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APPLICATION NUMBER:

203696Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 13, 2012
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	203-696
Applicant	Abbott Laboratories
Date of Submission	February 15, 2012
PDUFA Goal Date	December 15, 2012
Proprietary Name / Established (USAN) names	Lupaneta Pack Leuprolide acetate for depot suspension and norethindrone acetate (NETA)
Dosage forms / Strength	Leuprolide acetate (LA) for depot suspension and NETA tablets co-package kits: 1 Month: 3.75 mg LA injection/5 mg NETA tablets (30 tablets/bottle) kit 3 Month: 11.25 mg LA injection/5 mg NETA tablets (90 tablets/bottle) kit
Proposed Indication(s)	Initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms
Recommended:	Approval

1. Introduction

Leuprolide acetate (LA) for depot suspension is a gonadotropin-releasing hormone (GnRH) agonist used to treat the sex steroid-dependent gynecologic conditions of endometriosis and uterine fibroids. LA is available for the gynecologic indications in two doses; a 3.75 mg dose that is administered monthly, and an 11.25 mg dose administered every three months. Administration of LA results in an initial elevation, followed by prolonged suppression, of pituitary gonadotropins (Follicle-Stimulating Hormone [FSH] and Luteinizing Hormone [LH]). This causes decreased secretion of gonadal hormones such as estrogen, which has a beneficial impact on the symptoms of endometriosis and fibroids. Limited duration of use of LA has been recommended due to the adverse impact on bone mineral density (BMD) of the resultant hypoestrogenic state. Co-administration with a progestin, norethindrone acetate (NETA), has been shown to mitigate the effect of LA on BMD, as well as other associated side effects such as hot flashes, and this treatment regimen has been approved for a number of years. In this application, the Applicant seeks approval for co-packaging of the two drug products, LA and NETA. Two co-packaged kits are proposed, corresponding to the one-month and the three-month administration regimens.

2. Background

2.1 DESCRIPTION OF PRODUCT

Leuprolide acetate is approved in the following formulations and for various indications:

- Lupron – leuprolide acetate for depot suspension (3.75, 1-month administration and 11.25 mg, 3-month administration, **NDA 19-943**), indicated for “management of endometriosis, including pain relief and reduction of endometriotic lesions” and “preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.”
- Lupron Depot - leuprolide acetate for depot suspension, indicated for
 - Management of endometriosis and preoperative hematologic improvement of anemia caused by uterine fibroids (3.75 mg, 1-month administration, **NDA 20-011** and 11.25 mg, 3-month administration, **NDA 20-708**)
 - palliative treatment of advanced prostate cancer (7.5 mg, 1-month administration, NDA 19-732 and multiple higher doses for 3-, 4- and 6-month administration, NDA 20-517)
- Lupron Depot-Ped - leuprolide acetate for depot suspension (multiple doses for once-monthly weight-based dosing, NDA 20-263), indicated for treatment of children with central precocious puberty
- Viadur – leuprolide acetate implant (NDAs 21-088), indicated for palliative treatment of advanced prostate cancer
- Eligard – leuprolide acetate suspension for subcutaneous injection (NDAs 21-343, 21-379, 21-488 and 21-731 and a number of generic ANDAs), indicated for palliative treatment of advanced prostate cancer

Norethindrone acetate is a 19-nortestosterone derived progestin that is widely used as a component of hormone therapy and oral contraceptive products. In the 5 mg dose, it is approved as Aygestin (in 1982) and several generic products, for the indications of secondary amenorrhea and abnormal uterine bleeding.

2.2 REGULATORY HISTORY

Initial approval of leuprolide acetate was in the 1990s, for uterine fibroids (leiomyomata) and endometriosis. Adverse impact of LA on BMD led to a limit on the duration of use (for endometriosis) to six months.

Co-administration of LA and NETA was approved in September 2001 under NDAs 20-011 and 20-708, and a modified endometriosis indication was labeled: “indicated for initial management of endometriosis and for management of recurrence of symptoms.” Due to the mitigation of BMD decreases when NETA was co-administered with LA, the duration of treatment now specifies six months for initial treatment and six months for retreatment.

