CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20-992

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter			X	
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI			X	
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)			X	
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20-992

Trade Name: CENESTIN TABLETS 0.625 mg and 0.9 mg

Generic Name:(synthetic conjugated estrogens, A)

Sponsor: Duramed Pharmaceuticals, Inc.

Approval Date: March 24, 1999

Indication: Provides for the use of Cenestin (synthetic conjugated estrogens, A) Tablets for use in the treatment of moderate-to-severe vasomotor symptoms associated with the menopause

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-992

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-992

MAR 24 1999

Duramed Pharmaceuticals, Inc.
Attention: Mr. John R. Rapoza, M.S., R. Ph.
Vice President, Regulatory Affairs
5040 Lester Road
Cincinnati, OH 45213

Dear Mr. Rapoza:

Please refer to your new drug application (NDA) dated March 27, 1998, received March 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cenestin™ (synthetic conjugated estrogens, A) Tablets 0.625 mg and 0.9 mg.

We acknowledge receipt of your submissions dated April 6, May 7 and 27, June 19, September 22, October 30 (2), November 20, December 8, 9 and 15, 1998; January 20, February 2, 4 and 10 and March 1, 4, 15, 17, 19, 22 and 23, 1999. The User Fee goal date for this application is March 30, 1999.

This new drug application provides for the use of Cenestin™ (synthetic conjugated estrogens, A) Tablets for use in the treatment of moderate-to-severe vasomotor symptoms associated with the menopause.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that this drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved for the 0.625 mg and 0.9 mg tablets only, effective on the date of this letter. Please note that the dosing regimen allows for a range of doses including 0.625 mg through 2 X 0.625 mg.

In order to approve a 0.3 mg strength of Cenestin™ for this indication, a placebo-controlled study must be performed in a population of women with moderate-to-severe vasomotor symptoms associated with the menopause with adequate numbers of subjects randomized to the 0.3 mg strength to demonstrate the safety and effectiveness of this dose.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted March 23, 1999, immediate container and carton labels submitted March 15, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-992." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-992

FINAL PRINTED LABELING

APPROVED
3/24/99 DM

Cenestin™

(synthetic conjugated estrogens, A) Tablets

℞ only

PRESCRIBING INFORMATION

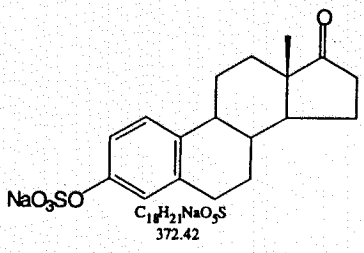
ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

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 natural estrogens are more or less hazardous than synthetic estrogens at equivalent estrogen doses.

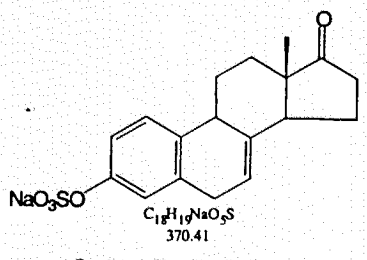
DESCRIPTION

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.

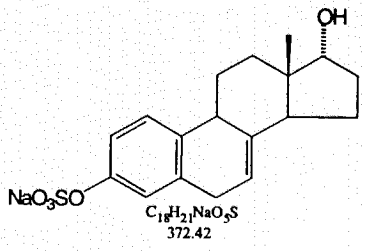
The structural formulae for these estrogens are:



