

# What to Do if Breast MRI Isn't a Screening Option

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Denver Bureau

SAN ANTONIO — Combining annual breast ultrasound with mammography and clinical breast examination is the next best option when MRI isn't available for screening a woman at high hereditary risk of breast cancer, Ellen Warner, M.D., said at a breast cancer symposium sponsored by the Cancer Therapy and Research Center.

Annual breast MRI is clearly the best approach in screening high-risk women. In the two prospective comparative trials reported to date—the Dutch national study and a large single-center trial led by Dr. Warner at Sunnybrook and Women's College Health Sciences Centre, Toronto—annual MRI for detection of early breast cancer displayed a sensitivity of 71% and 84%, respectively.

In contrast, annual mammography—the cornerstone of current U.S., French,

and U.K. national guidelines for screening high-risk women—had a sensitivity of just 40% as a solo screening modality in the Dutch national study (N. Engl. J. Med. 2004;351:427-37) and 30% in the Toronto study.

The Toronto investigators found, however, that by adding an annual breast ultrasound on the same day as mammography and clinical breast examination, the sensitivity climbed to 57%. This is not nearly as good as MRI, but markedly bet-

ter than mammography plus clinical breast examination, which had a sensitivity of just 38%.

Best of all was the combination of annual MRI, mammography, and ultrasound. It had a sensitivity of 97% in the ongoing 437-woman study that included 318 breast cancer mutation carriers. A total of 37 cancers was found. Dr. Warner provided updated findings from the study, the earlier results of which were previously published (JAMA 2004;292:1317-25).

"Without clinical breast examination we wouldn't have missed a single cancer. Mammography and ultrasound each found two cancers not found by any other modality; without either one of those tools the sensitivity would have dropped to 92%. Omit MRI and the sensitivity drops to 57%," the medical oncologist said.

Screening women who are at high hereditary risk for breast cancer poses two major challenges: It has to start at a very young age, because a 30-year-old BRCA1 mutation carrier has the same annual risk as a 60-year-old woman in the general population. And a very high-sensitivity screening tool is required.

"If we screened 100 women in the general population with a screening regimen with a sensitivity of 80%, we would only miss two cancers. If we screened 100 BRCA1 mutation carriers with a regimen with the same sensitivity, we'd miss 13," she explained.

The price to be paid for MRI's outstanding sensitivity has been a high false-positive rate. In the Dutch study, MRI generated nearly three times more false-positive breast biopsies than did mammography. But MRI experts are well along in developing novel screening protocols expected to greatly reduce that problem, according to Dr. Warner.

The Dutch and Toronto studies are among six prospective studies evaluating the usefulness of screening MRI in high-risk women that were launched in North America and Europe in the mid- to late-1990s. They were constructed so that upon completion they will be amenable to metaanalyses.

The next phase of the Dutch and Toronto studies will examine whether screening MRI confers a survival benefit. The expectation is that it does, because it detects significantly smaller, lower-stage cancers than does mammography.

Dr. Warner offered "a guesstimate" of screening MRI's cost benefit, with the large caveat that there are no survival data yet. She assumed that MRI screening reduces breast cancer mortality from 30% to 10%, and that survivors live an average of 25 additional years. Given those assumptions, annual MRI screening of the estimated 620,000 high-risk American women aged 30-60 years at a cost of \$1,200 per scan would cost \$24,000 per year of life saved.

"Since up to \$50,000 per year of life saved is considered an acceptable cost for medical interventions, even if I've overestimated the benefit of MRI by a factor of two, the cost is still reasonable," she said.

## Menostar™ (estradiol transdermal system)

### Rx only

#### BRIEF SUMMARY OF PRESCRIBING INFORMATION

**ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER**  
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, Endometrial cancer.**)

**CARDIOVASCULAR AND OTHER RISKS**  
Estrogens with and without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)  
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**).  
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies**).  
Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

#### INDICATIONS AND USAGE

Menostar™ is indicated for the prevention of postmenopausal osteoporosis. Therapy should be considered only for women at significant risk of osteoporosis. Non-estrogen medications should be carefully considered.

