ESTRA-50- estradiol pellet pellet, implantable
ESTRA-25- estradiol pellet pellet, implantable
Advanced Pharmaceutical Technology, Inc.

Estra-50 & Estra-25

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]The risk was independent of 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 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 in 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 persistant 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 progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have 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]epithelial changes of the 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 cannot be presumed they would not 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, hormones withdrawl 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. There is no considerable evidence from well controlled studies that progestogens are effective for these uses.

If Estrogen 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:

Estradiol N.F. Pellets contain N.F. 25mg and 50mg for subcutaneous implantation. The pellets are sterile unless vial has been opened or damaged.

Estradiol Pellets are cylindrical, with an approximate diameter of 3.2mm. Pellet therapy has the advantage of high efficiency from the standpoint of the quality of the hormone administered and the further advantage that a single treatment has effect continuously for several months.

CLINICAL PHARMACOLOGY:

Estradiol is one of the more potent of the known estrogenic compounds, identical with the primary estrogenic hormone produced by the human ovary. Estradiol exerts a developmental action on the female generative tract, has an inhibitory effect upon the pituitary in large doses, and produces a marked constitutional effect with an increase in muscular strength, body vigor, and mental acumen. It supplies follicular hormone in cases where estrogenic activity is depressed, insufficient, or absent.

INDICATIONS:

Estradiol is indicated in the treatment of:

1. Estrogen deficiency in Hysterectomized Women.

(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 approximately selected women and men with metastatic disease.

8. Postpartum breast engorgement - Although estrogens have been widely used for the

prevention of postpatum 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 or puerperal thromboembolism associated with the use of large doses of estrogen. [20,22]

ESTRADIOL 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-dependant 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 prostatic malignancy).

WARNINGS:

1. Induction of malignant neoplasma. Long term continuous administration of natural and synthetic estrogen in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is new 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 heed for caution, in prescribing estrogens for women with a strong history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. Gallbladder 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-progestogen oral contraceptives. There are several serios adverse effects or 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.

a. Thromboembolic disease. It is now we establish that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular disease, such as thrombophlebitis, pulminary 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 increase risk of post surgery thromboembolic complications has also been reported in users of oral contrceptives. [34,35]if feasable, 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 estrogen has not been found, [18,36]this does not rule out that such an increase may be present or that subgroups of women having underlying risk factors or who are receiving relatively large doses of estrogen may have an increased risk. Therefore estrogens should not be used in persons with active thrombophlebitis or thromboembolic disorders and they should not be used (except in treatent 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 estrogens (5mg 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 thromboembolicand 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 may 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. [39]The relationship of this malignancy to these drugs is not know 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 the use of estrogens in 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. Administration of estrogens may lead to severe hypercalceemia 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 initiation of any estrogen therapy. The pretreatment and periodic physical examination should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papnicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without a physical examination being performed.

2. Fluid retention - Because estrogens may cause some degree of fluid retention, conditions which may be influenced by this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develope 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 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 estrogen therapy when relevent specimens are submitted.

7. Patients with a history of jaundice during pregnancy have an increased risk of reccurance 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 phosphorous, 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 sullobromophthalein retention.

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

c. Increased thyroid binding globulin (TGB) 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 elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose toerance.

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 principal, 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 cantraceptives:

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 candidas; 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; aggrevation 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 withdrawl bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

Menopausal Syndrome: In all cases the objective should be determination of the

minimum amount of hormone that will maintain the patient symptom-free. With adequate clinical improvement, usually obtainable in two weeks or less, gradual reduction in dosage are advisable. Subcutaneous implantation- implant one 25mg, Estradiol Pellet and repeat when necessary. The pellets provide constant estrogen levels for approximately 3 months.

Hypogenitalism and Sexual Infantilism: - 1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly two to three times weekly. Subcutaneous implantation - implant one 25mg, Pellet and repeat when necessary.

Amenorrhea and Oligomenorrhea Associated with Hypogonadism: 1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly two to three times weekly during the first two weeks of an arbitrary 28-day menstrual cycle; progesterone is given the last two weeks of the theoretical cycle. This regimen is continued for 3-6 months. The patient then is allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy as outlined should be prescribed.

