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RESEARCH**

APPLICATION NUMBER:

203696Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203696 SS# 0000
Supporting document/s: 0
Applicant's letter date: 2/15/2012
CDER stamp date: e-submission 2/15/2012
Product: Leuprolide acetate for depot suspension &
norethindrone acetate tablets co-packaged kits
1 Month 3.75 mg inj/5 mg tab (30 tab/bottle) kit
& 3 Month 11.25 mg inj/5 mg tab/bottle) kit
Indication: Endometriosis (b) (4). The
product is indicated for initial management of the
painful symptoms of endometriosis (b) (4)
(b) (4)
Applicant: Abbott Endocrine Inc.
Review Division: Reproductive & Urologic Drug Products
Reviewer: Krishan L. Raheja, D.V. M., Ph.D.
Through Expert Reviewer: Alex Jordan, Ph.D.
Division Director: Audrey Gassman, M.D.
Project Manager: Kimberly P. Shiley
Entered in DARRTS : 5/7/2012

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203696 are owned by Abbott Endocrine Inc. or are data for which Abbott Endocrine Inc has obtained a written right of reference.

Any information or data necessary for approval of NDA 203696 that Abbott Endocrine Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203696.

1 Executive Summary

1.1 Introduction: This new drug application submission is for co-packaged two approved drug products leuprolide acetate for depot suspension and norethindrone acetate (NETA) tablets for the treatment of endometriosis with addback therapy. The product is indicated for the initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms. The configurations of the two co-packaged kits is as described below:

One month co-packaged kit contents:

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

The three month co-packaged kit contents:

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

1.2 Brief Discussion of Nonclinical Findings

No preclinical studies have been submitted and none were requested.

Lupron Depot has previously been approved for use in combination with norethindrone acetate for endometriosis add-back indication in the following NDA applications:

- Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg for 1-month administration: sNDA 020011/S-021; approved 9/21/2001

- Lupron Depot (leuprolide acetate for depot suspension) 11.25 mg for 3-month administration. sNDA 020708/S-011; approved 9/21/2001.

During the Pre-IND meeting on 11/10/2011, the Agency agreed that it is acceptable to cross-reference the historical Lupron Depot NDAs that supported the approval of Lupron Depot endometriosis add-back indication and that no additional documentation was needed for Module 2 and 4 of the submission.

For Norethindrone Acetate 5 mg tablets, sponsor has referred to Glenmark ANDA 91-090 for generic norethindrone acetate tablets packaged in HDPE bottles containing 30 tablets/bottle and 90 tablets/bottle. Glenmark received approval from the Office of Generic Drugs on 1/17/2012 under ANDA 91-090/S-002 to provide for norethindrone acetate 5 mg; 30 tables/bottle and 90 tablets/bottle configurations.

1.3 Recommendations

1.3.1 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.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Label is submitted in SLP format integrating approved labels for leuprolide acetate injection and norethindrone acetate tablets.

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/s/

KRISHAN L RAHEJA
05/07/2012

ALEXANDER W JORDAN
05/07/2012

**45 Day NDA Meeting Checklist
Pharmacology/Toxicology**

NDA Number: 203696

Date: 3/7/2012

Drug Name: Leuprolide acetate for depot suspension & norethindrone acetate tablets co-packaged kits as 1 Month 3.75 mg inj/5 mg tab (30 tab/bottle kit & 3 Month 11.25 mg inj/5 mg tab (90 tab/bottle) kit

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Sponsor: Abbott Laboratories, Abbott Park, IL

Date CDER Received: 2/15/2012

Filing Date: 4/15/2012

User Fee Date:

Expected Date of Draft Review:

On initial overview of the Pharm/Tox portion of the NDA application

ITEM	YES / NO	COMMENTS
1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?	NA This submission constitutes active ingredients leuprolide acetate injection and norethindrone acetate tablets as co-packaged kits. Both leuprolide acetate 3.75 mg and 11.25 mg injection and norethindrone acetate tablets are FDA approved products under several NDAs. As such adequate preclinical toxicity information is available for their safety for human use. Sponsor has referred to their approved NDAs for leuprolide acetate and Glenmark ANDA 91-090 for norethindrone acetate.. In accordance with FDA Guidance for Industry on "Nonclinical Safety Evaluation of Drug or Biologic Combinations", no additional P/T information is required.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	NA
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can begin? Has the data been presented in an appropriate manner?	NA
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	NA

5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	NA	
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	NA	
7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	NA	
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	NA	
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m ² or comparative serum/plasma AUC levels?	Yes yes NA	The draft physician package inserts for the 1-month and 3-month kits integrate the currently approved label language for both Lupron Depot (leuprolide acetate for depot suspension) and norethindrone acetate tablets.
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	
11)	Reasons for refusal to file:		

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/s/

KRISHAN L RAHEJA
04/06/2012

ALEXANDER W JORDAN
04/06/2012