Cenestin®

(synthetic conjugated estrogens, A) Tablets

Rx only

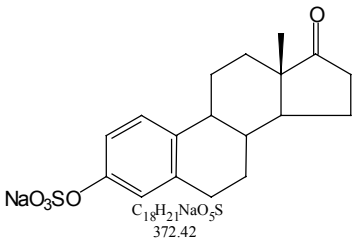
ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

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 currently no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

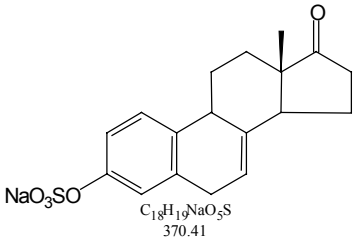
DESCRIPTION

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.

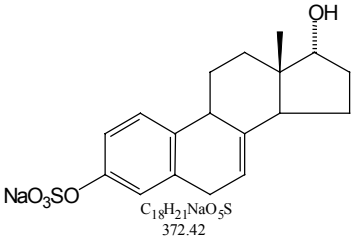
The structural formulae for these estrogens are:



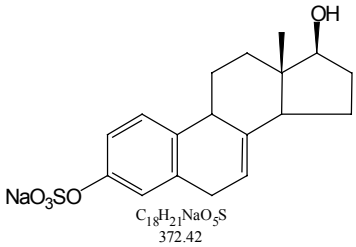
Sodium Estrone Sulfate



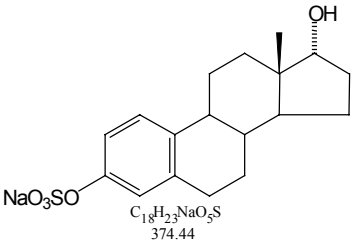
Sodium Equilin Sulfate



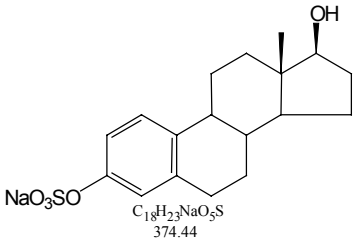
Sodium 17α-Dihydroequilin Sulfate



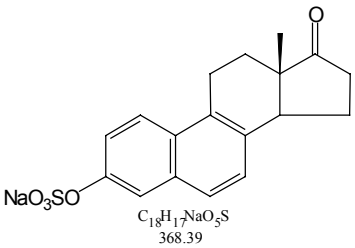
Sodium 17β-Dihydroequilin Sulfate



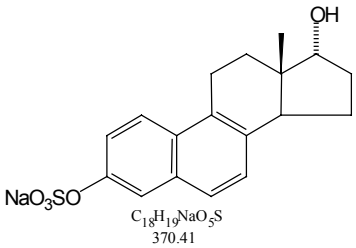
Sodium 17α-Estradiol Sulfate



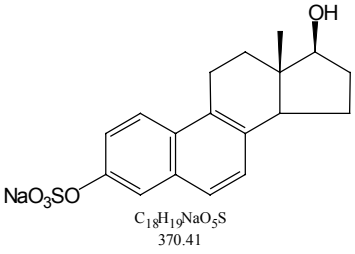
Sodium 17β-Estradiol Sulfate



Sodium Equilenin Sulfate



Sodium 17α-Dihydroequilenin Sulfate



Sodium 17β-Dihydroequilenin Sulfate

Tablets for oral administration, are available in 0.3 mg, 0.625 mg, 0.9 mg and 1.25 mg strengths of synthetic conjugated estrogens, A. Tablets also contain the following inactive ingredients: ethylcellulose, hydroxypropyl methylcellulose, 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.

-0.625 mg tablets also contain: FD&C Red No. 40 aluminum lake.