Postpartum Breast Engorgement: - 1.5mg of estradiol or 1.66mg of estradiol benzoate is administered intramuscularly daily begining at the first sign of engorgement and continuing until the symptoms are controlled. Restriction of fluids and a tight binder should also be employed.

Inoperable Breast Carcinoma in Postmenopausal Women: - 1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly three or more times weekly according to the severity of the pain.

Carcinoma of the Prostate: - 1.5mg of estradiol or 1.66mg of estradiol benzoate intramuscularly three times weekly. Subcutaneous Implantation - Implant one 25mg pellet and repeat when necessary.

Senile Vaginitis; Pruritis Vulvae; Kraurosis Vulvae: - 1.0 to 1.5mg of estradiol or 1.0 to 1.66mg of estradiol benzoate intramuscularly three times weekly for two or three injections, then 0.5 to 1.0mg of estradiol or 0.33 to 1.0mg of estradiol benzoate twice weekly for maintainance.

The pellets may be implanted conveniently and quickly by means of an injector or they may be administered by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure, and all aseptic precautions must be observed.

BY INJECTOR: The pellet may be quickly and easily implanted by means of the Bardani or Bartor Pellet Injectors. The areas usually selected for implantation are the intrascapular region or the posterior axillary line. Aseptic precautions must be observed for any surgical procedure. The skin is carefully cleaned, followed by the application of iodine and alcohol. The area is infiltrated with procaine 1:100. Make a very small incision (about 2mm long and 1mm deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The injector needle of the Kearns injector, with sharp plunger in place, is inserted into the incision and gently forced into the subcutaneous tissue at the desired site of implantation. The sharp plunger is withdrawn, and the pellet inserted into the hollow needle. The simplest method for placing the pellet in the needle is to allow the pellet to slide from the vial in which it is packed into the slot provided in the needle. The pellet is pushed as far as possible through the needle by means of the blunt plunger and held in place with the plunger while the needle is gently withdrawn. When the needle

comes in contact with the knob of the plunger, both are withdrawn together. When the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient.

BY INCISION: The intrascapular region or the posterior axillary line are convenient site for implanting pellets. The operative field is prepared in the usual manner with iodine and alcohol and the area is infiltrated with procaine 1:100 solution. An incision about 1 centimeter in length is made. With blunt dissection, a pocket about two centimeters in depth is prepared in the subcutaneous tissue below and away from the incision. The edges of the pocket may be held apart by a smal dilator and the pellet inserted into the bottom of the pocket with small forceps. Force should not be used when inserting pellets. The incision is closed with one or two sutures.

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.

PACKAGING:

ESTRA-25 & ESTRA-50 are supplied simply in sealed glass ampoules, each pack

contains 10 sterile pellets.

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ADVANCED PHARMACEUTICAL TECHNOLOGY

132 South Central Avenue, Elmsford, NY 10523

Package Leaflet

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 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 erosion 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:

Menopausal Syndrome: In all cases the objective should be determination of the minimum amount of hormone that will maintain the patient symptom-free. With adequate clinical improvement, usually obtainable in two weeks or less, gradual reduction in dosage are advisable. Subcutaneous implantation – implant one 25 mg. Estradiol Pellet and repeat when necessary.

Hypogenitalism and Sexual Infantilism: – 1.5 mg. of estradiol or 1.66 mg. of estradiol benzoate intramuscularly two or three times weekly. Subcutaneous implantation – implant one 25 mg. Pellet and repeat when necessary.

Amenorrhea and Oligomenorrhea Associated with Hypogonadism: 1.5 mg. of estradiol or 1.66 mg. of estradiol benzoate intramuscularly two or three times weekly during the first two weeks of an arbitrary 28-day menstrual cycle; progesterone is given during the last two weeks of the theoretical cycle. This regimen is continued for 3-6 months. The patient then is allowed to go untreated for 2 months to determine whether or not she can maintain the cycle without hormonal therapy. If not, additional courses of therapy as outlined should be prescribed.

Postpartum Breast Engorgement: – 1.5 mg. of estradiol or 1.66 mg. of estradiol benzoate is administered intramuscularly daily beginning at the first sign of engorgement and continuing until symptoms are controlled. Restriction of fluids and a tight binder should also be employed.

Inoperable Breast Carcinoma in Postmenopausal Women: – 1.5 mg. of estradiol or 1.66 mg. estradiol benzoate intramuscularly three or more times weekly according to the severity of the pain.

