IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0868/007/002
Case No: 2051977

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Rottapharm Ltd

Damastown Industrial Park, **Mulhuddart**, **Dublin 15**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

EPIESTROL - Septem 50 micrograms/24 hours Transdermal Patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **01/12/2008**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

EPIESTROL -Septem 50 micrograms/24hours Transdermal Patch.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains:
5.16 mg of estradiol hemihydrate equivalent to 5.0 mg estradiol/22.50 cm^2 delivering 50 µg of estradiol in 24 hours.

Excipient(s):
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch. Each patch is transparent, colourless, slightly opaque with an elliptical shape and a printed identification code, and covered by a rectangular, transparent protective liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.
The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology
EPIESTROL-Septem is an estrogen-only patch applied to the skin once weekly in order to ensure a continuous supply of estradiol to the body; thus each used system is removed after seven days and replaced by a new one.
Three strengths of EPIESTROL-Septem are available, i.e. EPIESTROL-Septem 25, 50, 75.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration *(see also Section 4.4)* should be used.
Treatment is usually initiated with EPIESTROL-Septem 25.
If after a treatment of 1-2 months with EPIESTROL-Septem 25 applied once weekly the symptoms of estrogen deficiency appear not to be neutralised, a higher dosage can be given.
In case of undesirable effects or symptoms of overdose (e.g. breast tenderness and/or vaginal bleeding), the dose should be reduced.

In women with an intact uterus, a progestagen approved for addition to estrogen treatment must be additionally administered for at least 12-14 days every month/28 day cycle to oppose the development of an estrogen-stimulated hyperplasia of the endometrium *(see Section 4.4 Special Warnings and Special Precautions for Use).*
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

Two therapeutic regimens can be used:

a) Cyclic: EPIESTROL-Septem is dosed cyclically with a treatment-free interval, usually 21 days on and 7 days off. The progestagen is usually added for 12-14 days of the cycle. Withdrawal bleeding may appear during this period.

b) Continuous sequential: EPIESTROL-Septem is dosed continuously. The progestagen is usually added for 12-14 days

(or more) of every 28 day cycle, in a sequential manner.
Continuous sequential treatment may be recommended in cases when marked symptoms of estrogen deficiency recur during the treatment-free period.
Withdrawal bleeding may occur when the progestagen is withdrawn.

The treatment with EPIESTROL-Septem may be initiated at any convenient time for women who are not currently on any estrogen therapy. Women currently using cyclic or sequential estrogen/progestagen therapy should complete the ongoing treatment cycle before beginning treatment with EPIESTROL-Septem; the appropriate time to begin treatment with EPIESTROL-Septem would be the first day of a withdrawal bleeding.
Women who are already using continuous combined estrogen/progestagen therapy may be switched to EPIESTROL-Septem directly.

Method of administration
Apply EPIESTROL-Septem to the skin of the hip, upper quadrant of the buttock, lumbar region or abdomen and press firmly over the whole surface and along the edges to ensure good adhesion.
The absorption capacity of the skin is the rate-determining factor in the release of estradiol from EPIESTROL-Septem.
The application on another (higher) skin region than on the mentioned preferred regions is not recommended, as this might have an influence on the release of estradiol.
The skin of the application site should be clean, dry, not-greasy and free of redness or irritation. Areas of the body which form folds or are subject to friction during movement should be avoided.
EPIESTROL-Septem *should not be applied on or near the breasts.*

Patches should not be applied twice consecutively to the same skin site.

If the patch is correctly applied, it will adhere to the skin for the required one-week period without problems. In the event that a patch does come off, it should be replaced with a new patch for the rest of the one-week dosing period. The patch should then be changed again at the regular time to re-establish the patient's routine schedule. Similarly, if the patch is not changed on the scheduled day, it should be replaced as soon as possible and changed again on the next scheduled day. Forgetting to apply a new patch at the scheduled time may increase the likelihood of break-through bleeding and spotting.