-0.9 mg tablets do not contain any 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 µg 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. Estrogen replacement therapy acts 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

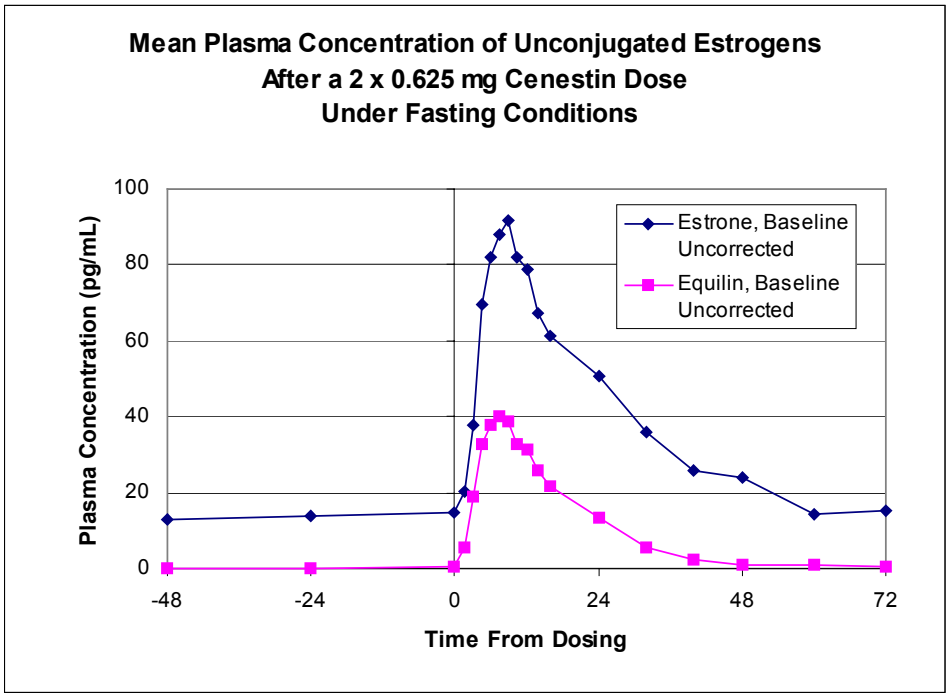
Pharmacokinetic Parameters of Unconjugated Estrogens Following a Dose of 2 x 0.625 mg Cenestin

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.

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.

Special Populations

Cenestin was investigated in postmenopausal women. No pharmacokinetic studies were conducted in other special populations.

Clinical Studies

Effects on vasomotor symptoms

A randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of Cenestin for the treatment of vasomotor symptoms in 120 menopausal women. 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, 8 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 all time points (4, 8, and 12 weeks).

Table 2
Clinical Response*
Mean Change in Reduction of Vasomotor Symptoms

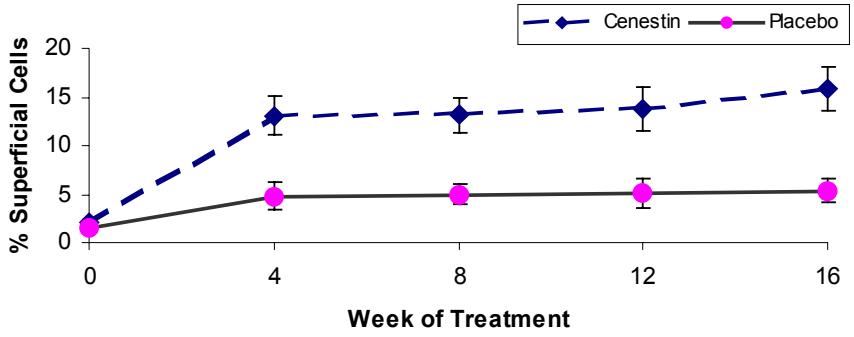
	Cenestin (n=70)	Placebo (n=47)	Difference
Baseline			
Mean # (SD)	96.8 (42.6)	94.1 (33.9)	-
Week 4			
Mean # (SD)	28.7 (28.8)	45.7 (36.8)	-
Mean Change	-68.1 (43.9)	-48.4 (46.2)	-19.9
Week 8			
Mean # (SD)	18.6 (25.0)	39.8 (39.1)	-
Mean Change	-78.3 (49.0)	-54.3 (49.2)	-24.6
Week 12			
Mean # (SD)	16.5 (25.7)	37.8 (38.7)	-
Mean Change	-80.3 (50.3)	-56.3 (48.0)	-24.7

