# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 21-103

# Pharmacology Review(s)

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS:

Reviewer Name: Ronald W. Steigerwalt, Ph.D. Pharmacology Team Leader
Division Name: Division of Metabolic and Endocrine Drug Products (DMEDP)
HFD#510
Review Completion Date: August 5, 1999
Review number: 1

**IND/NDA NUMBER: NDA 21-103**
Serial number/date/type of submission: Initial NDA submission June 11, 1999
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Novo Nordisk Pharmaceuticals, Inc; 100 Overlook Center – Ste. 200; Princeton, NJ 08540-7810

**DRUG**
Generic Name:
Estradiol hemihydrate, Ph.Eur.; Estradiol, USP
Norethisterone acetate, Ph.Eur Norethindrone acetate, USP
Trade Name: Activelle-Osteoporosis
Chemical Name:
estra-1,3,5 (10)-triene-3,17β-diol hemihydrate (Estradiol (0.5 mg))
17βacetoxy-19-nor-17α-pregen-4-20-yn-3-one (Norethindrone Acetate (1 mg))
CAS Registry Number:
Estradiol: 50-28-2
Norethisterone: 51-98-9
Molecular Formula/ Molecular Weight:
Estradiol: $C_{18}H_{24}O_2 \cdot 1/2$ H20; MW 281.4
Norethindrone acetate: $C_{22}H_{28}O_3$ MW 340.5

Relevant INDs/NDAs/DMFs: Sponsor cites NDA 20-907 for nonclinical support data.

Indication: Prevention [redacted] of osteoporosis

Clinical formulation: (listed as contents/tablet)

| Active Ingredients: | |
|---|---|
| Estradiol hemihydrate | 1.00 mg |
| Norethisterone acetate | 0.5 mg |
| Inactive Ingredients | |
| Lactose monohydrate | [redacted] |
| Maize starch | |
| Copolyvidone | |
| Talc | |
| Magnesium stearate | |
| Film Coating | |
| | |
| Talc | - |
| Triacetin | |

Route of administration: Oral

Proposed clinical protocol or Use: NDA supplement for use in prevention [redacted] of osteoporosis.

Previous clinical experience: Both Norethindrone acetate and estradiol are approved drugs. Activelle was approved in numerous European countries for postmenopausal symptoms in 1998. It was approved in Norway for use in osteoporosis on January 8, 1999. A high dose combination of 2-mg norethindrone acetate and 1 mg estradiol has been marketed outside the United States for 13 years. Activelle was approved in the United States under NDA 20-907 for treatment of postmenopausal symptoms in November, 1998.

Studies reviewed within this submission: Studies were previously reviewed under NDA 20-907. No further review was necessary under this supplement.

**OVERALL SUMMARY AND EVALUATION:**

Introduction: Activelle is currently approved under NDA 20-907 for relief of menopausal symptoms. The current NDA provides studies to support use in prevention [redacted] of osteoporosis. The components of the product have had extensive use in humans and are approved drugs. Outside the United States, a combination of 2-mg norethindrone acetate and 1 mg estradiol has been marketed for 13 years. Activelle was approved in numerous European countries for postmenopausal symptoms in 1998. It was approved in Norway for use in osteoporosis on January 8, 1999. Under NDA 20-907, it was determined that an extensive preclinical toxicology package was not necessary for approval for the relief of menopausal symptoms (see attached copy of Dr. Jordan's review). Under the current Division guidance for treatments for osteoporosis, preclinical studies assessing bone quality are not necessary to support approval of an osteoporosis indication for this combination of estradiol and norethindrone acetate provided adequate clinical data are available. Therefore, no additional preclinical review of this NDA is necessary.

Conclusions: No further preclinical evaluation of this NDA is necessary.

COMMUNICATION REVIEW:
Labeling Review (NDA): Current labeling in Pregnancy, Nursing mothers, and Carcinogenicity, Mutagenicity and Fertility sections is adequate.

**RECOMMENDATIONS:**

Pharmacology recommends **approval** of norethindrone acetate and estradiol (Activelle) for the treatment [redacted] of osteoporosis. No further action is necessary from pharmacology.

/S/

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader
8/5/99

cc: IND Arch
HFD510
HFD510/Steigerwalt/Hedin
Review Code: AP
Filename: 21103.000.doc
Attachment: Pharmacology Review of NDA 20-907

NDA 20-907 12/23/97

DEC 23 1997

Novo Nordisk Pharm

Submission: November 7, 1997

**Pharmacology Review of NDA**

Drug: Norethindrone Acetate (1 mg) and Estradiol (0.5 mg).

Indication: Relief of menopausal symptoms and the prevention of osteoporosis.

Both norethindrone acetate and estradiol are approved drugs. A high dose combination of 2 mg norethindrone acetate and 1 mg estradiol has been marketed outside the US for 13 yrs.

The sponsors conducted several preclinical studies including three single dose studies with the combination in rat and monkey which resulted in no unusual toxicity.

**Toxicity study by oral (gavage) administration to CD rats for four weeks.**
Novo Nordisk study no. 940265, 1997.

Groups of 20 female CD (Sprague-Dawley) rats received a combination of estradiol and norethindrone acetate by gavage daily for 4 weeks. There were two sets of doses; four or two parts E2 to one part NETA. Doses selected were 0.02+0.005 or 0.02+0.01 mg/kg/day for the low dose; 0.2+0.05 or 0.2+0.1 mg/kg/day for the mid-dose and 2.0+0.5 or 2.0+1.0 mg/kg/day for the high dose.

Mortality: None

Clinical signs: transient salivation after dosing in MD and HD and from wk 3, piloerection in the HD.

Body weight: Decrease bw gain in both HD gps.

Ophthalmoscopy: No effects.

Hematology: Prolonged prothrombin times in animals treated with either combination at the MD and HD. There was prolonged activated 0partial thromboplastin times and low mean cell volumes in both HD gps and slightly low packed cell vol in the HD receiving 2.0+1.0 mg/kg.

Clinical chemistry: No toxicological significant changes.

Urinalysis: Low urinary sodium and low specific gravity compared to controls in MD and HD.

Organ weights: Increased liver wts in both HD gps. Low thymus and ovary wts and high adrenal wts were seen in some HD animals. Rel kidney wts were increased in HD.

Gross pathology: No effects.

Histopathology: Effects seen only in the HD included centriacinar glycogenic vacuolation of the liver, acinar hyperplasia of the mammary gland, ovarian atrophy and luteal cysts, hyperplasia and focal squamous metaplasia of the uterine epithelium, and in a few animals, vacuolation of the vaginal epithelium.

Conclusion: This 4 week toxicity study in rats did not reveal any unexpected toxicities of the combination of norethindrone acetate and estradiol.

Labeling: Satisfactory.

Conclusion: Pharmacology recommends approval of norethindrone acetate and estradiol for treatment of menopausal symptoms.

/S/ 12/23

Alex Jordan, PhD

NDA 20-907
HFD-580