Cenestin®

(synthetic conjugated estrogens, A) Tablets

Rx 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 at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms**, *Endometrial cancer*.)

CARDIOVASCULAR AND OTHER RISKS

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders**.)

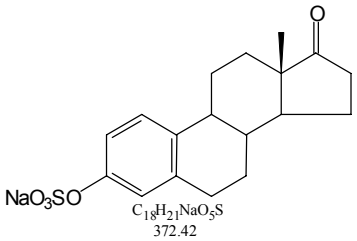
The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated equine estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies**.)

Other doses of oral conjugated estrogens with medroxyprogesterone, 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.

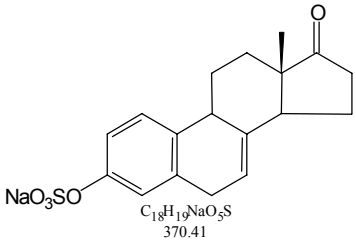
DESCRIPTION

Synthetic conjugated estrogens, A tablets contain a blend of nine (9) synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate.

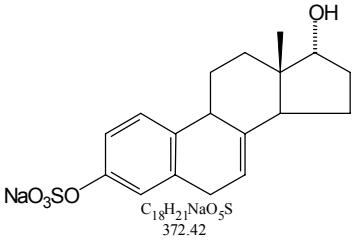
The structural formulae for these estrogens are:



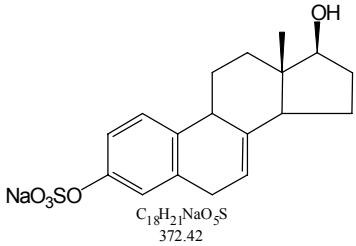
Sodium Estrone Sulfate



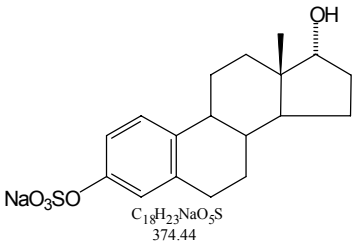
Sodium Equilin Sulfate



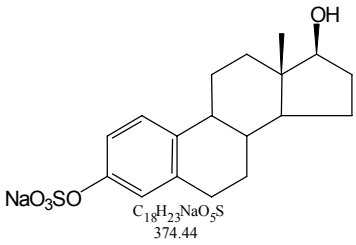
Sodium 17α-Dihydroequilin Sulfate



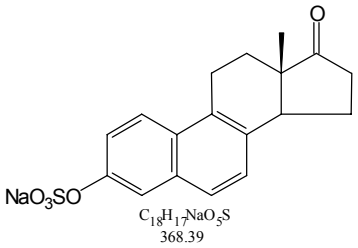
Sodium 17β-Dihydroequilin Sulfate



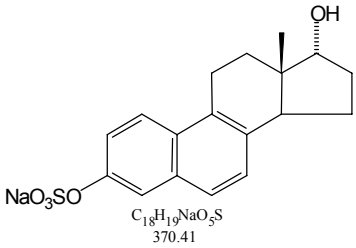
Sodium 17α-Estradiol Sulfate



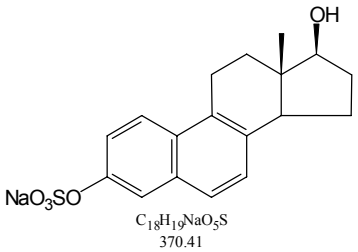
Sodium 17β-Estradiol Sulfate



Sodium Equilenin Sulfate



Sodium 17α-Dihydroequilenin Sulfate



Sodium 17β-Dihydroequilenin Sulfate

Tablets for oral administration, are available in 0.3 mg, 0.45mg, 0.625 mg, 0.9 mg and 1.25 mg strengths of synthetic conjugated estrogens, A. Tablets also contain the following inactive ingredients: ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate.

