CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203696Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	December 14, 2012
From	Audrey Gassman, MD
NDA #	203696
Applicant name	Abbott Endocrine, Inc.
Date of receipt of original submission	February 15, 2012
PDUFA goal date	December 21, 2012
Proprietary name/established name	Lupaneta Pack (leuprolide acetate for depot suspension, for intramuscular use and norethindrone acetate tablets for oral use)
Dosage Form/strength	Leuprolide acetate for depot suspension and norethindrone acetate oral tablets/ leuprolide acetate for injection supplied as 3.75 mg for monthly administration and 11.25 mg for 3-month administration and norethindrone acetate 5 mg tablets taken daily
Proposed Indications	1) Initial management of the painful symptoms of endometriosis and 2) Management of recurrence of symptoms
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Lisa Soule, MD
Medical Officer Review	Ronald Orleans, MD
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Krishan Raheja, DVM, PhD Alexander Jordan, PhD
Clinical Pharmacology Review	Li Li, PhD Myong-Jin Kim, PhD
ONDQA Review	Zhengfang Ge, PhD Moo-Jhong Rhee, RPh
DMEPA	Manizheh Siahpoushan, PharmD Zachary Oleszczuk, PharmD Carol Holquist, RPh
DMPP	Robin Duer, MBA, BSN, RM Melissa Hulett, RN, BSN, MSBA LaShawn Griffiths, RN, MSHS-PH, BSN
OPDP	Carrie Newcomer, PharmD
OSI	Not requested (no clinical data submitted)
SEALD	Eric Brodsky, MD Laurie Burke RPh, MPH

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPP – Division of Professional Promotion
DDTCP – Division of Direct-to-Consumer Promotion
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

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1. Introduction

Lupaneta Pack is a kit consisting of the co-packaging of two approved drug products previously approved to be used concomitantly for the initial management and retreatment of endometriosis. The first drug product is Lupron Depot (leuprolide acetate for depot suspension) and the second drug product is norethindrone acetate (NETA) tablets. Lupron Depot is a synthetic polypeptide analog of gonadotropin-releasing hormone (GnRH). NETA is a synthetic orally active progestin. Abbot Endocrine Inc. (the Applicant) has proposed two different package configurations of Lupaneta Pack in this NDA that will consist of: 1) a 1- month kit of Lupron Depot 3.75 mg and NETA 5 mg (30 tablets); or 2) a 3-month kit of Lupron Depot 11.25 mg and NETA 5 mg (90 tablets).

Lupron Depot 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 as monotherapy are indicated for the initial management of endometriosis. The recommended duration of initial treatment with the Lupron Depot 1-month or 3- month formulation alone is not to exceed six months.

NETA is a progestin hormone that is in the pharmacologic class of 19-nortestosterone derivatives. NETA 5 mg tablets are FDA-approved as a monotherapy for the treatment of endometriosis. The initial daily dosage for the endometriosis indication is 5 mg for two weeks. Dosage can be increased by 2.5 mg per day every two weeks until a maximum dose of 15 mg per day is reached. Therapy with NETA alone may be continued at this dose for six to nine additional months. Other FDA approved indications for NETA include treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology.

The use of Lupron Depot with concomitant NETA as “add-back” therapy for initial management of endometriosis and retreatment was approved by the FDA in 2001. The purpose of the “add-back” of NETA to Lupron Depot was to mitigate the adverse effects of estrogen suppression of Lupron Depot, the most important being the bone mineral

density (BMD) loss which occurs during Lupron Depot treatment. Clinical trials supporting the efficacy and safety of both the individual drug products and concomitant use of Lupron Depot 3.75 mg and NETA 5 mg were previously submitted, reviewed, and determined to be acceptable (See Approval letter for NDA 20011/S-021 for the co-administration of Lupron Depot 3.75 mg and NETA 5 mg).

