CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-538/S-006

FINAL PRINTED LABELING

JAN

APPROVED

Noven Estradiol Transdermal System
Continuous delivery for twice-weekly application

℞ Only

Prescribing Information

1. **ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.**
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. **ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.**
Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

   There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

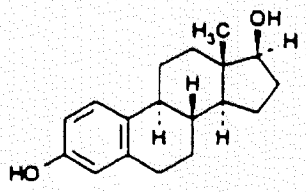
DESCRIPTION

The Noven® Estradiol Transdermal System contains estradiol in a multipolymeric adhesive. The system is designed to release 17ß-estradiol continuously upon application to intact skin.

Four systems are available to provide nominal in vivo delivery of 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 3.75, 5.0, 7.5, or 10.0 cm^2 contains 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP, respectively. The composition of the systems per unit area is identical.

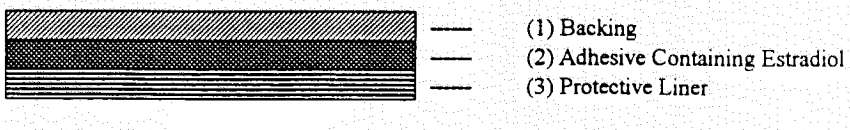
Estradiol USP (17ß-estradiol) is a white, crystalline powder, chemically described as estra-1,3,5 (10)-triene-3,17ß-diol.

The structural formula is:



The molecular formula of estradiol is $C_{18}H_{24}O_2$. The molecular weight is 272.39.

The Noven Estradiol Transdermal System comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, povidone and dipropylene glycol, and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

The Noven Estradiol Transdermal System provides systemic estrogen replacement therapy. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver, and bone of women. Among numerous effects, estradiol is largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics. By a direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, it causes enlargement of the breasts through promotion of ductal growth, stromal development, and the accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and pigmentation of the nipples and genitals.

Estrogens are intricately involved with other hormones, especially progesterone, in the processes of the ovulatory menstrual cycle and pregnancy, and affect the release of pituitary gonadotropins.

Loss of ovarian estradiol secretion after menopause can result in instability of thermoregulation, causing hot flushes associated with sleep disturbance and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol replacement therapy alleviates many of these symptoms of estradiol deficiency in the menopausal woman.

Pharmacokinetics

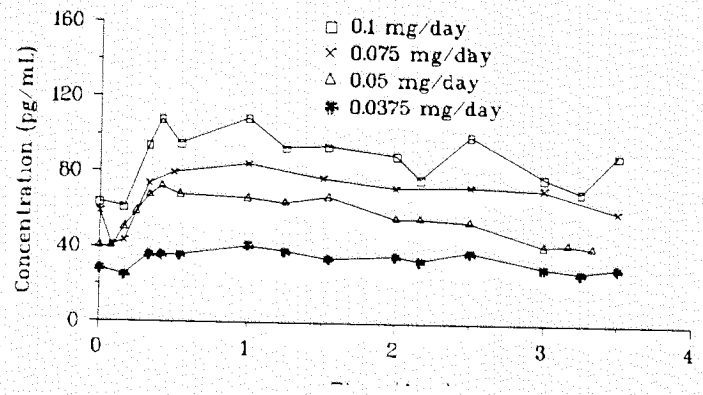
The skin metabolizes estradiol only to a small extent. In contrast, orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. Therefore, transdermal administration produces therapeutic plasma levels of estradiol with lower circulation levels of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

Absorption

In a multiple-dose study consisting of three consecutive patch applications of the original formulation (Vivelle® system) which was conducted in 17 healthy, postmenopausal women, blood levels of estradiol and estrone were compared following application of these units to sites on the abdomen and buttocks in a crossover fashion. Patches that deliver nominal estradiol doses of approximately 0.0375 mg/day and 0.1 mg/day were applied to abdominal application sites while the 0.1 mg/day doses were also applied to sites on the buttocks. These systems increased estradiol levels above baseline within 4 hours and maintained respective mean levels of 25 and 79 pg/mL above baseline following application to the abdomen; slightly higher mean levels of 88 pg/mL above baseline were observed following application to the buttocks. At the same time, increases in estrone plasma concentrations averaged about 12 and 50 pg/mL, respectively,

following application to the abdomen and 61 pg/mL for the buttocks. While plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours following removal of the patches in this study, results from another study show these levels to return to baseline values within 24 hours following removal of the patches.