-0.3 mg tablets also contain: FD&C Blue No. 2 aluminum lake and D&C Yellow No. 10 aluminum lake.
-0.45 mg tablets also contain FD&C Yellow No. 6/Sunset Yellow FCF lake.
-0.625 mg tablets also contain: FD&C Red No. 40 aluminum lake.

-0.9 mg tablets do not contain additional color additives.
-1.25 mg tablets also contain FD&C Blue No. 2 aluminum lake.

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 hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

Synthetic conjugated estrogens, A are soluble in water and are well absorbed from the gastrointestinal tract after release from the drug formulation. The Cenestin tablet releases the synthetic conjugated estrogens, A slowly over a period of several hours. The effect of food on the bioavailability of synthetic conjugated estrogens, A from Cenestin has not been studied.

Table 1
PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS IN HEALTHY POSTMENOPAUSAL WOMEN UNDER FASTING CONDITIONS

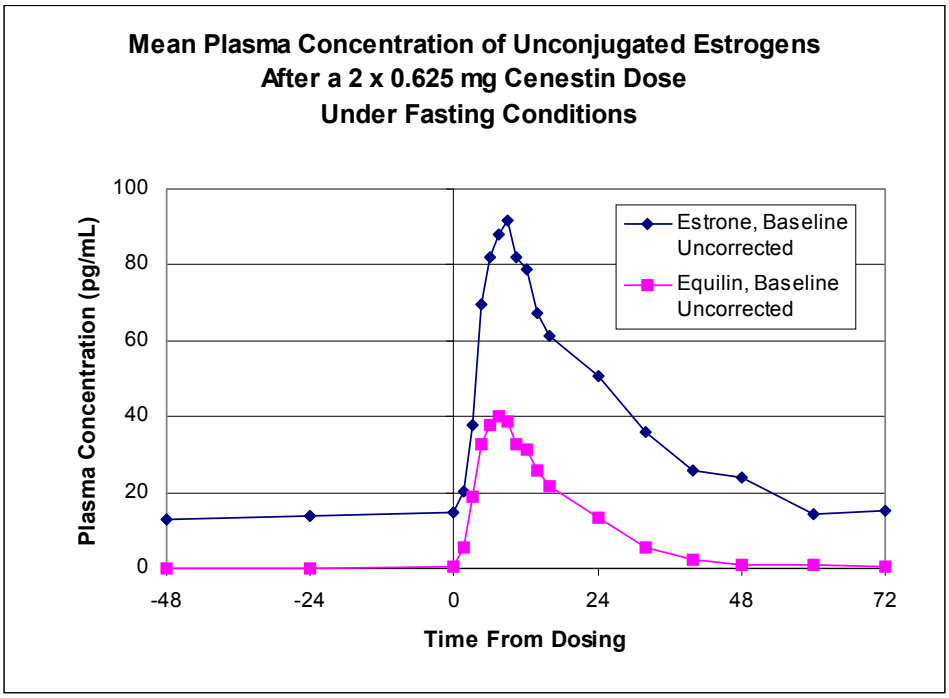
Pharmacokinetic Parameters of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin

Drug	C_{max} (pg/mL) CV%	t_{max} (h) CV%	$AUC_{0\text{-}72h}$ (pg·hr/mL) CV%
Baseline-corrected estrone	84.5 (41.7)	8.25 (35.6)	1749 (43.8)
Equilin	45.6 (47.3)	7.78 (28.8)	723 (67.9)

Pharmacokinetic Parameters of Conjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin

Drug	C_{max} (ng/mL) CV%	t_{max} (h) CV%	$t_{½}$ (h) CV%	$AUC_{0\text{-}72h}$ (ng·hr/mL) CV%
Baseline-corrected estrone	4.43 (40.4)	7.7 (30.3)	10.6 (25.4)	69.89 (39.2)
Equilin	3.27 (43.5)	5.8 (31.1)	9.7 (23.0)	46.46 (47.5)

Figure 1



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 concentrations 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 portion of the circulating estrogens exist 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

Cenestin was investigated in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers and 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

A randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of Cenestin for the treatment of moderate to severe vasomotor symptoms in 120 postmenopausal women between 38 and 66 years of age (68% were Caucasian). Patients were randomized to receive either placebo or 0.625 mg Cenestin daily for 12 weeks. Dose titration was allowed after one week of treatment. The starting dose was either doubled (2 x 0.625 mg Cenestin or placebo taken daily) or reduced (0.3 mg Cenestin or placebo taken daily), if necessary. Efficacy was assessed at 4 and 12 weeks of treatment. By week 12, 10% of the study participants remained on a single 0.625 mg Cenestin tablet daily while 77% required two (0.625 mg) tablets daily. The results in Table 2 indicate that compared to placebo, Cenestin produced a reduction in moderate to severe vasomotor symptoms at weeks 4 and 12.

A second randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of 0.45 mg Cenestin tablets, for the treatment of moderate to severe vasomotor symptoms in 104 menopausal women between 52 and 74 years of age (76% were Caucasian). Patients were randomized to receive either placebo or 0.45 mg Cenestin daily for 12 weeks. Efficacy was assessed at 4 and 12 weeks of treatment. The mean change in the number of moderate to severe hot flushes per week shown in Table 3 indicate that compared to placebo, 0.45 mg Cenestin produced a reduction in moderate to severe vasomotor symptoms at weeks 4 and 12. A corresponding reduction in the severity of hot flushes was demonstrated at weeks 5 and 12.

Table 2
Clinical Response[a]
Mean Change in the Number of Moderate to Severe Hot Flushes Per Week, 0.625 mg and 2 x 0.625 mg Cenestin, ITT Population

	Cenestin[b] 0.625 mg and 2 x 0.625 mg (n=70)	Placebo (n=47)	
Baseline			
Mean # (SD)	96.8 (42.6)	94.1 (33.9)	-
Week 4			
Mean # (SD)	28.7 (28.8)	45.7 (36.8)	-
Mean Change from Baseline (SD)	-68.1 (43.9)	-48.4 (46.2)	
P-value vs. Placebo	p=.022		
Week 12			
Mean # (SD)	16.5 (25.7)	37.8 (38.7)	-
Mean Change from Baseline (SD)	-80.3 (50.3)	-56.3 (48.0)	
P-value vs. Placebo	p=.010		

Mean = Arithmetic Mean, SD = Standard Deviation
[a] Intent-to-treat population = 117
[b]: Combined results for 0.625 mg and 0.625 mg Cenestin tablets.

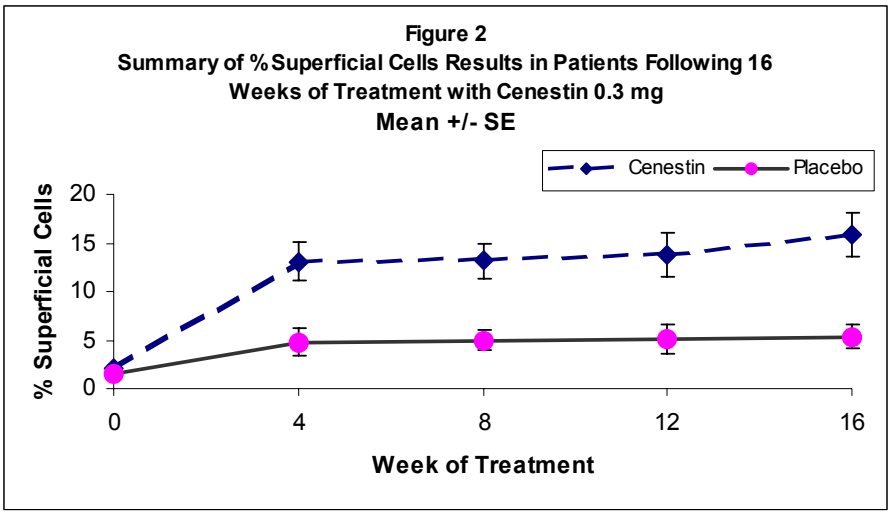
Table 3
Clinical Response*
Mean Change in the Number of Moderate to Severe Hot Flushes Per Week, 0.45 mg Cenestin, ITT Population

