CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

83-723/S030

Trade Name: PREMARIN Vaginal Cream, 0.625 mg/g

Generic Name: (conjugated estrogens)

Sponsor: Wyeth-Ayerst Laboratories.

Approval Date: May 10, 1990

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-723/S030

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL LETTER

83-723/S030

ANDA 83-273/S-030

MAY 10 1990

Wyeth-Ayerst Laboratories
For Ayerst Laboratories Inc.
Attention: Paul V. Uses
P.O. Box 8299
Philadelphia, PA 19101-1245

Dear Sir:

Reference is made to your supplemental new drug application submitted pursuant to Section 314.70 of the Regulations, dated January 17, 1990, regarding your abbreviated new drug application for PREMARIN (Conjugated Estrogens) Vaginal Cream, 0.625 mg/g.

The supplemental application provides for revised professional and patient package insert labeling reflecting editorial changes.

We have completed the review of this supplemental application and it is approved. Our letter of October 16, 1978, detailed the conditions relating to the approval of this abbreviated application.

The material submitted is being retained as part of your application.

Sincerely yours,

Kent T. Johnson /fc 5-10-90

Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research

cc:
HFD-82 Y Mille 5/9/90
HFD-630
YMille/TPoux/mkg/5/8/90/8866A
F/T: 5/9/90
Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-723/S030

LABELING

5. Unscrew applicator from tube.
6. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.
TO CLEANSE: Pull plunger out from barrel. Wash with mild soap and warm water.
DO NOT BOIL OR USE HOT WATER.

exposure occurs, see your doctor.

Other Effects of Estrogens

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.

2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.

3. *Effects on the uterus.* Estrogens may cause benign fibroid tumors of the uterus to get larger.

4. *Effects on liver.* Women taking oral contraceptives develop, on rare occasions, a tumor of the liver which can rupture and bleed into the abdomen and may cause death. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain or tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as asthma, epilepsy, migraine, heart disease, or kidney disease.

Summary

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while you were taking estrogens.

You can use estrogens as safely as possible by understanding that your doctor will require regular physical examinations while you are taking them, will try to discontinue the drug as soon as possible, and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest, sudden shortness of breath, or coughing blood.
3. Severe headache, dizziness, faintness, or changes in vision.
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).
6. Mental depression.

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

How Supplied

Premarin (conjugated estrogens) Vaginal Cream—Each gram contains 0.625 mg conjugated estrogens, USP. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz (42.5 g) tube with one plastic applicator calibrated in 1 g increments to a maximum of 4 g (NDC 0046-0872-93).
Also Available—Refill package: Each contains Net Wt. 1½ oz (42.5 g) tube (NDC 0046-0872-01).

Store at room temperature (approximately 25° C).

Instructions For Use of Premarin®
(conjugated estrogens)
Vaginal Cream Applicator:

1. Remove cap from tube.
2. Puncture dispensing end of tube with plastic spike on cap.
3. Screw nozzle end of applicator onto tube.
4. *Gently* squeeze tube to force sufficient cream into the barrel to provide the prescribed dose.
5. Unscrew applicator from tube.
6. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE: Pull plunger out from barrel. Wash with mild soap and warm water.
DO NOT BOIL OR USE HOT WATER.

AYERST LABORATORIES INC.
New York, NY 10017
Revised October 26, 1989 CI 3819-4 Printed in USA

AYERST LABORATORIES INC.
New York, NY 10017
Revised October 26, 1989 CI 3819-4 Printed in USA

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Ayerst® A.H.F.S. Category 68:16

Premarin® (conjugated estrogens)
Vaginal Cream *in a nonliquefying base*

CI 3819-4

MAY 10 1990

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INFORMATION FOR THE PATIENT

APPROVED

What You Should Know About

CI 3819-4

Ayerst®

A.H.F.S. Category 68:16

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Premarin® (conjugated estrogens) Vaginal Cream *in a nonliquefying base*

CI 3819-4

MAY 10 1990

CAUTION: Federal law prohibits dispensing without prescription.

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent, case-controlled studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[3] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semi-annual basis, to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration.[3] It therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equi-estrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a nonsteroidal estrogen, have an increased risk of developing, in later life, a form of vaginal or cervical cancer that is ordinarily extremely rare.[5,6] This risk has been estimated as not greater than 4 per 1,000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30% to 90%) have been found to have vaginal adenosis,[8-12] epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb-reduction defects.[13-16] One case-controlled study [16] estimated a 4.7-fold increased risk of limb-reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb-reduction defects in exposed fetuses is somewhat less than 1 per 1,000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

If Premarin (conjugated estrogens) Vaginal Cream is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

Description

Each gram of Premarin® (conjugated estrogens) Vaginal Cream contains 0.625 mg conjugated estrogens, USP, in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. Premarin Vaginal Cream is applied intravaginally.

Premarin (conjugated estrogens) is a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 α-dihydroequilin, together with smaller amounts of 17 α-estradiol, equilenin, and 17 α-dihydroequilenin as salts of their sulfate esters.

Clinical Pharmacology

Estrogens are important in the development and maintenance of the female reproductive system and secondary sex characteristics. They promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they contribute to: the shaping of the skeleton; maintenance of tone and elasticity of urogenital structures; changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination; growth of axillary and pubic hair; and pigmentation of the nipples and genitals. Decline of estrogenic activity at the end of the menstrual cycle can bring on menstruation, although the cessation of progesterone secretion is the most important factor in the mature ovulatory cycle. However, in the preovulatory or nonovulatory cycle, estrogen is the primary determinant in the onset of men-

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INFORMATION FOR THE PATIENT

APPROVED

CI 3819-4

What You Should Know About Estrogens

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and, therefore, much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you should ask your doctor for more information, or you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

Uses of Estrogen

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN.

