CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	22-001	Brand Name	Activella®
OCPB Division	II	Generic Name	estradiol + norethindrone acetate
Medical Division	DMEP, HFD-510	Drug Class	Hormones
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	Prevent postmenopausal osteoporosis
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Tablet
Date of Submission	28-FEB-2006	Dosing Regimen	1 tab (0.5 mg E_2 + 0.1 mg NETA)/day
Estimated Due Date of OCPB Review	7-NOV-2006	Route of Administration	oral
PDUFA Due Date	1-JAN-2007	Sponsor	novo nordisk
Division Due Date	5-DEC-2006	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; multi dose:	x	1		**Study ALD-1640**
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x	1		**Study ALD-1640**
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	
Comments to-be-sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS	
NDA:	**22-001**
Compounds:	Estradiol/norethindrone acetate (tablet; Activella® —)
Sponsor:	novo nordisk
Submission Date:	February 28, 2006
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

NDA 22-001 seeks approval of the combination 0.5 mg estradiol (E_2) and 0.1 mg norethindrone acetate (NETA) tablet for the prevention of postmenopausal osteoporosis (PMO) with the Division of Metabolism and Endocrine Products (DMEP). NDA 20-907 SE2-009 seeks approval of the same combination tablet for the relief of vasomotor symptoms due to menopause with the Division of Reproductive and Urologic Products (DRUP). Activella® (1 mg E_2 and 0.5 mg NETA) was approved for the relief of vasomotor symptoms due to menopause under NDA 20-907 on November 18, 1998. Activella® was approved for the prevention of PMO under NDA 21-103 on April 11, 2000.

Findings

NDA 22-001 does not have efficacy and safety data for the proposed prevention of PMO indication on the combination 0.5 mg E_2 and 0.1 mg NETA tablet. The sponsor claims that Studies KLIM/PD/11/USA and EST/PD/4/N+S in NDA 21-103 showed that unopposed 0.5 mg E_2 is effective in preventing PMO. Additionally, Study KLIM/PD/11/USA showed that NETA does not counteract E_2's positive effect on bone and has additional effect on bone. The sponsor also claims that per agreement with DMEP on December 4, 2002, they did not need to have additional studies for the efficacy and safety of combination 0.5 mg E_2 and 0.1 mg NETA tablet.

Combination 0.5 mg E_2 and 0.1 mg NETA tablet's formulation is, ——————— qualitatively similar to the Activella®. The sponsor conducted Study ALD-1640 (single dose, 3-way crossover) to assess the bioequivalence (BE) of the following 3 formulations and link the to-be-marketed tablet Activella® — tablet to the approved Activella® tablet:

- 2 combination 0.5 mg E_2 and 0.1 mg NETA tablets (to-be-marketed Activella® — as test formulation)
- 2 combination 0.5 mg E_2 and 0.25 mg NETA tablets (test formulation)
- 1 combination 1 mg E_2 and 0.5 mg NETA tablet (marketed Activella® as reference formulation))

Study ALD-1640 contains the in vitro dissolution data for the above 3 formulations. The sponsor used the regulatory approved Activella® in vitro dissolution methods to conduct the dissolution test in Study ALD-1640 (per Dr. Suarez).

