SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
ESTRING® Vaginal Ring

COMPOSITION:
Each vaginal ring contains 2.0 mg estradiol hemihydrate.

The other ingredients are:
Silicone elastomer A, silicone elastomer B, silicone fluid and barium sulphate.

PHARMACOLOGICAL CLASSIFICATION:
A 21.8.1 Oestrogens

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
The active ingredient, synthetic 17ß-estradiol, is identical to endogenous human estradiol.
Estradiol vaginal ring maintains low systemic plasma concentrations.

Pharmacokinetic properties:
Absorption:
After a brief initial peak, the release of estradiol from the vaginal ring is constant (7.5 µg/24 hr),
according to Fick’s law, for at least 90 days. As a consequence of the initial release peak, plasma levels
of estradiol reach about 200 pmol/l within 3 hours.

After this initial peak, plasma estradiol concentrations decline after 48 hours and constant levels are
achieved after 2 - 3 days. These levels are maintained at, or near, the quantification limit (20 - 30 pmol/l)
throughout the rest of the treatment period.
Metabolism:

Estradiol is mainly metabolised in the liver. Its main metabolites are estriol, estrone, and their conjugates. The plasma half-life of estradiol is 1 to 2 hours. Metabolic plasma clearance varies between 450 - 625 ml/min/m². The metabolites are mainly excreted via the kidneys as glucuronides and sulphates. Oestrogens also undergo enterohepatic circulation.

Excretion:

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

INDICATIONS:

Treatment of post-menopausal atrophic vaginitis.

CONTRAINDICATIONS:

ESTRING is contraindicated in individuals with any of the following conditions:

- Known hypersensitivity to estradiol hemihydrate or to any of the excipients of ESTRING. Known or suspected oestrogen-dependent malignancy, e.g. endometrial carcinoma or other oestrogen-dependent tumours.
- Undiagnosed genital bleeding.
- Endometrial hyperplasia.
- Known, suspected, or family history of cancer of the breast.
- Known or suspected oestrogen-dependent neoplasia.
- Active deep vein thrombosis, pulmonary embolism or history of these conditions.
- Active or recent arterial thromboembolic disease (e.g., stroke, myocardial infarction).
- Liver dysfunction or disease.
- Known or suspected pregnancy.
- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).
- Porphyria.

WARNINGS AND SPECIAL PRECAUTIONS:

Safety update to CDS Version 5.0 dated 15 December 2014
Response to MCC Clinical Committee Recommendation dated 11 May 2016 submitted 28 October 2016
Approved 17 February 2017
History and physical examination:

A complete medical and family history should be taken prior to the initiation of ESTRING therapy. Pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, including cervical cytology.

ESTRING is only suitable for the treatment of urogenital complaints due to oestrogen deficiency. There is no significant systemic effect and therefore it is not suitable for post-menopausal complaints which require a systemically active dose of oestrogen (e.g. vasomotor symptoms), neither is it suitable for osteoporosis prophylaxis.

Patients on long-term corticosteroid treatment of Cushing’s Disease, may be unsuitable for treatment as they may have vaginal atrophy unresponsive to oestrogen therapy.

The Women’s Health Initiative (WHI) clinical trial (see Pharmacodynamic properties) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5.2 years of treatment with oral conjugated equine oestrogens combined with medroxyprogesterone acetate relative to placebo. The WHI trial also reported increased risks of stroke and deep vein thrombosis in postmenopausal women during 6.8 years of treatment with oral CEE-alone, relative to placebo.

The following warnings, precautions, and adverse reactions associated with oral oestrogen and/or progestin therapy should be considered in the absence of comparable data with other dosages and forms of oestrogens and/or progestins.

Malignant neoplasms:

Endometrial cancer:

The use of unopposed oestrogens in women with intact uteri is associated with an increased risk of endometrial cancer. The reported endometrial cancer risk among users of unopposed oestrogen is about 2- to 12-fold greater than in non-users and appears to be dependent on the duration of treatment and dose. A woman with an intact uterus should be monitored closely for signs of
endometrial hyperplasia or carcinoma. Appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurrent abnormal vaginal bleeding.

**Breast cancer:**
The use of oestrogen-alone or combined oestrogen/progestin by postmenopausal women has been reported to increase the risk of breast cancer. The excess risk increased with duration of use.

**Ovarian cancer:**
Use of oestrogen-only products in a woman without an intact uterus, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer in some epidemiological studies.

**Cardiovascular disorders:**
ESTRING should not be used for the prevention of cardiovascular disease. Several randomised prospective trials on the long-term effects of oestrogen-alone or a combined oestrogen/progestin regimen in postmenopausal women have reported an increased risk of cardiovascular events such as myocardial infarction, coronary heart disease, stroke, and venous thromboembolism.

**Stroke:**
There is an increased risk of stroke in women receiving CEE/MPA compared to women receiving placebo. The increase in risk was already observed in year one and persisted over the observation period.

**Venous thromboembolism/pulmonary embolism:**
Hormonal replacement therapy (HRT) is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e., deep vein thrombosis (DVT) or pulmonary embolism (PE).

**Dementia:**
Several epidemiological studies showed an increased risk of developing dementia and mild cognitive impairment (MCI) in postmenopausal women 65 years of age or older.
Angioedema:

ESTRING may induce or exacerbate symptoms of angioedema.

