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

EVALON/EVALON FORTE

1. Generic Name

Estriol USP 1 mg or 2 mg tablets

2. Qualitative and quantitative composition

EVALON 1 mg Tablets

Each uncoated tablet contains:

Estriol USP……. 1mg

Excipients……...q.s

The excipients used are Amylopectin, Magnesium stearate, Potato starch, Lactose monohydrate.

EVALON FORTE 2 mg Tablets

Each uncoated tablet contains:

Estriol USP…… 2 mg

Excipients ……..q.s

The excipients used are Potato starch, Povidone, Silica colloidal anhydrous, Magnesium stearate, Lactose monohydrate.

3. Dosage form and strength

Dosage Form: Uncoated Tablets

Strength: 1 mg, 2 mg

4. Clinical particulars

4.1 Therapeutic indication

Estrogen deficiency symptoms due to menopause.

4.2 Posology and method of administration

EVALON/EVALON FORTE is an estrogen-only product that may be given to women with or without a uterus.

Posology

- For treatment of estrogen deficiency symptoms: 4-8 mg per day during the first weeks, followed by a gradual reduction. The lowest effective dosage should be used. In case of long-term treatment in women with an intact uterus, monitoring of the endometrium or, alternatively, concomitant use of a progestagen is recommended.
- A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be taken at the normal time.

Method of administration

The tablets should be swallowed with some water or other drink, preferably at the same time every day. It is important that the total daily dose is taken at once.

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
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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 favourable 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/EVALON FORTE, 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 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

Endometrial hyperplasia and carcinoma

Clinical studies showed that the use of divided daily doses and long term use of high dose of estriol (more than 8 mg daily) may lead to endometrium stimulation. In addition, one reported epidemiological study has shown that long-term treatment with low doses of oral estriol may increase the risk for endometrial cancer. The risk increased with the duration of treatment and disappeared within one year after the treatment was stopped. The increased risk mainly concerned less invasive and highly differentiated tumors. In women with an intact uterus, the following precautions should be taken:

- The total daily dose should be taken at one time.
- The patient should be informed to contact a doctor if vaginal bleeding occurs. Vaginal bleeding during medication should always be investigated.
- During long- term treatment, the endometrium should be monitored at least annually. Alternatively, a progestagen should be added, for at least 12-14 days of each calendar month. The increased breast cancer risk associated with combined estrogen-progestagen treatment should be considered, when making a decision to either monitor the endometrium or add a progestagen. There are no indications that treatment with oral estriol alone increases the risk for breast cancer.

Breast cancer

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

Combined estrogen-progestagen therapy

The reported 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 estrogen-progestagen for HRT that becomes apparent after about 3 years.

Estrogen-only therapy

The reported 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/EVALON FORTE carries the same risk. In a reported population-based case-control 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. Longterm (at least 5-10 years) use of estrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. Some studies including the reported WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk. It is uncertain whether long-term use of low potency estrogens (such as EVALON/EVALON FORTE) 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 (see section 'Undesirable Effects'). These studies did not include EVALON/EVALON FORTE and, in the absence of data, it is unknown whether EVALON/EVALON FORTE 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 reported 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, 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 .

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/EVALON FORTE is not intended for contraceptive use.

4.5 Drugs interactions

No examples of interactions between EVALON/EVALON FORTE and other medicines have been reported in clinical practice. Although data are limited, interactions between EVALON/EVALON FORTE 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/EVALON FORTE.

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P_{450} 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.)

Pregnancy

EVALON/EVALON FORTE is not indicated during pregnancy. If pregnancy occurs during medication with EVALON/EVALON FORTE, 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/EVALON FORTE 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 Ovestin 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	Flu-like symptoms

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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.
- 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 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

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. Therefore, toxic symptoms are not expected to occur if several tablets are taken simultaneously. In cases of acute overdose, nausea, vomiting, and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary

5 Pharmacological properties

5.1 Mechanism of Action

EVALON/EVALON FORTE 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/EVALON FORTE has only rarely been reported.

5.3 Pharmacokinetic properties

Absorption

After oral administration estriol is rapidly and almost completely absorbed from the gastrointestinal tract.

Distribution

Peak plasma levels of unconjugated estriol are reached of 8 mg estriol, Cmax is approximately 200 ng/ml, Cmin is approximately 20 ng/ml and Caverage approximately 40 ng/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

For 1 mg tablet: Round and flat tablets with bevelled edges and a diameter of 6 mm, coded DG above 7 below a single break line on one side and blank on the other side. The excipients used are Amylopectin, Magnesium stearate, Potato starch, Lactose monohydrate.

For 2 mg tablet: Round and flat tablets with bevelled edges and a diameter of 6 mm, coded DG above 8 below a single break line on one side and blank on the other side. The excipients used are Potato starch, Povidone, Silica colloidal anhydrous, Magnesium stearate, Lactose monohydrate.

The break line is only to facilitate breaking for ease of swallowing and not to divide in equal doses.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

3 years

8.3 Packaging information

EVALON/EVALON FORTE tablets are packed in push through strips of PVC film backed by aluminium foil provided with heat seal coating on the side in contact with the tablets. Each push through strip contains 30 tablets. The strips are packed in cardboard boxes.