Carcinoma of the Prostate: – 1.5 mg. of estradiol or 1.66 mg. of estradiol benzoate intramuscularly three times weekly. Subcutaneous Implantation – Implant one 25 mg pellet and repeat when necessary.

Senile Vaginitis; Pruritus Vulvae: Kraurosis Vulvae: - initially, 1.0 to 1.5 mg. of estradiol or 1.0 to 1.66 mg. of estradiol benzoate intramuscularly three times weekly for two or three injections, then 0.5 to 1.0 mg. of estradiol or 0.33 to 1.0 mg. of estradiol benzoate twice weekly for maintenance.

The pellets may be implanted conveniently and quickly by means of an injector or they may be administered by making an incision in the skin. Either method, though readily carried out in the physician's office, is a minor surgical procedure, and all aseptic precautions must be observed.

BY INJECTOR: The pellet may be quickly and easily implanted by means of the Bardani or Interpel injector available through APT. The areas usually selected for implantation are the intrascapular region or the posterior axillary line. Aseptic precautions must be observed as for any surgical procedure. The skin is carefully cleaned, followed by the application of iodine and alcohol. The area is infiltrated with procaine 1:100. Make a very small incision (about 2 mm. long and 1 mm. deep) into the skin with a sharp scalpel to allow free passage of the large injector needle. The injector needle of the Kearns injector, with sharp plunger in place, is inserted into the incision and gently forced into the subcutaneous tissue at the desired site of implantation. The sharp plunger is withdrawn, and the pellet inserted into the hollow needle. The simplest method for placing the pellet in the needle is to allow the pellet to slide from the vial in which it is packed into the slot provided in the needle. The pellet is pushed as far as possible through the needle by means of the blunt plunger and held in place with the plunger while the needle is gently withdrawn. When the needle comes in contact with the knob of the plunger, both are withdrawn together. When the injector has been withdrawn, the wound may be closed with a single stitch or a skin clip. In many instances, apposition of the edges of the wound with adhesive tape is sufficient.

BY INCISION: The intrascapular region or the posterior axillary line are convenient sites for implanting pellets. The operative field is prepared in the usual manner with iodine and alcohol and the area is infiltrated with procaine 1:100 solution. An incision about one centimeter in length is made. With blunt dissection, a pocket about two centimeters in depth is prepared in the subcutaneous tissue below and away from the incision. The edges of the pocket may be held apart by a small dilator and the pellet inserted into the bottom of the pocket with small forceps. Force should not be used in inserting pellets. The incision is closed with one or two sutures.

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.

PACKAGING: ESTRA-25 & ESTRA-50 are supplied simply in sealed glass ampoules, each pack contains 10 sterile pellets.

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ESTRA-25 PELLETS ESTRA-50 PELLETS

Brand of Estradiol N.F.

25MG and 50MG PELLETS

PRODUCT INFORMATION

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] The risk was independent of 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 progestogens, 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] epithelial changes of the 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 cannot be presumed they would not 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.[13-15] 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, hormones 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 There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses.

If Estrogen 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:

Estradiol N.F. Pellets contain estradiol N.F. 25 mg. and 50 mg. for subcutaneous implantation. The pellets are sterile unless vial has been opened or damaged.

Estradiol Pellets are cylindrical, with an approximate diameter of 3.2mm. Pellet therapy has the advantage of high efficiency from the standpoint of the quantity of hormone administered and the further advantage that a single treatment has effect continuously for several months.

CLINICAL PHARMACOLOGY:

Estradiol is one of the more potent of the known estrogenic compounds, identical with the primary estrogenic hormone produced by the human ovary, Estradiol exerts a developmental action on the female generative tract, has an inhibitory effect upon the pituitary in large doses, and produces a marked constitutional effect with an increase in muscular strength, bodily vigor, and mental acumen. It supplies follicular hormone in cases where estrogenic activity is depressed, insufficient, or absent.