	Cenestin 0.45 mg (n=53)	Placebo (n=51)	
Baseline			
Mean # (SD)	95.9 (37.0)	95.9 (41.6)	-
Week 4			
Mean # (SD)	45.7 (45.9)	59.4 (46.2)	-
Mean Change from Baseline (SD)	-50.3 (35.4)	-36.5 (42.9)	
P-value vs. Placebo	p=.014		
Week 12			
Mean # (SD)	26.1 (43.0)	50.5 (48.4)	-
Mean Change from Baseline (SD)	-69.9 (38.1)	-45.4 (44.7)	
P-value vs. Placebo	p<.001		

Mean = Arithmetic Mean, SD = Standard Deviation
*Intent-to-treat population = 104

Effects on vulvar and vaginal atrophy

The effects of 0.3 mg Cenestin on moderate to severe symptoms of vulvar and vaginal atrophy were confirmed in a 16-week, randomized, placebo-controlled, multicenter clinical study in 72 postmenopausal women between 30 and 77 years of age (53% were Caucasian). Patients were randomized to receive either placebo or 0.3 mg Cenestin daily for 16 weeks. Efficacy was assessed at weeks 12 and 16 for vaginal wall cytology and week 16 for vaginal pH. Results for percent of superficial cells from a maturation index of the vaginal mucosa are shown in Figure 2. Mean vaginal pH decreased from a baseline of 6.20 to 5.14 for Cenestin and increased to 6.15 from a baseline of 6.03 for placebo.



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 oral 0.625 mg conjugated equine estrogens (CE) per day alone or the use of oral 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate (MPA) per day compared to placebo in 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 CE or CE/MPA on menopausal symptoms.

The CE-only substudy is continuing and results have not been reported. The CE/MPA 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 CE/MPA 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 4 below:

Table 4

Relative and Absolute Risk Seen in the Estrogen/Progestin Substudy of the WHI[a]

Event[c]	Relative Risk Conjugated Equine Estrogens/Medroxyprogesterone Acetate vs Placebo at 5.2 years (95% CI*)	Placebo n = 8102	CEE/MPA 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 women-years in the group treated with CE/MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10,000 women-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 women-years. There was no difference between the groups in terms of all-cause mortality. (See **BOXED WARNINGS, WARNINGS,** and **PRECAUTIONS**.)

INDICATIONS AND USAGE

Cenestin therapy is indicated for the:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
    - 0.45 mg Cenestin
    - 0.625 mg Cenestin
    - 0.9 mg Cenestin
    - 1.25 mg Cenestin
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.
    - 0.3 mg Cenestin

CONTRAINDICATIONS

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

WARNINGS

See **BOXED WARNINGS.**

1. Cardiovascular disorders.

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

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

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

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

In the same substudy of WHI, an increased risk of stroke was observed in women receiving CE/MPA compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

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

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

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

In the CE/MPA substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE/MPA compared to women receiving placebo. The rate of VTE was 34 per

10,000 women-years in the CE/MPA group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted.

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

2. Malignant neoplasms

a. *Endometrial cancer*. The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 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 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 CE/MPA substudy of the Women's Health Initiative (WHI) study, a 26% increase of invasive breast cancer (38 vs 30 per 10,000 women-years) after an average of 5.2 years of treatment was observed in women receiving CE/MPA compared to women receiving placebo. The increased risk of breast cancer became apparent after 4 years on CE/MPA. The women reporting prior postmenopausal use of estrogen and/or estrogen with progestin had a higher relative risk for breast cancer associated with CE/MPA than those who had never used these hormones. (See **CLINICAL PHARMACOLOGY**, **Clinical Studies**.)