Mean = Arithmetic Mean, SD = Standard Deviation
Difference = Difference between treatment LSMeans (Cenestin – Placebo).
*Intent-to-treat population = 117

Effects on vulvar and vaginal atrophy

The effect of Cenestin on vulvar and vaginal atrophy was confirmed in a 16-week, randomized, placebo-controlled, multicenter clinical study in 72 postmenopausal women. 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.

Figure 2
Summary of % Superficial Cells Results in Patients Following 16 Weeks of Treatment with Cenestin 0.3 mg
Mean +/- SE



Effects on Lipids

The effect of Cenestin 0.3 mg on lipid parameters was evaluated in a 16-week placebo-controlled trial of healthy postmenopausal women at low risk for cardiovascular disease reporting vulvar and vaginal atrophy. Results are shown in Table 3.

Table 3

Effects on Lipids Following Treatment with Cenestin 0.3 mg at 16 Weeks

	Cenestin 0.3 mg N=34	Placebo N=29	Treatment Differences
	Mean (SD)	**Mean (SD)**	**Mean**
Total Cholesterol (mg/dL)	-16.6 (20.9)	-0.3 (20.4)	-7.6%
HDL Cholesterol (mg/dL)	4.2 (6.0)	0.7 (7.3)	4.9%
LDL Cholesterol (mg/dL)	-15.4 (14.0)	1.6 (14.0)	-17.1%
Triglycerides (mg/dL)	6.6 (38.6)	-2.7 (38.2)	7.7%
Total/HDL Cholesterol	-0.5 (0.5)	-0.04 (0.62)	-11.9%
LDL/HDL Cholesterol	-0.5 (0.5)	-0.02 (0.5)	-21.0%

INDICATIONS AND USAGE

Cenestin therapy is indicated for the:

1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
   - 0.625 mg Cenestin
   - 0.9 mg Cenestin
   - 1.25 mg Cenestin
2. Treatment of vulvar and vaginal atrophy.
   - 0.3 mg Cenestin

CONTRAINDICATIONS

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

1. Known or suspected pregnancy. See **PRECAUTIONS**. Estrogens may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast.
4. Known or suspected estrogen-dependent neoplasia.
5. Active deep vein thrombosis/pulmonary embolism or a history of these conditions.
6. Known hypersensitivity to any of the components of Cenestin.

WARNINGS

1. Induction of Malignant Neoplasms.

a. ***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.

b. ***Breast Cancer.*** While some epidemiologic studies suggest a very modest increase in breast cancer risk for estrogen-alone users versus non-users, other studies have not shown any increased risk. The addition of progestin to estrogen may increase the risk for breast cancer over that noted in non-hormone users more significantly (by about 24% to 40%), although this is based solely on epidemiologic studies, and definitive conclusions await prospective, controlled clinical trials.

Women without a uterus who require hormone replacement should receive estrogen-alone therapy, and should not be exposed unnecessarily to progestins. Women with a uterus who are candidates for short-term combination estrogen/progestin therapy (for relief of vasomotor symptoms) are not felt to be at a substantially increased risk for breast cancer. Women with a uterus who are candidates for long-term use of estrogen/progestin therapy should be advised of potential benefits and risks (including the potential for an increased risk of breast cancer). All women should receive yearly breast exams by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled as suggested by providers based on patient age and risk factors.

2. Thromboembolic Disorders.

The physician should be aware of the possibility of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism, and pulmonary embolism) during estrogen replacement therapy and be alert to their earliest manifestations. Should any of these occur or be suspected, estrogen replacement therapy should be discontinued immediately. Patients who have risk factors for thrombotic disorders should be kept under careful observation.

a. ***Venous thromboembolism.*** Several epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions

for VTE, such as past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2 to 3 cases per 10,000 women per year.

b. ***Cerebrovascular disease.*** Embolic cerebrovascular events have been reported in postmenopausal women receiving estrogens.