INDICATIONS:

Estradiol is indicated in the treatment of:

1. **Estrogen deficiency in Hysterectomized Women.**
(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. 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.[20,23]

ESTRADIOL 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. Gallbladder 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[19] similar to the 2-fold increase previously noted in users of oral contraceptives.[10,24] In the case of oral contraceptives the increased risk appeared after two years of use.[24]

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EPI-3
MG #6839 **ADVANCED PHARMACEUTICAL TECHNOLOGY** Rev. 8/25/14
132 South Central Avenue, Elmsford, NY 10523

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 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 we 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.[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 postsurgery 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 estrogen may have an 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 he 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 may 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.[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 the 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. 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 examination 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 which 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 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 estrogen therapy when relevant specimens are submitted.
7. Patients with a 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.

ESTRA-25 PELLETS ESTRA-50 PELLETS
Brand of Estradiol N.F.
25MG and 50MG PELLETS
PATIENT INFORMATION

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of

estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we

know, all these estrogens have similar properties and therefore much the same usefulness, side effects,

and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved

in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information.

If you want to know more, you can ask your doctor or pharmacist to let you read the package insert

prepared for the doctor.

USES OF ESTROGEN

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it,

in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop

producing estrogens, generally between the ages of 45 and 55: this is called the menopause.)

2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically

before the natural menopause.

3. To prevent pregnancy. (Estrogens are given along with a progestagen, another female hormone:

these combinations are called oral contraceptives or birth control pills. Patient labeling is available to

women taking oral contraceptives and they will not be discussed in this leaflet.)

4. To treat certain cancers in woman and men.

5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

THERE IS NO PROPER USE OF ESTROGEN IN A PREGNANT WOMAN.

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production.

This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may

need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease, many women may develop typical

symptoms: Feelings of warmth in the face, neck and chest or sudden intense episodes of heat and

sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes

very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis")

which cause discomfort, especially during and after intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that

considerably more than half of all women undergoing the menopause have only mild symptoms or

no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few

months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer

than six months. In an attempt to avoid over-stimulation of the uterus (womb), estrogens are usually

given cyclically during each month of use, that is three weeks of pills followed by one week without pills.

Sometimes women experience nervous symptoms or depression during menopause. There is no

evidence that estrogens are effective for such symptoms and they should not be used to treat them,

although other treatment may be needed.

You may have heard that taking estrogens for long periods (years) after the menopause will keep your

skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such

long-term treatment carries important risks.

ESTROGENS TO PREVENT SWELLING OF THE BREASTS AFTER PREGNANCY

If you do not breast feed your baby after delivery, your breasts may fill up with milk and become

painful and engorged. This usually begins about 3 to 4 days after delivery and may last for a few days to

up to a week or more. Sometimes the discomfort is severe, but usually it is not and can be controlled by

pain relieving drugs such as aspirin and by binding the breasts up tightly. Estrogens can be used to try

to prevent the breasts from filling up. While this treatment is sometimes successful, in many cases the

breasts fill up to some degree in spite of treatment. The dose of estrogens needed to prevent pain and

swelling of the breasts is much larger than the dose needed to treat symptoms of the menopause and

this may increase your chances of developing blood clots in the legs or lungs (see below). Therefore,

it is important that you discuss the benefits and the risks of estrogen use with your doctor if you have

decided not to breast feed your baby.

THE DANGERS OF ESTROGENS

1. Cancer of the uterus. If estrogens are used in the postmenopausal period for more than a year,

there is an increased risk of endometrial cancer (cancer of the uterus). Women taking estrogens have

roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put

this another way, while a postmenopausal woman not taking estrogens has 1 chance in 1,000 each

year of getting cancer of the uterus, a woman taking estrogens, has 5 to 10 chances in 1,000 each year.

For this reason, it is important to take estrogens only when you really need them.

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when

larger doses are taken. For this reason it is important to take the lowest dose of estrogen that will control

symptoms and to take it only as long as it is needed. If estrogens are needed for longer periods of time,

your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding

may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed

vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is

no cancer of the uterus.

If you have had your uterus completely removed (total hysterectomy), there is no danger of developing

cancer of the uterus.

2. Other possible cancers. Estrogens can cause development of other tumors in animals, such as

tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good

evidence that women using estrogen in the menopause have an increased risk of such tumors, but

there is no way yet to be sure they do not: and one study raises the possibility that use of estrogens in

the menopause may increase the risk of breast cancer many years later. This is a further reason to use

estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your

doctor at least once a year for a physical examination. Also, if members of your family have had breast

cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor may wish

to carry out more frequent examinations of your breasts.

