CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-355

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-355
Review number: 1
Serial number/date/type of submission: 000/12-14-2001/original submission
Information to sponsor: Yes ( ) No (*)
Sponsor and/or agent: Berlex Drug Development and Technology, Berlex Laboratories, Montville, NJ
Manufacturer for drug substance:

Reviewer name: Krishan L. Raheja, D.V.M., Ph.D.
Division name: Reproductive and Urologic Drug Products
HFD #: 580
Review completion date: 4-3-2002

Drug:

Trade name: Angeliq (drospirenone plus 17B-estradiol)

Drospirenone

Generic name (list alphabetically): Drospirenone
Code name: ZK 30595
Chemical name: 6R,7R,8R,9S,10R,13S,14S,15S,16S17S)-1,3,4,6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-6,7:15,16]cyclopental[a]phenanthrene-17,2(5H)-furon]3,5(2H)-dione)
CAS registry number: 67392-87-4
Mole file number:
Molecular formula/molecular weight:$C_{24}H_{30}O_3$/366.5

Estradiol
Generic name: 17B-estradiol
Code name:
Chemical name: (Estra-1,3,5(10)-triene-3,17-diol,17B)
CAS registry number:
Mole file number:
Molecular formula/molecular weight: $C_{18}H_{24}O_2$/272.39

Structure:

Drospirenone 17B-estradiol

Relevant INDs/NDAs/DMFs: IND [redacted] NDA 21-098 (Yasmin); DMF 12138 (drospirenone)

Drug class: Steroid hormones (progesterone and estrogen)

Indication: Oral hormone replacement therapy

Clinical formulation: Film coated tablets each containing [redacted], of drospirenone and 1.0 mg of estradiol The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropylmethyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment NF.

Route of administration: oral

Proposed use: Sponsor is seeking approval for the following indications:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause
2. Treatment of vulvar and vaginal atrophy

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

OVERALL SUMMARY AND EVALUATION:

For the following items see attached copy of NDA 21-098 review for Yasmin (drospirenone 3 mg and ethinyl estradiol 0.030 mg) tablets for oral contraception indication. The present NDA contains [redacted] of drospirenone plus 1 mg of 17B-estradiol as oral hormone replacement therapy.

Introduction:

Safety evaluation:

Safety issues relevant to clinical use:

Other clinically relevant issues:

Conclusions:

Communication review:

Labeling review:

RECOMMENDATIONS: Since all pre-clinical pharmacology/toxicology is referred to the sponsor's approved NDA 21-098 for Yasmin (3 mg drospirenone plus 0.030 mg ethinyl estradiol) as an oral contraceptive and as the dosage of drospirenone in Angeliq is equal or lower than that approved for Yasmin and 1 mg 17-B-estradiol is an approved dosage, Pharmacology recommends approval of NDA 21-355 for oral hormone replacement therapy.

Internal comments: none

External recommendations (to sponsor): none

Draft letter content for sponsor (if not same as above):

NDA issues: none

Reviewer signature:

Team leader signature [concurrence/non-concurrence]:

cc:
Original NDA 21-355
HFD-580
HFD-580/A.Jordan/L.Furlong/K.Raheja/A.Reddy

Memorandum of non-concurrence (if appropriate, attached):

Addendum to review (if necessary): see original NDA 21-098 review dated 2-11-2000

Studies reviewed within this submission: none

Studies not reviewed within this submission: All studies previously reviewed under NDA 21-098 for Yasmin (drospirenone plus ethinyl estradiol) as oral contraceptive.

Introduction and drug history: see review for NDA 21-098

TABLE OF CONTENTS

PHARMACOLOGY:

See review dated 2-11-2000 for the original NDA 21-098 submission dated 5-4-1999

SAFETY PHARMACOLOGY:

See review for NDA 21-098

PHARMACOKINETICS/TOXICOKINETICS:

See review for NDA 21-098

TOXICOLOGY:

See review for NDA 21-098

Histopathology Inventory for NDA # 21-355

Same as submitted under NDA 21-098. See review dated 2-11-2000

Study				
Species				
Adrenals				
Aorta				
Bone Marrow smear				
Bone (femur)				
Brain				
Cecum				
Cervix				
Colon				
Duodenum				
Epididymis				
Esophagus				
Eye				
Fallopian tube				
Gall bladder				
Gross lesions				
Harderian gland				
Heart				
Ileum				
Injection site				
Jejunum				
Kidneys				
Lachrymal gland				

Larynx				
Liver				
Lungs				
Lymph nodes, cervical				
Lymph nodes mandibular				
Lymph nodes, mesenteric				
Mammary Gland				
Nasal cavity				
Optic nerves				
Ovaries				
Pancreas				
Parathyroid				
Peripheral nerve				
Pharynx				
Pituitary				
Prostate				
Rectum				
Salivary gland				
Sciatic nerve				
Seminal vesicles				
Skeletal muscle				
Skin				
Spinal cord				
Spleen				
Sternum				
Stomach				
Testes				
Thymus				
Thyroid				
Tongue				
Trachea				
Urinary bladder				
Uterus				
Vagina				
Zymbal gland				
Standard List				

X, histopathology performed
*, organ weight obtained

GENETIC TOXICOLOGY:
See review for NDA 21-098

CARCINOGENICITY:
See review for NDA 21-098

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:
See review for NDA 21-098

SPECIAL TOXICOLOGY STUDIES:
See review for NDA 21-098

ADDENDUM TO REVIEW:
(if necessary)

APPENDIX/ATTACHMENTS:

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

/s/

Krishan L. Raheja
4/29/02 04:49:03 PM
PHARMACOLOGIST

Alexander W. Jordan
4/30/02 10:18:42 AM
PHARMACOLOGIST

NDA 21-355
Drug: Angeliq™ (drospirenone/17β-estradiol)

CAC/ECAC Report

This new drug application was not the subject of a CAC/ECAC report.

aur 10/15/10