Statements of Material Facts, Bribery, and Illegal Gratuities," also known as the "FDA Fraud Policy."

We attended a briefing on conjugated estrogens presented by CDER focusing on: (1) an overview of conjugated estrogens; (2) historical review of the regulation of estrogen drug products by FDA; (3) estrogen chemistry; and (4) generic conjugated estrogens. We reviewed the NDA file for Premarin containing: data submitted by Wyeth-Ayerst, FDA's review of these data, correspondence between FDA and Wyeth-Ayerst, minutes of meetings between FDA and Wyeth-Ayerst representatives, minutes of FDA internal meetings, internal FDA correspondence, and other related documents.

We interviewed FDA staff responsible for reviewing data on Premarin as well as supervisory and management officials. We also obtained reports of inspections of Wyeth-Ayerst manufacturing facilities conducted by FDA staff. In addition, we reviewed citizen petitions filed by Wyeth-Ayerst with FDA pertaining to Premarin and various analyses and responses to these petitions. We did not review pending applications for generic versions of Premarin.

Our review was limited to addressing questions posed by the Subcommittee and thus did not include an overall assessment of the internal controls over FDA's procedures for processing new drug and generic drug applications and for handling citizen petitions. Further, our review did not include an evaluation of the scientific merits of decisions made regarding Premarin, Prempro, and related generic versions of these products. We provided FDA with a draft copy of this report, and incorporated its comments where appropriate.

Our review, performed during September 1996 through January 1997, was conducted in accordance with generally accepted government auditing standards.

RESULTS OF REVIEW

The following paragraphs present a brief summary of our findings in the areas covered by our review: Premarin, Prempro, the citizen petition, and generic versions of Premarin. Following the summaries is a more detailed discussion of each of these areas presented in a question-and-answer format.

Premarin: According to FDA, there have been no unapproved formulations of Premarin. Regarding the issue of bioequivalency among the formulations, however, we found that FDA does not have evidence demonstrating that the currently marketed formulation of Premarin is bioequivalent to the version tested for osteoporosis in the late 1970's. This is because no in vivo bioequivalence requirement was in effect for conjugated estrogens at that time. Concerned about lack of bioequivalency data and the continued safety and effectiveness of Premarin, FDA, in 1993, directed Wyeth-Ayerst to conduct a new dose-ranging study of the drug. As of January 1997, 818 women, or about 30 percent of the total planned enrollment, have entered into the multi-year study.

Prempro: The Premarin tablet formulation used in the combination drug Prempro (Premarin/medroxyprogesterone acetate) slightly differed from the marketed Premarin, but Wyeth-Ayerst submitted in vivo bioequivalence data to demonstrate that the new and currently marketed formulations were bioequivalent.

Citizen Petition and Generic Versions of Premarin: The FDA is in the process of reviewing the claims and data associated with Wyeth-Ayerst's citizen petition, which was submitted to the agency over 2 years ago. The FDA has thus far found deficiencies in the design of studies submitted to support Wyeth-Ayerst's claims, but no misrepresentations in data in the firm's studies have been identified. Regarding the Subcommittee's concern that FDA may have held generic drug firms to a higher standard than the brand-name maker of Premarin, Wyeth-Ayerst, we noted that the agency was also concerned about possible differing standards in terms of bioequivalency requirements for the generic and brand name versions. However, upon further investigation, FDA determined there were no unapproved reformulations of the brand name Premarin that would have required Wyeth-Ayerst to submit additional bioequivalency data.

Beyond the Subcommittee's specific questions, we identified other concerns regarding the citizen petition process--namely that the process has been extended for an excessive period of time for the Wyeth-Ayerst case; and FDA does not have policies and procedures governing such an important process, one which can impact the marketability of generic versions of Premarin.

PREMARIN

This section addresses the questions raised by the Subcommittee regarding possible unapproved reformulations; whether the reformulations were bioequivalent; and the basis on which FDA allowed the continued marketing of Premarin.

Question 1: Did reformulations of Premarin receive prior approval from FDA? Does FDA have data from Wyeth-Ayerst to support the changes in the Premarin formulation through the years?

We identified two reformulations--both received prior FDA approval and Wyeth-Ayerst submitted adequate data to support the reformulations.

We identified another "apparent" reformulation involving the Premarin shellac coating. Wyeth-Ayerst did not consider this to be a reformulation, and the firm was able to demonstrate to FDA why it was not a reformulation.

An FDA inspection conducted in September 1993 found there were no unapproved reformulations of Premarin; however, the agency did not document its inspection results.

Two Reformulations

Reformulation Involving Microcrystalline Cellulose

The first reformulation--which received prior FDA approval and was supported by adequate documentation required at the time--occurred in the mid-1970's when Wyeth-Ayerst automated its Premarin tablet coating process. To switch from a manual to an automated coating process, Wyeth-Ayerst replaced about nine coat filler ingredients used in the manual coating process with microcrystalline cellulose. Wyeth-Ayerst filed supplemental new drug applications for this reformulation with FDA on September 25, 1972, and September 6, 1974.

In response to an FDA telephone request, Wyeth-Ayerst, on February 25, 1975, filed in vitro (i.e., within a glass or artificial environment) disintegration data for 0.3, 0.625, 1.25, and 2.5 mg. tablet batches made by both the manual and automated coating process as well as in vitro dissolution data for batches made by both methods for the 1.25 mg. tablet strength. On the basis of this data, FDA permitted this reformulation on April 22, 1975.

Reformulation Involving Rubidium Bromide

Subsequent to the FDA September 1993 inspection of its facility, Wyeth-Ayerst reformulated Premarin by removing talc triturate containing rubidium bromide from the tablet and replacing it with an equal amount of lactose. To support this reformulation, Wyeth-Ayerst submitted the results of an in vivo bioequivalence study comparing the different formulations. The FDA, on December 23, 1994, found the study acceptable and approved the reformulation.

"Apparent" Reformulation: Shellac Coating

According to FDA, in approximately 1989 or 1990, Wyeth-Ayerst instituted a reduction in the amount of shellac content in the Premarin tablet. The FDA was concerned that this reduction may have affected the dissolution profile of the tablet and cause Premarin to be released faster in the human body. Wyeth-Ayerst did not view the changes made to the shellac to constitute a reformulation, and was able to demonstrate to FDA's satisfaction that there was no change to the drug product.