Several substantive labeling supplements (SLRs) have been reviewed since the 2001 approval; these include:

- SLR 029 – proposed addition of “convulsions” to the Adverse Reactions - Postmarketing section of labeling
- SLR 030 – submitted in response to a Supplement Request letter from the Division, proposed addition of serious venous and arterial thromboembolic and thrombotic events to the Adverse Reactions - Postmarketing section of labeling

- SLR 032 - submitted in response to a Supplement Request letter from the Division, proposed removal of a statement indicating that BMD loss in six months of treatment is not likely to be clinically significant, and adding 95% confidence intervals to the mean percent change in BMD data provided
- SLR 033 - submitted in response to a Supplement Request letter from the Division, proposed adding “serious liver injury” to the Adverse Reactions - Postmarketing section of labeling

Initial discussions of an application for co-packaging of LA and NETA were (b) (4)

The Applicant proposed to provide labeling that included information about each component in a single PLR document, and the Division concurred.

A pre-NDA meeting was held on November 10, 2011. The Applicant was asked to provide the most recent Periodic Safety Update Report and a 120-day safety update to the NDA. Further discussion about the format of labeling was held.

2.3 PRIMARY MEDICAL REVIEWER’S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Ron Orleans, stated in his review dated November 15, 2012:

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.

Team Leader Comment:

I concur with Dr. Orleans’ recommendation.

Dr. Orleans did not recommend any postmarketing risk evaluation and mitigation strategies or postmarketing studies.

3. CMC/Device

Information about the drug substance for LA was cross-referenced to NDA 19-010 and information about the drug product LA was cross-referenced to NDA 20-011 (3.75 mg dose) and NDA 20-708 (11.25 mg dose). The Applicant also had a letter of authorization to cross-reference ANDA 91-090 for the NETA tablets supplied by Glenmark. Relevant DMFs for both LA and NETA have been reviewed previously and determined to be adequate.

The primary Chemistry Reviewer, Zhengfang Ge, Ph.D., made the following recommendations in her review dated October 2, 2012:

The Applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity and quality of the drug product.

*However, the Office of Compliance has **not** issued an overall “Acceptable” recommendation.*

*Labeling issues also have **not** been resolved as of this review.*

*Therefore, from the ONDQA perspective, this NDA is **not** recommended for “Approval” in its present form per 21 CFR 314.125(b)(6) until all the pending issues are resolved.*

Two manufacturing sites for the LA drug substance and drug product were requested to be evaluated by the Office of Compliance and were found to be acceptable. The manufacturing site for the NETA drug substance was found acceptable based on profile on March 19, 2012. The Office of Compliance issued an overall “Acceptable” recommendation on December 6, 2012.

Following completion of the inspections and agreement upon CMC sections of labeling, Dr. Ge submitted an amendment to her review, dated December 12, 2012, in which she concluded:

*This NDA is **now** recommended for **Approval** from the ONDQA perspective.*

No post-marketing commitments or risk management steps were recommended.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted by the Applicant. The primary Toxicology Reviewer, Krishan Raheja, D.V.M., Ph.D., made the following recommendations in his review dated May 7, 2012:

Recommendations on approvability: Pharmacology/Toxicology recommends approval of Abbott Inc. NDA 203696 from the P/T perspective for leuprolide acetate injection/norethindrone acetate tablets as 1-month and 3-month co-packaged kits for the treatment of endometriosis

Additional Non Clinical Recommendations for nonclinical studies: None

Recommendations on labeling: Label is submitted in SLP format integrating approved labels for leuprolide acetate injection and norethindrone acetate tablets.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical or clinical pharmacology studies were submitted in this application. The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., stated the following in her review dated November 15, 2012:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) finds NDA 203696 acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert.

6. Clinical Microbiology

No clinical microbiology consult was requested for this co-packaged product, which contains two drugs that are currently approved and marketed.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

No clinical studies were conducted for this NDA because it only provided for co-packaging of two previously approved products that have already been approved for co-administration and prescribed since 2001.

