

Estradiol

CONTRAINDICATIONS: (cont'd)

4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS:

Transdermal System, Vaginal Cream, and Tablets

1. 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 prolonged use—with increased risks of 15- to 24-fold for five to ten 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).

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 risks of 1.3-2.0) 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 fetal congenital reproductive tract disorders, and possibly other birth defects. Studies of women who have received 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. Although some of these changes are benign, others are precursors of malignancy.

2. Gallbladder disease. Two studies have reported a 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens.

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. 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.

Transdermal System

Effects Similar to Those Caused by Estrogen-Progestogen Oral Contraceptives

There are several serious adverse effects of oral contraceptives and other high-dose oral estrogen treatments, most of which have not, up to now, been documented as consequences of postmenopausal estrogen replacement therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women.

Thromboembolic Disease. It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular disease, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found, this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving relatively large doses of estrogens may have increased risk. Therefore, estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders, and they should not be used in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

Hepatic Adenoma. Benign hepatic adenomas have been associated with the use of oral contraceptives. Although benign and rare, these tumors may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.

Glucose Tolerance. A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

Vaginal Cream and Tablets

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.

PRECAUTIONS:

Transdermal System, Vaginal Cream, and Tablets

General

1. Addition of a progestin. Studies of the addition of of estrogen administration have reported a lowered Morphological and biochemical studies of endometrium are needed to provide maximal maturation any hyperplastic changes. Whether this will provide has not been clearly established. There are possible with the inclusion of progestin in estrogen replacement adverse effects on carbohydrate and lipid metabolism may be important in minimizing these adverse effect

2. Physical examination. A complete medical and far initiation of any estrogen therapy. The pretreatment should include special reference to blood pressure, b should include a Papanicolaou smear. As a general r longer than one year without reexamining the patient

3. Fluid Retention. Because estrogens may cause so which might be exacerbated by this factor, such as renal dysfunction, require careful observation.

4. Uterine bleeding and mastodynia. Certain patients of estrogenic stimulation, such as abnormal uterine bl

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

Information for the Patients. See text of Patient Packa Drug/Laboratory Test Interactions

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

2. Increased thyroid-binding globulin (TBG) leading hormone, as measured by protein-bound iodine (PBI) or T3 levels by radioimmunoassay. T3 increased TBG. Free T4 and free T3 concentrations are

3. Other binding proteins may be elevated in serum (CBG), sex hormone-binding globulin (SHBG), leading and sex steroids, respectively. Free or biologically changed. Other plasma proteins may be increased (a antitrypsin, ceruloplasmin).

4. Increased plasma HDL and HDL-2 subfraction 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 species increases the frequency of carcinomas of the t liver. See CONTRAINDICATIONS, and WARNINGS

Pregnancy Category X. Estrogens should not be used DICATIONS and BOXED WARNING.

Nursing Mothers. As a general principle, the administ should be done only when clearly necessary since man

Transdermal System

Prolonged administration of unopposed estrogen ther risk of endometrial hyperplasia in some patients. Est patients who have or have had endometriosis.

Oral contraceptives, appear to be associated with an sion. Although it is not clear whether this is due to the of the contraceptive, patients with a history of depress Preexisting uterine leiomyomata may increase in size occurs, estrogen therapy should be discontinued while t

In patients with a history of jaundice during pregn jaundice will recur with the use of estrogen-conta develops in any patient receiving estrogen, the medica cause is investigated.

Because the prolonged use of estrogens influences the n estrogens should be used with caution in patients w with hypercalcemia and in patients with renal insufficie

Vaginal Cream and Tablets

Hypercoagulability. Some studies have shown that wo apy have hypercoagulability, primarily related to decre appears dose- and duration-dependent and is less pron contraceptive use. Also, postmenopausal women tend, eters at baseline compared to premenopausal women. I postmenopausal mestranol may increase the risk of thr of studies (of primarily conjugated estrogens users) rep cient information on hypercoagulability in women wh disease.

Familial hyperlipoproteinemia. Estrogen therapy may be plasma triglycerides leading to pancreatitis and other c defects of lipoprotein metabolism.

Laboratory Tests. Estrogen administration should gener the smallest dose, rather than laboratory monitoring indications in which symptoms are observable. For pre DOSAGE AND ADMINISTRATION section.

Nursing Mothers. Estrogen administration to nursing m quantity and quality of the milk.

Tablets

Estradiol tablets USP, 2 mg, contain FD&C Yellow No. 6 dye-type reactions (including bronchial asthma) in cert the overall incidence of FD&C Yellow No. 5 (tartrazine) is low, it is frequently seen in patients who also have as