FDA On-Site Verification of Premarin Formulations

In 1991, FDA officials began raising concern as to whether there had been unapproved formulations of Premarin. To address this issue, in September 1993, CDER staff accompanied an ORA inspector to the Rouses Point, New York facility of Wyeth-Ayerst, where Premarin is manufactured. As a result of this for-cause inspection, FDA concluded that there appeared to be no unapproved formulations or manufacturing changes to Premarin. This conclusion was included in a written technical review of a supplement to Wyeth-

Ayerst's NDA for Premarin tablets. The FDA, however, could not provide us with a written report or other documentation to support this conclusion.

Even though this for-cause inspection appeared to partially resolve several years worth of serious concerns about the safety and effectiveness of Premarin, FDA did not have in its files a written report documenting the CDER staff's findings, nor any other documentation explaining why these concerns were dispelled. It also did not have a summary of the meeting held in October 1993 with CDER management to discuss these findings. The CDER staff who conducted the inspection informed us that other work precluded their preparing an inspection report and meeting summary.

Question 2: ***Are there data showing bioequivalence between the version of Premarin marketed today and the version tested in the Lindsay study, which examined the lowest effective dose for osteoporosis prevention?***

The FDA acknowledges that there are no bioequivalency data linking the version of Premarin marketed today with the one used in the Lindsay study conducted in the late 1970's. Furthermore, bioequivalency to the drug tested in the Lindsay study is not likely to ever be demonstrated, according to FDA, because of the inability of Wyeth-Ayerst to replicate the manual coating process of the Premarin formulation used over 20 years ago for the Lindsay study tablets.

At the time that Wyeth-Ayerst reformulated Premarin with microcrystalline cellulose, FDA did not require in vivo bioequivalence testing when drug manufacturers changed their product. Thus, FDA cannot know with certainty that the Premarin tablets marketed today are bioequivalent to the tablets used in the Lindsay study. However, as described below, scientific literature published over many years has shown that estrogen products, including the current version of Premarin, are effective in the prevention and management of osteoporosis.

Question 3: ***Given that there are no data linking the currently marketed Premarin product to the version used in the pivotal Lindsay study, what data has FDA used to justify its determination that Premarin is effective and safe for the treatment of osteoporosis? Why has the agency not rescinded Premarin's osteoporosis indication?***

The FDA has relied on the scientific literature regarding estrogens to justify that Premarin is effective for the prevention and management of osteoporosis. Numerous clinical studies published in the scientific literature since the pivotal studies were conducted in the 1970's continue to show that Premarin is effective in reducing bone mineral loss.

In terms of safety, the scientific literature suggests that use of estrogens, including Premarin, is associated with health risks. Numerous studies confirm the association of post-menopausal use of estrogens with an increased risk of endometrial cancer--a risk that appears dependent on duration of treatment and on the dose (i.e., the risk increases with higher doses and the

length of duration). In addition, recent studies, such as one whose results were published in the June 1995 issue of the New England Journal of Medicine, have shown that women who use estrogens are at greater risk than non-estrogens users for developing breast cancer. The literature also demonstrates that, because of the risks of developing endometrial cancer by using Premarin by itself, the drug should be taken only by the woman whose uterus is not intact. For the woman whose uterus is intact, the literature suggests that Premarin be taken with progestin to reduce the risks of developing endometrial cancer.

Another serious safety issue deals with the recommended dose of Premarin. Internal FDA documents indicate that in 1991, CDER officials, based on published studies, began to question whether the recommended dose of Premarin--0.625 mg.--was too high and might pose a health hazard in terms of endometrial and breast cancer for long-term users. In 1993, CDER officials considered withdrawing the osteoporosis indication. Their concerns focused on the lack of bioequivalency data between the currently marketed version of Premarin to the tablet used in the Lindsay study and the lowest effective dose of the drug.

The FDA decided not to withdraw the osteoporosis indication, but instead opted to rely on the published literature. At a meeting held in October 1993 between FDA and Wyeth-Ayerst, FDA agreed to accept a supplement to the NDA for the osteoporosis indication provided that the firm conduct a new dose-ranging study of Premarin. This supplement was based on published research showing that short-acting estrogens, including Premarin, were effective for the prevention and management of osteoporosis. While the published literature appears to have demonstrated the efficacy of Premarin for osteoporosis, it still remains to be proven whether a lower dose may be safer and just as effective for osteoporosis as the currently recommended dose.

Such information, however, will not be available until Wyeth-Ayerst completes its multi-year dose-ranging study. The new dose-ranging study was initiated in August 1995. As of January 1997, 818 women, or about 30 percent of the total planned enrollment of 2,688, have entered into the multi-year study. The target date for completion of the dose-ranging study will be approximately 2 years from the enrollment of the last study subject.

Question 4: Has FDA conducted validity assessments on Premarin following the discovery of different formulations?

The FDA did not conduct a validity assessment[4] on Premarin following the permitted reformulation in 1975, nor after the discovery of the apparent change in shellac content that occurred in the late 1980's. According to FDA, validity assessments are geared more towards verifying generic drug applications rather than reformulations of brand name drugs.

[4] A validity assessment is a means to verify that drug applications adequately characterize the actual manufacturing of the drug product.

In 1993, FDA identified an apparent reduction in the shellac content of Premarin tablets; and in September 1993, initiated a for-cause inspection to: (1) determine whether the amount of shellac used for sealing tablet cores had an effect on the way the tablets dissolved; and (2) collect records to identify other possible unapproved reformulations. As a result, FDA determined that the shellac that was used at the time of the inspection did not affect the in vitro dissolution rate of Premarin tablets and that there were no other unapproved reformulations.

As noted above in Question #1, FDA was deficient in documenting the results of this for-cause inspection and a related staff meeting.

PREMPRO

This section responds to a question raised by the Subcommittee regarding Prempro, a recently marketed Wyeth-Ayerst product combining estrogen with progestin. This combination is designed to reduce the risks of endometrial cancer.

Question: ***If there is not a reference drug[5] for conjugated estrogens on the market, what data did Wyeth-Ayerst submit to FDA to win approval for the osteoporosis indication for Prempro, its recently approved combination product?***

According to FDA, the reference drug used for Prempro was the currently marketed version of Premarin, except the Premarin used in Prempro does not include talc triturate and rubidium bromide. These ingredients were removed from the Premarin tablet and replaced by an equal amount of lactose. Because of this reformulation, FDA required that Wyeth-Ayerst conduct an in vivo study to show that the two formulations were bioequivalent. According to FDA, during 1994, the firm submitted a bioequivalency study that included data on 52 women, which demonstrated that the old and new formulations were bioequivalent. While the two most recent formulations have been shown to be bioequivalent, it must be noted, as we discussed above, that data does not exist linking these formulations to the Premarin used in the Lindsay study.

