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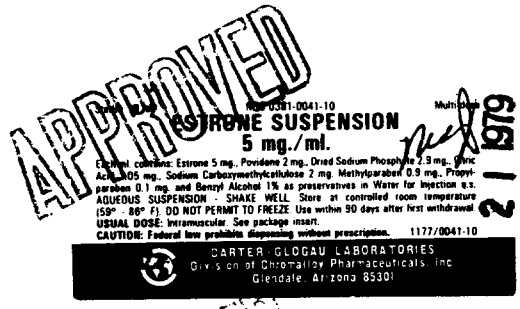
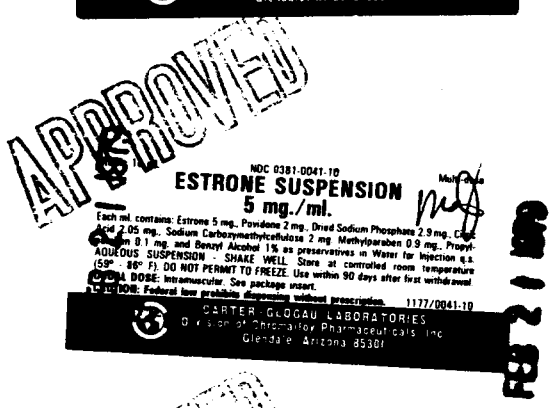
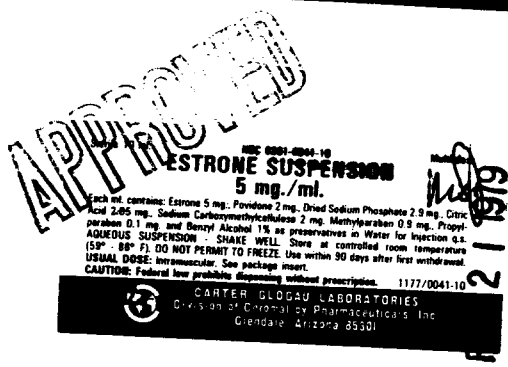






ESTRONE SUSPENSION

WARNING

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

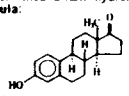
The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis[8-12] with epithelial changes of vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it is reasonable to presume they would induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.[13-16] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. These data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: Estrone occurs as small, white crystals or as a white to creamy white, crystalline powder. It is odorless, and is stable in air. It melts at about 260°. Estrone is practically insoluble in water. It is soluble in alcohol, in acetone, in dioxane, and in vegetable oils. It is slightly soluble in solutions of fixed alkali hydroxides. Estrone has the structural formula:



$C_{18}H_{22}O_2$ 270.37

Estra-1,3,5(10)-trien-17-one, 3-hydroxy-

3-Hydroxyestra-1,3,5(10)-trien-17-one

CATEGORY: ESTROGEN

Available as: Sterile aqueous suspension of Estrone for intramuscular injection containing Estrone 2 mg. or 5 mg. per ml. with Sodium Carboxymethylcellulose 2 mg., Povidone 2 mg., Dried Sodium Phosphate 2.9 mg., Citric Acid 2.05 mg., Methylparaben 0.9 mg., Propylparaben 0.1 mg., Benzyl Alcohol 1% as preservatives in Water for Injection q.s.

CLINICAL PHARMACOLOGY: Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, growth of axillary and pubic hair, and pigmentation of the nipples and genitals. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of menstruation. Estrogens also affect the release of pituitary gonadotropins.

The pharmacologic effects of conjugated estrogens are similar to those of endogenous estrogens. They are soluble in water and may be absorbed from mucosal surfaces after local administration.

In responsive tissues (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogen action, specific RNA and DNA syntheses occurs. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is minimal.

INDICATIONS: Estrone is indicated in the treatment of:

1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no 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. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease.

ESTRONE HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Active thrombophlebitis or thromboembolic disorders.
6. A past history of thrombophlebitis, thrombosis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: 1. Induction of malignant neoplasms. Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[18] although a recent long-term followup of a single physician's practice has raised this possibility.[18A] Because of the animal data, there is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. Gall bladder disease. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[18] similar to the 2-fold increase previously noted in users of oral contraceptives.[19-24] In the case of oral contraceptives the increased risk appeared after two years of use.[24]

3. Effects similar to those caused by estrogen-progestagen oral contraceptives. There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[20-23]

a. Thromboembolic disease. It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic disease, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[24-31] 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.[32/33] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[34/35] 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,[18,36] 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 (except in treatment of malignancy) 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[37] 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.

b. Hepatic adenoma. Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[38-40] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestagen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[39] The relationship of this malignancy to these drugs is not known at this time.

c. Elevated blood pressure. Increased blood pressure is not uncommon in women using oral contraceptives. There is now a report that this may occur with use of estrogens in the menopause[41] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. 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.

4. Hypercalcemia. The 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: A. General Precautions.

1. 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 Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention – Because estrogens may cause some degree of fluid retention, conditions might be influenced by

this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression.[24] Although it is not clear whether this is due to the estrogenic or progestagenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine leiomyomata may increase in size during estrogen use.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

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

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. Pregnancy Category X. See Contraindications and Boxed Warning.

C. 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.

ADVERSE REACTIONS: (See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. Genitourinary system.
Breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical eversion and in degree of cervical secretion; cystitis-like syndrome.
2. Breasts.
Tenderness, enlargement, secretion.
3. Gastrointestinal.
Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice.
4. Skin.
Chloasma or melasma which 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. CNS.
Headache, migraine, dizziness; mental depression; chorea.
7. Miscellaneous.
Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: Numerous reports of ingestion of large doses of estrogen-containing oral contraceptives by young children indicate that serious ill effects do not occur. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION: Shake vial and syringe well prior to withdrawal and injection (using a 21-23 gauge needle) to properly suspend medication.

1. Replacement Therapy of Estrogen-Deficiency Associated Conditions
The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

Initial relief of symptoms may be achieved through the administration of 0.1 mg. to 1 mg. of estrone weekly in single or divided doses. Some patients may require 0.5 mg. to 2 mg. weekly.

Note: Continual therapy with Estrogen alone may induce functional uterine bleeding.

2. Senile Vaginitis and Kraurosis Vulvae
Will generally respond to injection of 0.1 mg. to 0.5 mg. of estrone two or three times weekly. Administration should be cyclic (e.g., 3 weeks on and 1 week off.)

3. Abnormal Uterine Bleeding Due to Hormone Imbalance
May respond to brief courses of intensive estrogen therapy. Dosage in the range of 2 mg. to 5 mg. daily for several days.

4. Given chronically:
Inoperable progressing prostatic cancer.

For palliation in prostatic cancer, estrone may be employed at a dosage level of 2 mg. to 4 mg. two or three times weekly. If a response to estrogen therapy is going to occur, it should be apparent within 3 months of the beginning of therapy. If a response does occur, the hormone should be continued until the disease is again progressive.

Inoperable progressing breast cancer in appropriately selected men and post-menopausal women. (See Indications)

The usual dosage is 5 mg. 3 or more times weekly according to severity of pain.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: Multiple dose vials of 10 ml. and 30 ml. containing 2 mg. per ml. in aqueous suspension and 10 ml. containing 5 mg. per ml. in aqueous suspension.

CAUTION Federal law prohibits dispensing without prescription.

Literature Revised May 1977

Product No. 0039-10, 0039-30 0041-10

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