For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

EVALON CREAM

1. Generic Name

Estriol Cream BP 1 mg

2. Qualitative and quantitative composition

Each gram contains:

Estriol BP…….1 mg

Chlorhexidine Hydrochloride BP……0.1 mg (as preservative)

Cream base…….. q.s.

The excipients used are Octyldodecanol, Cetyl palmitate, Glycerol, Cetyl alcohol, Stearyl alcohol, Polysorbate 60, Sorbitan stearate, Lactic acid, Chlorhexidine dihydrochloride, Sodium hydroxide, Purified water.

3. Dosage form and strength

Dosage Form: Cream

Strength: Estriol: 1 mg and Chlorhexidine Hydrochloride: 0.1 mg

4. Clinical particulars

4.1 Therapeutic indication

Estrogen deficiency symptoms due to menopause.

4.2 Posology and method of administration

Evalon Cream is an estrogen-only product that may be given to women with or without a uterus.

Posology

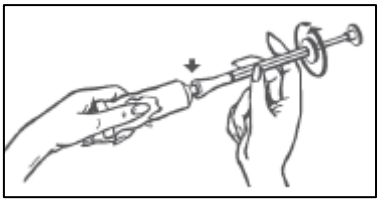
- For atrophy of the lower urogenital tract: application per day for the first weeks, followed by a gradual reduction, based on relief of symptoms, until a maintenance dosage (e.g. 1 application twice a week) is reached.

Method of administration

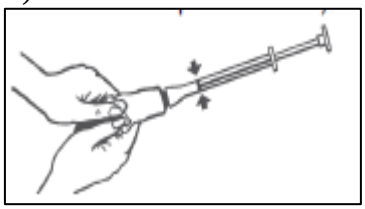
- Evalon Cream should be administered intra vaginally by means of a calibrated applicator before retiring at night.
- 1 application (applicator filled to the ring mark) contains 0.5 g Evalon Cream which corresponds to 0.5 mg estriol.

Instructions for use for the patient

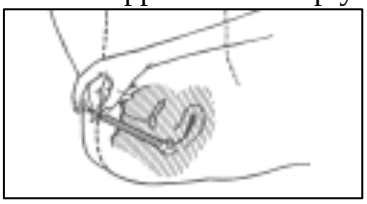
1. Remove cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube. Make sure the plunger is fully inserted into the barrel



3. Squeeze tube slowly to fill the applicator with the cream until the plunger stops (at the red ring, see arrows in the picture below).



4. Unscrew applicator from tube and put cap back on tube.
5. To apply cream, lie down, insert end of applicator deep into the vagina.
6. Slowly push plunger all the way in until applicator is empty.



7. After use, pull plunger out of barrel beyond the point of resistance and wash both in warm, soapy water. Do not use detergents. Rinse well afterwards. DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.
8. The applicator can be re-assembled by fully inserting the plunger into the barrel beyond the point where resistance is felt. Discard the applicator once the tube is empty.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected estrogen-dependent malignant tumors (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Acute liver disease, or a history of liver disease as long as liver function tests failed to return to normal
- Hypersensitivity to the active substance or to any of the excipients.
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favorable than in older women.

Medical examination/follow-up

Before initiation or reinstituting HRT, a complete personal and family medical history should be taken.

Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman.

Women should be advised what changes in their breast should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Evalon Cream, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumors, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0.5 mg estriol) nor should this maximum dose be used for longer than several weeks. One epidemiological study has shown that long-term treatment with low doses of oral estriol, but not vaginal estriol, may increase the risk for endometrial cancer. This risk increased with the duration of treatment and disappeared within one year after the treatment was terminated. The increased risk mainly concerned less invasive and highly differentiated tumors. Vaginal

bleeding during medication should always be investigated. The patient should be informed to contact a doctor if vaginal bleeding occurs.

Breast cancer
The overall evidence suggests an increased risk of breast cancer in women taking combined estrogenprogestagen and possibly also estrogen-only HRT, that is dependent on the duration of taking HRT.

Combined estrogen-progestagen therapy
The randomized placebo-controlled trial (Women's Health Initiative study (WHI)), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined estrogenprogestagen for HRT that becomes apparent after about 3 years.