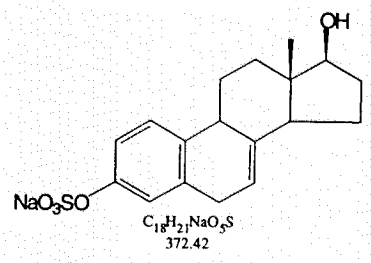
Sodium Estrone Sulfate



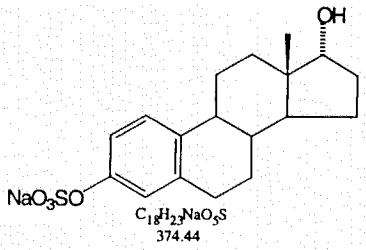
Sodium Equilin Sulfate



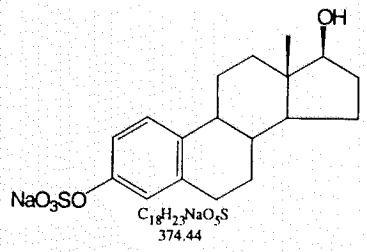
Sodium 17α-Dihydroequilin Sulfate



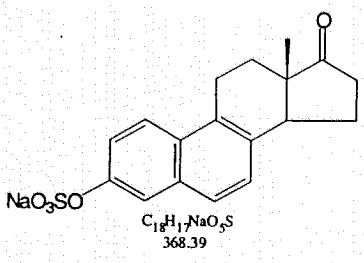
Sodium 17β-Dihydroequilin Sulfate



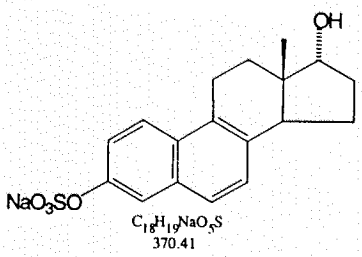
Sodium 17α-Estradiol Sulfate



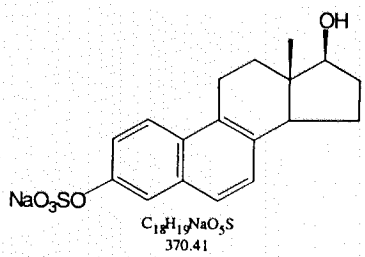
Sodium 17β-Estradiol Sulfate



Sodium Equilenin Sulfate



Sodium 17α-Dihydroequilenin Sulfate



Sodium 17β-Dihydroequilenin Sulfate

Tablets for oral administration, are available in 0.625 mg and 0.9 mg strengths of synthetic conjugated estrogens. 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.

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

-0.9 mg tablets do not contain any color additives.

CLINICAL PHARMACOLOGY

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.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, leutinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

Absorption

Synthetic conjugated estrogens 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. Maximum plasma concentrations of conjugated and unconjugated estrogens are attained within 4 to 16 hours after oral administration.

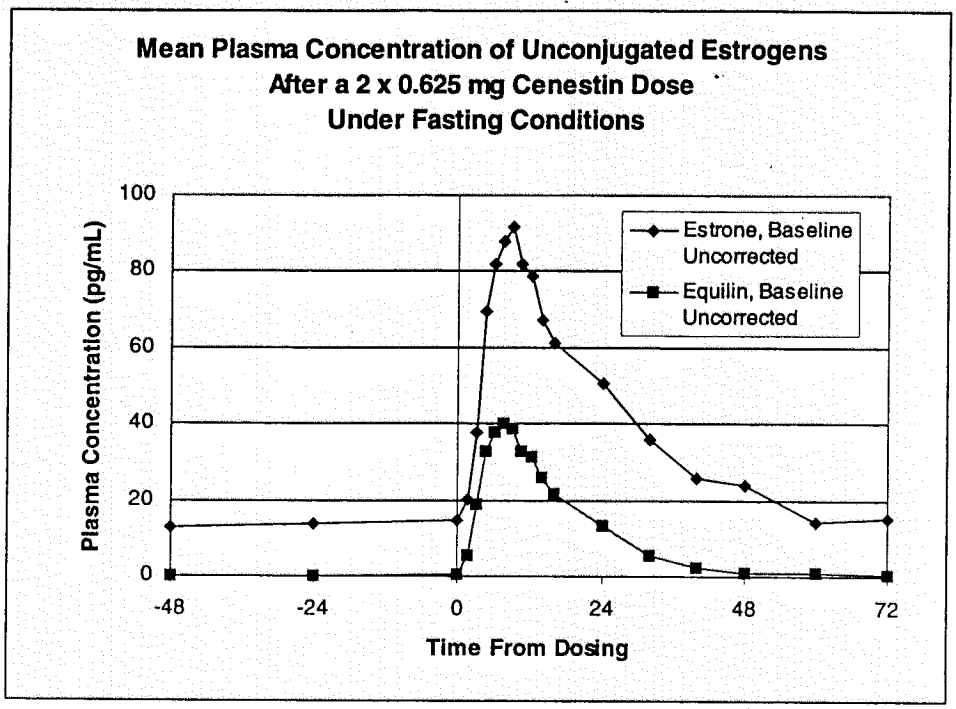
Table 1
PHARMACOKINETIC PARAMETERS FOR UNCONJUGATED AND CONJUGATED ESTROGENS IN HEALTHY POSTMENOPAUSAL WOMEN UNDER FASTING CONDITIONS

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)



Food-Drug Interactions

The effect of food on the 0.625 and 0.9 mg tablets has not been studied.

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. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to a lesser degree to albumin. Conjugated estrogens bind mainly to albumin while the unconjugated estrogens bind to both albumin and sex-hormone binding globulin (SHBG).

