CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-472/S-003

Trade Name: Estring 2 mg

Generic Name: estradiol vaginal ring

Sponsor: Pharmacia and Upjohn Company

Approval Date: 01/05/2000

Indications: For the treatment of urogenital symptoms associated with post-menopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-472/S-003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 20-472

Food and Drug Administration
Rockville MD 20857

JAN -5 2000

Pharmacia & Upjohn
Attention: Daniel G. Chirby, M.Sc.
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Chirby:

Please refer to your supplemental new drug application dated August 17, 1999, received August 18, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estring, (estradiol vaginal ring) 2mg.

This "Changes Being Effected" supplemental new drug application provides for a revised package insert regarding the addition of a "Geriatric Use" subsection to the labeling of human prescription products.

The supplement provides for the revisions in the **PRECAUTIONS** section of the labeling as follows:

G. Geriatric Use

Of the total number of subjects in clinical studies of ESTRING (including subjects treated with ESTRING, placebo, and comparator drug; n-951), 25% were 65 and over, while 4% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 17, 1999).

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 supplement NDA 20-472/S-003." Approval of this submission by FDA is not required before the labeling is used.

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 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, call Dornette Spell-LeSane, Project Manager, at (301) 827-4260.

Sincerely,

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

cc:
Archival NDA 20-472
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Mann/Slaughter/van der Vlugt/Rhee/Lin/Raheja/Jordan/Parekh
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: dsl/December 28, 1999
Initialed by:
final:
filename: APSLR003.DOC

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-472/S-003

LABELING

JAN -5 2000

APPROVED

Estring®
Vaginal Ring

Pharmacia
&Upjohn

estradiol vaginal ring

2 mg

PHYSICIAN'S LEAFLET

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

   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 equi-estrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

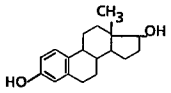
   There is no indication for estrogen therapy during pregnancy or during immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

   Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that the use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

DESCRIPTION

ESTRING (estradiol vaginal ring) is a slightly opaque ring with a whitish core containing a drug reservoir of 2 mg estradiol. Estradiol, silicone polymers and barium sulfate are combined to form the ring. When placed in the vagina, ESTRING releases estradiol, approximately 7.5 µg/24 hours, in a consistent stable manner over 90 days. ESTRING has the following dimensions: outer diameter 55 mm; cross-sectional diameter 9 mm; core diameter 2 mm. One ESTRING should be inserted into the upper third of the vaginal vault, to be worn continuously for three months.

Estradiol is chemically described as estra-1,3,5(10)-triene-3,17ß-diol. The molecular formula of estradiol is $C_{18}H_{24}O_2$ and the structural formula is:



The molecular weight of estradiol is 272.39.

CLINICAL PHARMACOLOGY

Pharmacokinetics

ABSORPTION

Estrogens used in therapeutics are well absorbed through the skin, mucous membranes, and the gastrointestinal (GI) tract. The vaginal delivery of estrogens circumvents first-pass metabolism possibly reducing the induction of several other hepatic proteins.

In a Phase I study of 14 postmenopausal women, the insertion of ESTRING (estradiol vaginal ring) rapidly increased serum estradiol (E_2) levels attesting to the rapid absorption of estradiol via the vaginal mucosa. The time to attain peak serum estradiol levels (T_{max}) was 0.5 to 1 hour. Peak serum estradiol concentrations post-initial burst declined rapidly over the next 24 hours and were virtually indistinguishable from the baseline mean (range: 5 to 22 pg/mL). Serum levels of estradiol and estrone (E_1) over the following 12 weeks during which the ring was maintained in the vaginal vault remained relatively unchanged (see Table 1).

The initial estradiol peak post-application of the second ring in the same women resulted in ~ 38% lower C_{max}, apparently due to reduced systemic absorption via the revitalized vaginal epithelium. The relative systemic exposure from the initial peak of ESTRING accounted for approximately 4% of the total estradiol exposure over the 12 week period.

The constant and stable release of estradiol from ESTRING was demonstrated in a Phase II study of 166 - 222 post-menopausal women who inserted up to four rings consecutively at three month intervals. Low dose systemic delivery of estradiol from ESTRING resulted in mean steady state serum estradiol estimates of 7.8, 7.0, 7.0, 8.1 pg/mL at weeks 12, 24, 36, and 48, respectively. Similar reproducibility is also seen in levels of estrone. Lower systemic exposure to estradiol and estrone is further supported by serum levels measured during a pivotal Phase III study.

