CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-167

PHARMACOLOGY REVIEW

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Type 6 NDA

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: February 4, 2000
Review number: 1

IND/NDA NUMBER: NDA 21-167
Serial number/date/type of submission: Type 6 NDA submission October 20, 1999
Information to sponsor: Yes ( ) No (X)
Sponsor (or agent): Novartis Pharmaceuticals Corporation; 59 Route 10; East Hanover, NJ 07936-1080

DRUG
Generic Name:
Estradiol hemihydrate, Ph.Eur.; Estradiol, USP
Trade Name: Vivelle® (estradiol transdermal system)
Chemical Name:
estra-1,3,5 (10)-triene-3,17β-diol hemihydrate (Estradiol (0.5 mg))
CAS Registry Number:
Estradiol: 50-28-2
Molecular Formula/ Molecular Weight: Estradiol: $C_{18}H_{24}O_2$; MW 272.39

Relevant INDs/NDAs/DMFs: Sponsor cites NDA 20-323 for nonclinical safety data.

Indication: Prevention of postmenopausal osteoporosis

Clinical formulation: (copied from sponsor label)
The Vivelle estradiol transdermal system contains estradiol in a multipolymeric adhesive. The system is designed to release 17ß-estradiol continuously upon application to intact skin. Five systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 7.25, 11.0, 14.5, 22.0, or 29.0 cm^2 contains 2.17, 3.28, 4.33, 6.57, or 8.66 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.
Estradiol USP (17ß-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39. The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer and epoxy resin, (2) an adhesive formulation containing estradiol, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3 butylene glycol, styrene-butadiene rubber, oleic acid, lecithin, propylene glycol, bentonite, mineral oil, and dipropylene glycol, and (3) a polyester release liner that is attached to the adhesive surface and must be removed before the system can be used

Route of administration: Transdermal patch

Proposed clinical protocol or Use: Type 6 NDA for use in prevention of postmenopausal osteoporosis.
Previous clinical experience: Estradiol is an approved drug. Vivelle was approved under NDA 20-323 for use at treating severe postmenopausal symptoms.
Studies reviewed within this submission: Studies were previously reviewed under NDA 20-323 No further review was necessary under this supplement. There were no preclinical studies submitted to support the

new indication. The decision regarding efficacy and safety will be determined in the review of the clinical data presented.

OVERALL SUMMARY AND EVALUATION:

Introduction: Vivelle is currently approved under NDA 20-323 for relief of menopausal symptoms. The current NDA provides studies to support use in prevention of postmenopausal osteoporosis. The components of the product have had significant use in humans and are approved under the original NDA. Under the current Division guidance for treatments for postmenopausal osteoporosis, preclinical studies assessing bone quality are not necessary to support approval of an osteoporosis indication for estradiol provided adequate clinical data are available. Therefore, no additional preclinical review of this NDA is necessary.

Conclusions: Preclinical toxicology was reviewed under the original approved NDA 20-323. 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. No changes are required.

RECOMMENDATIONS:

Pharmacology recommends **approval** of estradiol transdermal patch (Vivelle) for the prevention of postmenopausal osteoporosis. No further action is necessary from pharmacology.

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Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP

cc: IND Arch
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APPEARS THIS WAY
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