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. The apparent terminal elimination half-life ($t_{1/2}$) of conjugated estrone ranges from 4 to 18.5 hours and conjugated equilin from 4 to 17 hours.

Drug-Drug Interactions

There are no known drug interactions with estrogens.

Clinical Studies

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

INDICATIONS AND USAGE

Cenestin (synthetic conjugated estrogens, A) Tablets are indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause.

CONTRAINDICATIONS

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

1. Known or suspected pregnancy (see PRECAUTIONS).
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast (except in appropriately selected patients being treated for metastatic disease).
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

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 8-15 years after estrogen therapy is discontinued.
   b. **Breast Cancer.** While the majority of studies have not shown an increased risk of breast cancer in women who have ever used estrogen replacement therapy, there are conflicting data whether there is an increased risk in women using estrogens for prolonged periods of time, especially in excess of 10 years.
2. **Venous thromboembolism.** Three 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 findings were similar for ERT alone or with added progestin and pertain to commonly used ERT types and doses, including 0.625 mg or more per day orally of conjugated estrogens, 1 mg or more per day orally of estradiol, and 50 μg or more per day of transdermal estradiol. 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 2-3 cases per 10,000 women per year.
3. **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.
4. **Hypercalcemia.** Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.
5. **Gallbladder disease.** A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

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.

There are, however, possible risks which may be associated with the use of progestins in estrogen replacement regimens. These include:

(a) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL)

(b) impairment of glucose tolerance; and

(c) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point.

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

2. **Elevated blood pressure**
Substantial increases in blood pressure during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens in a small number of case reports. A generalized effect of estrogen therapy on blood pressure was not found in the one randomized, placebo-controlled study that has been reported.

3. **Familial hyperlipoproteinemia.**
Estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.

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

B. INFORMATION FOR THE PATIENT.

See text of PATIENT LABELING, below.

C. LABORATORY TESTS.

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

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) 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 triglycerides 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 and WARNINGS.

F. **PREGNANCY.**
Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethylstilbestrol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

G. **NURSING MOTHERS.**
As a general principle, 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.**
Safety and efficacy of Cenestin for the treatment of vasomotor symptoms due to hypoestrogenism in pediatric patients have not been established.

ADVERSE REACTIONS

See WARNINGS and PRECAUTIONS regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure and hypercalcemia. In a 12-week clinical trial that included 72 women treated with Cenestin and 48 women treated with placebo, the following adverse events occurred at a rate ≥ 5% (see Table 3).

Table 3

Number (%) of Patients with Adverse Events With a Greater than 5% 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)
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)
Urogenital System			
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)

The following additional adverse reactions have been reported with estrogen therapy:

1. *Genitourinary system.* Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.
2. *Breasts.* Tenderness, enlargement.
3. *Gastrointestinal.* Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.
4. *Skin.* Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. *Eyes.* Steepening of corneal curvature: intolerance to contact lenses.
6. *Central Nervous System.* Headache, migraine, dizziness; mental depression; chorea.
7. *Miscellaneous.* Increase or decrease in weight; reduced carbohydrate tolerance; aggravation or porphyria; edema; changes in libido.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

HOW SUPPLIED

Cenestin (synthetic conjugated estrogens, A) Tablets,

-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.

Store at 25°C (77°F); 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.

INFORMATION FOR THE PATIENT
Cenestin™
(synthetic conjugated estrogens, A) Tablets
PATIENT PACKAGE INSERT

INTRODUCTION

This leaflet describes when and how to use estrogens, and the risks and benefits of estrogen treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks are acceptable in comparison to the benefits. If you use estrogens, check with your doctor to be sure you are using the lowest possible dose that works, and that you don't use them longer than necessary. How long you need to use estrogens will depend on the reasons for use.

ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS

If you use any drug that contains estrogen, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Vaginal bleeding after menopause may be a warning sign of uterine cancer. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

USES OF CENESTIN

To reduce moderate or severe menopausal symptoms.

Estrogens are hormones made by the ovaries of normal women. Between ages 45 and 55, the ovaries normally stop making estrogens. This leads to a drop in body estrogen levels which causes the "change of life" or menopause (the end of monthly menstrual periods). If 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 intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms. Most women have only mild menopausal symptoms or none at all and do not need to use estrogen drugs for these symptoms. Others may need to take estrogens for a few months while their bodies adjust to lower estrogen levels. The majority of women do not need estrogen replacement for longer than six months for these symptoms.