Estrogen-only therapy
The WHI trial found no increase in the risk of breast cancer in hysterectomized women using estrogen only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of estrogen-progestagen combinations.
The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment. HRT, especially estrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer. Clinical studies reported that the likelihood of developing increased mammographic density was lower in subjects treated with estriol than in subjects treated with other estrogens. It is unknown whether Evalon Cream carries the same risk. In a population-based casecontrol study in 3,345 women with invasive breast cancer and 3,454 controls, estriol was found not to be associated with an increased risk of breast cancer, in contrast to other estrogens. However, the clinical implications of these findings are as yet unknown. Therefore, it is important that the risk of being diagnosed with breast cancer is discussed with the patient and weighed against the known benefits of HRT.

Ovarian cancer
Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of Estrogen-only. HRT products has been associated with a slightly increased risk of ovarian cancer (see undesirable effects). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see undesirable effects). It is uncertain whether long-term use of low potency estrogens (such as Evalon Cream) confers a different risk than other estrogen only products.

Venous thromboembolism
HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later. These studies did not include Evalon Cream and, in the absence of data, it is unknown whether Evalon Cream carries the same risk.
Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients.
Generally recognized risk factors for VTE include, use of estrogens, older age, major surgery, prolonged immobilization, obesity (Body Mass Index >30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilization is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended.
Treatment should not be restarted until the woman is completely mobilized.
In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counseling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g., antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated. Women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)
There is no evidence from randomized controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined estrogen-progestagen or estrogen-only HRT.

Combined estrogen-progestagen therapy
The relative risk of CAD during use of combined estrogen-progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to estrogen-progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

Estrogen-only
Randomized controlled data found no increased risk of CAD in hysterectomized women using estrogen-only therapy.

Ischemic stroke
Combined estrogen-progestagen and estrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see undesirable effects).

Other conditions
- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Estriol is a weak gonadotropin inhibitor without other significant effects on the endocrine system.
- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.
- Evalon Cream is not intended for contraceptive use.
- Evalon Cream contains acetyl alcohol and stearyl alcohol. This may cause local skin reactions (e.g. contact dermatitis)

4.5 Drugs interactions

No examples of interactions between Evalon Cream and other medicines have been reported in clinical practice. Although data are limited, interactions between Evalon Cream and other medicinal products may occur. The following interactions have been described with use of combined oral contraceptives which may also be relevant for Evalon Cream.

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St John's wort (Hypericum Perforatum) may induce the metabolism of estrogens. Clinically, an increased metabolism of estrogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Fertility

Evalon Cream is intended for the treatment in postmenopausal (naturally and surgically induced) women only.

Evalon Cream is not indicated during pregnancy. If pregnancy occurs during medication with Evalon Cream, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or fetotoxic effects.

Lactation

Evalon Cream is not indicated during lactation. Estriol is excreted in breast milk and may decrease milk production.

4.7 Effects on ability to drive and use machines

There is no information to suggest that Evalon cream affects a patient's ability to drive or operate machinery.

4.8 Undesirable effects

From literature and safety surveillance monitoring, the following adverse reactions have been reported:

System organ class	Adverse reactions*
Metabolism and nutrition disorders	Fluid retention
Gastrointestinal disorders	Nausea
Reproductive system and breast disorders	Breast discomfort and pain Postmenopausal spotting Cervical discharge
General disorders and administration site conditions	Application site irritation and pruritus Flu-like symptoms

MedDRA version 15.1

These adverse reactions are usually transient, but may also be indicative of too high a dosage. Other adverse reactions have been reported in association with estrogen/ progestagen treatment:

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer. For further information see sections "Contraindications" and "Warnings and Precautions"
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 'Warnings and Precautions').

Breast cancer risk

An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined estrogen-progestagen therapy for more than 5 years.

Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen progestagen combinations.

The level of risk is dependent on the duration of use (see section 'Warnings and Precautions').

Results of the reported largest randomized placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years use.

Age range (years)	Additional cases per 1000 never-users of HRT over a 5 years period	Risk ratio#	Additional cases per 1000 HRT users over 5 years (95 % CL)
Estrogen only HRT			
50-65	9-12	1.2	1.2 (0-3)
Combined estrogen-progestagen			
50-65	9-12	1.7	6 (5-7)

Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.