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries stop producing a majority of her estrogens, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (With the menopause, which generally occurs between the ages of 45 and 55, women produce a much smaller amount of estrogens.)
2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
3. To prevent pregnancy. (Estrogens are given along with a progestogen, another female hormone; these combinations are called oral contraceptives, or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet.)
4. To treat certain cancers in women and men.
5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

Estrogens in the Menopause

In the natural course of their lives, all women eventually experience a decrease

of mental depression [4a] Although it is not clear whether this is due to the estrogen a hist- 6

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PREMARIN® (conjugated estrogens) VAGINAL CREAM *in a nonliquefying base*

CI 3819-3

CAUTION: Federal law prohibits dispensing without prescription.

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The pharmacologic effects of conjugated estrogens are similar to those of endogenous estrogens. They are soluble in water and may be absorbed from mucosal surfaces after local administration.

In responsive tissues (female genital organs, breasts, hypothalamus, pituitary) estrogens enter the cell and are transported into the nucleus. As a result of estrogen action, specific RNA and protein synthesis occurs.

Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted into the bile; however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and, therefore, ionized in body fluids, which favor excretion through the kidneys since tubular reabsorption is

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PREVIOUS VERSION

INFORMATION FOR THE PATIENT

MAY 10 1990 APPROVED

INSTRUCTIONS FOR USE OF PREMARIN® (conjugated estrogens) VAGINAL CREAM APPLICATOR:

1. Remove cap from tube.
2. Puncture dispensing end of tube with plastic spike on cap.
3. Screw nozzle end of applicator onto tube.
4. *Gently* squeeze tube to force sufficient cream into the barrel to provide the prescribed dose.
5. Unscrew applicator from tube.
6. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.

TO CLEANSE: Pull plunger out from barrel. Wash with mild soap and warm water. DO NOT BOIL OR USE HOT WATER.

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have similar properties and, therefore, much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

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USES OF ESTROGEN

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Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries stop producing a majority of her estrogens, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (With the menopause, which generally occurs between the ages of 45 and 55, women produce a much smaller amount of estrogens.)
2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.
3. To prevent pregnancy. (Estrogens are given along with a progestogen, another female hormone; these combinations are

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

83-273/S030

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FPL Package Inserts Labeling Satisfactory 5/1/90

WYETH-AYERST LABORATORIES

P.O. BOX 8299, PHILADELPHIA, PA 19101-1245 • (215) 341-2239

Division of American Home Products Corporation

REGULATORY AFFAIRS

S-030

January 17, 1990

ANDA No. 83-273

NDA SUPPL AMENDMENT

S-027

FPL

Mr. Richard A. Terselic, Acting Director
Division of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Special Supplement - Changes Being Effected

Dear Mr. Terselic:

Reference is made to our approved Abbreviated New Drug Application No. 83-273 for "Premarin® (conjugated estrogens, USP) Vaginal Cream" and to FDA's letter of February 12, 1988 requesting relocation of two sections of text in the package insert.

Further reference is made to our correspondence dated October 16, 1989 and to a subsequent telephone conversation between representatives of Wyeth-Ayerst Laboratories and the Division of Generic Drugs in which Wyeth-Ayerst Laboratories agreed to implement the above referenced changes to the package insert at the time of the next printing, whether or not new guidelines for labeling estrogen-containing drug products were available.

Accordingly, we are filing this supplemental application in order to provide for the relocation of text in the Premarin Vaginal Cream package insert exactly as requested by FDA in the February 12, 1988 letter as follows:

1. The final paragraph in the "Dosage and Administration" section beginning "Tested patients with ... " has been relocated to appear before "INSTRUCTIONS FOR USE OF APPLICATOR."

2. "Instructions For Use of Premarin Vaginal Cream Applicator" were relocated to appear beneath the text required by the Federal Register notice.

Additionally, please note that while there is no perforation in the final printed specimens provided herewith, this labeling, when used in production, is perforated for easy separation of the patient and physician inserts.

In support of this supplemental application, we are pleased to provide herewith twelve copies of revised final printed labeling. A copy of the package insert currently in use with this product is provided for your convenience.

The newly revised package insert is scheduled for use in production on February 1, 1990.

We trust you will find this labeling satisfactory and will so advise us at your earliest convenience.

Sincerely

WYETH-AYERST LABORATORIES

Paul V. Uses
Associate Director
Drug Regulatory Affairs

JEB/PVU/sdj
M7567

Attachment

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date; August 31,1989.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 C.F.R. Part 314).*

NAME OF APPLICANT	DATE OF SUBMISSION
Ayerst Laboratories	1/17/90
ADDRESS *(Number, Street, City, State and Zip Code)*	TELEPHONE NO. *(Include Area Code)*
P.O. Box 8299 Philadelphia, PA 19101-1245	215 341-2207
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
conjugated estrogens, USP	Premarin®

CODE NAME *(If any)*	CHEMICAL NAME

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
cream	topical	0.625 mg of conjugated estrogens per gram

PROPOSED INDICATIONS FOR USE

For the treatment of atrophic vaginitis and kraurosis vulvae

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, AND DRUG MASTER FILES *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

☐ THIS SUBMISSION IS A FULL APPLICATION *(21 CFR 314.50)* ☒ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

STATUS OF APPLICATION *(Check one)*

☐ PRESUBMISSION ☐ ORIGINAL APPLICATION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☒ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS *(Check one)*

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT *(Rx)* ☐ APPLICATION FOR AN OVER - THE - COUNTER PRODUCT *(OTC)*

FORM FDA 356h (3/87)