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RESEARCH**

APPLICATION NUMBER:

203696Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA Number:	203696
Submission Date:	02/15/2012
Brand Name:	Lupaneta Pack
Generic Name:	Leuprolide acetate for depot suspension & norethindrone acetate tablets
OCP Reviewer:	Li Li, Ph.D
OCP Team Leader:	Myong Jin Kim, Pharm. D
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Reproductive and Urologic Products
Sponsor:	Abbott Endocrine Inc.
Submission Type; Code:	Original; Type 4 Combination
Formulation and Dosing regimen:	Lupron Depot®: one intramuscular injection every month or every 3 month; Norethindrone acetate tablet: once daily
Indication:	Treatment of endometriosis

Executive Summary

The Sponsor submitted a New Drug Application (NDA) to copackage two approved drug products, Lupron Depot® (leuprolide acetate for depot suspension) and norethindrone acetate (NETA) tablets, for the treatment of endometriosis. The configurations of co-packaged kit are listed below:

- One-month co-packaged kit:
 - Lupron Depot® 3.75 mg (for 1-month administration) syringe/needle/alcohol swabs
 - NETA 5 mg tablets; 30 tablets/bottle
- Three-month co-packaged kit:
 - Lupron Depot® 11.25 mg (for 3-month administration) syringe/needle/alcohol swabs
 - NETA 5 mg tablets; 90 tablets/bottle

Lupron Depot® 3.75 mg and 11.25mg formulation will be administered by intramuscular injection every month and every 3 month, respectively. NETA 5mg tablet will be administered once daily.

Lupron Depot® 3.75 mg was approved on October 22, 1990 under NDA 020011 and Lupron Depot® 11.25 mg was approved on March 7, 1997 under NDA 020708. NETA 5 mg tablets co-packaged in the proposed NDA are the currently marketed generic drug supplied by Glenmark (ANDA 91090, approved on January 17, 2012). FDA has approved the add-back indication for Lupron Depot® 3.75mg and Lupron Depot® 11.25mg co-administered with NETA 5mg daily in the Lupron NDAs mentioned above.

There are no new clinical pharmacology studies in the current NDA. The only component of this NDA relevant for Clinical Pharmacology review is the Sponsor's proposed labeling.

Recommendations

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.

Detailed Labeling Recommendations

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----CONTRAINDICATIONS-----

- Hypersensitivity to [Gonadotropin-releasing hormone \(GnRH\)](#), GnRH agonist or any of the excipients in leuprolide acetate for depot suspension or norethindrone acetate (4.1)
- Undiagnosed abnormal (b) (4) bleeding (4.2)
- Pregnancy (b) (4) (4.3, 8.1)
- Use in women who are breastfeeding (4.4)
- Known, suspected or history of cancer of the breast (4.5)
- (b) (4) thromboembolic disease (4.6)
- Impaired liver functions or liver disease (4.7)

(b) (4)

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

(b) (4)

No pharmacokinetic-based drug-drug interaction studies have been conducted with [leuprolide acetate](#) (b) (4). [However, drug interactions associated with cytochrome P-450 enzymes or protein binding would not be expected to occur. \[see Clinical Pharmacology \(12.3\)\]](#)

(b) (4)

Norethindrone Acetate

No pharmacokinetic drug interaction studies investigating any drug-drug interactions with norethindrone acetate have been conducted. [Drugs or herbal products that induce or inhibit](#) (b) (4) [, including CYP3A4, may decrease or increase the serum concentrations of norethindrone.](#)

7.12 Drug/Laboratory Test Interactions

(b) (4)

Administration of (b) (4) in therapeutic doses results in suppression of the pituitary-gonadal system. Normal function is usually restored within three months after treatment is discontinued. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment and for up to three months after discontinuation of (b) (4) may be [affected](#) (b) (4)

(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Leuprolide Acetate for Depot Suspension

(b) (4)

Leuprolide acetate for depot suspension is a long-acting GnRH analog. A single injection of (b) (4) results in an initial elevation followed by a prolonged suppression of pituitary gonadotropins. Repeated dosing at quarterly intervals results in decreased secretion of gonadal steroids; consequently, tissues and functions that depend on gonadal steroids for their maintenance become quiescent. This effect is reversible on discontinuation of drug therapy.

Norethindrone Acetate

Norethindrone acetate induces secretory changes in an estrogen-primed endometrium.

12.2 Pharmacodynamics

In a pharmacokinetic/pharmacodynamic study of healthy female subjects (N=20), the onset of estradiol suppression was observed for individual subjects between day 4 and week 4 after dosing. By the third week following the injection, the mean estradiol concentration (8 pg/mL) was in the menopausal range. Throughout the remainder of the dosing period, mean serum estradiol levels ranged from the menopausal to the early follicular range.