3. Gall bladder disease. Women who use estrogens after menopause are more likely to develop gall

bladder disease needing surgery as women who do not use estrogens. Birth control pills have a similar effect.

4. Abnormal blood clotting. Oral contraceptives increase the risk of blood clotting in various parts of

the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel of

the heart), or a pulmonary embolus (a clot which forms in the leg or pelvis, then breaks off and travels

to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has

not been fully studied, and there could still prove to be such a risk. It is recommended that if you have

had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control

pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If

you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with

great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

The larger doses of estrogen used to prevent swelling of the breasts after pregnancy have been

reported to cause clotting in the legs and lungs.

SPECIAL WARNING ABOUT PREGNANCY

You should not receive estrogen if you are pregnant. If this should occur, there is a greater than usual

chance that the developing child will be born with a birth defect, although the possibility

remains fairly small.

A female child may have an increased risk of developing cancer of the vagina or cervix later in life in the

teens or twenties. Every possible effort should be made to avoid exposure to estrogens during pregnancy.

If exposure occurs, see your doctor.

OTHER EFFECTS OF ESTROGENS

In addition to the serious known risks of estrogens described above, estrogens have the following

side effects and potential risks:

1. Nausea and vomiting. The most common side effect of estrogen therapy is nausea. Vomiting is

less common.

2. Effect on breasts. Estrogens may cause breast tenderness or enlargement and may cause the

breasts to secrete a liquid. These effects are not dangerous.

3. Effects on the uterus. Estrogens may cause benign fibroid tumors of the uterus to get larger.

Some women will have menstrual bleeding when estrogens are stopped. But if the bleeding occurs

on days you are still taking estrogens you should report this to your doctor.

4. Effects on liver. Women taking oral contraceptives develop on rare occasions a tumor of the liver

which can rupture and bleed into the abdomen. So far, these tumors have not been reported in women

using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in

the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get

jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. Other effects. Estrogens may cause excess fluid to be retained in the body. This may make some

conditions worse, such as epilepsy, migraine, heart disease, or kidney disease.

SUMMARY

Estrogens have important uses, but they have serious risks as well. You must decide, with your

doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your

doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should

not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal

vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in

the legs or lungs in the past while you were taking estrogens.

You can use estrogens as safely as possible by understanding that your doctor will require regular

physical examinations while you are taking them and will try to discontinue the drug as soon as possible

and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.

2. Pains in the calves or chest or sudden shortness of breast, or coughing blood (indicating possible

clots in the legs, heart, or lungs).

3. Severe headache, dizziness, faintness, or changes in vision (indicating possible developing clots

in the brain or eye).

4. Breast lumps (you should ask your doctor how to examine your own breasts).

5. Jaundice (yellowing of the skin).

6. Mental depression.

Based on his or her assessment of your medical needs, your doctor has prescribed this drug for you.

Do not give the drug to anyone else.

HOW SUPPLIED

ESTRA-25 & ESTRA-50 are supplied simply in sealed glass ampoules, each pack contains 10 sterile pellets.

ADVANCED PHARMACEUTICAL TECHNOLOGY

132 South Central Avenue, Elmsford, NY 10523

ESTRA-25 PELLETS ESTRA-50 PELLETS

Brand of Estradiol N.F.

25MG and 50MG PELLETS

PATIENT INFORMATION

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several diferent kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

USES OF ESTROGEN

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop producing estrogens, generally between the ages of 45 and 55: this is called the menopause.)
2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
3. To prevent pregnancy. (Estrogens are given along with a progestagen, another female hormone: these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet.)
4. To treat certain cancers in woman and men.
5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

THERE IS NO PROPER USE OF ESTROGEN IN A PREGNANT WOMAN.

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a decrease in estrogen production. This usually occurs between ages 45 and 55 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause." When the amount of estrogen in the blood begins to decrease, many women may develop typical symptoms: Feelings of warmth in the face, neck and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during and after intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than six months. In an attempt to avoid over-stimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, that is three weeks of pills followed by one week without pills. Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms and they should not be used to treat them, although other treatment may be needed.

You may have heard that taking estrogens for long periods (years) after the menopause will keep your skin soft and supple and keep you feeling young. There is no evidence that this is so, however, and such long-term treatment carries important risks.