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

3. **Gallbladder disease.** A 2 to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal 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.

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 which may be associated with the use of progestins in estrogen replacement regimens. These include adverse effects on lipoprotein metabolism (e.g., lowering HDL and raising LDL) and impairment of glucose tolerance.

The choice of progestin, its dose, and its regimen may be important in minimizing these adverse effects.

2. ***Cardiovascular Risk.***
The effects of estrogen replacement on the risk of cardiovascular disease have not been adequately studied. However, data from the Heart and Estrogen/Progestin Replacement Study (HERS), a controlled clinical trial of secondary prevention of 2,763 post-menopausal women with documented heart disease, demonstrated no benefit. During an average follow-up of 4.1 years, treatment with oral conjugated estrogen plus medroxyprogesterone acetate did not reduce the overall rate of coronary heart disease (CHD) events in postmenopausal women with established coronary disease. There were more CHD events in the hormone treated group than in the placebo group in year 1, but fewer events in years 3 through 5.

3. ***Elevated blood pressure.***
In a small number of case reports, substantial increases in blood pressure during estrogen replacement therapy 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.

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

5. ***Impaired liver function.***
Estrogens may be poorly metabolized in patients with impaired liver function.

6. ***Hypothyroidism.***
Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum

concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

7. ***Fluid retention.***
Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine and cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.

8. ***Exacerbation of endometriosis.***
Endometriosis may be exacerbated with administration of estrogen therapy.

9. ***Hypocalcemia.***
Estrogens should be used with caution in individuals with severe hypocalcemia.

B. Patient Information

See text of Patient Information Insert after the **HOW SUPPLIED** section.

C. Laboratory Tests.

Estrogen administration should be guided by clinical response at the lowest dose, for the treatment of vasomotor symptoms and vulvar and vaginal atrophy.

D. Drug/Laboratory Test Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen/progestin combinations (oral contraceptives):

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) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered.
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 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.
7. Reduced serum folate concentration.

E. Carcinogeneses, Mutagenesis, and 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 **CONTRAINDICATIONS.**

F. Pregnancy Category X.
Cenestin should not be used in pregnancy. See **CONTRAINDICATIONS.**

G. Nursing Mothers.
The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

H. Pediatric Use.
Cenestin is not indicated for use 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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial 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 appears to be related to drug use and for approximating rates.

See **WARNINGS** regarding induction of malignant neoplasms, thromboembolic disorders, gallbladder disease, and hypercalcemia. See **PRECAUTIONS** regarding cardiovascular risk and elevated blood pressure.

In a 12-week clinical trial that included 72 women treated with Cenestin and 48 women treated with placebo, adverse events that occurred at a rate of ≥ 2% are summarized in Table 4.

Table 4

Number (%) of Patients with Adverse Events With ≥ 2% Occurrence Rate By Body System and Treatment Group

Body System Adverse Event	Cenestin 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)
Allergic Reaction	0 (0)	1 (2)	1 (1)
Asthenia	24 (33)	20 (42)	44 (37)
Back Pain	10 (14)	6 (13)	16 (13)
Chest Pain	1 (1)	1 (2)	2 (2)
Chills	0 (0)	1 (2)	1 (1)
Fever	1 (1)	3 (6)	4 (3)
Flu Syndrome	3 (4)	1 (2)	4 (3)
Headache	49 (68)	32 (67)	81 (68)
Infection	10 (14)	5 (10)	15 (13)
Neck Pain	2 (3)	1 (2)	3 (3)
Neck Rigidity	1 (1)	1 (2)	2 (2)
Pain	8 (11)	9 (19)	17 (14)
Cardiovascular System			
Cardiovascular Disorder	0 (0)	1 (2)	1 (1)
Migraine	0 (0)	1 (2)	1 (1)
Palpitation	15 (21)	13 (27)	28 (23)
Vasodilation	1 (1)	2 (4)	3 (3)
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)
Gastrointestinal Disorder	0 (0)	1 (2)	1 (1)
Mouth Ulceration	0 (0)	1 (2)	1 (1)
Nausea	13 (18)	9 (19)	22 (18)
Periodontal Abscess	0 (0)	1 (2)	1 (1)
Vomiting	5 (7)	1 (2)	6 (5)
Hemic and Lymphatic System			
Ecchymosis	0 (0)	1 (2)	1 (1)
Metabolic and Nutritional			
Generalized Edema	3 (4)	2 (4)	5 (4)
Peripheral Edema	7 (10)	6 (13)	13 (11)
Weight Gain	0 (0)	1 (2)	1 (1)
Musculoskeletal System			