WHO SHOULD NOT USE CENESTIN

Cenestin should not be used:

- **During pregnancy.**
  If you think you may be pregnant, do not use any form of estrogen-containing drug. Using some types of estrogens while you are pregnant may cause your unborn child to have birth defects. Estrogens do not prevent miscarriage.
- **If you have unusual vaginal bleeding which has not been evaluated by your doctor (see Boxed Warning).**
  Unusual vaginal bleeding can be a warning sign of cancer of the uterus, especially if it happens after menopause. Your doctor must find out the cause of the bleeding so that he or she can recommend the proper treatment.
- **If you have had cancer.**
  Since estrogens may increase the risk of certain types of breast and uterine cancer, you should not use estrogens unless your doctor recommends that you take it. (For certain patients with breast or prostate cancer, estrogens may help.)
- **If you have any circulation problems.**
  Men and women with abnormal blood clotting conditions should avoid estrogen use (see DANGERS OF ESTROGENS, below).
- **After childbirth or when breastfeeding a baby.**
  Estrogens should not be used to try to stop the breasts from filling with milk after a baby is born. Such treatment may increase the risk of developing blood clots (see DANGERS OF ESTROGENS, below).

DANGERS OF ESTROGENS

- **Cancer of the uterus.**

  Your risk of developing cancer of the uterus gets higher the longer you use estrogens and the larger doses you use. Because of this risk, it is important to take the lowest dose that works and to take it only as long as you need it.

  Using progestin therapy together with estrogen therapy may reduce the higher risk of uterine cancer related to estrogen use (see also OTHER INFORMATION, below).

  If you have had your uterus removed (total hysterectomy), there is no danger of developing cancer of the uterus.

- **Cancer of the breast.**

  Most studies have not shown a higher risk of breast cancer in women who have ever used estrogens. However, some studies have reported that breast cancer developed more often (up to twice the usual rate) in women who used estrogens for long periods of time (especially more than 10 years), or who used higher doses for shorter time periods.

  Regular breast examinations by a health professional and monthly self-examination are recommended for all women. Yearly mammography is recommended for women beginning at age 50.

- **Abnormal blood clotting.**

  Taking estrogens may cause changes in your blood clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in your bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include stroke (by cutting off blood to the brain), heart attack (by cutting off blood to the heart), a pulmonary clot (by cutting off blood to the lungs), or other problems. Any of these conditions may cause death or serious long term disability.

- **Gallbladder disease.**

  Women who use estrogens after menopause are more likely to develop gallbladder disease needing surgery than women who do not use estrogens.

SIDE EFFECTS

In addition to the risks listed above, the following side effects have been reported with estrogen use:

Nausea and vomiting.

Breast tenderness or enlargement.

Enlargement of benign tumors of the uterus (fibroids).

Retention of excess fluid.

Spotty darkening of the skin, particularly on the face.

USE IN CHILDREN

Cenestin has not been shown either effective or safe for use by infants, children, or adolescent boys or girls.

REDUCING THE RISKS OF ESTROGEN USE

If you use estrogens, you can reduce your risks by doing these things:

- **See your doctor regularly.**
  While you are using estrogens, it is important to visit your doctor at least once a year for a check-up. If you develop vaginal bleeding while taking estrogens, you may need further evaluation.
- **Reassess your need for estrogens.**
  You and your doctor should reevaluate whether or not you still need estrogens every three to six months.
- **Be alert for signs of trouble.**
  If any of these warning signals (or any other unusual symptoms) happen while you are using estrogens, call your doctor immediately:

Abnormal bleeding from the vagina (possible uterine cancer)

Pains in the calves or chest, sudden shortness of breath, or coughing blood (possible clot in the legs, heart, or lungs)

Severe headache or vomiting, dizziness, faintness, changes in vision or speech, weakness or numbness of an arm or leg (possible clot in the brain or eye)

Breast lumps (possible breast cancer; ask your doctor or health professional to show you how to examine your breasts monthly)

Yellowing of the skin or eyes (possible liver problems)

Pain, swelling, or tenderness in the abdomen (possible gallbladder problem)

OTHER INFORMATION

Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Taking progestins, another hormone drug, with estrogens lowers the risk of developing this condition. Therefore, if your uterus has not been removed, your doctor may prescribe a progestin for you to take together with the estrogen.

Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.

Keep this and all drugs out of the reach of children. In case of overdose, call your doctor, hospital or poison control center immediately.

HOW SUPPLIED

Cenestin (synthetic conjugated estrogens, A) Tablets,

-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, ϕ, 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,ϕ, and number, 43.

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

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

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