The graph illustrates the mean plasma concentrations of estradiol at steady-state during application of these patches at four different dosages.



The original formulation that was tested in clinical trials has been revised to reduce the patch sizes and the revised formulation was shown to be bioequivalent to the original formulation.

The corresponding pharmacokinetic parameters are summarized in the table below.

Steady-State Estradiol Pharmacokinetic Parameters for Systems Applied to the Abdomen (mean ± standard deviation)
Nonbaseline-corrected data*

Dosage (mg/day)	C_{max}† (pg/mL)	C_{avg}‡ (pg/mL)	C_{min} (84 hr)§ (pg/mL)
0.0375	46 ± 16	34 ± 10	30 ± 10
0.05	83 ± 41	57 ± 23#	41 ± 11#
0.075	99 ± 35	72 ± 24	60 ± 24
0.1	133 ± 51	89 ± 38	90 ± 44
0.1¶	145 ± 71	104 ± 52	85 ± 47

*Mean baseline estradiol concentration = 11.7 pg/mL
†Peak plasma concentration
‡Average plasma concentration
§Minimum plasma concentration at 84 hr
#Measured over 80 hr
¶Applied to the buttocks

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to lesser degree to albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The half-life values calculated after dosing with the Noven Estradiol Transdermal Systems ranged from 5.9 to 7.7 hours. After removal of the transdermal systems, serum concentrations of estradiol and estrone returned to baseline levels within 24 hours.

Special Populations

The Noven Estradiol Transdermal Systems were investigated in postmenopausal women. No other special populations of volunteers were investigated.

Drug Interactions

No drug interaction studies were conducted with the Noven Estradiol Transdermal Systems, since estradiol is well characterized.

INDICATIONS AND USAGE

The Noven Estradiol Transdermal System is indicated in the following:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions.

2. Treatment of vulval and vaginal atrophy.

3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use the Noven Estradiol Transdermal System.

Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogen may cause fetal harm when administered to a pregnant woman.

2. Undiagnosed abnormal genital bleeding.

3. Known or suspected cancer of the breast.

4. Known or suspected estrogen-dependent neoplasia.

5. Active thrombophlebitis or thromboembolic disorders, or a documented history of these conditions.

WARNINGS

1. **Induction of malignant neoplasms**. Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogen therapy at higher doses or for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the 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. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred six months after estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. **Gallbladder disease**. Two studies have reported a 2- to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.

3. **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. These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. **Elevated blood pressure**. Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally administered estradiol does not affect renin substrate.

5. **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.

PRECAUTIONS

A. General.

1. **Addition of a progestin**. 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. Morphologic and biochemical studies of endometria suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are, however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include:

(1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL) which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below);

(2) impairment of glucose tolerance; and

(3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiologic data are available to address this point (see PRECAUTIONS, below).

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. **Cardiovascular risk**. A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy without added progestins and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

(1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socioeconomic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus, ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.

(2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of

added progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

(3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS, above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. **Physical examination**. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

4. **Hypercoagulability**. Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose- and duration-dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. Epidemiological studies, which employed primary orally administered estrogen products, have suggested that hormone replacement therapy (HRT) may be associated with an increased relative risk of developing venous thromboembolism (VTE), i.e., deep venous thrombosis or pulmonary embolism. Risk/benefit should therefore be carefully weighed in consultation with the patient when prescribing either oral or transdermal HRT to women with a risk factor for VTE.

5. **Familial hyperlipoproteinemia**. Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

6. **Fluid retention**. Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

7. **Uterine bleeding and mastodynia**. Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. **Impaired liver function**. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

B. Information for the Patient. See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

C. Laboratory Tests. Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

D. Drug/Laboratory Test Interactions.

Some of these drug/laboratory test interactions have been observed only with estrogen progestin combinations (oral contraceptives):

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex; and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.

3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

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, cervix, vagina, testis, and liver (see CONTRAINDICATIONS and WARNINGS).