Serum estradiol was suppressed to ≤ 20 pg/mL in all subjects within four weeks and remained suppressed (≤ 40 pg/mL) in 80% of subjects until the end of the 12-week dosing interval, at which time two of these subjects had a value between 40 and 50 pg/mL. Four additional subjects had at least two consecutive elevations of estradiol (range 43-240 pg/mL) levels during the 12-week dosing interval, but there was no indication of luteal function for any of the subjects during this period.

12.3 Pharmacokinetics

Absorption

Leuprolide Acetate for Depot Suspension

(b) (4)

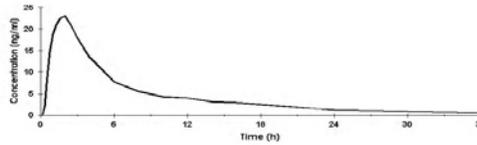
Following a single injection of the three month formulation of leuprolide acetate for depot suspension in female subjects, a mean plasma leuprolide concentration of 36.3 ng/mL was observed at 4 hours. Leuprolide appeared to be released at a constant rate following the onset of steady-state levels during the third week after dosing and mean levels then declined gradually to near the lower limit of detection by 12 weeks. The mean (\pm standard deviation) leuprolide concentration from 3 to 12 weeks was 0.23 ± 0.09 ng/mL. However, intact leuprolide and an inactive major metabolite could not be distinguished by the assay which was employed in the study. The initial burst, followed by the rapid decline to a steady-state level, was similar to the release pattern seen with the monthly formulation.

Norethindrone Acetate

Norethindrone acetate is deacetylated to norethindrone (b) (4) after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate is absorbed from norethindrone acetate tablets, with maximum plasma concentration of norethindrone generally occurring at about 2 hours post-dose. The pharmacokinetic parameters of norethindrone following single oral administration of 5 mg norethindrone acetate under fasting conditions in 29 healthy female volunteers are summarized in Table 5.

Table 5 Pharmacokinetic Parameters after a Single Dose of Norethindrone Acetate in Healthy Women	
Norethindrone Acetate (n=29)	Arithmetic Mean \pm SD
Norethindrone (b) (4)	
AUC (0-inf) (ng/ml*h)	166.90 \pm 56.28
C _{max} (ng/ml)	26.19 \pm 6.19
t _{max} (h)	1.83 \pm 0.58
t _{1/2} (h)	8.51 \pm 2.19
AUC = area under the curve, C _{max} = maximum plasma concentration, t _{max} = time at maximum plasma concentration, t _{1/2} = half-life, SD = standard deviation	

(b) (4) Mean Norethindrone Plasma Concentration Profile after (b) (4) Single Dose of 5 mg Administered to 29 Healthy Female Volunteers under Fasting Conditions



Effect of Food

The effect of food administration on the pharmacokinetics of norethindrone acetate has not been studied.

Distribution

Leuprolide Acetate for Depot Suspension (b) (4)

The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

Norethindrone Acetate

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is about 4 L/kg.

Metabolism

Leuprolide Acetate for Depot Suspension (b) (4)

In healthy male volunteers, a 1 mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 7.6 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

In rats and dogs, administration of ¹⁴C-labeled leuprolide was shown to be metabolized to smaller inactive peptides, a pentapeptide (Metabolite I), tripeptides (Metabolites II and III) and a dipeptide (Metabolite IV). These fragments may be further catabolized.

In a pharmacokinetic/pharmacodynamic study of endometriosis patients, intramuscular 11.25 mg leuprolide acetate for depot suspension (n=19) every 12 weeks or intramuscular 3.75 mg leuprolide acetate for depot suspension (n=15) every 4 weeks was administered for 24 weeks. There was no statistically significant difference in changes of serum estradiol concentration from baseline between the 2 treatment groups.

M-I plasma concentrations measured in 5 prostate cancer patients reached maximum concentration 2 to 6 hours after dosing and were approximately 6% of the peak parent drug concentration. One week after dosing, mean plasma M-I concentrations were approximately 20% of mean leuprolide concentrations.

Norethindrone Acetate

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Excretion

Leuprolide acetate for Depot Suspension (b) (4)

Following administration of leuprolide acetate for depot suspension 3.75 mg for 1-month administration to 3 patients, less than 5% of the dose was recovered as parent and M-I metabolite in the urine.

Norethindrone Acetate

Plasma clearance value for norethindrone is approximately 0.4 L/hr/kg. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of norethindrone following a single dose administration of norethindrone acetate is approximately 9 hours.

