

POLICY & PRACTICE

Funding Stem Cell Research

Some states are looking to follow in California's footsteps by attracting scientists to their states to conduct research on human embryonic stem cells. The governors of New Jersey and Connecticut have already announced their proposals to spend millions to entice stem cell researchers to their states, and a New York state senator wants to ask the state's voters for approval of a \$1 billion stem cell research initiative. California voters recently approved a measure to spend nearly \$3 billion on embryonic stem cell research over the next 10

years. Sean Tipton, spokesman for the Coalition for the Advancement of Medical Research said these activities are good news, given the federal policy on stem cell research; however, his organization questions whether a state-by-state approach makes sense. Researchers will have to figure out the different rules for grants in each state and could waste time and money on these administrative hurdles, he said.

Contaminated Stem Cells Lines

The currently available lines of human embryonic stem cells are contaminated

with a nonhuman molecule that compromises their potential use in humans, according to a new study from researchers at the University of California, San Diego, and the Salk Institute in La Jolla, Calif. The study was published in the online Jan. 23 issue of the journal *Nature Medicine*. Supporters of expanding the federal policy on stem cell research touted the research as evidence that the current policy isn't working. In August 2001, President Bush announced a policy allowing federal funding for human embryonic stem cell research but only on a limited number of stem cell lines that were derived before Aug. 9, 2001. "Stem cell policy in 2005 should not

be based on 2001 policy," Rep. Mike Castle (R-Del.), said in a statement. "An expansion of this policy is critical to our scientists and researchers who need access to the best stem cell lines available and who want the important ethical guidance of the National Institutes of Health." Rep. Castle, along with Rep. Diana DeGette (D., Colo.), has been pushing for an easing of the 2001 federal policy.

The State of Cervical Cancer

Most U.S. states are falling behind when it comes to cervical cancer screening rates, coverage of routine screening tests in public insurance programs, and legislation on cervical cancer, according to a new report from Women in Government. In the best-performing states, at least 80% of women in the appropriate age range have been screened in the last 3 years, and Medicaid programs cover both Pap testing and HPV tests in routine screening of women aged 30 and older. However, while 46 states and the District of Columbia cover HPV testing through Medicaid when medically necessary, many physicians are not routinely offering it, said J. Thomas Cox, M.D., director of the Women's Clinic at the University of California, Santa Barbara. "Therefore, it is imperative to inform doctors and women about HPV, and to ensure access to HPV testing and to the vaccine for HPV when it become available," he said in a statement. A copy of the report is available online at www.womeningovernment.org.

Focus on Folic Acid

Women of childbearing age with a family history that puts their potential children at high risk for neural tube defects should supplement their diets with 4 mg of folic acid each day, according to the U.S. Surgeon General. But the increased folic acid should be taken through folic acid supplements, not by increasing the number of multivitamins, the Surgeon General said, because of the risk of vitamin A poisoning. The Surgeon General made these recommendations while announcing his agenda for 2005. Women of childbearing age without family history of neural tube defects should supplement their diets with 400 mcg of folic acid each day, said Surgeon General Richard H. Carmona, M.D.

MedPAC: Give Doctors a 2% Hike

Medicare should increase physician payments by 2.7% in 2006 to keep pace with the cost of providing care, the Medicare Payment Advisory Commission recommended. Such an increase will help physicians continue to treat Medicare patients. John Nelson, M.D., president of the American Medical Association, said in a statement. "Unless Medicare payments keep up with the cost of providing care, there is a real concern that some physicians will be forced to stop taking new Medicare patients," he said. However, unless Congress fixes a flaw in Medicare's physician payment formula, doctors face a 5% cut next year and cumulative cuts of 30% through 2012. Several MedPAC commissioners supported the idea of taking outpatient or Part B drugs from the formula, although the Government Accountability Office has warned that this solution would not prevent several years of declines in physician payments.