If the patch is correctly applied, the patient may bathe or shower. However, the patch may become detached after a very hot bath or sauna. If this occurs, the patch should be replaced with a new one (as described above). Possibly the sauna should be planned for a day scheduled for the change of the patch.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- 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 have failed to return to normal;
- Known hypersensitivity to the active substances 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.

Medical examination/follow-up
Before initiating 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 breasts should be reported to their doctor or nurse *(see 'Breast cancer' below)*. Investigations, including 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 EPIESTROL-Septem, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below)
- Risk factors for estrogen dependent tumours, 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

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods *(see section 4.8)*. The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
  For patches releasing more than 50 µg/day, the endometrial safety of added progestagens have not been studied.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed estrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years *(see Section 4.8)*.

For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but

returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.
- Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- 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 randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years.
It is estimated that for women who use conjugated estrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate =1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5-10 years) use of estrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

Other conditions

- Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in EPIESTROL-Septem is increased.
- Women with pre-existing hypertriglyceridemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.
- Estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).
- There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamezapin) 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.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied estrogens might be less affected than oral hormones by enzyme inducers.

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

4.6 Pregnancy and lactation

EPIESTROL-Septem is not indicated during pregnancy. If pregnancy occurs during medication with EPIESTROL-Septem treatment should be withdrawn immediately.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Lactation
EPIESTROL-Septem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

EPIESTROL-Septem has no known effects on the ability to drive or use machines.

4.8 Undesirable effects

Approximately 10 to 17% of the patients treated with EPIESTROL-Septem in clinical trials experienced systemic adverse reactions, which were mild and transient. Breast tenderness was reported in 20-35% of patients. Local reactions at the application site, mostly mild erythema with or without pruritus, occurred in 10-25% of patients.
The table below lists the adverse reactions observed with EPIESTROL-Septem and HRT products containing 17β-estradiol.

Organ system class	Common ADRs, >1/100, <1/10	Uncommon ADRs, >1/1,000, <1/100	Rare ADRs >1/10,000, <1/1000
Psychiatric disorders	- Depression		
Central nervous system	- Irritability - Headache	- Migraine - Dizziness	- Changes in libido - Worsening of epilepsy
Vascular disorders		- Increase in blood pressure	- Venous thromboembolism
Gastro-intestinal disorders	- Nausea - Abdominal cramps - Meteorism	- Vomiting	
Hepatobilary disorders		- Disturbed or abnormal liver function tests	
Skin and subcutaneous tissue disorders (1)			- Allergic-contact dermatitis - Reversible post-inflammatory pigmentation - Generalised pruritus and exanthema
Reproductive system and breast disorders	- Breast tenderness and breast pain - Break-through bleeding - Changes in vaginal secretions - Endometrial hyperplasia		- Uterine tumours
General disorders	- Fluid retention with edema - Feeling of heaviness in the legs	- Alterations in glucose tolerance and blood coagulation	- Ocular irritation during contact lenses use - Anaphylactic reactions (sometimes in patients with allergic reactions

	- Weight increase or decrease		in the anamnesis)

(1) Skin reactions are less frequent if EPIESTROL-Septem is applied on the outer upper quadrant of the buttock, changing the site at each application

Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.

For *oestrogen plus progestagen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be
  - For users of *oestrogen-only* replacement therapy
    - between 0 and 3 (best estimate = 1.5) for 5 years' use
    - between 3 and 7 (best estimate = 5) for 10 years' use.
  - For users of *oestrogen plus progestagen* combined HRT,
    - between 5 and 7 (best estimate = 6) for 5 years' use
    - between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestagen combined* HRT (CEE + MPA) per 10,000 women years.
According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
  - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA), the number of *additional* cases would be
  - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) *(see section 4.4).*

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial

cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with estrogen/progestagen treatment:

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer *(see Section 4.4 Special Warnings and Special Precautions for Use).*
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, *see section 4.3 Contraindications and 4.4 Special Warnings and Special Precautions for Use*.
- Myocardial infarction and stroke *(see Section 4.4 Special Warnings and Special Precautions for Use).*
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia *(see Section 4.4 Special Warnings and Special Precautions for Use).*

4.9 Overdose

Overdose symptoms generally lead to breast tenderness**,** abdominal or pelvis swelling, anxiety, irritability or fluid retention. Flatulence may also occur as a symptom of overdosage.
Break-through bleeding may occur as a result of relative estradiol overdosage during progestagen administration (i.e. underdosage of the progestagen).
These symptoms disappear when the transdermal patch is removed or when the dose is reduced.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CA03
Urogenital system and sex hormones

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms.