Pregnancy Category X. Estrogens should not be used during pregnancy (see CONTRAINDICATIONS and Boxed Warning).

Nursing Mothers. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure, and hypercalcemia.

The most commonly reported systemic adverse event with the Noven Estradiol Transdermal Systems was mild headache. Topical irritancy evaluations showed that for the majority of the subjects, no erythema was observed at the application sites after removal of the systems. No occurrence of erythema was greater than mild in severity.

The following additional adverse reactions have been reported with estrogen therapy:

1. Genitourinary system. Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.

2. Breasts. Tenderness, enlargement.

3. Gastrointestinal. Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.

4. Skin. Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.

5. Eyes. Steepening of corneal curvature; intolerance to contact lenses.

6. Central Nervous System. Headache, migraine, dizziness; mental depression; chorea.

7. Miscellaneous. Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Noven Estradiol Transdermal System should be placed on a clean, dry area of the abdomen. *The Noven Estradiol Transdermal System should not be applied to the breasts.* The Noven Estradiol Transdermal System should be replaced twice weekly. The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued.

Initiation of Therapy

For treatment of moderate-to-severe vasomotor symptoms and vulval and vaginal atrophy associated with the menopause, start therapy with the Noven Estradiol Transdermal System 0.05 mg/day applied to the skin twice weekly. In order to use the lowest dosage necessary for the control of symptoms, decisions to increase dosage should not be made until after the first month of therapy. Some women taking the 0.0375 mg/day dosage may experience a delayed onset of efficacy. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with the Noven Estradiol Transdermal System may be initiated at once. In women who are currently taking oral estrogens, treatment with the Noven Estradiol Transdermal System should be initiated 1 week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear in less than 1 week.

Therapeutic Regimen

The Noven Estradiol Transdermal System may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, the Noven Estradiol Transdermal System may be given on a cyclic schedule (e.g., three weeks on drug followed by one week off drug).

HOW SUPPLIED

Noven Estradiol Transdermal System, 0.0375 mg/day - each 3.75 cm^2 system contains 0.585 mg of estradiol USP for nominal* delivery of 0.0375 mg of estradiol per day.

Patient Calendar Pack of 8 Systems	NDC 57616-081-11
Carton of 6 Patient Calendar Packs of 8 Systems	NDC 57616-081-12
Carton of 24 Systems	NDC 57616-081-13
Institutional Carton of 100 Systems	NDC 57616-081-31

Noven Estradiol Transdermal System, 0.05 mg/day - each 5.0 cm^2 system contains 0.78 mg of estradiol USP for nominal* delivery of 0.05 mg of estradiol per day.

Patient Calendar Pack of 8 Systems	NDC 57616-082-11
Carton of 6 Patient Calendar Packs of 8 Systems	NDC 57616-082-12
Carton of 24 Systems	NDC 57616-082-13
Institutional Carton of 100 Systems	NDC 57616-082-31

Noven Estradiol Transdermal System, 0.075 mg/day - each 7.5 cm^2 system contains 1.17 mg of estradiol USP for nominal* delivery of 0.075 mg of estradiol per day.

Patient Calendar Pack of 8 Systems	NDC 57616-083-11
Carton of 6 Patient Calendar Packs of 8 Systems	NDC 57616-083-12
Carton of 24 Systems	NDC 57616-083-13
Institutional Carton of 100 Systems	NDC 57616-083-31

Noven Estradiol Transdermal System, 0.1 mg/day - each 10.0 cm^2 system contains 1.56 mg of estradiol USP for nominal* delivery of 0.1 mg of estradiol per day.

Patient Calendar Pack of 8 Systems	NDC 57616-084-11
Carton of 6 Patient Calendar Packs of 8 Systems	NDC 57616-084-12
Carton of 24 Systems	NDC 57616-084-13
Institutional Carton of 100 Systems	NDC 57616-084-31

*See DESCRIPTION.

Store at controlled room temperature at 25°C (77°F).
Do not store unpouched. Apply immediately upon removal from the protective pouch.

Noven Pharmaceuticals, Inc. Printed in U.S.A. (October 1998)
Miami, FL 33186