ESTROGENS TO PREVENT SWELLING OF THE BREASTS AFTER PREGNANCY

If you do not breast feed your baby after delivery, your breasts may fill up with milk and become painful and engorged. This usually begins about 3 to 4 days after delivery and may last for a few days to up to a week or more. Sometimes the discomfort is severe, but usually it is not and can be controlled by pain relieving drugs such as aspirin and by binding the breasts up tightly. Estrogens can be used to try to prevent the breasts from filling up. While this treatment is sometimes successful, in many cases the breasts fill up to some degree in spite of treatment. The dose of estrogens needed to prevent pain and swelling of the breasts is much larger than the dose needed to treat symptoms of the menopause and

this may increase your chances of developing blood clots in the legs or lungs (see below). Therefore, it is important that you discuss the benefits and the risks of estrogen use with your doctor if you have decided not to breast feed your baby.

THE DANGERS OF ESTROGENS

1. Cancer of the uterus. If estrogens are used in the postmenopausal period for more than a year, there is an increased risk of endometrial cancer (cancer of the uterus). Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a postmenopausal woman not taking estrogens has 1 chance in 1,000 each year of getting cancer of the uterus, a woman taking estrogens, has 5 to 10 chances in 1,000 each year. For this reason, it is important to take estrogens only when you really need them.

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason *it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed.* If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus.

If you have had your uterus completely removed (total hysterectomy), there is no danger of developing cancer of the uterus.

2. *Other possible cancers.* Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogen in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not: and one study raises the possibility that use of estrogens in the menopause may increase the risk of breast cancer many years later. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year for a physical examination. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x- rays), your doctor may wish to carry out more frequent examinations of your breasts.

3. *Gall bladder disease.* Women who use estrogens after menopause are more likely to develop gall bladder disease needing surgery as women who do not use estrogens. Birth control pills have a similar effect.

4. *Abnormal blood clotting.* Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the leg or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied, and there could still prove to be such a risk. It is recommended that if you have had clotting in the legs or lungs or a heart attack or stroke while you were using estrogens or birth control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate). If you have had a stroke or heart attack or if you have angina pectoris, estrogens should be used with great caution and only if clearly needed (for example, if you have severe symptoms of the menopause).

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HOW SUPPLIED

ESTRA-25 & ESTRA-50 are supplied simply in sealed glass ampoules, each pack contains 10 sterile pellets.

EPPL-1
MG #6840

ADVANCED PHARMACEUTICAL TECHNOLOGY
132 South Central Avenue, Elmsford, NY 10523

Rev. 8/25/14

NDC: 57377-050-01

ESTRA-50
Brand of Estradiol Pellets
10 Sterile Pellets
For subcutaneous implantation

50mg Each pellet contains:
50mg estradiol

Read accompanying package directions carefully.

