Ogen advertisement.

[s.l.]: [s.n.], 1975

When beginning or reinstating estrogen therapy, consider OGEN®

(PIPERAZINE ESTRONE SULFATE TABLETS, N.F.)

Ogen helps you taper therapy to the minimum needed for relief of symptoms.

Scored tablets

permit half-step adjustments up

or down.

One prescription can help

minimize symptoms
minimize medication
minimize side effects.

See following pages for Brief Summary

ABBOTT

7033175

OGEN .625
(piperazine estrone sulfate 0.75 mg., calculated as sodium estrone sulfate 0.625 mg.)

OGEN 1.25
(piperazine estrone sulfate 1.5 mg., calculated as sodium estrone sulfate 1.25 mg.)

OGEN 2.5
(piperazine estrone sulfate 3 mg., calculated as sodium estrone sulfate 2.5 mg.)

OGEN 5
(piperazine estrone sulfate 6 mg., calculated as sodium estrone sulfate 5 mg.)

7033175

OGEN®

PIPERAZINE ESTRONE SULFATE TABLETS, N.F.

Tablets

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. OGEN SHOULD NOT BE USED DURING PREGNANCY.

According to some investigators, the use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. Studies have reported 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] In one of these studies, this risk was estimated as not greater than 4 per 1000 exposures.[7] Furthermore, there are reports that a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these reported changes are histologically benign, the investigators have not determined whether they are precursors of adenocarcinoma.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies in the offspring, including 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. The 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. OGEN has not been studied for these uses, and therefore should not be used during pregnancy. There is no evidence from well controlled studies that progestogens are effective for these uses.

If OGEN (piperazine estrone sulfate tablets) 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 question of continuation of the pregnancy should be addressed.

INDICATIONS

OGEN (piperazine estrone sulfate tablets) is indicated for the treatment of estrogen deficiency associated with:

1. Moderate to severe *vasomotor* symptoms of 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.

OGEN (piperazine estrone sulfate tablets) is also indicated for the prevention of postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.[20,21]

OGEN (PIPERAZINE ESTRONE SULFATE TABLETS) HAS NOT BEEN TESTED FOR EFFICACY FOR ANY PURPOSE DURING PREGNANCY. SINCE ITS EFFECT UPON THE FETUS IS UNKNOWN, IT CANNOT BE RECOMMENDED FOR ANY CONDITION DURING PREGNANCY (SEE BOXED WARNING).

CONTRAINDICATIONS

OGEN should not be used in women with any of the following conditions:

1. Known or suspected cancer of the breast.
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.

WARNINGS

1. *Induction of malignant neoplasms.* Long-term continuous administration of natural and synthetic estrogens in certain animal species has been reported by some investigators to increase 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,[17] although a recent long-term followup of a single physician's practice has raised this possibility.[18] Therefore, caution should be exercised when administering estrogens to women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. Careful breast examinations should be performed periodically.

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,[17] similar to the 2-fold increase previously noted in users of oral contraceptives.[19,22] In the case of oral contraceptives, the increased risk appeared after two years of use.[22]

3. *Effects similar to those caused by estrogen-progestogen 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 postpartum breast engorgement would be more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in women receiving estrogens for postpartum breast engorgement.[20,21]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[22-29] 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.[30,31] An increased risk of post-surgery thromboembolic complications has also been reported in users of oral contraceptives.[32,33] If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism; it should also be discontinued during periods of prolonged immobilization.

While an increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has not been found[17,34] 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[35] 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 contracep-

tive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[36-38] 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 progestogen 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.[37] 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[39] 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.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

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 — Estrogens may cause some degree of fluid retention. Therefore, patients with conditions such as epilepsy, migraine, and cardiac or renal dysfunction, which might be influenced by this factor, 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.[22] Although it is not clear whether this is due to the estrogenic or progestogenic 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 the patient's use 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. OGEN cannot be recommended for use during pregnancy. See Contraindications and Boxed Warning.

C. Nursing Mothers. Estrogens have been reported to be excreted in human breast milk.

ADVERSE REACTIONS

(See Warnings regarding reports of possible induction of neoplasia, unknown effects upon 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. *Breast.*

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.