All clinical data submitted to support the efficacy and safety of co-treatment of Lupron Depot and NETA for management and retreatment of endometriosis were obtained with the 3.75 mg formulation of Lupron (Reference NDA 20011/S-021). A separate study conducted as part of a phase 4 commitment (Study M96-506) for the approval of the Lupron Depot 11.25 mg formulation was submitted and reviewed as part of the approval of concomitant use of Lupron Depot 11.25 mg and NETA (See NDA 20708/S-011). The clinical reviewer concluded in his review of S-011 dated September 21, 2001, that the data from this phase 4 study 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 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 as the 3.75 mg formulation, so Lupron Depot 11.25 mg with concomitant NETA 5 mg was also approved for management of endometriosis and retreatment of symptoms (See NDA 20708/S-011) on September 21, 2001.

For this application, the Applicant sought approval of two separate kits, one containing the co-package of 3.75 mg Lupron Depot and 30 NETA 5 mg tablets (1-month kit) and the other the co-package of 11.25 mg Lupron Depot and 90 NETA 5 mg tablets (3-month kit) for initial management of endometriosis and retreatment of symptoms. No significant efficacy or safety issues were identified during the review of these co-packaged kits for the stated indications. There are no outstanding clinical pharmacology, nonclinical toxicology, or chemistry, manufacturing and control (CMC) issues. Drug product labeling was primarily based on integrating the currently approved labels for Lupron Depot and NETA tablets. Final agreed upon product labeling was submitted by the Applicant on December 13, 2012. Both the primary Clinical Reviewer and the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendations.

2. Background

Lupron Depot was initially approved for use in the United States for the palliative treatment of advanced prostate cancer in 1985. In 1990, Lupron Depot was approved for the management of pain and its use was restricted in maximum duration of treatment to 6 months. This restriction in duration of treatment was primarily because of a concern that longer periods of treatment or retreatment with GnRH analogs would lead to clinically significant irreversible bone loss from prolonged periods of hypoestrogenism.

Treatment protocols to extend the duration of treatment beyond the initial 6 months of treatment and allow retreatment with Lupron Depot primarily focused on addition of sex-

steroid hormones to ameliorate the hypoestrogenic effects. The concomitant use of Lupron Depot with sex steroid hormones, such as progestins, was referred to as "add-back" therapy. In an effort to safely increase the permissible duration of treatment as well as to safely permit retreatment, the Sponsor of Lupron Depot conducted 2 new clinical trials of "add-back" therapy (M92-878 and M97-777) in which women were treated with Lupron Depot 3.75 mg plus NETA 5 mg for up to 1 year. The Applicant also provided data from a phase 4 clinical trial (M96-506) to support concomitant use of either Lupron Depot 3.75 mg or 11.25 mg in women with endometriosis. Trial M96-506 provided assessments of clinical efficacy (reduction in the painful symptoms of endometriosis), general safety, changes in BMD and pharmacokinetic/pharmacodynamic assessments (serum concentrations of leuprolide and estradiol). After review by the Agency, both the Lupron Depot 3.75 mg and 11.25 mg doses were approved for concomitant use with daily NETA 5 mg tablets for management of endometriosis and retreatment of symptoms (See NDAs 20011/S-021 and NDA 20708/S-011 approved on September 21, 2001). To date, there has been no fixed-dose combination or co-packaging of Lupron Depot and NETA for the endometriosis indications.

3. Chemistry, Manufacturing and Controls

This drug product, Lupaneta Pack, is a co-packaged kit containing two approved drug products, leuprolide acetate for depot suspension (tradename Lupron Depot) and NETA tablets (tradename Aygestin). Lupaneta Pack will be provided in two package configurations: 1) 1 month package of Lupron Depot 3.75 mg with 30 tablets of 5 mg norethindrone acetate tablets and 2) 3 month package of Lupron Depot with 90 days of 5 mg norethindrone acetate tablets.

The Lupron Depot products (i.e. both the 3.75 mg and 11.25 mg products) to be supplied in Lupaneta Pack were cross-referenced by the Applicant to NDA 20011 and NDA 20708, respectively, for the CMC information. Abbott Endocrine Inc. is the holder of both NDA 20-011 and NDA 20708. In addition, the Applicant owns and cross-referenced NDA 19-010, for the CMC information of the drug substance leuprolide acetate.