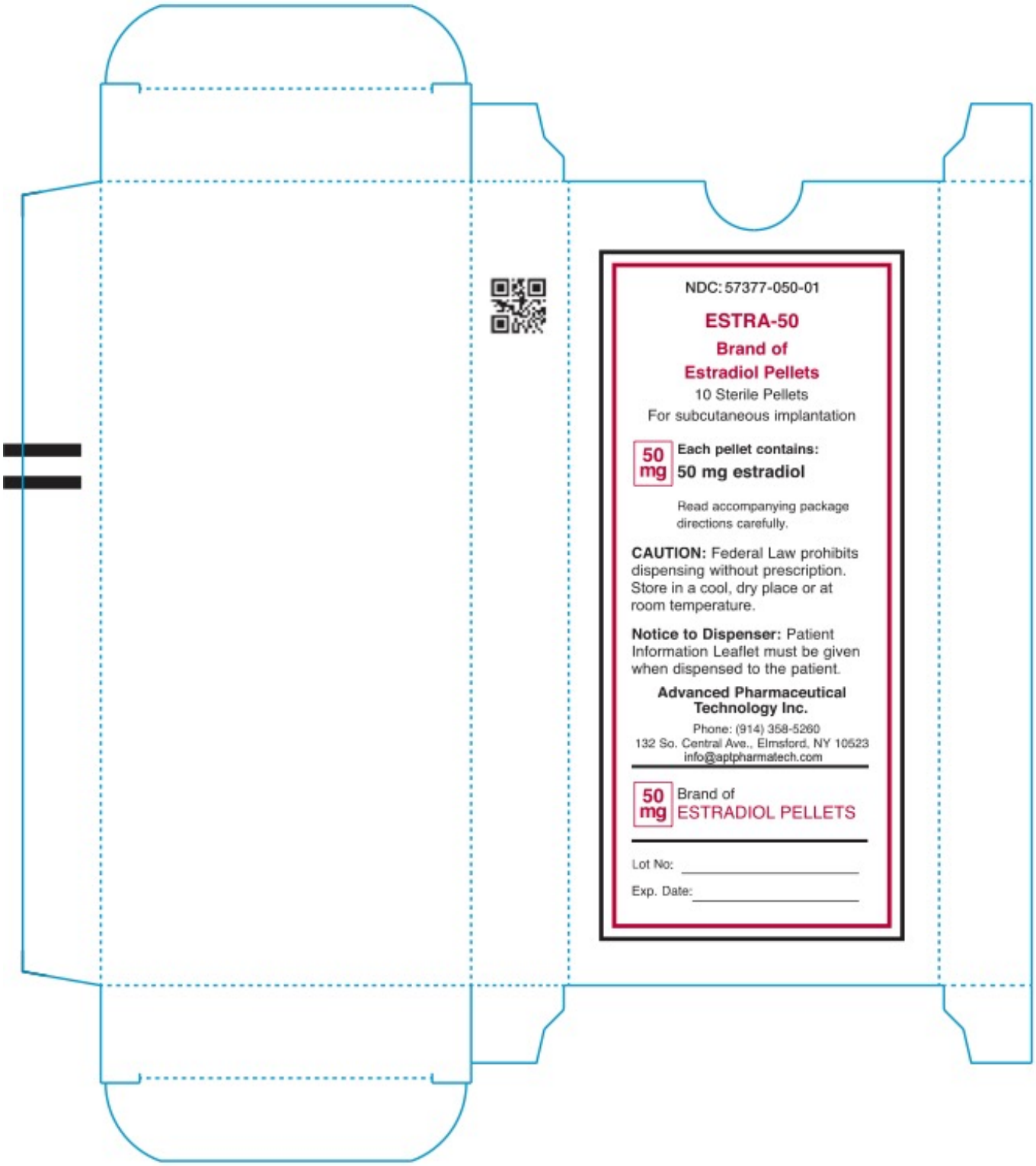
Caution:Federal Law prohibits dispensing without prescription.
Store in a cool, dry place or at room teperature.

Notice to Dispenser:Patient information Leaflet must be given when dispensed to patient.

Advanced Pharmaceutical
Technology Inc.
Phone: (914) 358-5260
132 So.Central Ave., Elmsford, NY 10523
info@aptpharmatech.com

50mg Brand of
Estradiol Pellets

Lot No:
Exp. Date:



NDC: 57377-025-01

ESTRA-25
Brand of Estradiol Pellets
10 Sterile Pellets
For subcutaneous implantation

25mg Each pellet contains:

25mg estradiol

Read accompanying package directions carefully.