#### CONTRAINDICATIONS

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

- Undiagnosed abnormal genital bleeding.
- Known, suspected, or history of cancer of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
- Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- Menostar™ should not be used in patients with known hypersensitivity to its ingredients.
- Known or suspected pregnancy. There is no indication for Menostar™ in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

#### WARNINGS

##### See **BOXED WARNINGS**.

##### 1. Cardiovascular disorders.

Estrogen and estrogen/progestin therapy have been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogens should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of VTE, obesity, and venous stasis erythematosa) should be managed appropriately.

##### 2. Coronary heart disease and stroke.

In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving CE compared to placebo. These observations are preliminary (See **CLINICAL PHARMACOLOGY, Clinical Studies**).

In the CE/MPA substudy of WHI an increased risk of coronary heart disease (CHD) events (defined as non-fatal myocardial infarction and CHD death) was observed in women receiving CE/MPA compared to women receiving placebo (37 vs. 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs. 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS) treatment with CE/MPA (0.625mg/2.5mg per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE/MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE/MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty-one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE/MPA group and the placebo group in HERS, HERS II, and overall.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

##### 3. Venous thromboembolism (VTE)

In the Women's Health Initiative (WHI) study, an increase in VTE has been observed in women receiving CE/MPA compared to women receiving placebo. These observations are preliminary. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

##### 2. Malignant neoplasms

##### a. Endometrial cancer

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 10 to 15 years or more and the risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Clinical surveillance of all women taking estrogen/progestin combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

##### b. Breast cancer

The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomized clinical trial providing information about this issue is the Women's Health Initiative (WHI) substudy of CE/MPA (see **CLINICAL PHARMACOLOGY, Clinical Studies**). The results from observational studies are generally consistent with those of the WHI clinical trial and report no significant variation in the risk of breast cancer among different estrogens or progestins, doses, or routes of administration.

The CE/MPA substudy of WHI reported an increased risk of breast cancer in women who took CE/MPA for a mean follow-up of 5.6 years. Observational studies have also reported an increased risk for estrogen/progestin combination therapy, and a smaller increased risk for estrogen alone therapy, after several years of use. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk appeared to return to baseline in about five years after stopping treatment. In addition, observational studies suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy.

In the CE/MPA substudy, 26% of the women reported prior use of estrogen alone and/or estrogen/progestin combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for CE/MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for CE/MPA compared with placebo. In the same substudy, invasive breast cancers were larger and diagnosed at a more advanced stage in the CE/MPA group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

##### 3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), 4,532 generally healthy postmenopausal women 65 years of age and older were studied, of whom 35% were 70 to 74 years of age and 18% were 75 or older. After an average follow-up of 4 years, 40 women being treated with CE/MPA (1.8%, n=2,229) and 21 women in the placebo group (0.9%, n=2,303) received diagnoses of probable dementia. The relative risk for CE/MPA versus placebo was 2.05 (95% confidence interval 1.21-3.48), and was similar for women with and without histories of menopause on hormone use before WHIMS. The absolute risk of probable dementia for CE/MPA versus placebo was 45 versus 22 cases per 10,000 women-years, and the absolute excess risk for CE/MPA was 23 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL PHARMACOLOGY, Clinical Studies and Geriatric Use**.)

It is unknown whether these findings apply to estrogen alone therapy.

##### 4. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

##### 5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

##### 6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be discontinued.

#### PRECAUTIONS

##### A. General

##### 1. Addition of a progestin when a woman has not had a hysterectomy.

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lower incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

##### 2. Elevated blood pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with estrogen use.

##### 3. Familial hyperlipoproteinemia

In patients with familial defects of lipoprotein metabolism, oral estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

##### 4. Impaired liver function and past history of cholelithiasis/ jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholelithiasis associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

##### 5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T<sub>4</sub> and T<sub>3</sub> serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

##### 6. Fluid retention

Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

##### 7. Hypocalcemia

Estrogens should be used with caution in individuals with severe hypocalcemia.

##### 8. Ovarian cancer

The CE/MPA sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE/MPA versus placebo was 1.58 (95% confidence interval 0.77-3.24) but was not statistically significant. The absolute risk for CE/MPA versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiological studies, the use of estrogen alone, in particular for ten or more years, has been associated with an increased risk of ovarian cancer. Other epidemiologic studies have not found these associations.

##### 9. Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogens. A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

##### 10. Exacerbation of other conditions

Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

#### B. PATIENT INFORMATION

Physicians are advised to discuss the PATIENT INFORMATION leaflet with patients for whom they prescribe Menostar™.