In the WHI, no increased risk of breast cancer in CE-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 increase risk of breast cancer in association with increasing duration of postmenopausal treatment with estrogens with or without a progestin. This association was reanalyzed in original data from 51 studies that involved various doses and types of estrogens, with and without progestins. 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 5 years or longer. Some later studies have suggested that postmenopausal 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 health care provider and perform monthly self-examinations. In addition, mammography examinations should be scheduled based on patient age and risk factors.

3. Gallbladder disease

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

4. 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.

5. 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 renal vascular lesions, estrogens should be permanently 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 in estrogen replacement regimens. These include:

   a. A possible increased risk of breast cancer.
   b. Adverse effects on lipoprotein metabolism (e.g., lowering HDL, raising LDL).
   c. 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 a 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 estrogen/progestin combination therapy in postmenopausal women.

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.*** Estrogens 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.

B. Patient Information

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

C. Laboratory Tests

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

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 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

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

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

F. Pregnancy

Cenestin should not be used in 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 Cenestin is administered to a nursing woman.

H. Pediatric Use

Cenestin is not indicated in children.

I. Geriatric Use

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

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.

In a 12-week clinical trial that included 72 women treated with 0.625 mg and 2 x 0.625 mg Cenestin and 48 women treated with placebo, adverse events that occurred at a rate of ≥ 5% are summarized in Table 5.

Table 5

Number (%) of Patients with Adverse Events With ≥ 5% Occurrence Rate By Body System and Treatment Group

Body System **Adverse Event**	Cenestin* 0.625 mg and 2 x 0.625 mg **n (%)**	**Placebo** **n (%)**	**Total** **n (%)**
Number of Patients Who Received Medication	72 (100)	48 (100)	120 (100)
Number of Patients With Adverse Events	68 (94)	43 (90)	111 (93)
Number of Patients Without Any Adverse Events	4 (6)	5 (10)	9 (8)
Body As A Whole			
Abdominal Pain	20 (28)	11 (23)	31 (26)
Asthenia	24 (33)	20 (42)	44 (37)
Back Pain	10 (14)	6 (13)	16 (13)
Fever	1 (1)	3 (6)	4 (3)
Headache	49 (68)	32 (67)	81 (68)
Infection	10 (14)	5 (10)	15 (13)
Pain	8 (11)	9 (19)	17 (14)
Cardiovascular System			
Palpitation	15 (21)	13 (27)	28 (23)
Digestive System			
Constipation	4 (6)	2 (4)	6 (5)
Diarrhea	4 (6)	0 (0)	4 (3)
Dyspepsia	7 (10)	3 (6)	10 (8)
Flatulence	21 (29)	14 (29)	35 (29)
Nausea	13 (18)	9 (19)	22 (18)
Vomiting	5 (7)	1 (2)	6 (5)
Metabolic and Nutritional			
Peripheral Edema	7 (10)	6 (13)	13 (11)
Musculoskeletal System			
Arthralgia	18 (25)	13 (27)	31 (26)
Myalgia	20 (28)	15 (31)	35 (29)
Nervous System			
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)
Hypertonia	4 (6)	0 (0)	4 (3)
Insomnia	30 (42)	23 (48)	53 (44)
Leg Cramps	7 (10)	3 (6)	10 (8)
Nervousness	20 (28)	20 (42)	40 (33)
Paresthesia	24 (33)	15 (31)	39 (33)
Vertigo	12 (17)	12 (25)	24 (20)
Respiratory System			
Cough Increased	4 (6)	1 (2)	5 (4)
Pharyngitis	6 (8)	4 (8)	10 (8)
Rhinitis	6 (8)	7(15)	13 (11)
Skin and Appendages			

Body System Adverse Event	Cenestin* 0.625 mg and 2 x 0.625 mg n (%)	Placebo n (%)	Total n (%)
Rash	3 (4)	3 (6)	6 (5)
Urogenital System			
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)

* Combined results for 0.625 mg and 2 x 0.625 mg Cenestin Tablets

In a second 12-week clinical trial that included 52 women treated with 0.45 mg Cenestin and 51 women treated with placebo, adverse events that occurred at a rate of >5% are summarized in Table 6