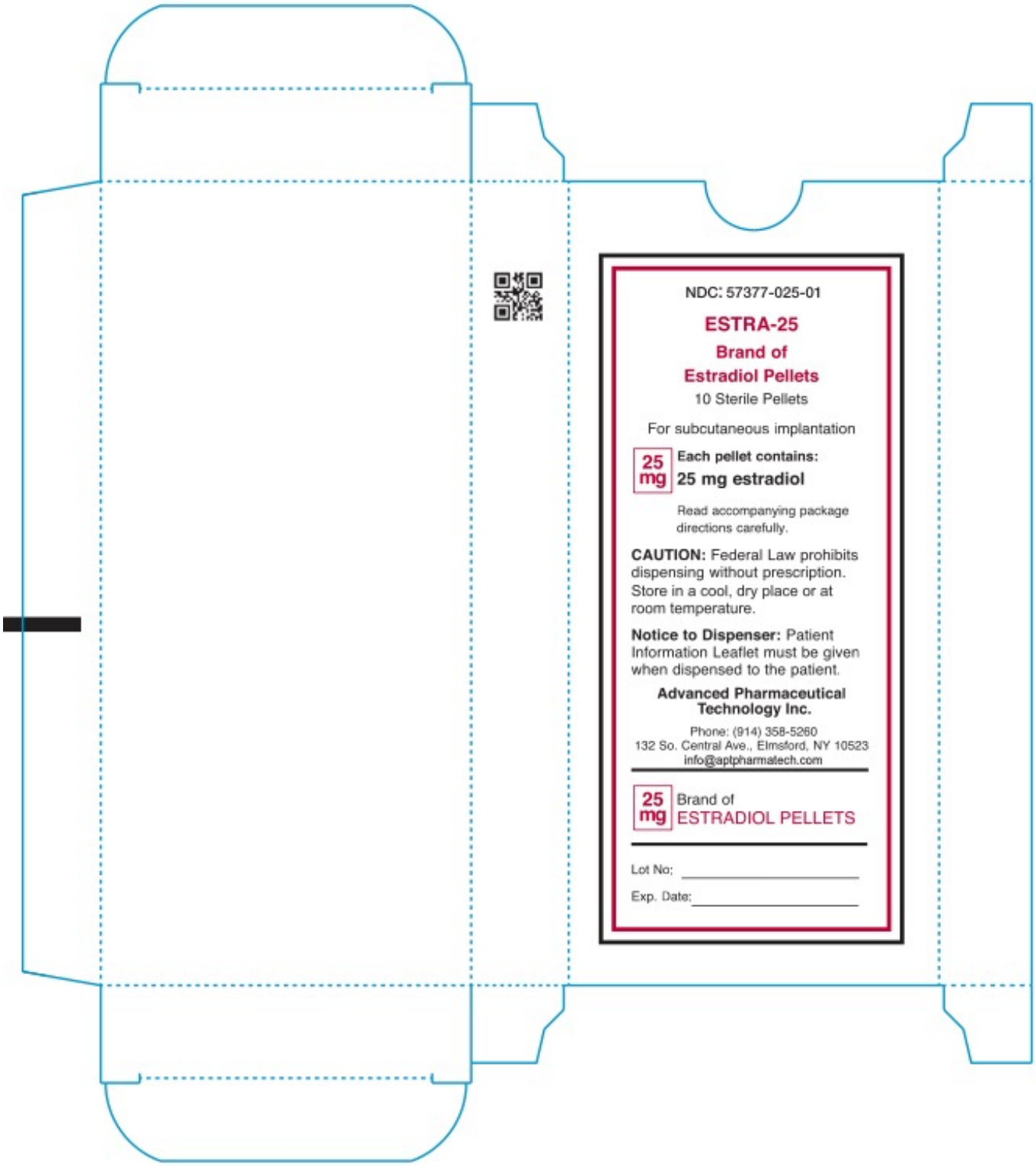
Caution:Federal Law prohibits dispensing without prescription.
Store in a cool, dry place or at room teperature.

Notice to Dispenser:Patient information Leaflet must be given when dispensed to patient.

Advanced Pharmaceutical Technology Inc.
Phone: (914) 358-5260
132 So.Central Ave., Elmsford, NY 10523
infor@aptpharmatech.com

25mg Brand of
ESTRADIOL PELLETS

Lot No:
Exp date:



ESTRA-50

estradiol pellet pellet, implantable

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57377-050
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
STEARIC ACID (UNII: 4ELV7Z65AP)	
POVIDONE (UNII: FZ989GH94E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:57377-050-01	10 in 1 AMPULE; Type 0: Not a Combination Product	01/01/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Export only		01/01/2017	

ESTRA-25

estradiol pellet pellet, implantable

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57377-025
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ESTRADIOL (UNII: 4TI98Z838E) (ESTRADIOL - UNII:4TI98Z838E)	ESTRADIOL	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
STEARIC ACID (UNII: 4ELV7Z65AP)	
POVIDONE (UNII: FZ989GH94E)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start**	**Marketing End**

#	Item Code	Package Description	Date	Date
1	NDC:57377-025-01	10 in 1 AMPULE; Type 0: Not a Combination Product	01/01/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Export only		01/01/2017	

Labeler - Advanced Pharmaceutical Technology, Inc. (023237884)

Establishment

Name	Address	ID/FEI	Business Operations
Advanced Pharmaceutical Technology, Inc.		023237884	manufacture(57377-050, 57377-025)

Revised: 9/2024 Advanced Pharmaceutical Technology, Inc.