In post-menopausal women, mean dose of estradiol systemically absorbed unchanged from ESTRING is ~ 8% [95% CI: 2.8-12.8%] of the daily amount released locally. Low systemic exposure to estradiol and estrone resulting from ESTRING should elicit lower estrogen-dependent effects.

DISTRIBUTION

Circulating, unbound estrogens are known to modulate pharmacological response. Estrogens circulate in blood bound to sex-hormone binding globulin (SHBG) and albumin. A dynamic equilibrium exists between the conjugated and the unconjugated forms of estradiol and estrone, which undergo rapid interconversion.

METABOLISM

Exogenously delivered or endogenously derived estrogens are primarily metabolized in the liver to estrone and estriol, which are also found in the systemic circulation. Estrogen metabolites are primarily excreted in the urine as glucuronides and sulphates. Of the several estrogen metabolites, urinary estrone and estrone sulphate (E_1S), post-ESTRING use, are in the normal post-menopausal range.

EXCRETION

Mean percent dose excreted in the 24-hour urine as estradiol, 4 and 12 weeks post-application of ESTRING in a Phase I study was 5 and 8%, respectively, of the daily released amount.

Drug-Drug Interactions
No formal *drug-drug* interactions studies have been done with ESTRING. It is anticipated that lower exposure to systemic estrogens may reduce the potential for drug interactions thus maintaining the benefit to risk ratio of concomitant drugs.

TABLE 1: PHARMACOKINETIC MEAN ESTIMATES FOLLOWING ESTRING APPLICATION

Estrogen	C_{max} (pg/mL)	$C_{ss\text{-}48\ hr}$ (pg/mL)	$C_{ss\text{-}4w}$ (pg/mL)	$C_{ss\text{-}12w}$ (pg/mL)
Estradiol (E_2)	63.2[a]	11.2	9.5	8.0
Baseline-adjusted E_2[b]	55.6	3.6	2.0	0.4
Estrone (E_1)	66.3	52.5	43.8	47.0
Baseline-adjusted E_1	20.0	6.2	-2.4	0.8

[a] n=14 [b] Based on means

Pharmacodynamics
In-vivo, estrogens diffuse through cell membranes, distribute throughout the cell, bind to and activate the estrogen receptors, thereby eliciting their biological effects. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalamus, liver and bone of women. ESTRING delivers estradiol constantly at a mean rate of ~ 7.5 µg/24 hours for a period of up to 90 days. Its use in post-menopausal patients in Phase I and II studies showed no apparent effects on systemic levels of hepatic protein SHBG, or FSH. Lowering of the pretreatment vaginal pH from a mean of 6.0 to a mean of 4.6 (as found in fertile women) over the 12 to 48 week treatment period, and improvements evident in the vaginal mucosal epithelium seen in all studies attest to the local dynamic effects of estrogens.

INDICATIONS AND USAGE

ESTRING (estradiol vaginal ring) is indicated for the treatment of urogenital symptoms associated with post-menopausal atrophy of the vagina (such as dryness, burning, pruritus and dyspareunia) and/or the lower urinary tract (urinary urgency and dysuria).

CLINICAL STUDIES

Two pivotal controlled studies have demonstrated the efficacy of ESTRING (estradiol vaginal ring) in the treatment of post-menopausal urogenital symptoms due to estrogen deficiency.

In a U.S. study where ESTRING was compared with conjugated estrogens vaginal cream, no difference in efficacy between the treatment groups was found with respect to improvement in the physician's global assessment of vaginal symptoms (83% and 82% of patients receiving ESTRING and cream, respectively) and in the patient's global assessment of vaginal symptoms (83% and 82% of patients receiving ESTRING and cream, respectively) after 12 weeks of treatment. In an Australian study, ESTRING was also compared with conjugated estrogens vaginal cream and no difference in the physician's assessment of improvement of vaginal mucosal atrophy (79% and 75% for ESTRING and cream, respectively) or in the patient's assessment of improvement in vaginal dryness (82% and 76% for ESTRING and cream, respectively) after 12 weeks of treatment.