CITIZEN PETITION AND GENERIC VERSIONS OF PREMARIN

This section responds to questions raised by the Subcommittee about Wyeth-Ayerst's and FDA's handling of issues related to the citizen petitions and generic drug versions of Premarin:

[5] A reference drug is the FDA-approved drug upon which a drug applicant is basing its new drug product.

Question 1: ***Has FDA applied its fraud policy to examine the veracity of claims made by Wyeth-Ayerst in its citizen petition filed with FDA in November 1994, that "alleged but did not provide supportive data that DHES had some biological activity?"***

The FDA has not invoked the fraud policy to analyze Wyeth-Ayerst's claims. According to a cognizant FDA official, the fraud policy is more directed to misrepresentation-of data in application submissions, rather than differing scientific opinions.

In terms of Wyeth-Ayerst's contention that DHES has some biological activity, and thus should be required to be included in generic versions, the firm has submitted to FDA clinical and pharmacokinetic study data that it believes supports this claim. The agency concluded that the clinical study was scientifically deficient for, among other things, not having a control group. The FDA's Division of Scientific Investigations has performed audits on data from the following two studies: (1) "A Pilot Study on the Clinical Effect of Delta 8,9, Dehydroestrone Sulfate Alone or in Combination with Estrone Sulfate;" and (2) "A Comparative Bioavailability Study of Premarin (0.625 mg.) and Estratab (0.625 mg.) in Healthy Post-Menopausal Females." Although the studies were found to be deficient, we are not aware of any misrepresentation in Wyeth-Ayerst's data provided to FDA regarding issues in its citizen petition.

Because the citizen petition has been under review for over 2 years by FDA, Wyeth-Ayerst has been able to provide FDA additional data to further substantiate its claims. Also, the agency has allowed the public, including drug companies seeking to develop generic versions of Premarin, to review and comment on Wyeth-Ayerst's claims. These mechanisms could serve as an additional method to identify the possibility of inaccurate data.

Question 2: ***Were generic drug applications in the 1980's and those that have been subsequently received held to an apparent higher standard than brand name Premarin?***

An FDA official involved in conjugated estrogens issues has cited possible differing standards for generic versions of Premarin marketed prior to 1991 and the brand name (innovator) product. However, a review of the history related to bioequivalence testing for both generic versions and brand name Premarin does not support this supposition.

Generic versions of Premarin were required in 1986 to show in vivo bioequivalence to brand name Premarin; however such bioequivalence could not be established because the generic products released faster in the body than the brand name version. As a result, in 1991, FDA required the generic products to be removed from the market. In 1993, this FDA official acknowledged bioequivalency issues were also associated with Premarin in that there were no bioequivalency data linking suspected reformulations of the product. The FDA official stated for the record:

> "Ironically, the same bioequivalence questions first raised by Wyeth-Ayerst [regarding generic versions on the market in the 1980's] now cast doubt upon

the safety and efficacy of Premarin. It would be neither consistent nor ethical, however, for FDA to apply a more lenient standard to the innovator firm now than was applied to the generic sponsors in 1990-91, when bioequivalence issues are virtually identical."

In 1993, FDA followed up on possible unapproved reformulations, and determined there were none. Had such unapproved reformulations been identified, and FDA not required Wyeth-Ayerst to submit additional bioequivalence data, then one could conclude that FDA had indeed applied a more lenient standard to Wyeth-Ayerst than the firms that had previously marketed generic versions of Premarin. Given that there were no unapproved reformulations, we could not substantiate the Subcommittee's concern that there were differing standards applied in this case.

Questions have been raised regarding the fast-releasing aspects of the drug because Wyeth-Ayerst, from 1967 to 1990, marketed in Canada a fast-releasing Premarin tablet that was similar to the generic versions marketed in the U.S. prior to 1991. However, according to FDA, Wyeth-Ayerst's fast-releasing product was not sold in the U.S. and FDA does not have regulatory oversight in a foreign country.

Regarding the generic versions currently being reviewed by FDA, we have not reviewed these pending applications, and thus we have no indications that they are being held to a higher standard than brand name Premarin.

Other Concerns about the
Citizen Petition Process

As a result of our review, we identified two significant concerns regarding the citizen petition process for the Premarin issue. First, in the Wyeth-Ayerst case, it appears that FDA has allowed the process to extend for an unacceptably long period of time--over 2 years. The regulations cited at 21 C.F.R. Section 10.30, require FDA to furnish a response to each petitioner within 180 days of receipt of the petition. The response will either: (1) approve the petition; (2) deny the petition; or (3) provide a tentative response. In this case, at the 180-day point, FDA informed Wyeth-Ayerst that the petition was "still under consideration."

In July 1995, FDA convened the Fertility and Maternal Health Drugs Advisory Committee to discuss the clinical effects of conjugated estrogens. This committee determined that there were insufficient data to assess whether or not DHES or any component must be present in generic versions of Premarin to achieve clinical safety and efficacy. The agency also established an ad hoc conjugated estrogens working group comprising scientific, legal, and policy experts to address the issues raised in the petition. Cognizant officials have indicated to us that the petition process has been extended to allow for the submission of public comments and analysis of data. Such data continued to be submitted to the agency up until December 1996. In December 1996, the firm amended its original petition to request that DHES be considered an "active" ingredient in Premarin.

Our second concern focuses on the absence of written policies and procedures for FDA's handling of citizen petitions. Such policies and procedures, we believe, are essential for any type of administrative process that can significantly impact the industries under FDA's regulatory purview. Although FDA has yet to decide whether it will approve Wyeth-Ayerst's citizen petition request, the Director of CDER announced on May 5, 1997, that the agency could not currently approve generic applications for synthetic versions of conjugated estrogens because the active ingredients of Premarin have not been adequately defined. According to CDER officials, CDER began developing a citizen petition policy several months ago and expects to complete it soon.

CONCLUSIONS

Premarin

The Subcommittee has raised serious questions regarding the safety and efficacy of Premarin--an important drug product used daily by millions of women. Regarding the formulations of Premarin, a September 1993 for-cause inspection confirmed there have been no unapproved reformulations of the drug product; however, FDA could not furnish documentation of its inspection results nor any other documentation explaining why its concerns about the drug's formulations were dispelled.