8.4 Storage and handing instructions

- Store below 25ºC, protect from light and moisture.
- Keep out of reach and sight of Children.

9. Patient Counselling Information

Package leaflet: Information for the user

EVALON/EVALON FORTE

Estriol USP 1 mg or 2 mg tablets

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/EVALON FORTE is and what it is used for

EVALON/EVALON FORTE 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/EVALON FORTE

Do not use EVALON/EVALON FORTE:

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

If this applies to you:

- Tell your doctor and don't take EVALON/EVALON FORTE.
- **Take special care with EVALON/EVALON FORTE**
- **Talk to your doctor before taking EVALON/EVALON FORTE:**
- **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/EVALON FORTE 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/EVALON FORTE, 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 taking EVALON/EVALON FORTE:

In women with an intact uterus, the following precautions should be taken:

- The total daily dose should be taken at one time.
- The patient should be informed to contact a doctor if vaginal bleeding occurs. Vaginal bleeding during medication should always be investigated.
- During long- term treatment, the endometrium should be
- monitored at least annually. Alternatively, a progestagen should be added, for at least 12-14 days of each calendar month. The increased breast cancer risk associated with combined estrogen-progestagen treatment should be considered, when making a decision to either monitor the endometrium or add a progestagen. There are no indications that treatment with oral estriol alone increases the risk for breast cancer.

→ 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/EVALON FORTE

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.

EVALON/EVALON FORTE is not intended for contraceptive use.

→ See a doctor as soon as possible.

Other medicines and EVALON/EVALON FORTE

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 dose of EVALON/EVALON FORTE. 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/EVALON FORTE 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/EVALON FORTE is not intended for contraceptive use.

EVALON/EVALON FORTE 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/EVALON FORTE 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/EVALON FORTE is not indicated during pregnancy. If pregnancy occurs during medication with EVALON/EVALON FORTE, 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/EVALON FORTE 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 Ovestin affects a patient's ability to drive or operate machinery.

9.3 How to use EVALON/EVALON FORTE

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/EVALON FORTE to take

It may take a while to find the best dose of EVALON/EVALON FORTE for you. The dose you take will depend on:

- your age
- whether you are taking EVALON/EVALON FORTE with other medicines
- whether you have any other problems.

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 take more EVALON/EVALON FORTE than your doctor tells you to.

- The usual effective dose of EVALON/EVALON FORTE is 4-8 mg per day during the first weeks, followed by a gradual reduction. The lowest effective dosage should be used. In case of long-term treatment in women with an intact uterus, monitoring of the endometrium or, alternatively, concomitant use of a progestagen is recommended.
- A missed dose should be taken as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be taken at the normal time.

How to take your dose of EVALON/EVALON FORTE

Take your dose of EVALON/EVALON FORTE as per your doctor advises. It can be taken with or without food.

- **Always take the full dose** that your doctor has prescribed. Never take only part of a tablet.

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.

Direction for use:

The tablets should be swallowed with some water or other drink, preferably at the same time every day. It is important that the total daily dose is taken at once

If you take more EVALON/EVALON FORTE than you should

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

If you take too much **EVALON/EVALON FORTE you may be more likely to have serious side effects which may be fatal.**

If you forget to take a single dose of EVALON/EVALON FORTE

→ Don't take extra tablets to make up for a missed dose. Just take your next dose at the usual time. In case you forget to take multiple doses of EVALON/EVALON FORTE.

→ **Ask your doctor for advice on how to start taking it again.** It's important that you do this.

Don't stop taking EVALON/EVALON FORTE without advice

EVALON/EVALON FORTE must be taken 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 tablets 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 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.

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/EVALON FORTE

Store below 25ºC, protect from light and moisture.

Keep out of reach and sight of children.

9.6 Contents of the pack and other information

What EVALON/EVALON FORTE contains:

EVALON 1 mg Tablets

Each uncoated tablet contains:

Estriol USP……. 1mg

Excipients……...q.s

Round and flat tablets with bevelled edges and a diameter of 6 mm, coded DG above 7 below a single break line on one side and blank on the other side. The excipients used are Amylopectin, Magnesium stearate, Potato starch, Lactose monohydrate.

EVALON FORTE 2 mg Tablets

Each uncoated tablet contains:

Estriol USP…… 2 mg

Excipients ……..q.s

Round and flat tablets with bevelled edges and a diameter of 6 mm, coded DG above 8 below a single break line on one side and blank on the other side. The excipients used are Potato starch, Povidone, Silica colloidal anhydrous, Magnesium stearate, Lactose monohydrate.

The break line is only to facilitate breaking for ease of swallowing and not to divide in equal doses.

10 Details of manufacturer

Manufactured by:

Aspen Global Incorporated, Mauritius

Under License Holding of Aspen Pharma Trading Limited, Ireland

At, Cyndea Pharma S.L, Poligono Industrial Emiliano Revilla Sanz,

Avenida De Agreda, 31. 42110 Olvega (Soria), Spain.

11 Details of permission or licence number with date

IL/FF-000413-RC/FF-002139

12 Date of revision

NA

Marketed by:

TORRENT PHARMACEUTICALS LTD.

Indrad-382721, Dist. Mehsana, India.

IN/EVALON/EVALON FORTE 1 mg, 2 mg/MAY-2021/01/PI