PPAC: Pricing System Needs Correction Plan

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WASHINGTON — Physicians should be reimbursed retroactively for any payment miscalculations that occurred under Medicare's new system for in-office infusions, the Practicing Physicians Advisory Council recommended.

The average sales price (ASP) is something federal regulators "are concocting, and they don't know how accurate it's going to be," said PPAC member Barbara L. McAneny, M.D., an oncologist from Albuquerque, N.M., who drew up the recommendation.

For that reason, the Centers for Medicare and Medicaid Services should establish a correction factor for each quarter it updates pricing on the ASP, to prevent physicians from treating patients at a loss or being put in the position of denying them medical treatment, she said. PPAC is an independent panel that advises CMS on issues related to physician payment.

The ASP was authorized by the Medicare Modernization Act of 2003, replacing the former system of overpayments for drugs and underpayments for their administration. The intent was to make fair payments for both services.

This year and next, Medicare will pay physicians the ASP plus 6%, although in 2006, physicians will have the option of obtaining the drugs directly from a supplier selected by Medicare through a competitive bidding process.

CMS officials told the panel that the agency would update pricing for the ASP on a quarterly basis. However, Dr. McAneny argued that this would not allow for any mistakes in pricing made along the way.

"Suppose the ASP is set at $60 for a drug, but you can only purchase that drug for $100," she later said in an interview. This means physicians would be getting paid only $60 for that drug from January through April—and losing $40 every time they administer the drug.

CMS might be able to correct the price on April 1, but that doesn't compensate for the losses physicians would have incurred over the first quarter of the year, Dr. McAneny said.

As a result, the agency could end up getting complaints from half the physicians in the country about the cost of a drug.

If the average sales price is set at $60, but physicians must pay $100 for the drug from January to June, they would 'lose $40 every time they administer' it.

By putting in a correction mechanism, the agency can make the change retroactive, she recommended.

A report from the Government Accountability Office indicated that physicians may not get shortchanged under the ASP. Medicare payments for cancer drugs may decline next year, but payments are actually expected to exceed physicians' costs by 6% on average, the GAO found. The American Society of Clinical Oncology responded that the study underreported some costs and the report's methodology was flawed.

"GAO has always said that everything's going to be fine" with the ASP, Dr. McAneny said. Nevertheless, "we need a plan B in case they're wrong."

The ASP replaces the average wholesale price, a number that drug makers had been giving to the government for each drug administered. Medicare in the past paid physicians 95% of the average wholesale price for in-office administration of a drug to a Medicare beneficiary; however, the physician was not paid an administration fee.

The ASP system comes with mixed benefits: Physicians now will get paid an administration fee but they won't be getting paid as much for the drugs themselves as they were under the average-wholesale-price system.

PPAC also requested that physicians be allowed Internet access to a list of drugs that CMS compiled by manufacturer to determine ASP.

"This will be very helpful to the physician community—not just oncology—but for everybody who wants to purchase drugs . . . under the average selling price, and [to] know who they can purchase these drugs from," Dr. McAneny said. ■

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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 of equivalent estrogen dose.

CARDIOVASCULAR AND OTHER RISKS

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated estrogens (0.625 mg) relative to placebo.

The 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 (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.)

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 to 5.2 years of treatment with oral conjugated estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

Other doses of conjugated estrogens and 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

Premarin (conjugated estrogens) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae.

CONTRAINDICATIONS

Premarin Vaginal Cream 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 (e.g., within past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6. Liver dysfunction or disease.
7. Premarin Vaginal Cream should not be used in patients with known hypersensitivity to its ingredients.
8. Known or suspected pregnancy. There is no indication for Premarin Vaginal Cream in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS.**)

WARNINGS

See **BOXED WARNINGS.**

Systemic absorption may occur with the use of Premarin Vaginal Cream. The warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

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 systemic lupus erythematosus) should be managed appropriately.

a. ***Coronary heart disease and stroke.*** In the Premarin tablets substudy of the Women's Health Initiative (WHI) study, an increase in the number of myocardial infarctions and strokes has been observed in women receiving Premarin compared to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.)

In the estrogen plus progestin substudy of WHI, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving PREMPRO (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) per day 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 the WHI, an increased risk of stroke was observed in women receiving PREMPRO 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 PREMPRO (0.625 mg conjugated estrogen plus 2.5 mg medroxyprogesterone acetate per day) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with PREMPRO did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the PREMPRO-treated group than in the placebo group in year 1, but not during the subsequent years. 2,321 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 PREMPRO 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 (VTE).*** In the Premarin tablets substudy of the Women's Health Initiative (WHI), an increase in VTE has been observed in women receiving Premarin compared to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information.)

In the estrogen plus progestin substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving PREMPRO compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the Prempro 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 five to ten years or more 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 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 postmenopausal 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) trial of estrogen plus progestin (see **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information). The results from observational studies are generally consistent with those of the WHI trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took estrogen plus progestin. 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. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with estrogen/progestin combination therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen/progestin combinations, doses, or routes of administration.