PHYSICIAN REFERENCES

1. Ziel, H. K. and W. D. Finkel, "Increased Risk of Endometrial Carcinoma Among Users of Conjugated Estrogens," *New England Journal of Medicine,* 293:1167-1170, 1975.
2. Smith, D. C., R. Prentic, D. J. Thompson and W. L. Hermann, "Association of Exogenous Estrogen and Endometrial Carcinoma," *New England Journal of Medicine,* 293:1164-1167, 1975.
3. Mack, T. M., M. C. Pike, B. E. Henderson, R. I. Pfeffer, V. R. Gerkins, M. Arthur and S. E. Brown, "Estrogens and Endometrial Cancer in a Retirement Community," *New England Journal of Medicine,* 294:1262-1267, 1976.
4. Weiss, N. S., D. R. Szekely and D. F. Austin, "Increasing Incidence of Endometrial Cancer in the United States," *New England Journal of Medicine,* 294:1259-1262, 1976.
5. Herbst, A. L., H. Ulfelder and D. C. Poskanzer, "Adenocarcinoma of Vagina," *New England Journal of Medicine,* 284:878-881, 1971.
6. Greenwald, P., J. Barlow, P. Nasca and W. Burnett, "Vaginal Cancer after Maternal Treatment with Synthetic Estrogens," *New England Journal of Medicine,* 285:390-392, 1971.
7. Lanier, A., K. Noller, D. Decker, L. Elveback and L. Kurland, "Cancer and Stilbestrol. A Follow-up of 1719 Persons Exposed to Estrogens In Utero and Born 1943-1959," *Mayo Clinic Proceedings,* 48:793-799, 1973.
8. Herbst, A., R. Kurman and R. Scully, "Vaginal and Cervical Abnormalities After Exposure to Stilbestrol In Utero," *Obstetrics and Gynecology,* 40:287-298, 1972.
9. Herbst, A., S. Robboy, G. Macdonald and R. Scully, "The Effects of Local Progesterone on Stilbestrol-Associated Vaginal Adenosis," *American Journal of Obstetrics and Gynecology,* 118:607-615, 1974.
10. Herbst, A., D. Poskanzer, S. Robboy, L. Friedlander and R. Scully, "Prenatal Exposure to Stilbestrol, A Prospective Comparison of Exposed Female Offspring with Unexposed Controls," *New England Journal of Medicine,* 292:334-339, 1975.
11. Stafl, A., R. Mattingly, D. Foley and W. Fetherston, "Clinical Diagnosis of Vaginal Adenosis," *Obstetrics and Gynecology,* 43:118-128, 1974.
12. Sherman, A. I., M. Goldrath, A. Berlin, V. Vakhariya, F. Banooni, W. Michaels, P. Goodman and S. Brown, "Cervical-Vaginal Adenosis After *In Utero* Exposure to Synthetic Estrogens," *Obstetrics and Gynecology,* 44:531-545, 1974.
13. Gal, I., B. Kirman and J. Stern, "Hormone Pregnancy Tests and Congenital Malformation," *Nature,* 216:83, 1967.
14. Levy, E. P., A. Cohen and F. C. Fraser, "Hormone Treatment During Pregnancy and Congenital Heart Defects," *Lancet,* 1:611, 1973.
15. Nora, J. and A. Nora, "Birth Defects and Oral Contraceptives," *Lancet,* 1:941-942, 1973.
16. Janerich, D. T., J. M. Piper and D. M. Glebatis, "Oral Contraceptives and Congenital Limb-Reduction Defects," *New England Journal of Medicine,* 291:697-700, 1974.
17. Boston Collaborative Drug Surveillance Program "Surgically Confirmed Gall Bladder Disease, Venous Thromboembolism and Breast Tumors in Relation to Post-Menopausal Estrogen Therapy," *New England Journal of Medicine,* 290:15-19, 1974.
18. Hoover, R., L. A. Gray, Sr., P. Cole and B. MacMahon, "Menopausal Estrogens and Breast Cancer," *New England Journal of Medicine,* 295:401-405, 1976.
19. Boston Collaborative Drug Surveillance Program, "Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gall Bladder Disease and Breast Tumors," *Lancet* 1:1399-1404, 1973.
20. Daniel, D. G., H. Campbell and A. C. Turnbull, "Puerperal Thromboembolism and Suppression of Lactation," *Lancet,* 2:287-289, 1967.