In terms of bioequivalency, there is no data link between the Premarin product tested in the late 1970's during a pivotal osteoporosis study and the product that is currently marketed. The FDA has relied on published data demonstrating Premarin's effectiveness for the prevention and management of osteoporosis, but has also raised concerns about the absence of bioequivalency data and the possibility that the dose of Premarin may be too high. To address these concerns, FDA directed Wyeth-Ayerst in October 1993 to conduct a new dose-ranging study of the drug. Until a new study is completed, the agency is relying on published data to demonstrate that Premarin is effective for osteoporosis.

Prempro

In terms of the recent Wyeth-Ayerst product, Prempro, the firm used the marketed version of Premarin as a reference drug in the new drug application, except the Premarin used in Prempro does not include talc triturate and rubidium bromide. These ingredients were removed from the Premarin tablet and replaced by an equal amount of lactose. Wyeth-Ayerst was able to demonstrate to FDA through in vivo testing that the two formulations were bioequivalent.

Citizen Petition Process and Generic Versions of Premarin

In terms of the Subcommittee's concern about possible fraudulent claims made by Wyeth-Ayerst in the citizen petition process, it appears that FDA has--and is using--appropriate

methods for identifying inaccuracies in the firm's data submissions. We did not identify instances where Wyeth-Ayerst received preferential treatment from FDA over generic drug sponsors. Our concerns with the citizen petition process focus on the length of time it has taken FDA to receive and analyze pertinent data in the Wyeth-Ayerst case and the absence of agency policies and procedures for handling such petitions.

Premarin®

(conjugated estrogens tablets, USP)

℞ only

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.

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 during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (see **CLINICAL PHARMACOLOGY, Clinical Studies**). Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations of estrogens and progestins were not studied in the WHI 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.

DESCRIPTION

Premarin® (conjugated estrogens tablets, USP) for oral administration contains a mixture of conjugated equine estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin. Tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, and 2.5 mg strengths of conjugated estrogens.

Premarin tablets contain the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid (not present in 0.45 mg tablet), sucrose, and titanium dioxide.

— 0.3 mg tablets also contain: D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 1.

— 0.45 mg tablets also contain: FD&C Blue No. 2; these tablets comply with USP Drug Release Test 1.

— 0.625 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40; these tablets comply with USP Drug Release Test 1.

— 0.9 mg tablets also contain: D&C Red No. 6, D&C Red No. 7; these tablets comply with USP Drug Release Test 2.

— 1.25 mg tablets also contain: black iron oxide, D&C Yellow No. 10, FD&C Yellow No. 6; these tablets comply with USP Drug Release Test 3.

— 2.5 mg tablets also contain: FD&C Blue No. 2, D&C Red No. 7; these tablets comply with USP Drug Release Test 3.

CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol, at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Pharmacokinetics

Absorption

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The Premarin tablet releases conjugated estrogens slowly over several hours. Table 1 summarizes the mean pharmacokinetic parameters for unconjugated and conjugated estrogens following administration of 2 x 0.3 mg, 2 x 0.45 mg, and 2 x 0.625 mg tablets to healthy postmenopausal women.

TABLE 1. PHARMACOKINETIC PARAMETERS FOR PREMARIN

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.3 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	82 (33)	7.8 (27)	54.7 (42)	5390 (50)
Baseline-adjusted estrone	58 (42)	7.8 (27)	21.1 (45)	1467 (41)
Equilin	31 (47)	7.2 (28)	18.3 (110)	652 (68)

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.3 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Estrone	2.5 (32)	6.5 (29)	25.4 (22)	61.0 (43)
Baseline-adjusted total estrone	2.4 (32)	6.5 (29)	16.2 (34)	40.8 (36)
Equilin	1.6 (40)	5.9 (27)	11.8 (21)	22.4 (42)

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.45 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	92 (32)	8.7 (28)	56.4 (68)	6344 (56)
Baseline-adjusted estrone	65 (40)	8.7 (28)	20.3 (38)	1940 (40)
Equilin	35 (49)	7.6 (33)	21.9 (113)	849 (60)

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.45 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total estrone	2.8 (46)	7.1 (27)	27.6 (35)	77 (34)
Baseline-adjusted total estrone	2.6 (46)	7.1 (27)	14.7 (42)	48 (38)
Total equilin	1.9 (53)	5.9 (32)	11.8 (32)	29 (55)

Pharmacokinetic Profile of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (pg•h/mL)
Estrone	139 (37)	8.8 (20)	28.0 (30)	5016 (34)
Baseline-adjusted estrone	120 (41)	8.8 (20)	17.4 (37)	2956 (39)
Equilin	66 (42)	7.9 (19)	13.6 (52)	1210 (37)

Pharmacokinetic Profile of Conjugated Estrogens Following a Dose of 2 x 0.625 mg

PK Parameter Arithmetic Mean (%CV)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC (ng•h/mL)
Total estrone	7.3 (41)	7.3 (24)	15.0 (25)	134 (42)
Baseline-adjusted total estrone	7.1 (41)	7.3 (24)	13.6 (23)	122 (38)
Total equilin	5.0 (42)	6.2 (26)	10.1 (26)	65 (44)

Distribution
The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentration in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism
Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant proportion of the circulating estrogens exists as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion
Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations
No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions
Data from a single-dose drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicate that the pharmacokinetic dispositions of both drugs are not significantly altered. No other clinical drug-drug interaction studies have been conducted with conjugated estrogens.

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

Clinical Studies
Effects on Vasomotor Symptoms
In the first year of the Health and Osteoporosis, Progestin and Estrogen (HOPE) Study, a total of 2805 postmenopausal women (average age 53.3 ± 4.9 years) were randomly assigned to one of eight treatment groups, receiving either placebo or conjugated estrogens with or without medroxyprogesterone acetate.

Efficacy for vasomotor symptoms was assessed during the first 12 weeks of treatment in a subset of symptomatic women (n = 241) who had at least 7 moderate to severe hot flushes daily or at least 50 moderate to severe hot flushes during the week before randomization. Premarin (0.3 mg, 0.45 mg, and 0.625 mg tablets) was shown to be statistically better than placebo at weeks 4 and 12 for relief of both the frequency and severity of moderate to severe vasomotor symptoms. Table 2 shows the adjusted mean number of hot flushes in the Premarin 0.3 mg, 0.45 mg, and 0.625 mg and placebo treatment groups over the initial 12-week period.