Table 6
Number (%) of Patients with a ≥5% Occurrence Rate by Body System and Treatment Group

Body System and Term	Cenestin 0.45 mg	Control	p-value
Any Adverse Event (%)	40 (75.5%)	39 (76.5%)	1.0000
Body as a whole	20 (37.7%)	24 (47.1%)	0.4275
Asthenia	6 (11.3%)	7 (13.7%)	0.7731
Headache	6 (11.3%)	8 (15.7%)	0.5748
Infection	1 (1.9%)	6 (11.8%)	0.0576
Pain	6 (11.3%)	1 (2.0%)	0.1128
Pain abdominal	5 (9.4%)	3 (5.9%)	0.7159
Cardiovascular	5 (9.4%)	10 (19.6%)	0.1695
Palpitations	3 (5.7%)	3 (5.9%)	1.0000
Vasodilations	2 (3.8%)	4 (7.8%)	0.4324
Digestive	8 (15.1%)	7 (13.7%)	1.0000
Nausea	5 (9.4%)	2 (3.9%)	0.4374
Metabolic and nutritional	5 (9.4%)	3 (5.9%)	0.7159
Weight increase	3 (5.7%)	2 (3.9%)	1.0000
Musculoskeletal	5 (9.4%)	6 (11.8%)	0.7582
Arthralgia	5 (9.4%)	5 (9.8%)	1.0000
Myalgia	2 (3.8%)	6 (11.8%)	0.1566
Neurological	15 (28.3%)	19 (37.3%)	0.4044
Anxiety	3 (5.7%)	1 (2.0%)	0.6179
Depression	2 (3.8%)	7 (13.7%)	0.0895
Insomnia	3 (5.7%)	5 (9.8%)	0.4839
Nervousness	2 (3.8%)	7 (13.7%)	0.0895
Paresthesia	4 (7.5%)	3 (5.9%)	1.0000
Vertigo	3 (5.7%)	3 (5.9%)	1.0000
Respiratory	10 (18.9%)	6 (11.8%)	0.4173
Upper Respiratory Tract Infection	7 (13.2%)	1 (2.0%)	0.0603
Rhinitis	3 (5.7%)	2 (3.9%)	1.0000
Pharyngitis	1 (1.9%)	3 (5.9%)	0.3581
Urogenital	19 (35.8%)	7 (13.7%)	0.0124
Endometrial thickening	10 (18.9%)	4 (7.8%)	0.1503
Vaginitis	4 (7.5%)	1 (2.0%)	0.3632

P-value by Fisher's Exact (2-tail) Test
If a subject experiences the same event more than once, the first occurrence is tabulated.

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; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

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

3. Cardiovascular

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

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

5. Skin

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

6. Eyes

Retinal vascular thrombosis; intolerance to contact lenses.

7. Central nervous system

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

8. Miscellaneous

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

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen containing drug products 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 with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be reevaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have 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 associated with the menopause.
   - Cenestin 0.45 mg
   - Cenestin 0.625 mg
   - Cenestin 0.9 mg
   - Cenestin 1.25 mg

   Patients should be started at Cenestin 0.45 mg daily. Subsequent dosage adjustment may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider. The lowest effective dose of Cenestin for the treatment of moderate to severe vasomotor symptoms has not been determined.

2. For 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.
   - Cenestin 0.3 mg daily

HOW SUPPLIED

Cenestin (synthetic conjugated estrogens, A) Tablets are available as:

0.3 mg: Round, green, film-coated, and are debossed with letters, ф, and number, 41.

Available in bottles of:

30	NDC 51285-441-30
100	NDC 51285-441-02
1000	NDC 51285-441-05

0.45 mg: Round, orange, film-coated, and are debossed with letters, ф, and number, 46.

Available in bottles of:

30	NDC 51285-446-30
100	NDC 51285-446-02
1000	NDC 51285-446-05

0.625 mg: Round, red, film-coated, and are debossed with letters, ф, and number, 42.