In the U.S. study, symptoms of dysuria and urinary urgency improved in 74% and 65%, respectively, of patients receiving ESTRING as assessed by the patient. In the Australian study, symptoms of dysuria and urinary urgency improved in 90% and 71%, respectively, of patients receiving ESTRING as assessed by the patient.

In both studies, ESTRING and conjugated estrogens vaginal cream had a similar ability to reduce vaginal pH levels and to mature the vaginal mucosa (as measured cytologically using the maturation index and/or the maturation value) after 12 weeks of treatment. In supportive studies, ESTRING was also shown to have a similar significant treatment effect on the maturation of the urethral mucosa.
Endometrial overstimulation, as evaluated in non-hysterectomized patients participating in the U.S. study by the progestogen challenge test and pelvic sonogram, was reported for none of the 58 (0%) patients receiving ESTRING and 4 of the 35 patients (11%) receiving conjugated estrogens vaginal cream.

Of the U.S. women who completed 12 weeks of treatment, 95% rated product comfort for ESTRING as excellent or very good compared with 65% of patients receiving conjugated estrogens vaginal cream, 95% of ESTRING patients judged the product to be very easy or easy to use compared with 88% of cream patients, and 82% gave ESTRING an overall rating of excellent or very good compared with 58% for the cream.

CONTRAINDICATIONS

1. Estrogens should not be used in women with any of the following conditions:
   a. Known or suspected pregnancy (see **BOXED WARNING**).
   b. Undiagnosed abnormal genital bleeding.
   c. Known or suspected cancer of the breast.
   d. Known or suspected estrogen-dependent neoplasia.
2. ESTRING (estradiol vaginal ring) should not be used in patients hypersensitive to any of its ingredients.

WARNINGS

1. **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, some have reported a moderately increased risk (relative risks of 1.3 to 2.0) in those taking higher doses or those taking lower doses for prolonged periods of time, especially in excess of ten years. Other studies have not shown this relationship.
2. **Other.**
   Congenital lesions with malignant potential, gallbladder disease, cardiovascular disease, elevated blood pressure and hypercalcemia have been associated with systemic estrogen treatment.

PRECAUTIONS

A. General

1. **Use of Progestins.**
   It is common practice with systemic administration of estrogen to add progestin for ten or more days during a cycle to lower the incidence of endometrial proliferation or hyperplasia. From the available clinical data, it seems unlikely that ESTRING would have adverse effects on the endometrium. Furthermore, addition of progestins to a patient being treated with ESTRING is not expected to result in vaginal bleeding.

2. **Physical Examination.**
A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than one year without reexamining the patient.

3. **Uterine Bleeding and Mastodynia.**
Although uncommon with ESTRING, certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

4. **Liver Disease.**
ESTRING should be used with caution in patients with impaired liver function.

5. **Location of ESTRING.**
Some women have experienced moving or gliding of ESTRING within the vagina. Instances of ESTRING being expelled from the vagina in connection with moving the bowels, strain, or constipation have been reported. If this occurs, ESTRING can be rinsed in lukewarm water and reinserted into the vagina by the patient.

6. **Vaginal Irritation.**
ESTRING may not be suitable for women with narrow, short, or stenosed vaginas. Narrow vagina, vaginal stenosis, prolapse, and vaginal infections are conditions that make the vagina more susceptible to ESTRING-caused irritation or ulceration. Women with signs or symptoms of vaginal irritation should alert their physician.

7. **Vaginal Infection.**
Vaginal infection is generally more common in postmenopausal women due to the lack of the normal flora of fertile women, especially lactobacillus, and the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy before initiation of ESTRING. If a vaginal infection develops during use of ESTRING, then ESTRING should be removed and reinserted only after the infection has been appropriately treated.

8. **Other.**
Hypercoagulability and hyperlipidemia have been reported in women on other types of estrogen replacement therapy but, these have not been seen with ESTRING patients.

Fluid retention is another known risk factor with estrogen therapy and may be harmful to patients with asthma, epilepsy, migraine and cardiac or renal dysfunction. ESTRING treatment has not been associated with any indication of increase in body weight up to 48 weeks of treatment.

B. Information for the Patient.
See text of **Information for Patients** which appears at the end of this insert.

C. Drug-Drug and Drug-Laboratory Interactions.
It is recommended that ESTRING be removed during treatment with other vaginally administered preparations.