TABLE 2. SUMMARY TABULATION OF THE NUMBER OF HOT FLUSHES PER DAY– MEAN VALUES AND COMPARISONS BETWEEN THE ACTIVE TREATMENT GROUPS AND THE PLACEBO GROUP: PATIENTS WITH AT LEAST 7 MODERATE TO SEVERE FLUSHES PER DAY OR AT LEAST 50 PER WEEK AT BASELINE, LOCF

Treatment[a] (No. of Patients)	---------- No. of Hot Flushes/Day ----------			
Time Period (week)	Baseline Mean ± SD	Observed Mean ± SD	Mean Change ± SD	p-Values vs. Placebo[b]
0.625 mg CE (n = 27)				
4	12.29 ± 3.89	1.95 ± 2.77	-10.34 ± 4.73	<0.001
12	12.29 ± 3.89	0.75 ± 1.82	-11.54 ± 4.62	<0.001
0.45 mg CE (n = 32)				
4	12.25 ± 5.04	5.04 ± 5.31	-7.21 ± 4.75	<0.001
12	12.25 ± 5.04	2.32 ± 3.32	-9.93 ± 4.64	<0.001
0.3 mg CE (n = 30)				
4	13.77 ± 4.78	4.65 ± 3.71	-9.12 ± 4.71	<0.001
12	13.77 ± 4.78	2.52 ± 3.23	-11.25 ± 4.60	<0.001
Placebo (n = 28)				
4	11.69 ± 3.87	7.89 ± 5.28	-3.80 ± 4.71	-
12	11.69 ± 3.87	5.71 ± 5.22	-5.98 ± 4.60	-

a: Standard errors based on assumption of equal variances.
b: Based on analysis of covariance with treatment as factor and baseline as covariate.

Effects on Vulvar and Vaginal Atrophy
Results of vaginal maturation indexes at cycles 6 and 13 showed that the differences from placebo were statistically significant ($p<0.001$) for all treatment groups (conjugated estrogens alone and conjugated estrogens/medroxyprogesterone acetate treatment groups).

Effects on Bone Mineral Density
In the 3-year, randomized, double-blind, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, the effect of Premarin 0.625 mg (conjugated estrogens tablets, USP), given alone or in combination with medroxyprogesterone acetate (MPA), on bone mineral

density (BMD) was evaluated in postmenopausal women. One of the regimens evaluated was continuous combined Premarin 0.625 mg/MPA 2.5 mg, a regimen similar to PREMPRO.

Intent-to-treat subjects

In the intent-to-treat subjects, BMD increased significantly ($p<0.001$) compared to baseline or placebo at both the hip and the spine in women assigned to Premarin or the continuous Premarin/MPA regimen. Spinal BMD increased 3.46% among women assigned to Premarin, increased 4.87% in women assigned to the Premarin/MPA regimen and decreased 1.81% in women assigned to placebo. At the hip, women assigned to Premarin gained 1.31%, women assigned to Premarin/MPA gained 1.94%, while women assigned to placebo lost 1.62%.

Adherent subjects

In the adherent subjects, BMD also increased significantly ($p<0.001$) compared to baseline or placebo at both the hip and the spine in women assigned to Premarin or continuous Premarin/MPA. Spinal BMD increased 5.16% among women assigned to Premarin, increased 5.49% in women assigned to Premarin/MPA and decreased 2.82% in women assigned to placebo. At the hip, women assigned to Premarin gained 2.60%, women assigned to Premarin/MPA gained 2.23%, while women assigned to placebo lost 2.17%.

These results are summarized in Tables 3 and 4 below.

TABLE 3. MEAN PERCENTAGE CHANGE FROM BASELINE IN BMD AT 36 MONTHS IN INTENT-TO-TREAT SUBJECTS**

	Spine			Hip		
Regimen	n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	175	+3.46%*†	2.78, 4.14	175	+1.31%*†	0.76, 1.86
Premarin 0.625 mg/ MPA 2.5 mg	174	+4.87%*†	4.21, 5.52	174	+1.94%*†	1.50, 2.39
Placebo	174	-1.81%*	-2.51, -1.12	173	-1.62%*	-2.16, -1.08

* Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.

** Includes all 523 women who were randomized to either Premarin, Premarin/MPA or Placebo whether or not they completed the study. If BMD was not available at 36 months, then the 12 months value was carried forward and analyzed. Baseline values were carried forward if 12 months and 36 months data were unavailable. Most patients who discontinued study medication were followed through month 36 and could have been off therapy for an extended period prior to their month 36 evaluation.

TABLE 4. MEAN PERCENTAGE CHANGES FROM BASELINE IN BMD AT 36 MONTHS IN ADHERENT SUBJECTS**						
	Spine			Hip		
Regimen	n	Mean % Change	95% CI	n	Mean % Change	95% CI
Premarin 0.625 mg	95	+5.16%*†	4.32, 6.00	95	+2.60%*†	1.97, 3.23
Premarin 0.625 mg/ MPA 2.5 mg	144	+5.49%*†	4.79, 6.18	144	+2.23%*†	1.75, 2.71
Placebo	124	-2.82%*	-3.54, -2.10	123	-2.17%*	-2.78, -1.56

* Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes mean percentage change from baseline is significantly different from placebo at the 0.001 level.

** Women who completed the study, had BMD reported at month 36, and took 80% or more of their prescribed medication.

In general, older women (55-64 years of age) taking placebo in the PEPI study lost bone at a lower rate than younger women (45-54 years of age). Conversely, older women receiving Premarin or Premarin 0.625 mg/MPA 2.5 mg had greater increases in BMD than younger women. Tables 5 and 6 present data for women 45 to 54 years of age and women 55 to 64 years of age.

TABLE 5. MEAN PERCENT CHANGE FROM BASELINE IN BMD FOR WOMEN 45 TO 54 YEARS OF AGE								
	Intent-To-Treat Subjects				Adherent Subjects			
Regimen	n	Mean % Change at the Spine	n	Mean % Change at the Hip	n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	74	+2.45%†**	74	+1.37%†**	43	+3.73%†**	43	+2.20%†**
Premarin 0.625 mg/ MPA 2.5 mg	69	+3.53%†**	69	+1.26%†**	58	+3.97%†**	58	+1.48%†**
Placebo	78	-2.82%**	78	-2.23%**	50	-4.02%**	50	-3.04%**

** Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes the mean percent change from baseline is significantly different from placebo at the 0.001 level.