Two clinical studies were conducted in women with endometriosis to support approval of co-administration of LA and NETA and to provide for a single retreatment course with maximum duration of six months. Both studies utilized the 3.75 once-monthly dose of LA. Extension of the indication for co-administration to the 11.25 every three-month dose of LA was made on the basis of an earlier study which did not reveal any differences between the two dose regimens on efficacy in treating painful symptoms of endometriosis or on the magnitude of BMD loss associated with use of LA.

Team Leader Comment:

The efficacy data in the Clinical Trials section of labeling should primarily reflect the effects on endometriosis symptoms and BMD reduction observed with the co-administration of LA and NETA.

8. Safety

No clinical trials were conducted in support of this NDA, so the safety review consists solely of review of postmarketing safety reports.

Team Leader Comment:

The Adverse Reactions section of labeling should mainly reflect findings associated with co-administration of LA and NETA.

8.1 POSTMARKETING SAFETY FINDINGS

The Applicant provided Periodic Safety Update Reports (PSURs) for LA the last 4.5 years in the initial submission, covering from early 2007 through mid-2011. The Applicant noted that a new risk management plan for the dosage form indicated for prostate cancer was submitted to the UK Medicines and Healthcare Regulatory Agency in 2011. Two studies were published in the reporting interval, one of which addressed suicidal behavior among patients treated with GnRH agonists. The other publication and an ongoing study addressed use of LA in children with precocious puberty.

Adverse reactions (ARs) noted for medical significance in the last four PSURs were:

- Cerebrovascular accident
- Coronary heart disease (including MI)
- Diabetes mellitus
- Embolism/thrombosis
- Injection site reaction

- BMD loss
- Hypertension
- Severe depression
- Convulsion

Team Leader Comment:

All of the “medically significant” ARs except diabetes and hypertension are described in labeling.

8.2 SAFETY UPDATE

A 120-day Safety Update Report was submitted on June 14, 2012, providing the most recent six-month PSUR and a safety update of the Applicant’s global safety database for LA that covered February through mid-April, 2012. The PSUR noted two deaths in women (a larger number were described in men), including a death from cardiopulmonary collapse in a woman with metastatic breast cancer being treated with LA for her breast cancer and a woman who died three months after initiating LA treatment “for control of excessive bleeding as a result of dialysis;” cause of death unknown. In a discussion of cumulative reports of serious and “noteworthy” ARs, the Applicant noted the following:

- Cerebrovascular accident – 57 of 181 reports were in women; the Applicant notes that confounding factors like smoking and hypertension must be considered
- Convulsion – 35 of 75 cases were in women; the Applicant will continue to monitor, but has not determined there to be a causal relationship
- Coronary heart disease (including MI) – 26 of 219 cases were in women, including 17 of 93 MI reports
- Diabetes mellitus – 75% of these cases were reported in males, typically in elderly patients with underlying diabetes
- Embolism/thrombosis – 101 of 479 cases were in women (this category overlaps with coronary heart disease and cerebrovascular accident); in women, the most common events were pulmonary emboli and deep vein thrombosis (66% of cases)
- Hypertension – 69 of 99 cases were in women; reports have indicated both hypotension and hypertension in females, indicating no clear pathophysiology
- Injection site reaction – the Applicant noted that the “vast majority” of the most serious of these ARs, abscesses, occur in elderly males and that a causality of hypersensitivity reaction may be involved
- Interstitial lung disease – only 8 of 197 cases reported in women; the majority are from Japan and may reflect coding issues
- BMD loss – 7 of 17 cases were in females
- Severe depression – 100 of 126 cases were in women, and included 56 reports of depression, 5 completed suicides, 23 suicide attempts and 16 cases of suicidal ideation
- Thyroid disorder – 15 of 19 cases reported in women, most often hyperthyroidism; however, the Applicant believes the number of reports is low in relation to the high background incidence of hyperthyroidism

- Dyslipidemia – four of 13 serious cases were in women; the Applicant again believes the number of reports is low compared to background incidence

Team Leader Comment:

Based on the Applicant's cumulative summary of "noteworthy" ARs, I believe the current labeling is generally adequate and appropriate for the female gynecologic indication. However, I believe that "hypertension" should be added to the Adverse Reactions section of labeling based on the cases reported in this submission.