Body System Adverse Event	Cenestin n (%)	Placebo n (%)	Total n (%)
Arthralgia	18 (25)	13 (27)	31 (26)
Bone Pain	0 (0)	1 (2)	1 (1)
Joint Disorder	0 (0)	1 (2)	1 (1)
Myalgia	20 (28)	15 (31)	35 (29)
Nervous System			
Agitation	0 (0)	1 (2)	1 (1)
Confusion	0 (0)	1 (2)	1 (1)
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)
Emotional Lability	1 (1)	2 (4)	3 (3)
Hypertension	2 (3)	2 (4)	4 (3)
Hypertonia	4 (6)	0 (0)	4 (3)
Hypesthesia	2 (3)	1 (2)	3 (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)
Somnolence	2 (3)	0 (0)	2 (2)
Vasodilation	0 (0)	1 (2)	1 (1)
Vertigo	12 (17)	12 (25)	24 (20)
Respiratory System			
Bronchitis	2 (3)	1 (2)	3 (3)
Cough Increased	4 (6)	1 (2)	5 (4)
Dyspnea	2 (3)	0 (0)	2 (2)
Laryngitis	0 (0)	1 (2)	1 (1)
Lung Function Decreased	0 (0)	1 (2)	1 (1)
Pharyngitis	6 (8)	4 (8)	10 (8)
Rhinitis	6 (8)	7(15)	13 (11)
Sinusitis	2 (3)	0 (0)	2 (2)
Skin and Appendages			
Alopecia	2 (3)	1 (2)	3 (3)
Puritus	2 (3)	2 (4)	4 (3)
Rash	3 (4)	3 (6)	6 (5)
Subcutaneous Nodule	1 (1)	1 (2)	2 (2)
Special Senses			
Abnormal Vision	0 (0)	1 (2)	1 (1)
Conjunctivitis	0 (0)	1 (2)	1 (1)
Dry Eyes	0 (0)	1 (2)	1 (1)
Ear Pain	0 (0)	2 (4)	2 (2)
Lacrimation Disorder	0 (0)	1 (2)	1 (1)
Urogenital System			
Breast Neoplasm	1 (1)	1 (2)	2 (2)
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)
Urinary Frequency	0 (0)	1 (2)	1 (1)

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

1. For treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. An initial dose of 0.625 mg daily is recommended with titration up to 1.25 mg. Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

2. For treatment of vulvar and vaginal atrophy - 0.3 mg daily.

HOW SUPPLIED

Cenestin (synthetic conjugated estrogens, A) Tablets,

-0.3 mg tablets are available in containers of 30 (NDC 51285-441-30), 100 (NDC 51285-441-02), and 1000 (NDC 51285-441-05).
Tablets are round, green colored, film-coated, and are debossed with letters, ф, and number, 41.

-0.625 mg tablets are available in containers of 30 (NDC 51285-442-30), 100 (NDC 51285-442-02), and 1000 (NDC 51285-442-05).
Tablets are round, red colored, film-coated, and are debossed with letters, ф, and number, 42.
-0.9 mg tablets are available in containers of 30 (NDC 51285-443-30), 100 (NDC 51285-443-02), and 1000 (NDC 51285-443-05).
Tablets are round, white, film-coated, and are debossed with letters, ф, and number, 43.
-1.25 mg tablets are available in containers of 30 (NDC 51285-444-30), 100 (NDC 51285-444-02), and 1000 (NDC 51285-444-05).