* Taken from baseline incidence rates in developed countries

US WHI studies-additional risk of breast cancer after 5 years' use

Age range(yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95% CI)
CEE estrogen-only			
5.-79	21	0.8 (0.7-1.0)	-4 (-6-0)*
CEE+MPA estrogen & progestagen‡			
50-79	17	1.2 (1.0-1.5)	+4 (0-9)

‡ When the analysis was restricted to women who had not used HRT prior to the reported study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

* WHI reported study in women with no uterus, which did not show an increase in risk of breast cancer.

Ovarian cancer

Long-term use of estrogen-only and combined estrogen progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women reported Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT. Results of the WHI studies are presented:

WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio and 95%CI**	**Additional cases per 1000 HRT users**
Oral estrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 - 10)
Oral combined estrogen-progestagen			
50-59	4	2.3 (1.2- 4.3)	5 (1 - 13)

***** Study in women with no uterus

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60.

Risk of ischemic stroke

The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischemic stroke. The risk of hemorrhagic stroke is not increased during use of HRT. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age.

WHI studies combined - Additional risk of ischemic stroke* over 5 years' use

Age range (years)	**Incidence per 1000 women in placebo arm over 5 years**	**Risk ratio and 95% CI**	**Additional cases per 1000 HRT users over 5 years**
50-59	8	1.3 (1.1-1.6)	3 (1-5)

* no differentiation was made between ischemic and hemorrhagic stroke.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

The acute toxicity of estriol in animals is very low. Overdose with Evalon Cream after vaginal administration is unlikely. However, in cases where large quantities are ingested, nausea, vomiting, and withdrawal bleeding in females may occur. No specific antidote is known. Symptomatic treatment can be given if necessary.

5 Pharmacological properties

5.1 Mechanism of Action

Evalon Cream contains the natural female hormone estriol. Unlike other estrogens, estriol is short acting since it has only a short retention time in the nuclei of endometrial cells. It substitutes for the loss of estrogen production in menopausal women and alleviates menopausal symptoms. Estriol is particularly effective in the treatment of urogenital symptoms. In case of atrophy of the lower urogenital tract estriol induces the normalization of the urogenital epithelium and helps to restore the normal microflora and the physiological pH in the vagina. As a result, it increases the resistance of the urogenital epithelial cells to infection and inflammation reducing vaginal complaints such as dyspareunia, dryness, itching, vaginal and urinary infections, miction complaints and mild urinary incontinence.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: natural and semisynthetic estrogens
ATC code: G03CA04
Clinical trial information

- Relief of menopausal symptoms was achieved during the first weeks of treatment.
- Vaginal bleeding after treatment with Evalon cream has only rarely been reported.

5.3 Pharmacokinetic properties

Absorption
Intravaginal administration of estriol ensures optimal availability at the site of action. Estriol is also absorbed into the general circulation, as is shown by a sharp rise in the plasma levels of unconjugated estriol.

Distribution
Peak plasma levels are reached 1-2 hours after application. After vaginal application of 0.5 mg estriol, Cmax is approximately 100 pg/ml, Cmin is approximately 25 pg/ml and Caverage is approximately 70 pg/ml. After 3 weeks of daily administration of 0.5 mg vaginal estriol, Caverage has decreased to 40 pg/ml

Biotransformation
Nearly all (90%) estriol is bound to albumin in the plasma and, in contrast with other estrogens, hardly any estriol is bound to sex hormone-binding globulin. The metabolism of estriol consists principally of conjugation and deconjugation during the enterohepatic circulation**.**

Elimination
Estriol, being a metabolic end product, is mainly excreted via the urine in the conjugated form. Only a small part (± 2%) is excreted via the feces, mainly as unconjugated estriol.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Non-stated

7 Description

EVALON cream is white, to nearly white homogeneous, smooth mass of creamy consistency. The excipients used are Octyldodecanol, Cetyl palmitate, Glycerol, Cetyl

alcohol, Stearyl alcohol, Polysorbate 60, Sorbitan stearate, Lactic acid, Chlorhexidine dihydrochloride, Sodium hydroxide, Purified water.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

36 months

8.3 Packaging information

Evalon Cream is filled in collapsible aluminium tubes of 15, 30 or 50 grams. Not all pack sizes may be marketed. The tubes are provided with a polyethylene screw cap.

