CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-538/S-015

MEDICAL REVIEW

Medical Officer Summary of NDA Supplement

1. NDA 20-538-S015 Submission Date: January 22, 2001
M.O. Review Review Completed: November 15, 2001

Drug: Estradiol transdermal system

Generic Name: 17-Beta estradiol

Trade name: Vivelle-Dot™

Chemical Name: Estradiol USP (estra-1,3,5, (10)-triene-3, 17β

Sponsor: Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Pharmacologic Category: Estrogen

Clinical Indication: Estrogen Replacement Therapy

Dosages and Route of Administration: 0.025mg per day, 0375 mg per day, 0.05 mg per day, 0.075 mg per day, and 0.1 mg per day

NDA Drug Class: 3S

Related Drugs: Approved estradiol trandermal patches are Estraderm®, Climara®, Vivellle®,Menorest®, Alora® and Esclim®.

Summary/Issues

The sponsor wishes to incorporate labeling changes that were approved for Vivelle® (estradiol transdermal system) on February 25, 2000. Vivelle-Dot™ is approved based upon demonstrating bioequalence to Vivelle®in supplement 006.

This supplement is submitted to obtain an osteoporosis indication. The sponsor conducted a two-year randomized controlled placebo trial that was reviewed in the Division of Metabolic and Endocrine Drug Products (DMEDP). With submission of this supplement, the sponsor also submitted a proposed draft label.
Novartis has submitted draft labeling to be consistent with Vivelle® and also to update the label for Vivelle-Dot™ in an effort to be consistent with the Draft Labeling Guidance for Estrogen and Estrogen/Progestin Products of 1995. Substantial changes have been made to most sections of the submitted draft label. The following is a detailed discussion of some of these changes:

The **Box Warning** has been updated and the two paragraphs under # 2 have been reworded and moved to the Precautions section of the label.

Under **Clinical Pharmacology** four paragraphs have been deleted.

The **Pharmacokinetic** section now includes a section for special populations and a specific section that reports adhesion data related to the adhesions studies from short-term clinical trials with Vivelle-Dot.

Under **Clinical Studies** an introductory statement states that Vivelle-Dot is bioequivalent to Vivelle.

Under **Contraindications**, the first sentence relating to hypersensitivity has been removed.

Under **Warnings**, this section has been significantly updated and renumbered. The following paragraphs show changes to this section:

1. Induction of malignant neoplasms.

a. **Endometrial cancer.** The reported endometrial cancer risk among unopposed estrogen users ———————— is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use with increased risks of 15- to 24-fold for five to 10 years or more, and this risk has been shown to persist for at least 8-15 years after estrogen therapy is discontinued.

b. **Breast Cancer.** While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24-40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. **Thromboembolic disorders.**
The physician should be aware of the possibliity of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) —— estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

Venous thromboembolism. Several epidemiologic studies have found an increased risk of — thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

Cerebrovascular disease. Embolic cerebrovascular events have been reported

Cardiovascular disease. large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

3. **Gallbladder disease.** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

4. **Hypercalcemia.** Administration of estrogen may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

The **Precautions** section is significantly updated and clinical conditions in this section are renumbered. Sections 1,2, and 3 are modified and this section now includes a Carcinogenesis, Mutagenesis, and Impairment of fertility section, Pregnancy Category X, a section on Nursing Mothers, a Pediatric Use, and a section on Geriatric Use.

A. General

~~1.~~ **Addition of a progestin when a woman has not had a hysterectomy.** Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lower incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include ~~—~~ adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and ~~—~~impairment of glucose tolerance. The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. **Cardiovascular risk.** The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 post-menopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in post-menopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. **Elevated blood pressure.** In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen.

6. **Hypothyroidism.** Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy, ~~———~~

8. **Exacerbation of endometriosis**. Endometriosis may be exacerbated with administration of estrogen therapy.

9. **Hypocalcemia**. Estrogens should be used with caution in individuals with severe hypocalcemia.

The following paragraphs show the revised format Carcinogenesis, Mutagenesis and Impairment to fertility, pregnancy category X, nursing mothers, pediatric and geriatric use:

E. **Carcinogenesis, Mutagenesis, And Impairment of Fertility.** Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver

F. **Pregnancy Category X** Vivelle-Dot™ should not be used during pregnancy see **CONTRAINDICATIONS.**

Nursing Mothers. The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Vivelle-Dot™ is not indicated for the prevention of postpartum breast engorgement

Pediatric Use. Estrogen replacement therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce gynecomastia

I. **Geriatric Use.**The safety and effectiveness in geriatric patients have not been established.

Under **Adverse reactions**, an introductory paragraph is inserted relating to adverse events and clinical trials. This paragraph reads:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Following this introductory paragraph, the following language should be inserted: "See **WARNINGS** regarding induction of malignant neoplasia, thromboembolic disorders, gallbladder disease, and hypercalcemia; see **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure".

The sponsor was also instructed to insert an adverse event table by Body System with clinical data originating in the Vivelle studies. Adverse events are to be reported which as (=/>2%).

INDICATIONS and **DOSAGE AND ADMINISTRATION** section

Under **Dosage and Administration** editorial changes are made to the first paragraph and under Initiation of therapy, the important dosage of 0.0375 mg/days without a delay in therapy is now introduced.

HFD-510 will review labeling relating to the osteoporosis indication.

Patient Package Insert

The patient package insert was substantial revised to fit a plain language format that has been introduced into more recently approved labels for estrogen products.

Recommendation:

The application is approvable pending submission by the sponsor of the recommended revised labeling changes to the Division of Reproductive and Urologic Drug Products (DRUDP).

Phill H. Price, M.D.

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

/s/

Phill H. Price
11/19/01 02:04:29 PM
MEDICAL OFFICER

Shelley Slaughter
11/19/01 02:10:29 PM
MEDICAL OFFICER
I concur with the medical officer review. See also team leader review

MEMO TO THE FILE

NDA 20-538S015
NDA 20-538S014

Item: Safety Update

The sponsor submitted a Safety Update for Vivelle-Dot™, S015 on May 25, 2001 and a second Safety Update for S014 on November 14, 2001. The sponsor stated that there was no new clinical trial information reported in either Safety Update.

Phill Price, M.D.
November 19 , 2001