—Mary Ellen Schneider

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 estrogen is important. Adequate diagnostic 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 profile than synthetic estrogens of 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 disease.**)
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thromboses in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated estrogens (CE 0.625mg/progesterone 0.625mg) 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:
1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5. Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Menostar™ should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Menostar™ in pregnancy. There appears to be little or no benefit 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 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 (eg, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (eg, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke
In the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and stroke was observed in women receiving conjugated estrogens plus progestin. 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 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 CHD (n = 2,783, 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) compared to placebo in women with CHD at baseline. 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 women receiving CE/MPA than in women receiving placebo 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 3.7 years. There was 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.

b. Venous thromboembolism
In the Women's Health Initiative (WHI) study, an increase in VTE 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, a 2-fold greater rate of VTE, including deep vein 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 for 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 uterus 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 five to ten years and this 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 combination is important. Adequate diagnostic 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 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 been conducted for estrogen and estrogen/progestin combination therapy. In the WHI trial and from observational studies, the excess risk increased with duration of use. From observational studies, the risk of breast cancer from CE/MPA was similar to that 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 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 1.08, 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 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 33% 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 mg, n=2,229) and 21 women in the placebo group (0.9 mg, 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 menopausal symptoms. The WHI substudy of CE/MPA compared to placebo 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 PRECAUTIONS, 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 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, to 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 case report, substantial increases in blood pressure have been attributed to diosyncratic 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 hypercholesterolemia
In patients with familial defects of lipoprotein metabolism, oral estrogen therapy may be associated with elevations of lipoproteins 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 women with a history of cholelithiasis, caution should be exercised with oral estrogen use, and 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 T₄ and T₃ 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 hormone therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone level 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 patients with severe hypocalcemia.

8. Ovarian cancer
The CE/MPA substudy of WHI reported that estrogen plus progestin increased the risk of ovarian cancer. The relative risk 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. These observations are preliminary. 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 shown such 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.

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

C. LABORATORY TESTS
Estrogen therapy should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (eg, estradiol, FSH).
1. Adequate diagnostic endometrial tissue, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VII coagulant activity, IX, X, XII, XIII, XII-VII complex, II-VII complex, and fibrinogen; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen-antifibrinogen complex; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone levels as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaffected. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum (ie, 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, alpha₂-macroglobulin, ceruloplasmin).
4. Increased plasma HDL and HDL₂ subfraction concentrations, reduced LDL cholesterol concentration, and in oral formulations increased triglyceride levels.
5. Impaired glucose tolerance.

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.

6. Pediatric Use
Efficacy 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, 32% (n=3,729) were 65 to 74 while 18% (n=803) were 75 and over. Most women (80%) had no prior history of estrogen 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. In postmenopausal women in the osteoporosis treatment trial in 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 following adverse reactions to Menostar™ are reported, provide a basis for identifying the adverse effects that appear to be related to drug use and for approximating rates.

Summary of Most Frequently Reported Treatment Emergent Adverse Experiences/Medical Events (≥5%) by Treatment Groups

AE per Body System	Menostar™ 14 mcg/day (n=2098)	Placebo (n=2098)
Body as a Whole	95 (46%)	100 (48%)
Abdominal Pain	17 (8%)	17 (8%)
Accidental Injury	29 (14%)	23 (11%)
Infection	11 (5%)	10 (5%)
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%)
Musculoskeletal System	25 (12%)	22 (11%)
Arthralgia	54 (26%)	51 (24%)
Arthritis	24 (12%)	13 (6%)
Myalgia	10 (5%)	6 (3%)
Nervous System	30 (14%)	23 (11%)
Headache	11 (5%)	6 (3%)
Respiratory System	62 (30%)	67 (32%)
Bronchitis	12 (6%)	9 (4%)
Upper Respiratory Infection	20 (10%)	25 (12%)
Skin and Appendages	50 (24%)	54 (26%)
Application Site Reaction	18 (9%)	18 (9%)
Pruritus	18 (9%)	18 (9%)
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 whitening/bleeding of floor; 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; cholestatic jaundice; increased incidence of gall bladder disease; pancreatitis; enlargement of hepatic hemangiomas.
- 5. Skin**
Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; 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**
Decrease or increase 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. Surgery if effects have not been reported following acute ingestion of large doses of estrogen-containing drugs by young children.

HOW SUPPLIED
Menostar™ (estradiol transdermal system), 14 mcg/day — each 3.25 cm² system contains 1 mg of estradiol USP.
NDC 504-065-04
3M Individual Cartons of 4 systems
3M Shelf Pack Carton of 6 Individual Cartons of 4 systems
Do not store above 86°F (30°C). Do not store unopened. Apply immediately upon removal from the protective pouch.

Made in USA
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Manufactured by:
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