The NETA tablets (both the 30 tablets and 90 tablets) to be supplied in both package configurations of Lupaneta Pack are generic drug products that will be supplied by Glenmark, ANDA 91090. ANDA 91090 was approved on Jan 17, 2012. LOA for ANDA 91-090 was provided in this NDA.

After an initial review of the NDA submission dated October 2, 2012, the chemistry reviewer concluded that, "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 21CFR 314.125(b)(6),(13) until all the pending issues are resolved."

In an addendum to his review dated December 12, 2012, the chemistry reviewer stated that the Office of Compliance had issued an "Acceptable" recommendation for the facilities involved in this NDA and that revised labeling was acceptable from ONDQA's perspective. He therefore concluded in his December 2012 addendum that, "This NDA is now recommended for Approval from the ONDQA perspective".

No Biopharmaceutics review was necessary for Lupaneta Pack as both drug products in this co-packaged kit are currently approved.

Comment: I concur that there are no outstanding CMC issues related to this application.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted or requested for this application. After review of the submission, the pharmacology/toxicology reviewer commented in his review dated May 7, 2012, that, "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."

Comment: I concur that there are no outstanding nonclinical issues related to this application.

5. Clinical Pharmacology

No new clinical pharmacology studies were submitted or requested for this application. After review of the submission, the clinical pharmacology reviewer in her review dated November 15, 2012, concluded that, "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."

Comment: I concur that there are no outstanding clinical pharmacology issues related to this application.

6. Clinical Microbiology

No new clinical microbiology review was submitted or requested for this application of previously approved and marketed drug products.

7. Efficacy/Statistics

No new clinical trials were requested or submitted for this application. The efficacy of Lupaneta Pack was cross-referenced to clinical trials originally submitted under NDAs 20011 and 20708. The clinical and statistical reviewers evaluated this co-packaging application and agreed that efficacy of concomitant use of Lupron Depot and NETA

products for initial management of endometriosis and retreatment of symptoms was previously determined to be acceptable. The clinical reviewer agreed with the Applicant that no additional efficacy data was necessary for approval of this co-packaged kit and stated in his November 15, 2012, review that, "…the Division has previously agreed that no new phase 3 clinical trials were needed for the proposed Lupron Co-Pack NDA submission." The statistical reviewer concurred with the clinical reviewer's assessment and concluded in his review dated November 15, 2012, that, "There was no new efficacy data submitted in support of this submission. Therefore, no statistical review was necessary."

Comment: I concur that there are no outstanding efficacy issues related to this application.

8. Safety

The safety database to support concomitant use of Lupron Depot and NETA was cross-referenced to clinical trials originally submitted under NDAs 20011 and 20708. The original clinical trial safety database consisted of 2 separate trials with 191 subjects that were treated with Lupron Depot 3.75 monthly and NETA 5 mg, with some subjects treated up to 1 year. The safety database demonstrated that the proportion of subjects experiencing adverse events and withdrawals from treatment was similar between subjects treated with Lupron Depot 3.75 monthly with NETA and those treated with Lupron Depot alone. In addition, co-treatment with NETA did not raise any new safety concerns that precluded approval of use of the concomitant use with Lupron Depot. Finally, use of Lupron Depot 11.25 mg was determined to be comparable by the Agency, if not pharmacokinetically equivalent to the 3.75 mg use for these indications based on results from study M96-506 (See NDAs 20011/S-021 and NDA 20708/S-011).

Therefore, the clinical reviewer focused his safety review on postmarketing data from two periodic safety update reports (27th PSUR/S-0001 and 28th PSUR/S-0005) submitted to this application. After review of the 27th PSUR, the clinical reviewer concluded:

> "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."

The 28th PSUR was submitted to this NDA as the 120-day Safety Update. After review of this PSUR, the clinical reviewer concluded that, "These reports do not suggest a trend or new safety signal." In addition, the clinical review also evaluated the applicant's review of the available literature for GnRH analogs with "add-back" therapy that was submitted with the 120-day safety update.