Drug-drug and drug-laboratory interactions have been reported with estrogen administration overall, but were not observed in clinical trials with ESTRING. However, the possibility of the following interactions should be considered when treating patients with ESTRING.

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 plasma HDL and HDL-2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglycerides levels.

D. Carcinogenesis, 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, and liver (see **CONTRAINDICATIONS** and **BOXED WARNING**).

G. Geriatric Use.

Of the total number of subjects in clinical studies of ESTRING (including subjects treated with ESTRING, placebo, and comparator drug; n = 951), 25% were 65 and over, while 4% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

E. Pregnancy Category X.

Estrogens should not be used during pregnancy (see **CONTRAINDICATIONS** and **BOXED WARNING**).

F. Nursing Mothers.

This product is not intended for 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.

ADVERSE REACTIONS

The biological safety of the silicone elastomer has been studied in various *in vitro* and *in vivo* test models. The results show that the silicone elastomer is non-toxic, non-pyrogenic, non-irritating, and non-sensitizing. Long-term implantation induced encapsulation equal to or less than the negative control (polyethylene) used in the USP test. No toxic reaction or tumor formation was observed with the silicone elastomer.

In general, ESTRING (estradiol vaginal ring) was well tolerated. In the two pivotal controlled studies, discontinuation of treatment due to an adverse event was required by 5.4% of patients receiving ESTRING and 3.9% of patients receiving conjugated estrogens vaginal cream. The most common reasons for withdrawal from ESTRING treatment due to an adverse event were vaginal discomfort and gastrointestinal symptoms.

The adverse events reported with a frequency of 3% or greater in the two pivotal controlled studies by patients receiving ESTRING or conjugated estrogens vaginal cream are listed in Table 2.

Table 2: Adverse Events Reported by 3% or More of Patients Receiving Either ESTRING or Conjugated Estrogens Vaginal Cream in Two Pivotal Controlled Studies

ADVERSE EVENT	**Estring (n=257)** %	**Conjugated Estrogens Vaginal Cream (n=129)** %
Musculoskeletal		
Back Pain	6	8
Arthritis	4	2
Arthralgia	3	5
Skeletal Pain	2	4
CNS/Peripheral Nervous System		
Headache	13	16
Psychiatric		
Insomnia	4	0
Gastrointestinal		
Abdominal Pain	4	2
Nausea	3	2
Respiratory		
Upper Respiratory Tract Infection	5	6
Sinusitis	4	3
Pharyngitis	1	3
Urinary		
Urinary Tract Infection	2	7
Female Reproductive		
Leukorrhea	7	3
Vaginitis	5	2
Vaginal Discomfort/Pain	5	5
Vaginal Hemorrhage	4	5
Asymptomatic Genital Bacterial Growth	4	6
Breast Pain	1	7
Resistance Mechanisms		
Genital Moniliasis	6	7
Body as a Whole		
Flu-Like Symptoms	3	2
Hot Flushes	2	3
Allergy	1	4
Miscellaneous		
Family Stress	2	3

Other adverse events (listed alphabetically) occurring at a frequency of 1 to 3% in the two pivotal controlled studies by patients receiving ESTRING include: anxiety, bronchitis, chest pain, cystitis, dermatitis, diarrhea, dyspepsia, dysuria, flatulence, gastritis, genital eruption, genital pruritus, hemorrhoids, leg edema, migraine, otitis media, skin hypertrophy, syncope, toothache, tooth disorder, urinary incontinence.

The following additional adverse events were reported at least once by patients receiving ESTRING in the worldwide clinical program, which includes controlled and uncontrolled studies. A causal relationship with ESTRING has not been established.

Body as a Whole: allergic reaction

CNS/Peripheral Nervous System: dizziness

Gastrointestinal: enlarged abdomen, vomiting

Metabolic/Nutritional Disorders: weight decrease or increase

Psychiatric: depression, decreased libido, nervousness

Reproductive: breast engorgement, breast enlargement, intermenstrual bleeding, genital edema, vulval disorder

Skin/Appendages: pruritus, pruritus ani

Urinary: micturition frequency, urethral disorder

Vascular: thrombophlebitis

Vision: abnormal vision

OVERDOSAGE

Given the nature and design of ESTRING (estradiol vaginal ring), it is unlikely that overdosage will occur. However, should overdosage occur, it may manifest itself as nausea, vomiting, and/or vaginal bleeding. Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing oral contraceptives by young children.