In the WHI trial of estrogen plus progestin, 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 estrogen plus progestin 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 estrogen plus progestin 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 estrogen plus progestin compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen plus progestin 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 observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of estrogens alone or estrogens plus progestins compared to never users, while the estrogen plus progestin sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

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), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomized to PREMPRO (0.625 mg/2.5 mg) or placebo. A population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to Premarin (0.625 mg) or placebo. In the planned analysis, pooling the events in women receiving Premarin or PREMPRO in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the estrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **PRECAUTIONS, Geriatric Use.**)

4. **Gallbladder disease.** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving postmenopausal 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 lowered 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, adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL) and impairment of glucose tolerance.

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. ***Hypertriglyceridemia.*** In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.

4. ***Impaired liver function and past history of cholestatic jaundice.*** Estrogens may be poorly metabolized in patients with impaired liver function. For patients with a history of cholestatic jaundice 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_4 and T_3 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 estrogen plus progestin substudy of WHI reported that after an average follow-up of 5.6 years, the relative risk for ovarian cancer for estrogen plus progestin versus placebo was 1.58 (95% confidence interval 0.77 -3.24) but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen-only products, 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 estrogen therapy.

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

11. ***Barrier contraceptives.*** Premarin Vaginal Cream exposure has been reported to weaken latex condoms. The potential for Premarin Vaginal Cream to weaken and contribute to the failure of condoms, diaphragms, or cervical caps made of latex or rubber should be considered.

B. Patient Information Physicians are advised to discuss the contents of the PATIENT INFORMATION leaflet with patients for whom they prescribe Premarin Vaginal Cream.

C. Laboratory Tests Estrogen administration should be guided by clinical response at the lowest dose for the treatment of postmenopausal vulvar and vaginal atrophy.

D. Drug/Laboratory Test Interactions

1. 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, XI, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Patients on thyroid replacement therapy may require higher doses of thyroid hormone.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total 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_2 cholesterol subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility (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.

F. Pregnancy Premarin Vaginal Cream should not be used during pregnancy. (See **CONTRAINDICATIONS.**)

G. Nursing Mothers Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of breast milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving the drug. Caution should be exercised when Premarin Vaginal Cream is administered to a nursing woman.

H. Pediatric Use Estrogen therapy has been used for the induction of puberty in adolescents with some forms of pubertal delay. Safety and effectiveness in pediatric patients have not otherwise been established.

Large and repeated doses of estrogen over an extended time period have been shown to accelerate epiphyseal closure, which could result in short adult stature if treatment is initiated before the completion of physiologic puberty in normally developing children. If estrogen is administered to patients whose bone growth is not complete, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended during estrogen administration.

Estrogen treatment of prepubertal girls also induces premature breast development and vaginal cornification, and may induce vaginal bleeding. In boys, estrogen treatment may modify the normal pubertal process and induce gynecomastia. See **INDICATIONS;** see **DOSAGE AND ADMINISTRATION** section in full Prescribing Information.

I. Geriatric Use Of the total number of subjects in the estrogen plus progestin substudy of the Women's Health Initiative study, 44% (n = 7,320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (See **CLINICAL PHARMACOLOGY, Clinical Studies** in full Prescribing Information). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomized to PREMPRO (0.625 mg/2.5 mg) or placebo. A population of 2,947 hysterectomized women, aged 65 to 79 years, was randomized to Premarin (0.625 mg) or placebo. In the planned analysis, pooling the events in women receiving Premarin or PREMPRO in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the estrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the estrogen-plus-progestin group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Dementia.**)

There have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin Vaginal Cream to determine whether those over 65 years of age differ from younger subjects in their response to Premarin Vaginal Cream.

ADVERSE REACTIONS

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

Systemic absorption may occur with the use of Premarin Vaginal Cream. Warnings, precautions, and adverse reactions associated with oral Premarin treatment should be taken into account.

The following additional adverse reactions have been reported with estrogen and/or progestin therapy:

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; vaginitis, including vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; application site reactions of vulvovaginal discomfort including burning and irritation; genital pruritus; ovarian cancer; endometrial hyperplasia; endometrial cancer; precocious puberty.
2. *Breasts:* Tenderness, pain, enlargement, secretion; breast cancer; fibrocystic breast changes.
3. *Cardiovascular:* Deep and superficial venous thrombosis, pulmonary embolism, myocardial infarction, stroke; increase in blood pressure.
4. *Gastrointestinal:* Nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; pancreatitis; increased incidence of gallbladder disease; 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; urticaria.
6. *Eyes:* Retinal vascular thrombosis; intolerance to contact lenses.
7. *Central Nervous System:* Headache; migraine; dizziness; nervousness; mood disturbances; irritability; mental depression; chorea; exacerbation of epilepsy; dementia.
8. *Miscellaneous:* Increase or decrease in weight; reduced carbohydrate tolerance; glucose intolerance; aggravation of porphyria; edema; changes in libido; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; angioedema; hypersensitivity; increased triglycerides; arthralgias; leg cramps.

OVERDOSAGE

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

This brief summary is based on PREMARIN® (conjugated estrogens) Vaginal Cream Prescribing Information W10413C005 ET01, revised August 9, 2004.

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