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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-103

Clinical Pharmacology and Biopharmaceutics Review

New Drug Application
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-103
Type of Submission:	SE1 (Supplement - New Indication)
Generic Name:	Estradiol/Norethindrone actetate
Formulation(s);	Tablets
Strength(s);	1mg/0.5mg
Route(s)	PO
Brand Name:	Activelle™
Sponsor:	Novo Nordisk Pharmaceuticals, Inc. Princeton, NJ
Submission Date(s):	June 10, 1999
Reviewer:	Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D.

I. SYNOPSIS

Indications

Activelle™ (estradiol/norethindrone actetate 1mg/0.5mg tablets) is an estrogen progestin fixed combination tablet that is currently approved for the following two indications in postmenopausal women with an intact uterus:

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

The present NDA supplement is for the **new indication**:

Prevention [redacted] of postmenopausal osteoporosis.

This indication is also limited to postmenopausal women with an intact uterus.

Dose

The dose for all indications is one tablet daily.

Submitted Information

There was no new biopharmaceutic, pharmacokinetic, drug metabolism, pharmacodynamic, or clinical pharmacology information in this submission. All previously submitted information has been previously reviewed and found acceptable.

Although studies were performed in post-menopausal women, there is a lack of information in the elderly and particularly the extreme elderly, and this population would be expected to use this medication. The currently approved labeling for geriatric use follows, and appropriately addresses dosing in this population in spite of the lack of information.

"GERIATRIC USE: Clinical studies of Activelle did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range,

reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy[1]".

Additional information would not be expected to alter the labeling and thus additional pharmacokinetic studies are not warranted.

II. RECOMMENDATION

The Division of Pharmaceutical Evaluation II of the Office of Clinical Pharmacology and Biopharmaceutics (OCPB/DPE-2) has reviewed NDA # 21-103 SE1, submitted June 10, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB.

This recommendation and the labeling comments should be sent to the sponsor as appropriate.

III. LABELING COMMENTS FOR SPONSOR

Please include descriptive statistics (mean, standard deviation, range) of patient age in the text of the pharmacokinetics section when discussing both the single and multiple dose studies.

IV. SIGNATURES

/S/ 7/30/99

Ronald Evan Kavanagh, B.S. Pharm., Pharm.D., Ph.D. — Date

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

RD - Hae-Young Ahn, Ph.D., Team Leader — Date

/S/ 7/30/99

~~FD~~ FT - Hae-Young Ahn, Ph.D., Team Leader — Date

OCPB Briefing Meeting: None

CC: **NDA 21-103 (orig., 1 copy)**
HFD-510 (Zawaldski, ~~Weber~~) Hecht
HFD-850 (Lesko, Huang)
HFD-870 (M. Chen, Kavanagh, Ahn)
HFD-340 (Vish)
HFD-580 (Parekh)
Central Document Room (Barbara Murphy)

[1] 21 CFR §201.57 (10)(ii)(A)