#### C. LABORATORY TESTS

Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g. estradiol, FSH).

- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antithrombin III and fibrinogen; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
- Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radioimmunoassay) or T<sub>3</sub> levels by radioimmunoassay. T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum (i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG) leading to increased circulating

corticosteroids and sex steroids, respectively. Free hormone concentrations may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

#### 4. Increased plasma HDL and HDL<sub>2</sub> subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglyceride levels.

#### 5. Impaired glucose tolerance.

#### 6. Reduced response to methyrapone test.

#### D. CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS and PRECAUTIONS**.)

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

#### E. PREGNANCY

Menostar™ should not be used during pregnancy. (See **CONTRAINDICATIONS**.)

#### F. NURSING MOTHERS

Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Menostar™ is administered to a nursing woman.

#### G. Pediatric Use

The safety and efficacy of Menostar™ in pediatric patients has not been established.

#### H. Geriatric Use

A total of 417 postmenopausal women 61-79 years old, with an intact uterus, participated in the osteoporosis trial. More than 50% of women receiving study drug, were considered geriatric (65 years or older). Efficacy in older (≥ 65 years) and younger (< 65 years) postmenopausal women in the osteoporosis treatment trial was comparable both at 12 and 24 months. Safety in older (≥ 65 years) and younger (< 65 years) postmenopausal women in the osteoporosis treatment trial was also comparable throughout the study.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of women that were older than 70. (See **WARNINGS, Dementia**.)

It is unknown whether these findings apply to estrogen alone therapy.

#### ADVERSE REACTIONS

##### See **BOXED WARNINGS, WARNINGS and PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

AE per Body System	Menostar™ 14 mcg/day (N=208)	Placebo (N=209)
Body as a Whole	85 (46%)	100 (48%)
Abdominal Pain	17 (8%)	17 (8%)
Accidental Injury	29 (14%)	13 (6%)
Infection	11 (5%)	20 (9%)
Pain	26 (13%)	26 (12%)
Cardiovascular	20 (10%)	19 (9%)
Digestive System	52 (25%)	44 (21%)
Constipation	11 (5%)	6 (3%)
Dyspepsia	11 (5%)	9 (4%)
Metabolic and Nutritional Disorders	25 (12%)	22 (11%)
Musculoskeletal System	54 (26%)	51 (24%)
Arthralgia	24 (12%)	13 (6%)
Arthritis	11 (5%)	15 (7%)
Myalgia	10 (5%)	6 (3%)
Nervous System	30 (14%)	23 (11%)
Dizziness	14 (7%)	6 (3%)
Respiratory System	62 (30%)	67 (32%)
Bronchitis	12 (6%)	9 (4%)
Upper Respiratory Infection	33 (16%)	35 (17%)
Skin and Appendages	50 (24%)	54 (26%)
Application Site Reaction	18 (9%)	18 (9%)
Breast Pain	10 (5%)	8 (4%)
Urogenital System	66 (32%)	40 (19%)
Cervical polyps	13 (6%)	4 (2%)
Leukorrhea	22 (11%)	3 (1%)

The following additional adverse reactions have been reported with estrogens:

##### 1. Genitourinary system

Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyoma; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

##### 2. Breasts

Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

##### 3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

##### 4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholelithiasis; increased incidence of gall bladder disease; pancreatitis; enlargement of hepatic hemangiomas.

##### 5. Skin

Chloasma or melasma, which may persist when drug is discontinued; hirsutism multififorme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; pruritus; pruritus, rash.

##### 6. Eyes

Retinal vascular thrombosis; intolerance to contact lenses.

##### 7. Central nervous system

Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia.

##### 8. Miscellaneous

Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgia; leg cramps; changes in libido; anaphylactoid/anaphylactic reactions including urticaria and angioedema; hypocalcemia; exacerbation of asthma; increased triglycerides.

#### OVERDOSAGE

Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females. Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children.

#### HOW SUPPLIED

Menostar™ (estradiol transdermal system), 14 mcg/day — each 3.25 cm<sup>2</sup> system contains 1 mg of estradiol USP

NDC 50419-455-04

Individual Carton of 4 systems

Shelf Pack Carton of 6 Individual Cartons of 4 systems