DOSAGE AND ADMINISTRATION

One ESTRING (estradiol vaginal ring) is to be inserted as deeply as possible into the upper one-third of the vaginal vault. The ring is to remain in place continuously for three months, after which it is to be removed and, if appropriate, replaced by a new ring. The need to continue treatment should be assessed at 3 or 6 month intervals.

Should the ring be removed or fall out at any time during the 90-day treatment period, the ring should be rinsed in lukewarm water and re-inserted by the patient, or, if necessary, by a physician or nurse.

Retention of the ring for greater than 90 days does not represent overdosage but will result in progressively greater underdosage with the attendant risk of loss of efficacy and increasing risk of vaginal infections and/or erosions.

Instructions for Use

ESTRING (estradiol vaginal ring) insertion

The ring should be pressed into an oval and inserted into the upper third of the vaginal vault. The exact position is not critical. When ESTRING is in place, the patient should not feel anything. If the patient feels discomfort, ESTRING is probably not far enough inside. Gently push ESTRING further into the vagina.

ESTRING use

ESTRING should be left in place continuously for 90 days and then, if continuation of therapy is deemed appropriate, replaced by a new ESTRING.
The patient should not feel ESTRING when it is in place and it should not interfere with sexual intercourse. Straining at defecation may make ESTRING move down in the lower part of the vagina. If so, it may be pushed up again with a finger.
If ESTRING is expelled totally from the vagina, it should be rinsed in lukewarm water and reinserted by the patient (or doctor/nurse if necessary).

ESTRING removal

ESTRING may be removed by hooking a finger through the ring and pulling it out.

For patient instructions, see **Information for Patients.**

HOW SUPPLIED

Each ESTRING (estradiol vaginal ring) is individually packaged in a heat-sealed rectangular pouch consisting of three layers, from outside to inside: polyester, aluminum foil, and low density polyethylene, respectively. The pouch is provided with a tear-off notch on one side.

NDC 0013-2150-36 ESTRING (estradiol vaginal ring) 2 mg - available in single packs.

STORAGE - Store at controlled room temperature 15° to 30° C (59° to 86° F).

CAUTION: Federal law prohibits dispensing without prescription.

INFORMATION FOR PATIENTS

INTRODUCTION

This leaflet describes when and how to use ESTRING (estradiol vaginal ring), and the risks and benefits of estrogen treatment. Please read this information carefully before starting treatment.

Estrogens have important benefits but also some risks. You must decide, with your doctor, whether the risks to you of estrogen use are acceptable because of their benefits. If you use estrogens, check with your doctor to be sure you are using the dose that is appropriate for you, and that you don't use them longer than necessary. How long you need to use estrogens should be decided by you and your doctor.

1. **ESTROGENS INCREASE THE RISK OF CANCER OF THE UTERUS IN WOMEN WHO HAVE HAD THEIR MENOPAUSE ("CHANGE OF LIFE")**

   If you use any estrogen-containing drug, 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.

2. **ESTROGENS SHOULD NOT BE USED DURING PREGNANCY**

   Estrogens do not prevent miscarriage (spontaneous abortion) and are not needed in the days following childbirth. If you take estrogens during pregnancy, your unborn child has a greater than usual chance of having birth defects. The risk of developing these defects is small, but clearly larger than the risk in children whose mothers did not take estrogens during pregnancy. These birth defects may affect the baby's urinary system and sex organs. Daughters born to mothers who took DES (an estrogen drug) have a higher than usual chance of developing cancer of the vagina or cervix when they become teenagers or young adults. Sons may have a higher than usual chance of developing cancer of the testicles when they become teenagers or young adults.

USES OF ESTROGEN

Estrogens are hormones made by the ovaries of women during their reproductive years. 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 results in what is known as "surgically induced 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. ESTRING (estradiol vaginal ring) DOES NOT PROVIDE ENOUGH ESTROGEN TO REDUCE THESE SYMPTOMS.

The declining estrogen levels associated with advancing age after menopause may also result in thinning and drying of the tissue in the urinary tract and vagina (urogenital atrophy). Vaginal symptoms of this condition include dryness in the vagina (atrophic vaginitis), genital itching and burning, and pain with intercourse. Urinary symptoms may include urinary urgency and pain on urination. Small amounts of estrogen delivered directly to the local tissue can be used to help reduce these symptoms.