Tablets are round, blue colored, film-coated, and are debossed with letters, ф, and number, 44.

Store at 25ºC (77ºF); excursions are permitted to 15°-30°C (59°-86°F) [See USP Controlled Room Temperature]

Dispense in tight container as defined in USP.

Dispense in child-resistant packaging.

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

PATIENT INFORMATION

Cenestin®
(synthetic conjugated estrogens, A) Tablets

INTRODUCTION

This leaflet describes the risks and benefits of treatment with Cenestin. Read this information before treatment. Read the information you get each time you get medicine because there may be new information. Talk with your healthcare provider if you have any questions about this medicine.

What Is The Most Important Information I Should Know About Cenestin?

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS

If you take any medicine containing estrogen, it is important to visit your healthcare provider regularly and report any unusual vaginal bleeding right away. 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.

What is Cenestin?

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

Cenestin Is Approved For The Following Uses:

- **To reduce moderate or severe menopausal symptoms.**

  Estrogens are hormones made by a woman's ovaries. Between ages 45 and 55, the ovaries normally stop making estrogens. 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 intense episodes of heat and sweating ("hot flashes" or "hot flushes"). In some women, estrogen therapy can help the body adjust to lower estrogen levels and reduce these symptoms. Most women do not need estrogen replacement for longer than six months.
- **To treat itching, burning, and dryness in and around the vagina due to menopause.**

Who Should Not Take Cenestin?

Do not take Cenestin if you:

- **think you may be pregnant**. Taking Cenestin while you are pregnant may harm your unborn child. Do not take Cenestin to prevent miscarriage.
- **have unusual vaginal bleeding**. If you develop vaginal bleeding while taking Cenestin, talk with your healthcare provider about proper treatment.
- **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 have had cancer, talk with your healthcare provider about taking Cenestin.
- **have circulation problems (blood clots or problems with blood flow).** Talk with your healthcare provider about your condition. Do not take Cenestin if you have blood clots or have had them in the past.
- **have recently had a baby.** Do not take Cenestin to stop your breast from filling with milk after a baby is born.
- **are allergic to Cenestin or any of the ingredients in it.** Your healthcare provider can give you a list of the ingredients in Cenestin.

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 you remember. However, if it is almost time for your next dose, skip the missed dose and take only your next regularly scheduled dose. Do not take two doses at the same time.

It is important to keep taking Cenestin for as long as your healthcare provider recommends it. Your length of treatment with Cenestin may be different than someone else's and will depend on why you are taking Cenestin.

What Are The Possible Risks And Side Effects of Cenestin?

Common side effects include:

- Breast pain
- Abdominal (stomach area) pain
- Nausea and vomiting
- Spotting or bleeding from the vagina

Less common but serious side effects include:

- Cancer of the uterus
- Breast cancer
- Blood clots
- Gallbladder disease

These are some of the warning signs of serious side effects:

- Unusual vaginal bleeding
- Breast lumps
- Pains in your legs
- Severe headaches and vomiting
- Dizziness and faintness
- Changes in vision or speech

If you have any of these warning signs, or other unusual symptoms that concerns you, call your healthcare provider right away.

What Can I Do to Lower My Chances of Getting a Serious Side Effect With Cenestin?

See your healthcare provider regularly. While you are taking Cenestin, it is important to visit your healthcare provider at least once a year for a check-up. If you develop vaginal bleeding while taking Cenestin, you may need further evaluation. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram (breast X-ray), you may need to have more frequent breast examinations.

General Information About Cenestin.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Your healthcare provider has prescribed this medicine for you and you alone. Do not give Cenestin to anyone else. Do not take Cenestin for conditions for which it was not prescribed.

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

Manufactured by: **Duramed Pharmaceuticals, Inc.**
Cincinnati, OH 45213 USA

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45213 U.S.A.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
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