In the safety update, no fatalities were reported; four serious unlisted reports were described, all in women. They included the following:

- A pulmonary embolus two months after the woman's second bi-monthly 7.5 mg dose of LA for endometriosis; negative workup for hypercoagulopathy
- Anaphylactic shock requiring ER treatment coincident with LA 3.75 mg treatment, also taking norethisterone acetate
- Left bundle branch block (LBBB) in a woman with severe mitral valve regurgitation taking LA 11.25 mg for fibroids
- Blood glucose increased and chest pain in a woman 1.5 months after starting LA 3.75 mg for fibroids; past history of high blood sugar

A review of the literature did not find any new clinical trials or publications relating to use of LA + NETA.

Team Leader Comment:

I concur with Dr. Orleans that no new safety signal is evident.

8.3 OVERALL ASSESSMENT OF SAFETY FINDINGS

The safety profile of co-administration of LA and NETA was determined to be acceptable when approved in 2001, and the co-packaging of these components will not alter the safety profile. Postmarketing safety data submitted subsequent to the 2001 approval has been reflected in labeling updates, where appropriate.

9. Advisory Committee Meeting

An Advisory Committee meeting was not needed for this application, which involved co-packaging of two previously approved products that have been used together for the indication for many years.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies in females < 17 years of age because studies are impossible or highly impractical due to the difficulty of enrolling pediatric patients. Because endometriosis is a disease specific to women, the Applicant also requested a waiver of studies in pediatric males. The Applicant provided background information indicating that the diagnosis of endometriosis takes an average of seven years in symptomatic women; because the condition does not occur prior to menarche, there would be very few females below 17 years of age with a diagnosis of endometriosis. The Division concurred with the Applicant's waiver request. The application did not meet criteria for review by the Pediatric Research Committee.

11. Other Relevant Regulatory Issues

No financial disclosure certification was provided because no clinical trials were conducted for this NDA.

12. Labeling

The Applicant submitted several proposed proprietary names; the name Lupaneta Pack was found to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Carton and container labeling was reviewed by CMC, DMEPA and the Office of Prescription Drug Promotion (OPDP), and comments provided to the Applicant were addressed in revised labeling.

The label was submitted in the format prescribed by the Physician Labeling Rule (PLR). Although both LA and NETA have approved labels, neither is currently in PLR format. The current LA label discussed concomitant use of NETA, but labeling information specific to NETA is not included in the LA label. Therefore, this label review involved the integration of two product labels and conversion to PLR format. In addition, the inclusion of information added to the current LA label based on several recent SLRs was addressed.

Major issues of discussion in labeling negotiations included the need to integrate sections of the label such as Contraindications and Warnings & Precautions to discuss the co-packaged product, rather than discussing each drug separately. Further work was required to develop Adverse Reactions and Clinical Trials sections that reported data relevant to the co-packaged product, rather than relying on data from the trials of LA alone. Data reported in these sections were verified by referring to the original 2001 clinical review of the data that supported the co-administration of LA and NEA. Finally, the Applicant did not initially submit patient labeling and was asked to develop this during the course of the review. The package insert and patient labeling were reviewed by DMEPA, OPDP, the Study Endpoints and Label Development (SEALD) team, and the Division of Medical Policy Programs (DMPP) Patient Labeling Team, and their comments were conveyed to the Applicant.

Labeling negotiations were finalized on December 13, 2012, with the submission of acceptable labeling by the Applicant.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that Lupaneta Pack be approved for the indication “initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms” provided that acceptable labeling is provided by the Applicant.

13.2 Risk Benefit Assessment

The risk/benefit profile for co-administration of LA and NETA has already been determined to be acceptable; co-packaging of the two drug products will not alter this profile but will provide greater convenience to healthcare providers and patients.

13.3 Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended.

13.4 Recommendation for other Postmarketing Study Requirements and Commitments

I do not recommend requiring any postmarketing studies.

13.5 Recommended Comments to Applicant

None

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/s/

LISA M SOULE
12/13/2012

AUDREY L GASSMAN
12/13/2012