USE OF ESTRING (estradiol vaginal ring)

ESTRING is a local estrogen therapy designed to relieve vaginal and urinary symptoms of postmenopausal estrogen deficiency for a full 90 days. ESTRING exerts its effect locally in the lower urogenital tract and has not been shown to have significant effects in other estrogen-sensitive organs or tissues of the body. Consequently, ESTRING PROVIDES RELIEF OF LOCAL SYMPTOMS OF MENOPAUSE ONLY.

DESCRIPTION

ESTRING (estradiol vaginal ring) contains a drug reservoir of 2 mg of the estrogen, estradiol, in its core. ESTRING releases estradiol into the vagina in a consistent, stable manner for 90 days. The soft, flexible ring is placed in the upper third of the vagina (by the physician or the patient) and worn continuously for 90 days, then removed and replaced if continuation of therapy is indicated.

WHO SHOULD NOT USE ESTRING (estradiol vaginal ring)

ESTRING should not be used:

During pregnancy (see **BOXED WARNING**).
Women who are definitely postmenopausal cannot become pregnant. Women whobelieve they are postmenopausal because their menstrual cycles have recently stopped should confirm that they are not pregnant before using any form of estrogen-containing drug. Using estrogens while pregnant may cause the unborn child to have birth defects. Estrogens do not prevent miscarriage.

In the presence of unusual vaginal bleeding which has not been evaluated by a doctor (see **BOXED WARNING**).
Unusual vaginal bleeding after menopause can be a warning sign of cancer of the uterus. Estrogens may increase the risk of cancer of the uterus in women who have had their menopause ("change of life"). If you use any estrogen-containing drug, it is important to visit your doctor regularly and report any unusual vaginal bleeding right away. Your doctor should evaluate any unusual vaginal bleeding to find out the cause.

If there is a history of certain types of cancer.
Estrogens may increase the risk of certain types of cancer. In general, ESTRING should not be used in women who have ever had cancer of the breast or uterus.

During treatment for vaginal infection with vaginal antimicrobial therapy.
It is recommended that ESTRING be discontinued while other vaginal medications are being used to treat a vaginal infection. Use of ESTRING can be resumed after termination of the other vaginal medication, and after first consulting with a physician.

After childbirth or when breastfeeding a baby.
ESTRING should not be used to try to stop the breasts from filling with milk after a baby is born. Women who are breast-feeding should avoid using any drugs because many drugs pass through to the baby in the milk. While nursing a baby, drugs should only be taken on the advice of your healthcare giver.

POSSIBLE RISKS FROM TREATMENT WITH ESTROGENS

The following risk factors apply to estrogens in general:

Cancer of the uterus.
Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus (endometrial cancer). The risk of endometrial cancer is greater in estrogen users than nonusers. Studies have shown that this increased risk depends on estrogen dose, duration of treatment, and treatment regimen.

If the uterus has been 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.

Gallbladder disease and abnormal blood clotting.
Gallbladder disease and abnormal blood clotting are risk factors associated with medium to high doses of estrogen. Most studies of low dose estrogen usage by women do not show an increased risk of these complications, and to date have not been seen with ESTRING (estradiol vaginal ring) treatment.

SIDE EFFECTS

Like all medications, ESTRING (estradiol vaginal ring) may cause side effects. The most frequently reported side effect is increased vaginal secretions. Many of these vaginal secretions are like those that occur normally prior to menopause and indicate that ESTRING is working. Vaginal secretions that are associated with a bad odor, vaginal itching, or other signs of vaginal infection are NOT normal and may indicate a risk or a cause for concern. Other side effects may include vaginal discomfort, abdominal pain, or genital itching.

Estrogens in General
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 ("fibroids") of the uterus.
- Retention of excess fluid. This may worsen some conditions, such as asthma, epilepsy, migraine, heart disease, or kidney disease.
- Spotty darkening of the skin, particularly on the face.

REDUCING RISK OF ESTROGEN USE

If you use estrogens, you may 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, call your doctor - 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.

Reassess your need for estrogens.
You and your doctor should reevaluate whether or not you still need estrogens at least every 6 months.

Be alert for warning signs.
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 skin or eyes (possible liver problem).
- Pain, swelling, or tenderness in the abdomen (possible gallbladder problem).