21. Bailar, J. C., "Thromboembolism and Oestrogen Therapy," *Lancet,* 2:560, 1967.
22. Royal College of General Practitioners, "Oral Contraception and Thromboembolic Disease," *Journal of the Royal College of General Practitioners,* 13:267-279, 1967.
23. Inman, W. H. W. and M. P. Vessey, "Investigation of Deaths from Pulmonary, Coronary, and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age," *British Medical Journal,* 2:193-199, 1968.
24. Vessey, M. P. and R. Doll, "Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report," *British Medical Journal,* 2:651-657, 1969.
25. Sartwell, P. E., A. T. Masi, F. G. Arthes, G. R. Greene and H. E. Smith, "Thromboembolism and Oral Contraceptives: An Epidemiological Case Control Study," *American Journal of Epidemiology,* 90:365-380, 1969.
26. Collaborative Group for the Study of Stroke in Young Women, "Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis," *New England Journal of Medicine,* 288:871-878, 1973.
27. Collaborative Group for the Study of Stroke in Young Women, "Oral Contraceptives and Stroke in Young Women: Associated Risk Factors," *Journal of the American Medical Association,* 231:718-722, 1975.
28. Mann, J. I. and W. H. W. Inman, "Oral Contraceptives and Death from Myocardial Infarction," *British Medical Journal,* 2:245-248, 1975.
29. Mann, J. I., M. P. Vessey, M. Thorogood and R. Doll, "Myocardial Infarction in Young Women with Special Reference to Oral Contraceptive Practice," *British Medical Journal,* 2:241-245, 1975.
30. Inman, W. H. W., V. P. Vessey, B. Westerholm and A. Engelund, "Thromboembolic Disease and the Steroidal Content of Oral Contraceptives," *British Medical Journal,* 2:203-209, 1970.
31. Stolley, P.D., J. A. Tonascia, M.S. Tockman, P. E. Sartwell, A. H. Rutledge and M. P. Jacobs, "Thrombosis with Low-Estrogen Oral Contraceptives," *American Journal of Epidemiology,* 102:197-208, 1975.
32. Vessey, M. P., R. Doll, A. S. Fairbairn and G. Glober, "Post-Operative Thromboembolism and the Use of the Oral Contraceptives," *British Medical Journal,* 3:123-126, 1970.
33. Greene, G. R. and P. E. Sartwell, "Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma or Infection," *American Journal of Public Health,* 62:680-685, 1972.
34. Rosenberg, L., M. B. Armstrong and H. Jick, "Myocardial Infarction and Estrogen Therapy in Postmenopausal Women," *New England Journal of Medicine,* 294:1256-1259, 1976.
35. Coronary Drug Project Research Group, "The Coronary Drug Project: Initial Findings Leading to Modifications of Its Research Protocol, *Journal of the American Medical Association,* 214:1303-1313, 1970.
36. Baum, J., F. Holtz, J. J. Bookstein and E. W. Klein, "Possible Association Between Benign Hepatomas and Oral Contraceptives," *Lancet,* 2:926-928, 1973.
37. Mays, E. T., W. M. Christopherson, M. M. Mahr and H. C. Williams, "Hepatic Changes in Young Women Ingesting Contraceptive Steroids, Hepatic Hemorrhage and Primary Hepatic Tumors," *Journal of the American Medical Association,* "235:730-782, 1976.
38. Edmondson, H. A., B. Henderson and B. Benton, "Liver Cell Adenomas Associated with the Use of Oral Contraceptives," *New England Journal of Medicine,* 294:470-472, 1976.
39. Pfeffer, R. I. and S. Van Den Noort, "Estrogen Use and Stroke Risk in Postmenopausal Women," *American Journal of Epidemiology,* 103:445-456, 1976.