Accidental displacement of ESTRING:

There have been incidences of both the ring falling out and of movement of the ring, generally during defaecation. Therefore, if the woman is constipated, she should remove the ring before defaecation. Removal of the ring prior to sexual intercourse may also be preferred. Advice for removal and reinsertion of the ring are provided in the Patient Information Leaflet.

Vaginal irritation:

ESTRING is not 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 estradiol-caused irritation or ulceration. Women with signs or symptoms of vaginal irritation should alert their medical practitioner. In addition, any woman with symptoms/signs of abnormal vaginal discharge, vaginal discomfort, or any vaginal bleeding should be examined fully to exclude ulceration, infection, or unresponsive atrophic vaginitis.

In any woman experiencing persistent or severe discomfort due to the presence of the ring or excessive movement of the ring, the ring should be discontinued. Treatment should be discontinued in patients with signs of ulceration or severe inflammation due to unresponsive atrophic vaginitis.

Vaginal infection:

In patients with vaginal infection being treated with systemic therapy, ESTRING may continue without interruption. However, removal of ESTRING should be considered while using other vaginal preparations.

The maximum duration of use during clinical trials was 2 years and, therefore, the maximum recommended duration of continuous therapy is 2 years.
Effects on ability to drive and use machines:

The effect of ESTRING on the ability to drive and use machinery has not been systemically evaluated.

INTERACTIONS:

No interaction studies have been done with ESTRING.

Removal of ESTRING is recommended when using other vaginal preparations.

PREGNANCY AND LACTATION:

Pregnancy:
ESTRING should not be used during pregnancy (see CONTRAINDICATIONS). If pregnancy occurs during ESTRING administration, treatment should be withdrawn immediately.

Lactation:
ESTRING should not be used by women breastfeeding their infants.

Oestrogens have been detected in the breast milk of mothers receiving these medicines, and the effect on breast-fed infants has not been determined. Suppression of lactation may occur.

DOSAGE AND DIRECTIONS FOR USE:

Adults (Post-menopausal women only):

One ring to be inserted into the upper third of the vagina, to be worn continuously for 3 months, then replaced by a new ring.

ESTRING can be used continuously without the addition of progestogens and consequently, no uterine bleeding will result from treatment.

The maximum duration of use during clinical trials was 2 years and, therefore, the maximum recommended duration of continuous therapy is 2 years.

Instructions for use are available in a Patient Information Leaflet enclosed in each pack.
The ring is easy to insert and remove. It lies in the posterior vaginal vault in contact with the vaginal mucosa and remains intact.

**SIDE EFFECTS:**

The biological safety of the silicone elastomer has been studied in various *in vitro* and *in vivo* test models.

In the two pivotal controlled studies, discontinuation of treatment due to an adverse event was required by 5.4% of patients receiving ESTRING. The most common reasons for withdrawal from ESTRING treatment due to an adverse event were vaginal discomfort and gastrointestinal symptoms.

Adverse reactions reported during clinical trials include in decreasing frequency: vulvovaginal infection, pressure symptoms in vagina or on bladder or rectum and increased sweating.

Cases of vaginal ulceration were reported in clinical trials. It is recommended that any patient who develops an ulcer should be withdrawn from treatment.

The adverse reactions reported with ESTRING patients across all studies, in order of decreasing frequency, are as follows:

Very common (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1 000, < 1/100) rare (> 1/10 000, <1/1 000), very rare (< 1/10 000)
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection, upper respiratory tract infection, sinusitis</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
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<td>Nervous system disorders</td>
<td>Headache</td>
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<td>Vascular disorders</td>
<td>Hot flushes</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain or discomfort, nausea</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthropathy (including arthralgia, arthritis, arthrosis), back pain</td>
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</tbody>
</table>
### System Organ Class

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Leukorrhoea</td>
<td>Vaginal bleeding, vaginal irritation/discomfort, vaginitis moniliasis, urogenital pruritus, breast symptoms (including breast engorgement, breast enlargement, breast pain)</td>
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<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Influenza-like symptoms</td>
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</tbody>
</table>

**Post marketing experience:**

The following side effects have been reported during post-marketing studies with ESTRING:
System Organ Class | Adverse Event
--- | ---
Immune system disorders | Hypersensitivity including anaphylaxis and angioedema
Reproductive system and breast disorders | Vaginal erosion/vaginal ulceration

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Given the nature and design of ESTRING, it is unlikely that overdosage will occur. However, should overdosage occur, it may cause nausea and vomiting. Withdrawal bleeding may occur in women. Treatment is symptomatic and supportive.

IDENTIFICATION:
A slightly opaque ring made of a silicone elastomer with a whitish core.

PRESENTATION:
Each ring is packed in a heat sealed pouch consisting of the following layers: polyester/aluminium foil/polyethylene. Each pouch is packed in a carton together with a Patient Information Leaflet and a Package Insert.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.
Keep out of reach of children.

REGISTRATION NUMBER:
29/21.8.1/0720

NAME AND BUSINESS ADDRESS OF THEHOLDER OF THE CERTIFICATE OF REGISTRATION:
Pfizer Laboratories (Pty) Ltd
85 Bute Lane
Sandton

Safety update to CDS Version 5.0 dated 15 December 2014
Response to MCC Clinical Committee Recommendation dated 11 May 2016 submitted 28 October 2016
Approved 17 February 2017
DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of registration: 07 December 1995

Date of last council approval: 17 February 2017

NAMIBIA: S2
Reg. No.: 04/21.8.1/0729