TABLE 6. MEAN PERCENT CHANGE FROM BASELINE IN BMD FOR WOMEN 55 TO 64 YEARS OF AGE								
	Intent-To-Treat Subjects				Adherent Subjects			
Regimen	n	Mean % Change at the Spine	n	Mean % Change at the Hip	n	Mean % Change at the Spine	n	Mean % Change at the Hip
Premarin 0.625 mg	101	+4.21%†‡**	101	+1.27%†**	52	+6.34%†‡**	52	+2.93%†**
Premarin 0.625 mg/ MPA 2.5 mg	105	+5.75%†‡**	105	+2.39%†**	86	+6.51%†‡**	86	+2.73%†**
Placebo	95	-1.01%*	94	-1.14%*	73	-2.04%‡**	72	-1.60%**

* Denotes a statistically significant mean change from baseline at the 0.05 level.

** Denotes a statistically significant mean change from baseline at the 0.001 level.

† Denotes the mean percent change from baseline is significantly different from placebo at the 0.001 level.

‡ Denotes the mean percent change from baseline in the older age group is significantly different from the mean percent change in the younger age group at the 0.05 level.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women to assess the risks and benefits of either the use of Premarin (0.625 mg conjugated equine estrogens per day) alone or the use of Prempro (0.625 mg conjugated equine estrogens plus 2.5 mg medroxyprogesterone acetate per day) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of Premarin or Prempro on menopausal symptoms.

The Premarin-only substudy is continuing and results have not been reported. The Prempro substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results of the Prempro substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic), after an average follow-up of 5.2 years are presented in Table 7 below.

Table 7. RELATIVE AND ABSOLUTE RISK SEEN IN THE PREMPRO SUBSTUDY OF WHI[a]

Event[c]	Relative Risk Prempro vs Placebo at 5.2 Years (95% CI*)	Placebo n = 8102	Prempro n = 8506
		Absolute Risk per 10,000 Person-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index [c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: Adapted from JAMA, 2002; 288:321-333

b: Includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer

c: A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes

d: Not included in Global Index

* Nominal confidence intervals unadjusted for multiple looks and multiple comparisons

For those outcomes included in the "global index," absolute excess risks per 10,000 person-years in the group treated with Prempro were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 person-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS, WARNINGS,** and **PRECAUTIONS.)**

INDICATIONS AND USAGE

Premarin therapy is indicated in the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

4. Treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

5. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

6. Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy. Postmenopausal women require an average of 1500 mg/day of elemental calcium. Therefore, when not contraindicated, calcium supplementation may be helpful for women with suboptimal dietary intake. Vitamin D supplementation of 400-800 IU/day may also be required to ensure adequate daily intake in postmenopausal women.

CONTRAINDICATIONS

Estrogens should not be used in individuals with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.

2. Known, suspected, or history of cancer of the breast except in appropriately selected patients being treated for metastatic disease.

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 tablets should not be used in patients with known hypersensitivity to their ingredients.

8. Known or suspected pregnancy. There is no indication for Premarin in pregnancy. There appears to be little or no increased risk of birth defects in women who have used estrogen and progestins from oral contraceptives inadvertently during pregnancy. (See **PRECAUTIONS.**)

WARNINGS
See **BOXED WARNINGS.**

The use of unopposed estrogens in women who have a uterus is associated with an increased risk of endometrial cancer.

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

   In the Prempro 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 Prempro compared to women receiving placebo (37 vs 30 per 10,000 person-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 Prempro compared to women receiving placebo (29 vs 21 per 10,000 person-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 equine 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. 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 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 risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

b. ***Venous thromboembolism (VTE).*** In the Premarin substudy of the Women's Health Initiative (WHI), an increase in VTE has been observed in women receiving Premarin compared to placebo. These observations are preliminary, and the study is continuing. (See **CLINICAL PHARMACOLOGY, Clinical Studies.)**

In the Prempro 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 woman-years in the Prempro group compared to 16 per 10,000 woman-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 with an intact uterus 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 the 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.*** Estrogen and estrogen/progestin therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the Prempro substudy of the Women's Health Initiative study (WHI), a 26% increase of invasive breast cancer (38 vs 30 per 10,000 woman-years) after an average of 5.2 years of treatment was observed in women receiving Prempro compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on Prempro. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with Prempro than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY, Clinical Studies.)**

In the Premarin substudy of the WHI study, no increased risk of breast cancer in estrogen-treated women compared to placebo was reported after an average of 5.2 years of therapy. These data are preliminary and that substudy of WHI is continuing.

Epidemiologic studies have reported an increased risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens, with or without progestin. This association was reanalyzed in original data from 51 studies that involved treatment with various doses and types of estrogens, with and without progestin. In the reanalysis, an increased risk of having breast cancer diagnosed became apparent after about 5 years of continued treatment, and subsided after treatment had been discontinued for about 5 years. Some later studies have suggested that treatment with estrogen and progestin increases the risk of breast cancer more than treatment with estrogen alone.

A postmenopausal woman without a uterus who requires estrogen should receive estrogen-alone therapy and should not be exposed unnecessarily to progestins. All postmenopausal women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

3. **Dementia.** In a study of women 65 years of age and older (a randomized controlled sub-study of the Women's Health Initiative, the Women's Health Initiative Memory Study; n=4,532, 54% older than 70), those treated with PREMPRO (0.625 mg, conjugated equine estrogen, plus 2.5 mg medroxyprogesterone acetate) were reported to have a two-fold increase in the risk of developing probable dementia. After an average follow-up of 4 years, the absolute risk of probable dementia was 45 per 10,000 woman-years in the PREMPRO group and 22 per 10,000 woman-years in the placebo group. It is unknown whether these findings apply to younger postmenopausal women.

   The estrogen-alone sub-study of the Women's Health Initiative Memory Study is currently ongoing. No data are available. 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 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 during 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. In the HOPE study, the mean percent increase from baseline in serum triglycerides after one year of treatment with Premarin 0.625 mg, 0.45 mg, and 0.3 mg compared with placebo were 34.3, 30.2, 25.1, and 10.7, respectively. After two years of treatment, the mean percent changes were 47.6, 32.5, 19.0, and 5.5, respectively.

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.***
   Use of estrogen-only products, in particular for ten or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies. Other studies did not show a significant association. Data are insufficient to determine whether there is an increased risk with combined estrogen/progestin therapy in postmenopausal women.

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-only therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

10. ***Exacerbation of other conditions.***
    Estrogens therapy 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 patients with these conditions.

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

C. Laboratory Tests
Estrogen administration should be initiated at the lowest dose for the treatment of postmenopausal moderate to severe vasomotor symptoms and moderate to severe symptoms of postmenopausal vulvar and vaginal atrophy and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH). Laboratory parameters may be useful in guiding dosage for the treatment of hypoestrogenism due to hypogonadism, castration and primary ovarian failure.