After review of the safety data from the Lupaneta Pack submission that included both PSURs and published literature, the clinical reviewer summarized his findings on safety in his November 15, 2012, review that, "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."

The CDTL provided the following overall assessment of safety findings for this application in her review dated December 13, 2012, "The safety profile of co-administration of leuprolide acetate 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."

Comment: I concur with the clinical reviewer and CDTL that there are no outstanding safety issues related to this application. I agree with the primary reviewer that there are adverse effects on a biomarker of cardiovascular outcomes, HDL cholesterol, associated with concomitant use of Lupron Depot and NETA. However, in my opinion, the limitation of duration of use of these products for this indication makes the risk/benefit for women without underlying risk factors for cardiovascular adverse events to be acceptable.

9. Advisory Committee Meeting

An Advisory Committee was not recommended by any of the review teams because both drug products have previously approved alone and in combination.

Comment: I concur with the recommendations of the review teams that there were no outstanding efficacy or safety concerns that required an Advisory Committee meeting.

10. Pediatrics

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 NETA 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 NETA tablets is currently approved for use in children.

The Division concurred with the Applicant's waiver request. The application did not meet the criteria for review by the Pediatric Research Committee.

11. Other Relevant Regulatory Issues

<u>Division of Medical Policy Programs (DMPP)</u>:

DMPP reviewed the Patient Package Insert (PPI) on November 28, 2012, and found it to be acceptable with several recommended changes. The Division discussed several of the recommendations with DMPP, and after minor editing, the agreed to recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information (PI) and the Patient Package Insert (PPI). OPDP completed their review of the PPI on December 3, 2012 and on the PPl and carton/container labeling on December 7, 2012. The Division discussed several of the recommendations with OPDP, and after editing, the agreed to recommendations were implemented.

Office of Scientific Investigations (OSI):

OSI inspection was not necessary for this co-packaging application because no new clinical data was submitted to support this new combination product NDA kit (See clinical review dated November 15, 2012)

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team provided a review on July 23, 2012, and a final addendum on November 1, 2012, of carton and container labels for areas of vulnerability that could lead to medication errors. DMEPA's recommendations were implemented.

DMEPA also assessed the proposed tradename "Lupaneta Pack" on October 25, 2012, and found it acceptable.

Financial Disclosures**:**

Financial Disclosure certificates were not required for this NDA because no new clinical data was submitted to support this new combination product NDA (See clinical review dated November 15, 2012).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team reviewed the prescriber information label and provided recommendations. These recommendations were implemented.

12. Labeling

Labeling discussions are complete and final agreed to labeling was submitted on December 14, 2012. Labeling for Lupaneta Pack (leuprolide acetate for depot suspension, for intramuscular use and NETA tablets for oral use) was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the Applicant.

Labeling was also reviewed by the Study Endpoints and Label Development (SEALD) Team and their recommendations were implemented.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer, and the Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical review teams that the Lupaneta Pack application should receive an Approval action.

Risk Benefit Assessment:

Lupron Depot and NETA were approved for concomitant use in 2001 as individual drug products with separate labeling for each product. Co-treatment of either the Lupron Depot 3.75 mg monthly or Lupron Depot 11.25 mg every three month products with NETA 5 mg tablets did not raise any new efficacy or safety concerns. No additional efficacy or safety evaluations were requested or provided for review with this application. No new safety concerns were identified in post-marketing data that precluded approval of the co-packaged kits. I also concur with the clinical reviewer and CDTL that the new co-packaged kits will likely facilitate concomitant use of the Lupron Depot and NETA products. Agreed to labels for the carton/container, prescriber information and patient package insert were completed on December 14, 2012.

Therefore, in my opinion, the risk/benefit assessment favors approval of Lupaneta Pack (leuprolide acetate for depot suspension, for intramuscular use and norethindrone acetate tablets) for use for: 1) Initial management of the painful symptoms of endometriosis and 2) Management of recurrence of symptoms.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- The review teams determined that a REMS was not necessary for these co-packaged product.
- The review teams also determined that no new postmarketing requirements or commitments are necessary for these co-packaged products.

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

/s/

AUDREY L GASSMAN
12/14/2012