AVAILABLE IN BOTTLES OF:

30	NDC 51285-442-30
100	NDC 51285-442-02
1000	NDC 51285-442-05

0.9 mg: Round, white, film-coated, and are debossed with letters, ф, and number, 43.

Available in bottles of:

30	NDC 51285-443-30
100	NDC 51285-443-02
1000	NDC 51285-443-05

1.25 mg: Round, blue, film-coated, and are debossed with letters, ф, and number, 44.

Available in bottles of:

30	NDC 51285-444-30
100	NDC 51285-444-02
1000	NDC 51285-444-05

Store at 20-25ºC (68-77ºF); excursions are permitted to15-30°C (59-86°F) [See USP Controlled Room Temperature].

Dispense in tight container.

Dispense in child-resistant packaging.

Pharmacist: Include one “Information for the patient” leaflet with each package dispensed.

PATIENT INFORMATION

Revised FEBRUARY 2004

Cenestin®
(synthetic conjugated estrogens, A) Tablets

Read this PATIENT INFORMATION before you start taking Cenestin and read what you get each time you refill Cenestin. 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 Cenestin (synthetic estrogen mixture)?

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

Report any unusual vaginal bleeding right away while you are taking estrogens. 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 attack, strokes, breast cancer, and blood clots. You and your healthcare provider should talk regularly about whether you still need treatment with Cenestin.

What is Cenestin?

Cenestin is a medicine that contains a mixture of synthetic estrogens made from a plant source.

What is Cenestin used for?

Cenestin 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 to 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 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 estrogens. In other women, symptoms can be more severe. You and your health care provider should talk regularly about whether you still need treatment with Cenestin.
- **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 Cenestin to control these problems. If you use Cenestin only to treat your dryness, itching, and burning in and around your vagina, talk with your healthcare provider about whether a topical vaginal product would be better for you.

Who Should Not Take Cenestin?

Do not start taking Cenestin if you:

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

TELL YOUR HEALTHCARE PROVIDER:

- **if you are breastfeeding.** The synthetic estrogen hormones in Cenestin 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, or 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 Cenestin works. Cenestin may also affect how your other medicines work.
- **if you are going to have surgery or will be on bed rest.** You may need to stop taking estrogens.

How Should I Take Cenestin?

Take one Cenestin tablet each day at about the same time. 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.

Start at the lowest dose and talk to your healthcare provider about how well that dose is working for you. 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 Cenestin.

What are the possible risks and side effects of estrogens?

Less common but serious side effects include:

- Breast cancer
- Cancer of the uterus
- Stroke
- Heart attack
- Blood clots
- 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 infection

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

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

- Talk with your healthcare provider regularly about whether you should continue taking Cenestin.
- 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 Cenestin.
- 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 safe and effective use of Cenestin.

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

Keep Cenestin out of the reach of children.

This leaflet provides a summary of the most important information about Cenestin. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Cenestin that is written for health professionals. You can get more information by calling the toll free number 877-405-0369.

What are the ingredients in Cenestin?

Tablets for oral administration, are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg and 1.25 mg strengths of synthetic conjugated estrogens, A. Tablets also contain the following inactive ingredients: ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate.

-0.3 mg tablets also contain: FD&C Blue No. 2 aluminum lake and D&C Yellow No. 10 aluminum lake.

-0.45 mg tablets also contain FD&C Yellow No. 6/sunset Yellow FCF lake.
-0.625 mg tablets also contain: FD&C Red No. 40 aluminum lake.

-0.9 mg tablets do not contain any additional color additives.
-1.25 mg tablets also contain FD&C Blue No. 2 aluminum lake.

Manufactured By:
Duramed Pharmaceuticals, Inc.
Subsidiary of Barr Pharmaceuticals, Inc.
Pomona, NY 10970

Revised FEBRUARY 2004
BR - 41, 46, 42, 43, 44