OTHER INFORMATION

1. Estrogens increase the risk of developing a condition (endometrial hyperplasia) that may lead to cancer of the lining of the uterus. Progestin, another hormone drug, is usually prescribed with higher-dose estrogen preparations to lower the risk of developing endometrial hyperplasia. Progestins are not usually needed for women using ESTRING (estradiol vaginal ring) alone.

2. Some women have experienced moving or sliding of ESTRING within the vagina. If this happens, ESTRING can be gently pushed back into position with a clean finger. Instances of ESTRING slipping out of the vagina have been infrequent and were usually associated with moving the bowels, straining, or constipation within the first few weeks of treatment. If this occurs, ESTRING can be washed with lukewarm (NOT hot) water and reinserted. If this happens repeatedly, you should consult with your doctor or healthcare giver and determine whether continued treatment is appropriate for you.

3. ESTRING may not be suitable for women with narrow, short, or stenosed (constricted) vaginas. A narrow vagina, vaginal stenosis (constriction), significant prolapse, and vaginal infections are conditions that make the vagina more susceptible to irritation or ulceration caused by ESTRING. Women with signs or symptoms of vaginal irritation should alert their doctor or healthcare giver.
4. Vaginal infection is generally more common in postmenopausal women. Vaginal infections should be treated with appropriate antimicrobial therapybefore initiation of ESTRING. If a vaginal infection develops during use of ESTRING, then ESTRING should be removed and reinserted only after the infection has been appropriately treated. See your doctor or healthcare giver if you have vaginal discomfort or suspect you have a vaginal infection.
5. Your doctor has prescribed this drug for you and you alone. Do not give the drug to anyone else.
6. Keep this and all drugs out of the reach of children.
7. This leaflet provides a summary of important information about ESTRING. If you want more information, ask your doctor or pharmacist to show you the professional labeling. The professional labeling is also published in a book called the "Physicians' Desk Reference®," which is available in book stores and public libraries. Generic drugs carry virtually the same labeling information as their brand name versions.

HOW SUPPLIED

Each ESTRING (estradiol vaginal ring) is individually packaged in a heat-sealed rectangular pouch. The pouch is provided with a tear-off notch on one side.

NDC 0013-2150-36 ESTRING (estradiol vaginal ring) 2 mg available in single units.

Storage: Store at controlled room temperature 15° to 30° C (59° to 86° F).

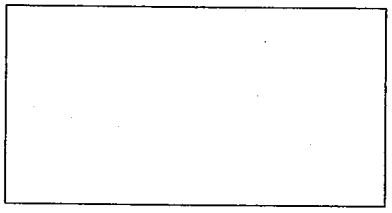
Caution: Federal law prohibits dispensing without prescription.

A Patient Guide to ESTRING

(estradiol vaginal ring) 2 mg

Insertion and Removal

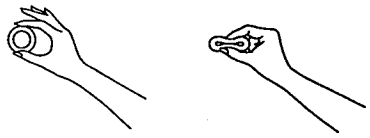
FEMALE ANATOMY



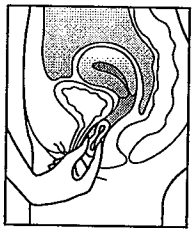
ESTRING INSERTION

ESTRING can be inserted and removed by you or your doctor. To insert ESTRING yourself, choose the position that is most comfortable for you: standing with one leg up, squatting, or lying down.

1. After washing and drying your hands, remove ESTRING from its pouch using the tear-off notch on the side. (Since the ring becomes slippery when wet, be sure your hands are dry before handling it.)
2. Hold ESTRING between your thumb and index finger and press the opposite sides of the ring together as shown.

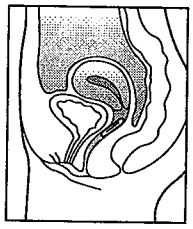


3. Gently push the compressed ring into your vagina as far as you can.



ESTRING PLACEMENT

The exact position of ESTRING is not critical, as long as it is placed in the upper third of the vagina.



When ESTRING is in place, you should not feel anything. If you feel uncomfortable, ESTRING is probably not far enough inside. Use your finger to gently push ESTRING further into your vagina.

There is no danger of ESTRING being pushed too far up in the vagina or getting lost. ESTRING can only be inserted as far as the end of the vagina, where the cervix (the narrow, lower end of the uterus) will block ESTRING from going any further (see diagram of Female Anatomy).