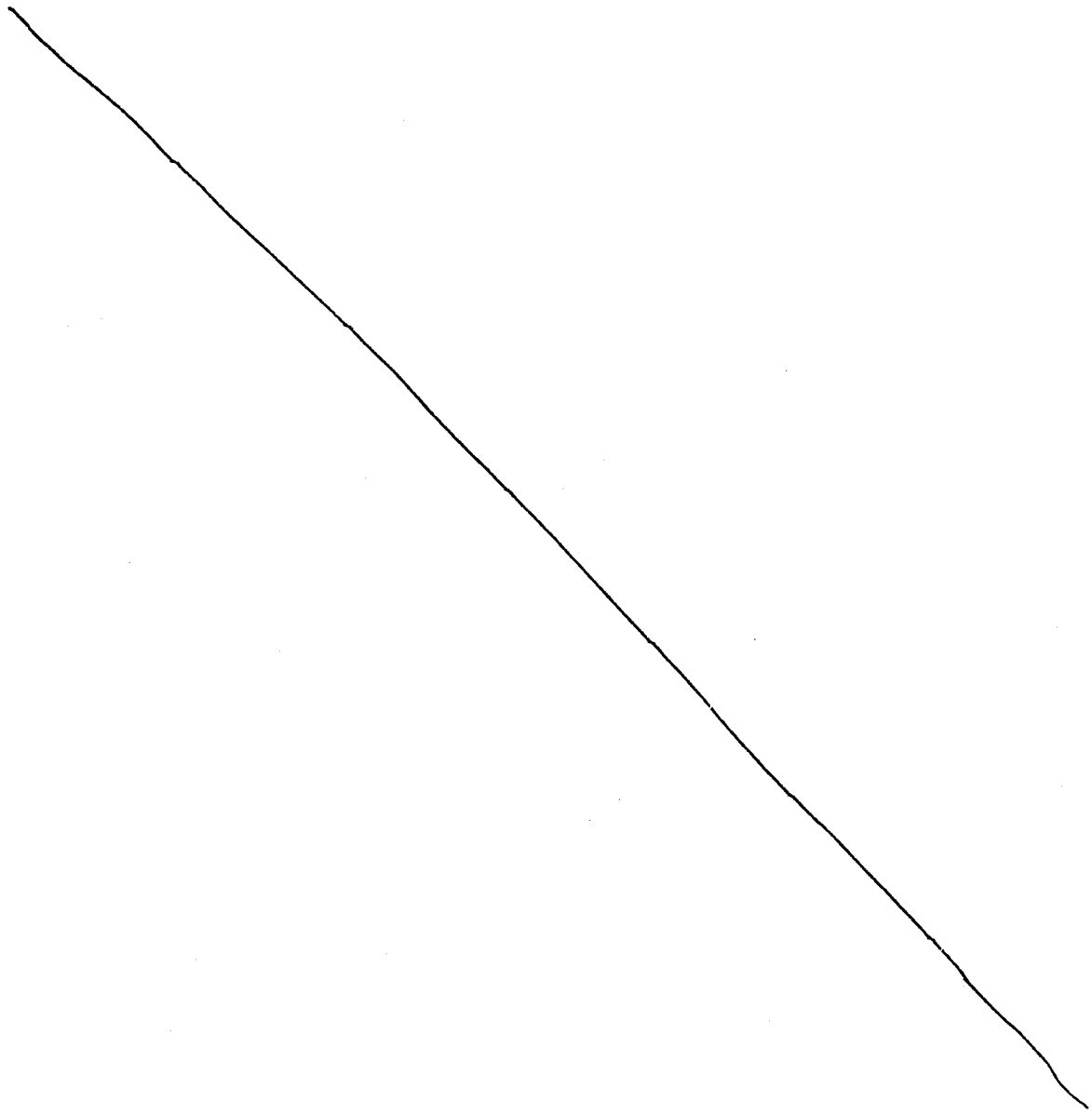
NDA 22-001 contains the following clinical pharmacology information:

- Study ALD-1640's report (including in vitro dissolution profiles comparisons)
- Study ALD-1640's bioanalytical validation report
- Study ALD-1640's electronic data sets
- Study KLIM/PD/11/USA's reports
- Study EST/PD/4/N+S's reports
- proposed labeling

Recommendations

NDA 22-001 is fileable from clinical pharmacology perspective. The sponsor should receive the following comment:

- Is it "Activella® [redacted]" or "Activelle [redacted]" that the sponsor intends to market? The application letter states "Activella® [redacted]," whereas the body uses "Activelle [redacted]



This reviewer has an agreement with DRUP's Clinical Pharmacology reviewer, Dr. Sandra Suarez, that Sandra will review Study ALD-1640 including the in vitro dissolution data.

The filing meeting was on April 19, 2006.

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/s/

S.W. Johnny Lau
5/9/2006 04:49:52 PM
BIOPHARMACEUTICS

Hae-Young Ahn
5/9/2006 04:52:54 PM
BIOPHARMACEUTICS

Memo to File
OFFICE OF CLINICAL PHARMACOLOGY

NDA	22-001
Submission Dates	February 28, 2006
Brand Name	ACTIVELLA®
Generic Name	Estradiol (0.5 mg) and norethindrone acetate (0.1 mg)
Reviewer	S.W. Johnny Lau
Team Leader	Hae-Young Ahn
OCP Division	DCP 2 (HFD-870)
ORM division	Metabolic and Endocrine Products (HFD-510)
Sponsor	novo nordisk
Relevant IND(s)	None (all European studies)
Submission Type; Code	6; S
Formulation; Strength(s)	Film-coated tablets 0.5 mg/0.1 mg
Indication	To prevent postmenopausal osteoporosis

Executive Summary

The sponsor submitted NDA 22-001 to seek approval of the combination 0.5 mg estradiol (E_2) and 0.1 mg norethindrone acetate (NETA) tablet (ACTIVELLA®) for the prevention of postmenopausal osteoporosis (PMO) with the Division of Metabolism and Endocrine Products (DMEP). NDA 20-907 SE2-009 seeks approval of the 0.5 mg E_2 and 0.1 mg NETA combination tablet for the relief of vasomotor symptoms due to menopause with the Division of Reproductive and Urologic Products (DRUP). ACTIVELLA® (1 mg E_2 and 0.5 mg NETA) was approved for the relief of vasomotor symptoms due to menopause under NDA 20-907 on November 18, 1998. ACTIVELLA® (1 mg E_2 and 0.5 mg NETA) was approved for the prevention of PMO under NDA 21-103 on April 11, 2000.

The Clinical Pharmacology and Biopharmaceutics information for NDA 22-001 is identical to those for NDA 20-907 SE2-009. Therefore, the review for NDA 22-001's Clinical Pharmacology and Biopharmaceutics information including labeling recommendation will be referred to those for NDA 20-907 SE2-009.

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by Hae-Young Ahn, Ph.D., Team Leader 11/ /06

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/s/

S.W. Johnny Lau
11/7/2006 02:10:59 PM
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Hae-Young Ahn
11/30/2006 10:25:04 PM
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