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, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor 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) levels leading to increased circulating total thyroid hormone levels 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 circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. 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 concentrations, increased triglyceride levels.

5. Impaired glucose tolerance.

6. Reduced response to metyrapone test.

E. Carcinogenesis, Mutagenesis, Impairment of Fertility.
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. (See **BOXED WARNINGS, CONTRAINDICATIONS,** and **WARNINGS).**

F. Pregnancy.
Premarin 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 the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Premarin 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 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** and **DOSAGE AND ADMINISTRATION** sections.

I. Geriatric Use.
Of the total number of subjects in the Prempro substudy of the Women's Health Initiative study, 44% (n=7320) were 65 years and over, while 6.6% (n=1,095) were 75 and over (see **CLINICAL PHARMACOLOGY, Clinical Studies**). No significant differences in safety were observed between subjects 65 years and over compared to younger subjects. There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to younger subjects.

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilizing Premarin to determine whether those over 65 years of age differ from younger subjects in their response to Premarin.

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.

During the first year of a 2-year clinical trial with 2333 postmenopausal women between 40 and 65 years of age (88% Caucasian), 1012 women were treated with conjugated estrogens and 332 were treated with placebo. Table 8 summarizes adverse events that occurred at a rate of ≥ 5%.

TABLE 8. NUMBER (%) OF PATIENTS REPORTING ≥ 5% TREATMENT EMERGENT ADVERSE EVENTS

	--Conjugated Estrogens Treatment Group--			
Body System Adverse event	0.625 mg (n = 348)	0.45 mg (n = 338)	0.3 mg (n = 326)	Placebo (n = 332)
Any adverse event	93%	90%	90%	85%
Body as a Whole				
Abdominal pain	16%	15%	17%	11%
Accidental injury	6%	12%	6%	9%
Asthenia	7%	7%	8%	5%
Back pain	14%	13%	13%	12%
Flu syndrome	11%	11%	10%	11%
Headache	26%	32%	29%	28%
Infection	18%	22%	23%	22%
Pain	17%	18%	20%	18%
Digestive System				
Diarrhea	6%	7%	6%	6%
Dyspepsia	9%	9%	11%	14%
Flatulence	7%	7%	6%	3%
Nausea	9%	6%	6%	9%
Musculoskeletal System				
Arthralgia	14%	12%	7%	12%
Leg cramps	5%	7%	3%	2%
Myalgia	5%	5%	9%	8%

TABLE 8. NUMBER (%) OF PATIENTS REPORTING ≥ 5% TREATMENT EMERGENT ADVERSE EVENTS

	--Conjugated Estrogens Treatment Group--			
Body System Adverse event	0.625 mg (n = 348)	0.45 mg (n = 338)	0.3 mg (n = 326)	Placebo (n = 332)
Nervous System				
Depression	7%	8%	5%	7%
Dizziness	5%	6%	4%	5%
Insomnia	6%	7%	7%	10%
Nervousness	3%	5%	2%	2%
Respiratory System				
Cough increased	4%	7%	4%	4%
Pharyngitis	10%	10%	12%	11%
Rhinitis	6%	9%	10%	13%
Sinusitis	6%	11%	7%	7%
Upper respiratory infection	12%	10%	9%	11%
Skin and Appendages				
Pruritus	4%	5%	5%	2%
Urogenital System				
Breast pain	11%	12%	7%	9%
Leukorrhea	5%	7%	4%	3%
Vaginal hemorrhage	14%	4%	2%	0
Vaginal moniliasis	6%	5%	5%	2%
Vaginitis	7%	6%	5%	1%

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

1. *Genitourinary system.*
Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting, dysmenorrhea.
Increase in size of uterine leiomyomata.
Vaginitis, including vaginal candidiasis.
Change in amount of cervical secretion.
Change in cervical ectropion.
Ovarian cancer.
Endometrial hyperplasia.
Endometrial cancer.

2. *Breasts.*
Tenderness, enlargement, pain, 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 gallbladder disease.
Pancreatitis.
Enlargement of hepatic hemangiomas.

5. *Skin.*
Chloasma or melasma that may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.
Pruritus, rash.

6. *Eyes.*
Retinal vascular thrombosis.
Steepening of corneal curvature.
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.
Arthralgias.
Leg cramps.
Changes in libido.
Urticaria, angioedema, anaphylactoid/anaphylactic reactions.
Hypocalcemia.
Exacerbation of asthma.
Increased triglycerides.

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

DOSAGE AND ADMINISTRATION
When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., at 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women with a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

1. For treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

   Patients should be treated with the lowest effective dose. Generally women should be started at 0.3 mg Premarin daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

   Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

2. For prevention of postmenopausal osteoporosis:

   When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should be considered only for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered. Patients should be treated with the lowest effective dose. Generally women should be started at 0.625 mg Premarin daily. Dosage may be adjusted depending on individual clinical and bone mineral density responses. This dose should be periodically reassessed by the healthcare provider.

   Premarin therapy may be given continuously with no interruption in therapy, or in cyclical regimens (regimens such as 25 days on drug followed by five days off drug) as is medically appropriate on an individualized basis.

3. For treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure:

   Female hypogonadism—0.3 mg to 0.625 mg daily, administered cyclically (e.g., three weeks on and one week off). Doses are adjusted depending on the severity of symptoms and responsiveness of the endometrium.

   In clinical studies of delayed puberty due to female hypogonadism, breast development was induced by doses as low as 0.15 mg. The dosage may be gradually titrated upward at 6 to 12 month intervals as needed to achieve appropriate bone age advancement and eventual epiphyseal closure. Clinical studies suggest that doses of 0.15 mg, 0.3 mg, and 0.6 mg are associated with mean ratios of bone age advancement to chronological age progression ($\Delta BA/\Delta CA$) of 1.1, 1.5, and 2.1, respectively. (Premarin in the dose strength of 0.15 mg is not available commercially). Available data suggest that chronic dosing with 0.625 mg is sufficient to induce artificial cyclic menses with sequential progestin treatment and to maintain bone mineral density after skeletal maturity is achieved.

   Female castration or primary ovarian failure—1.25 mg daily, cyclically. Adjust dosage, upward or downward, according to severity of symptoms and response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

4. For treatment of breast cancer, for palliation only, in appropriately selected women and men with metastatic disease:

   Suggested dosage is 10 mg three times daily for a period of at least three months.

