**Transdermal System, Vaginal Cream, and Tablets**

**CONTRAINDICATIONS:**

4. Known or suspected estrogen-dependent neoplasia.

5. Active thrombophlebitis or thromboembolic disorders.

**WARNINGS:**

1. **Transdermal System, Vaginal Cream, and Tablets**

   Induction of malignant neoplasms.

   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 premature estrogen users—women with incidence of 1.5 to 2.5 times the risk for ten or more years of use. In clinical studies, persistence of risk was demonstrated for 8 to 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 progesterin therapy may offset this risk but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

   Breast Cancer. While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, some have reported a moderately increased risk (relative risk of 1.3-2.3) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of 10 years. Other studies have not shown this relationship.

   Congenital lesions with malignant potential. Estrogen therapy during pregnancy is associated with an increased risk of fatal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who have received DES during pregnancy have shown the persistence of offspring with 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 undiagnosed abnormalities and possibly testicular cancer later in life. Although some of these changes are benign, others are precursors of malignancy.

   2. **Gaillaudet disease.** Two studies have reported a 2- to 4-fold increase in the risk of gastrointestinal and mesenteric vascular disease in women receiving estrogen for menopausal symptoms.

   3. **Cardiovascular disease.** Large doses of estrogen (5 mg conjugated estrogens per day) comparable to those used to treat breast cancer of the prostate and breast, have been shown in large prospective studies to reduce the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from women to men. However, to avoid the theoretical cardiovascular effects, women should be using 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. One study showed that postmenopausal estrogen users have higher blood pressure than nonusers. Two other studies showed slightly lower blood pressure among estrogen users compared to nonusers. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use.

   5. **Hypercalcemia.** Administration of estrogens 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:**

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**General**

1. **Addition of a progestin.** Studies of the addition of estrogen administration have reported a lowered Morphological and biochemical indices of endometrial proliferation are needed to provide maximal maximal any hyperplastic changes. Whether this will provide equivalent or increased protection than estrogen replacement therapy. The addition of a progestin in estrogen replacement therapy is dependent on the dose of estrogen used in reducing endometrial risk. The overall incidence of FD&C Yellow No. 5 (tartrazine) may be important in minimizing these adverse effects.

2. **Physical examination.** A complete medical and fat examination is performed. The examination should include special reference to blood pressure, body weight, and chest pain. As a general rule, a mammogram should be obtained every three years.

3. **Fluid Retention.** Because estrogens may cause severe fluid retention, the patient should be counseled about the necessity for diet and fluid restriction. However, the fluid retention may be self-limiting.

4. **Uterine bleeding and mastodynia.** Certain patients may experience episodic uterine bleeding or mastodynia.

5. **Impaired liver function.** Estrogens may be poorly liver function and should be administered with caution.

6. **Data for the Patient.** Estrogen administration is associated with a decrease in fat and an increase in lean body mass. These changes may be associated with an increase in the risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease. There is a suggestion that estrogens may be associated with an increased risk of thromboembolic disease.

**Nursing Mothers.** Estrogen administration to nursing mothers is not recommended. Estrogen therapy should be withheld from nursing mothers who are using estrogen replacement therapy.