Specific Populations

Hepatic Impairment

The effect of hepatic disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. However, norethindrone acetate is contraindicated in markedly impaired liver function or liver disease.

[The pharmacokinetics of the leuprolide acetate for depot suspension in hepatically impaired patients have not been determined.](#)

Renal Impairment

The effect of renal disease on the disposition of norethindrone after norethindrone acetate administration has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma norethindrone concentration was unchanged compared to concentrations in premenopausal women with normal renal function.

[The pharmacokinetics of the leuprolide acetate for depot suspension in renally impaired patients have not been determined.](#)

Race

The effect of race on the disposition of norethindrone after norethindrone acetate administration has not been evaluated.

(b) (4)

DRUG INTERACTIONS

Leuprolide Acetate for Depot Suspension

(b)
(4)

(b) (4)

(b) (4)

Leuprolide acetate for depot suspension is a peptide that is primarily degraded by peptidase and not by cytochrome P-450 enzymes as noted in specific studies, and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Reviewer's comment: *The Sponsor is currently evaluating the basis for contraindicating norethindrone in patients with markedly impaired liver functions. The related labeling language will be revised once the Sponsor provides the updated information.*

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/s/

LI LI
11/15/2012

MYONG JIN KIM
11/15/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence (BE) data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			x	
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			x	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			x	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?			x	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			x	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

Li Li

4/10/2012

Reviewing Clinical Pharmacologist

Date

Myong Jin Kim

4/10/2012

Team Leader/Supervisor

Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

NDA: 203696
Compound: Leuprolide acetate for depot suspension & norethindrone acetate tablets co-packaged kits
Sponsor: Abbott Laboratories
Date: 4/05/2012
Reviewer: Li Li, Ph.D.

Summary:

The Sponsor submitted a New Drug Application (NDA) to copackage two approved drug products, Lupron Depot® (leuprolide acetate for depot suspension) and norethindrone acetate (NETA) tablets, for the treatment of endometriosis with (b) (4). The configurations of co-packaged kit are listed below:

- One-month co-packaged kit:
 - Lupron Depot® 3.75 mg (for 1-month administration) syringe/needle/alcohol swabs
 - NETA 5 mg tablets; 30 tablets/bottle
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 - Lupron Depot® 11.25 mg (for 3-month administration) syringe/needle/alcohol swabs
 - NETA 5 mg tablets; 90 tablets/bottle

Lupron Depot® 3.75 mg and 11.25mg formulation will be administered by injection every month and every 3 month, respectively. NETA 5mg tablet will be administered once daily.

There are no new clinical pharmacology studies in the current NDA. The only component of this NDA for review is the Physician Labeling Rule (PLR) conversion.

Regulatory History:

- Approval for individual drug component
 - Lupron Depot® 3.75 mg: approved under Abbott NDA 020011 on October 22, 1990
 - Lupron Depot® 11.25 mg: approved under Abbott NDA 020708 on March 7, 1997
 - NETA: approved under Glenmark Generic's ANDA 091090 as 5mg tablets in 30 or 90 tablets/bottle. Glenmark Generic will provide Abbott with right to reference for their ANDA
- Approval for Co-administration

FDA has approved the add-back indication for Lupron Depot® 3.75mg and Lupron Depot® 11.25mg co-administered with NETA 5mg daily in the Lupron NDA 020011 and NDA 020708. Lupron Depot 3.75mg and Lupron Depot 11.25mg are indicated for the management of endometriosis, including pain relief and reduction of endometriotic lesions. Lupron Depot 3.75 mg with NETA 5mg daily are also indicated for initial management of endometriosis and for management of recurrence symptoms. Duration of initial treatment or retreatment should be limited to 6 months
- Interaction with Division of Reproductive and Urologic Products (DRUP)
 - The Sponsor had multiple regulatory interactions with DRUP relating to this drug product under Investigational New Drug Application (b) (4)
 - Pre-IND meeting on March 23, 2011
 - No new Phase 3 studies to support the proposed indication are required
 - No additional phase 1 drug-drug interaction studies of leuprolide acetate and NETA are required
 - Pre-NDA meeting (Type B teleconference) on November 10, 2011
 - Sponsor should submit integrated labeling in PLR format that includes both Lupron and NETA labeling pertinent to this product

Pediatric Waiver:

The Sponsor requests a full waiver for pediatric studies in patients aged 0-17 years inclusive.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 203696 is fileable. No comments need to be conveyed in the 74 day letter.

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/s/

LI LI
04/13/2012

MYONG JIN KIM
04/13/2012