5. For treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only:

   1.25 mg to 2.5 mg three times daily. The effectiveness of therapy can be judged by phosphatase determinations as well as by symptomatic improvement of the patient.

HOW SUPPLIED
Premarin (conjugated estrogens tablets, USP)

— Each oval purple tablet contains 2.5 mg, in bottles of 100 (NDC 0046-0865-81) and 1,000 (NDC 0046-0865-91).

— Each oval yellow tablet contains 1.25 mg, in bottles of 100 (NDC 0046-0866-81); 1,000 (NDC 0046-0866-91); and Unit-Dose packages of 100 (NDC 0046-0866-99).

— Each oval white tablet contains 0.9 mg, in bottles of 100 (NDC 0046-0864-81).

— Each oval maroon tablet contains 0.625 mg, in bottles of 100 (NDC 0046-0867-81); 1,000 (NDC 0046-0867-91); and Unit-Dose Packages of 100 (NDC 0046-0867-99).

— Each oval blue tablet contains 0.45 mg, in bottles of 100 (NDC 0046-0936-81); and Unit-Dose Packages of 100 (NDC 0046-0936-099).

— Each oval green tablet contains 0.3 mg, in bottles of 100 (NDC 0046-0868-81) and 1,000 (NDC 0046-0868-91).

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

Store at 20-25° C (68-77° F); excursions permitted to 15-30° C (59-86° F). [see USP Controlled Room Temperature]

Dispense in a well-closed container as defined in the USP.

PATIENT INFORMATION

Premarin ®
(conjugated estrogens tablets, USP)

Read this PATIENT INFORMATION before you start taking Premarin and read what you get each time you refill Premarin. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Premarin (an estrogen mixture)?

- Estrogens increase the chances of getting cancer of the uterus.

  Report any unusual vaginal bleeding right away while you are taking Premarin. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

- Do not use estrogens with or without progestins to prevent heart disease, heart attacks, or strokes.

  Using estrogens with or without progestins may increase your chances of getting heart attacks, strokes, breast cancer, and blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with estrogens.

What is Premarin?
Premarin is a medicine that contains a mixture of estrogen hormones.

Premarin is used after menopause to:

- **reduce moderate to severe hot flashes.** Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 and 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

  When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women the symptoms are mild, and they will not need to take estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Premarin.

- **treat moderate to severe dryness, itching, and burning, in and around the vagina.** You and your healthcare provider should talk regularly about whether you still need treatment with Premarin to control these problems.

- **help reduce your chances of getting osteoporosis (thin weak bones).** Osteoporosis from menopause is a thinning of the bones that makes them weaker and easier to break. If you use Premarin only to prevent osteoporosis from menopause, talk with your healthcare provider about whether a different treatment or medicine without estrogens might be better for you. You and your healthcare provider should talk regularly about whether you should continue with Premarin.

  Weight-bearing exercise, like walking or running, and taking calcium and vitamin D supplements may also lower your chances for getting postmenopausal osteoporosis. It is important to talk about exercise and supplements with your healthcare provider before starting them.

Premarin is also used to:

- **treat certain conditions in women before menopause if their ovaries do not make enough estrogen naturally.**
- **ease symptoms of certain cancers that have spread through the body, in men and women.**

Who should not take Premarin?

Do not start taking Premarin if you:

- **have unusual vaginal bleeding.**
- **currently have or have had certain cancers.** Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take Premarin.
- **had a stroke or heart attack in the past year.**
- **currently have or have had blood clots.**
- **are allergic to Premarin tablets or any of its ingredients.** See the end of this leaflet for a list of all the ingredients in Premarin.
- **think you may be pregnant.**

Tell your healthcare provider:

- **if you are breast feeding.** The hormones in Premarin can pass into your milk.
- **about all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

- **about all the medicines you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Premarin works. Premarin may also affect how your other medicines work.

- **if you are going to have surgery or will be on bedrest.** You may need to stop taking estrogens.

How should I take Premarin?

- Take one Premarin tablet at the same time each day.

- If you miss a dose, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.

- Estrogens should be used only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about whether you still need treatment with Premarin.

What are the possible side effects of Premarin?

Less common but serious side effects include:
- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- Dementia
- Gallbladder disease
- Ovarian cancer

These are some of the warning signs of serious side effects:
- Breast lumps
- Unusual vaginal bleeding
- Dizziness and faintness
- Changes in speech
- Severe headaches
- Chest pain
- Shortness of breath
- Pains in your legs
- Changes in vision
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptom that concerns you.

Common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach/abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

Other side effects include:

- High blood pressure
- Liver problems
- High blood sugar
- Fluid retention
- Enlargement of benign tumors of the uterus ("fibroids")
- Vaginal yeast infections

These are not all the possible side effects of Premarin. For more information, ask your healthcare provider or pharmacist.

What can I do to lower my chances of getting a serious side effect with Premarin?

- Talk with your healthcare provider regularly about whether you should continue taking Premarin.
- If you have a uterus, talk to your healthcare provider about whether the addition of a progestin is right for you.
- See your healthcare provider right away if you get vaginal bleeding while taking Premarin.
- Have a breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about the safe and effective use of Premarin

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take Premarin for conditions for which it was not prescribed. Do not give Premarin to other people, even if they have the same symptoms you have. It may harm them.

Keep Premarin out of the reach of children.

This leaflet provides a summary of the most important information about Premarin. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Premarin that is written for health professionals. You can get more information by calling the toll free number 800-934-5556.

What are the ingredients in Premarin?

Premarin contains a mixture of conjugated equine estrogens, which are a mixture of sodium estrone sulfate and sodium equilin sulfate and other components including sodium sulfate conjugates, 17 α-dihydroequilin, 17 α-estradiol, and 17 β-dihydroequilin. Premarin also contains calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, and titanium dioxide. The tablets come in different strengths and each strength tablet is a different color. The color ingredients are:

— 0.3 mg tablet (green color): D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, and FD&C Yellow No. 6.

— 0.45 mg tablet (blue color): FD&C Blue No. 2.

— 0.625 mg tablet (maroon color): FD&C Blue No. 2, D&C Red No. 27, and FD&C Red No. 40.

— 0.9 mg tablet (white color): D&C Red No. 6 and D&C Red No. 7.

— 1.25 mg tablet (yellow color): black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6.

— 2.5 mg tablet (purple color): FD&C Blue No. 2 and D&C Red No. 7.

The appearance of these tablets is a trademark of Wyeth Pharmaceuticals.

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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