ESTRING USE

Once inserted, ESTRING should remain in place in the vagina for 90 days.

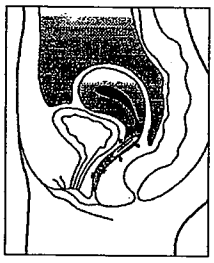
Most women and their partners experience no discomfort with ESTRING in place during intercourse, so it is NOT necessary that the ring be removed. If ESTRING should cause you or your partner any discomfort, you may remove it prior to intercourse (see ESTRING Removal, below). Be sure to reinsert ESTRING as soon as possible afterwards.

ESTRING may slide down into the lower part of the vagina as a result of the abdominal pressure or straining that sometimes accompanies constipation. If this should happen, gently guide ESTRING back into place with your finger.

There have been rare reports of ESTRING falling out in some women following intense straining or coughing. If this should occur, simply wash ESTRING with lukewarm (NOT hot) water and reinsert it.

ESTRING DRUG DELIVERY

Once in the vagina, ESTRING begins to release estradiol immediately. ESTRING will continue to release a low, continuous dose of estradiol for the full 90 days it remains in place.



It will take about 2 to 3 weeks to restore the tissue of the vagina and urinary tract to a healthier condition and to feel the full effect of ESTRING in relieving vaginal and urinary symptoms. If your symptoms persist for more than a few weeks after beginning ESTRING therapy, contact your doctor.

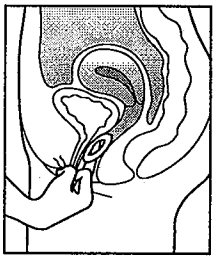
One of the most frequently reported effects associated with the use of ESTRING is an increase in vaginal secretions. These secretions are like those that occur normally prior to menopause and indicate that ESTRING is working. However, if the secretions are associated with a bad odor or vaginal itching or discomfort, be sure to contact your doctor.

ESTRING REMOVAL

After 90 days there will no longer be enough estradiol in the ring to maintain its full effect in relieving your vaginal or urinary symptoms. ESTRING should be removed at that time and replaced with a new ESTRING, if your doctor determines that you need to continue your therapy.

To remove ESTRING:

1. Wash and dry your hands thoroughly.
2. Assume a comfortable position, either standing with one leg up, squatting, or lying down.
3. Loop your finger through the ring and gently pull it out.
4. Discard the used ring in a waste receptacle. (Do not flush ESTRING).



If you have any additional questions about removing ESTRING, contact your doctor or healthcare giver.

Manufactured for:

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

612762

By:

Ferring AB
Malmö, Sweden

~~101021197~~

~~November 1997~~

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-472/S-003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 20-472/SLR-003
ESTRING Physician labeling label Review
Date received: August 18, 1999
Date revised: December 28, 1999

JAN -3 2000

The purpose of this "Changes Being effected" (CBE) supplement is to revise the physician package insert, in compliance with 21 CFR; 201.47(f)(10), to reflect the addition of a "Geriatric Use" subsection to the labeling of human prescription products.

The supplement provides for the revisions in the **PRECAUTIONS** section of the labeling as follows:

G. Geriatric Use

Of the total number of subjects in clinical studies of ESTRING (including subjects treated with ESTRING, placebo, and comparator drug; n-951), 25% were 65 and over, while 4% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This is acceptable

Proposed Regulatory Action (MO to complete)

☒ Approval

☐ Approvable

☐ Not Approvable

PM signature — Date: 12/28/99

Medical Officer Signature — Date: 12/28/99

Team Leader Signature — Date: 1/3/00

Deputy Director Signature — Date: 1/3/00

Archival NDA 20-472
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Mann/Slaughter/van der Vlugt/Rhee/Lin/Raheja/Jordan/Parekh/Rumble

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-472/S-003

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

AUG 25 1999

Attention: Daniel G. Chirby, M.Sc.
Regulatory Affairs Manager

Dear Mr. Chirby:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ESTRING® Vaginal Ring

NDA Number: 20-472

Supplement Number: S-003

Date of Supplement: August 17, 1999

Date of Receipt: August 18, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 17, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

FOR Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-472/S-003
HFD-580/Div. Files
HFD-580/CSO/Spelllesane

SUPPLEMENT ACKNOWLEDGEMENT