The CE-marked applicator consists of a styrene acrylonitril barrel and a polyethylene plunger. Each tube is packed, together with an applicator in a cardboard box.

8.4 Storage and handing instructions

Store below 25°C. Do not freeze.

Keep out of reach and site of children.

9. Patient Counselling Information

Package leaflet: Information for the user

EVALON CREAM

Estriol 1 mg

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet:

9.1 What EVALON CREAM is and what it is used for

EVALON belongs to a class of medicines called estrogen. It is used in Estrogen deficiency symptoms due to menopause.

9.2 What you need to know before you use EVALON CREAM

Do not use Evalon:

- **if you are allergic** to any of the other ingredients of this medicine.

Tell your doctor and don't take Evalon cream

- **Take special care with Evalon cream**
- **Talk to your doctor before taking Evalon cream:**
- **if you are already taking medicine that contains estrogen.**

If any of these applies to you:

Before initiation or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use.

→ **Tell your doctor**, who may decide to lower the dose or that EVALON cream is not suitable for you.

Important information therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

→ Read the description of these symptoms

The patient should be closely supervised. It should be taken into account that these conditions may reoccur or be aggravated during treatment with Evalon, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumors, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

→ **Contact your doctor immediately** if you experience any of the above symptoms while using Evalon:

→ See a doctor as soon as possible or go to the nearest hospital for help.

You may find it helpful to tell a family member, caregiver or close friend that you can become depressed or have significant changes in mood and ask them to read this leaflet. You might ask them to tell you if they are worried about your depression or other changes in your behaviour.

If you're taking EVALON

Please note that it's reported that increased risk of probable dementia in women who start using continuous combined or estrogen-only HRT after the age of 65.

→ See a doctor as soon as possible.

Other medicines and EVALON CREAM

Tell your doctor if you are taking, have recently taken or might take any other medicines including herbal medicines or other medicines bought without a prescription.

Your doctor needs to know if you are taking other medicines for any disease condition. This is to make sure you take the correct use of Evalon cream. These conditions include:

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.
- Estriol is a weak gonadotropin inhibitor without other significant effects on the endocrine system.
- HRT use does not improve cognitive function.

→ **Tell your doctor** if you may feel any of these conditions.

Some medicines interact with EVALON CREAM or make it more likely that people will have side effects. These include:

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepin) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St John's wort (Hypericum Perforatum) may induce the metabolism of estrogens.

Clinically, an increased metabolism of estrogens may lead to decreased effect and changes in the uterine bleeding profile.

→ **Tell your doctor** if you are taking any of these or if you start or stop taking any.

→ **Talk to your doctor**, who will discuss suitable methods of contraception with you. Because Evalon is not intended for contraceptive use.

EVALON can also affect the way hormonal contraceptives work, although it's unlikely to make them less effective. If you are using a hormonal contraceptive and you notice any changes in your menstrual pattern, such as breakthrough bleeding or spotting between periods:

→ **Tell your doctor.** These may be signs that EVALON cream is affecting the way your contraceptive is working.

Pregnancy and breast-feeding

→ If you are pregnant, think you may be pregnant or are planning to have a baby ask your doctor for advice before taking this medicine.

Evalon cream is not indicated during pregnancy. If pregnancy occurs during medication with Evalon cream, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or fetotoxic effects.

Evalon cream is not indicated during lactation. Estriol is excreted in breast milk and may decrease milk production

Driving and using machines

There is no information to suggest that Evalon cream affects a patient's ability to drive or operate machinery.

9.3 How to use EVALON CREAM

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor if you are not sure.

How much EVALON C REAM to use

Your doctor will prescribe a low dose to start and gradually increase the dose over a few weeks until you reach a dose that works for you (called the effective dose).

Never use more EVALON CREAM than your doctor tells you to.

For atrophy of the lower urogenital tract:
1 application per day for the first weeks, followed by a gradual reduction, based on relief of symptoms, until a maintenance dosage (e.g. 1 application twice a week) is reached.

How to use your EVALON CREAM

Use your EVALON CREAM as per your doctor advises.

- **Always use the cream** as per your doctor has prescribed.