Clinical trial Information
Relief of menopausal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

The average half-life of estradiol in plasma is about one hour. Plasma clearance is 650-900 litre/day/m^2. Estradiol is metabolised mainly in the liver, the most important metabolites are estriol, estrone and their conjugates (glucuronides, sulphates), which are much less active than estradiol. The metabolites of estradiol are eliminated mainly by the kidney as glucuronides and sulphates. The metabolites of estradiol are also found in faeces, due to an entero-hepatic circulation

Following cutaneous application of EPIESTROL-Septem, estradiol is released from the drug-containing adhesive matri through the skin and reaches the systemic circulation directly, avoiding first-pass metabolism by the liver. Consequently, the estradiol:estrone ratio in plasma, which falls to values below 1 after the menopause and during oral estrogen replacement therapy, return to pre-menopausal levels (approximately 1) with transdermal estradiol.

The nominal daily *in vivo* release rate of EPIESTROL-Septem 50 is 50 µg of estradiol; the system is active for one week. This release rate results in physiological estradiol serum concentrations, i.e. in the range of those observed during the premenopausal early follicular phase, which are constantly maintained throughout the patch application period.

Physiological concentrations of estradiol were achieved 6 hours after application of EPIESTROL-Septem 50 in postmenopausal women, with average concentrations over 257 pmol/l after 12 hours.

Following repeated applications of EPIESTROL-Septem 50 patches at one week intervals, mean maximum serum estradiol concentrations of 286 pmol/l were obtained at steady-state. The serum concentration of estradiol remained within the physiological levels of premenopausal women throughout the seven days of application and returned to

baseline within 12-24 hours after removal of the patch.

The average concentration of estradiol in steady-state conditions was 180 pmol/l. The C_{min} of estradiol, shown to be at the steady state, was 106 pmol/l.

5.3 Preclinical safety data

Animal studies with estradiol have shown expected estrogenic effects There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.
Local tolerance studies performed in the rabbit have demonstrated the good skin tolerability of the transdermal patch after single and repeated applications. The patch did not show any sensitisation potential in the guinea pig.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Estradiol-containing
Adhesive matrix: acrylic copolymers (Durotak 387-2353; Durotak 387-2287)
Backing foil: polyethylene terephthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Two years.

6.4 Special precautions for storage

Do not store above 25°C.
EPIESTROL-Septem should be stored in an intact sachet.

6.5 Nature and contents of container

EPIESTROL-Septem 50 is packed in a cardboard box containing 4 or 12 transdermal delivery systems sealed individually in protective sachets consisting of 4 layers: Surlyn, heat-sealable material (inner layer), aluminium foil, polyethylene and paper (outer layer).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Tear open the sachet at the indentation (do not use scissors to avoid damaging the patch) and remove the patch. Hold the patch between the thumb and index finger at the corner of the pull-off-tag. Detach the protective liner with the other hand and discard it.

Do not touch the adhesive side of the patch . Apply the patch to the skin holding between the thumb and index finger the part still covered by the protective liner. Detach the remaining part of the protective liner and press firmly for about 10 seconds on the whole surface of the patch.

Pass a finger along the edges to assure good adhesion.

After use, the patch should be folded with the adhesive part inside and discarded.

7 MARKETING AUTHORISATION HOLDER

Rottapharm Ltd.,
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8 MARKETING AUTHORISATION NUMBER

PA 868/7/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1 December 2008

10 DATE OF REVISION OF THE TEXT

September 2009