 months."

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

The Division had previously agreed that it was acceptable to cross-reference the historical Lupron Depot NDAs that supported the approval of Lupron Depot endometriosis add-back indication and that no additional information was needed for Module 2, 4 and 5 (with the exception of the PSURs that are included in Module 5). Therefore, no new clinical trial data were submitted to support this application.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

From a clinical perspective, this application is fileable.

Comment to Applicant:
The Applicant should be reminded that in spite of the fact there are no ongoing studies; the 120-day safety update is generally required for an NDA submission. This should include reviews of the current literature and a summary of postmarketing safety information. The PSUR may be sufficient to address postmarketing safety information provided the cut–date for the information in the report is close to the cut-date for the 120-day safety update.

Reviewing Medical Officer: Ronald J. Orleans, M.D. Date: April 10, 2012

Clinical Team Leader: Lisa M. Soule, M.D. Date: April 10, 2012

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

/s/

RONALD J ORLEANS
04/12/2012

LISA M SOULE
04/12/2012