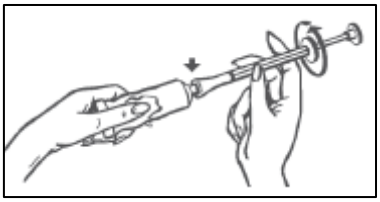
Your doctor may also advise you to start or stop taking other medicines, depending on what condition you're being treated for and the way you respond to treatment.

Method of administration

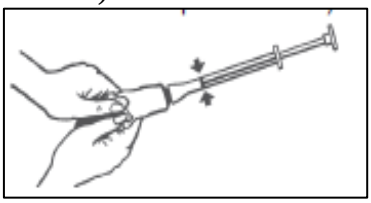
- Evalon Cream should be administered intra vaginally by means of a calibrated applicator before retiring at night.
- 1 application (applicator filled to the ring mark) contains 0.5 g Evalon Cream which corresponds to 0.5 mg estriol.

Instructions for use for the patient

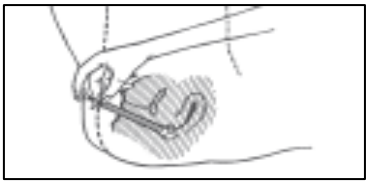
1. Remove cap from the tube, invert it, and use the sharp point to open the tube.
2. Screw the end of the applicator onto the tube. Make sure the plunger is fully inserted into the barrel



3. Squeeze tube slowly to fill the applicator with the cream until the plunger stops (at the red ring, see arrows in the picture below).



4. Unscrew applicator from tube and put cap back on tube.
5. To apply cream, lie down, insert end of applicator deep into the vagina.
6. Slowly push plunger all the way in until applicator is empty.



7. After use, pull plunger out of barrel beyond the point of resistance and wash both in warm, soapy water. Do not use detergents. Rinse well afterwards. DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.
8. The applicator can be re-assembled by fully inserting the plunger into the barrel beyond the point where resistance is felt. Discard the applicator once the tube is empty.

If you use more EVALON CREAM than you should

→ **Contact a doctor or nearest hospital emergency department immediately.** If possible, show them the EVALON cream.

If you use too much **EVALON CREAM you may be more likely to have serious side effects which may be fatal.**

Don't stop using EVALON CREAM without advice

EVALON CREAM must be used for as long as your doctor recommends. Don't stop unless your doctor advises you to.

9.4 Possible Side Effects

Like all medicines, these cream can cause side effects, although not everybody gets them.

- Estrogen-dependent neoplasms benign and malignant,
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65.
- Breast cancer risk
- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women using combined estrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of estrogen-only therapy is substantially lower than that seen in users of estrogen progestagen combinations.
- The level of risk is dependent on the duration of use.

Ovarian cancer

Long-term use of estrogen-only and combined estrogen progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the reported Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT.

Risk of coronary artery disease

The risk of coronary artery disease is slightly increased in users of combined estrogen-progestagen HRT over the age of 60 (see section 'Warnings and Precautions').

Risk of ischemic stroke

The use of estrogen-only and estrogen-progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischemic stroke. The risk of hemorrhagic stroke is not increased during use of HRT. This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store EVALON

Store below 25°C. Do not freeze.
Keep out of reach and site of children.

9.6 Contents of the pack and other information

What EVALON contains:

Each gram contains:

Estriol BP …….1 mg

Chlorhexidine Hydrochloride BP…….0.1 mg

(as preservative)

In a cream base…….q.s

The excipients are Octyldodecanol, Cetyl palmitate, Glycerol, Cetyl alcohol, Stearyl alcohol, Polysorbate 60, Sorbitan stearate, Lactic acid, Chlorhexidine dihydrochloride, Sodium hydroxide, Purified water.

10 Details of manufacturer

Manufactured by:

Aspen Global Incorporated, Mauritius

Under License Holding of Aspen Pharma Trading Limited, Ireland

At, Aspen Bad Oldesloe GmbH

Industriestrasse 32 - 36, 23843 Bad Oldesloe Germany

11 Details of permission or licence number with date

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12 Date of revision

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Marketed by:

TORRENT PHARMACEUTICALS LTD.

Indrad-382721, Dist. Mehsana, India.