SPECIALIST INFORMATION (Summary of Product Characteristics)

1) NAME OF THE MEDICINAL PRODUCT:

Estrogel®

2) QUALITATIVE AND QUANTITATIVE COMPOSITION:

1 Unit dose (1.25 g Estrogel®) contains 0.75 mg 17β-oestradiol (estradiol).

3) PHARMACEUTICAL FORM:

Hydroalcoholic gel (transdermal system)

4) CLINICAL PARTICULARS:

4.1. Therapeutic indications:

Estrogen deficiency symptoms because of natural or surgically induced menopause, which may include, for example, hot flushes, sleep disturbances, atrophic vaginitis, dyspareunia, urinary incontinence and accompanying emotional disturbances (e.g. depression). Also as second-line treatment for prevention of osteoporosis in postmenopausal women at high risk of future fractures, if these women are intolerant of other medicinal products for the prevention of osteoporosis or if these products are contraindicated in these women.

Exclusive use of this drug speciality during the menopause years should not be initiated unless the patient has had a hysterectomy.

4.2. Posology, method and duration of administration:

The usual daily dose is 2 unit doses (2.5 g Estrogel®). If symptoms are not relieved the dose can be increased to 4 unit doses (5 g Estrogel®) daily.

Treatment with Estrogel® is usually cyclic: 3 weeks treatment followed by a treatment free week. During the treatment free week breakthrough bleeding may occur. Continuous, non-cyclic treatment can be considered for women who have had a hysterectomy or in women who have severe estrogen deficiency symptoms during the treatment free interval.

In women with an intact uterus it is necessary to combine treatment with gestagen to oppose non-physiological stimulation of the endometrium (with the risk of carcinoma developing).

If estradiol using Estrogel® is given continuously it is advisable to take the accompanying gestagen for 10 - 12 consecutive days per month.

Cyclic application of estradiol can be carried out according to the following regimen: From 1st to 21st day of the cycle 2 unit doses of Estrogel® daily, combined with a gestagen dose for the last 10 - 12 days of estrogen use. The last 7 days of the cycle are free of treatment.
For both schemes a withdrawal bleed generally occurs after completion of the gestagen therapy.

The gel is applied to a skin area approx. the size of two hands (ca. 20 x 20 cm) (abdomen, shoulders, arms or thighs), and it should not be applied to the breasts. It is best applied in the morning or evening after washing. The gel does not have to be massaged in; it should be allowed to dry for about five minutes before covering with clothing.

4.3. Contraindications:

Pregnancy and lactation period; hypersensitivity to one of the ingredients; hormone-dependent tumours (e.g. carcinoma of the breast or endometrium, leiomyoma of the uterus, existing, treated or clinically suspected), endometriosis, undiagnosed vaginal bleeding, acute or history of thromboembolic disorders, serious cardiovascular diseases; sickle cell anaemia; severe liver disorder; jaundice or persistent pruritus during an earlier pregnancy; Dubin-Johnson syndrome, Rotor syndrome; previous or existing tumours of the liver; otosclerosis with deterioration in previous pregnancies. In women with an intact uterus, during the menopause it is necessary to combine treatment with concomitant regular administration of gestagen.

Particular caution and monitoring is necessary for: history of thrombophlebitis, status post myocardial infarction; varices, hypertension, heart failure or renal insufficiency, latent or manifest diabetes mellitus, epilepsy, cholelithiasis, cholecystitis, porphyria, migraine, depression, multiple sclerosis, chorea minor, bronchial asthma, tetany.

4.4. Special warnings and precautions for use:

Before initiating treatment pregnancy must be excluded.

As with any hormone replacement therapy a thorough general examination should be carried out before Estrogel® is prescribed and, for treatment over prolonged periods a gynaecological examination at least annually to include breast examination.

Tenderness in the breasts or breakthrough bleeding may be indicative of overdosage so that the lowest effective dose must be selected in all cases. Repeated episodes of bleeding not due to too high a dose must be investigated and diagnosed.

As prolonged use of exclusive estrogen treatment in postmenopausal women with an intact uterus may increase the risk of endometrial hyperplasia and carcinoma, the addition of a sequential progestogen therapy is essential for women receiving estrogen treatment. Sequential progestogen therapy protects the endometrium from the effect of estrogens described above.

Patients with heart failure, renal or hepatic dysfunction, severe hypertension or epilepsy should be monitored especially carefully.

Reasons for immediate discontinuation: first emergence of migraine-type headaches or frequent occurrence of unusually severe headaches; sudden onset of disturbances in vision and hearing; first signs of thromboembolisms, angina pectoris, elective surgery (four weeks beforehand); prolonged periods of immobilisation (e.g. following accidents); increase in epileptic attacks; significant increases in blood pressure; cholestasis, jaundice, hepatitis, pruritus.

6 months should elapse after viral hepatitis has subsided before using Estrogel®.
The risk of developing thromboembolism is increased by smoking, old age and taking oral estrogens for many years, there is no clinical experience on the use of Estrogel® in this regard.
Currently there is some indication that the relative risk of breast cancer may be slightly higher in postmenopausal women taking long-term hormone replacement therapy. It is important for the benefits to be weighed carefully against the risk before treatment is given for longer than 5 years.
Women with a positive family history of breast cancer have an increased risk of developing this disease. As there is so far no definite clarification of the influence of hormone replacement therapy on the risk, these women must be subject to careful medical supervision.

4.5. Interactions with other medicinal products:
Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone, rifampicin), may impair the activity of estrogens. By contrast oral estrogens can enhance the effect of benzodiazepines and antidepressants, glucocorticoids and theophylline and influence the effect of the following medicinal products: anticoagulants, antidiabetics, lipid lowering drugs and antihypertensive agents.

The extent of interference with transdermally administered estradiol is not known. It is known that orally administered estrogen has an influence on the following laboratory tests: Glucose tolerance, blood coagulation, metyrapone, thyroid function tests. These interactions cannot be ruled out for use of Estrogel®.

4.6. Pregnancy and lactation:
Estrogel® is contraindicated in pregnancy and during lactation.

4.7. Effects on ability to drive and use machines:
None known.

4.8. Undesirable effects:
Breast:  Tenderness, pain, enlargement.
Genital tract: Breakthrough bleeding, endometrial hyperplasia (when estrogen treatment is not supplemented by sequential gestagen therapy).
Local intolerance/skin irritation: occasional pruritus or mild and transient reddening at the site of application may be caused by the gel base.
Rarely:
CNS: Headaches (also migraine), depression.
Gastrointestinal tract: Nausea, abdominal cramps, sensation of pressure and bloating.
Others: Sodium and water retention, edema.
Systemic undesirable effects reported for orally administered estrogens such as weight gain, increase in blood pressure, disturbances of the coagulation system and liver function, change in glucose tolerance (especially at the start of therapy and in prediabetic patients) also cannot be ruled out for Estrogel®.
However, in view of the tiny amounts of estradiol transferred through the skin these undesirable effects are less likely. Orally administered estrogens may increase the risk of cholecystitis, cholelithiasis and possibly in very rare cases of liver tumours. So far there is no evidence that this is the case for Estrogel®.

4.9. Overdosage:

Symptoms: Tenderness in the breasts and/or breakthrough bleeding possibly also mood changes with anxiety are the general signs of an overdosage.

Therapy: Reduction in the dose.

5. PHARMACOLOGICAL PROPERTIES:

5.1. Pharmacodynamic properties:

Estrogel® permits transdermal administration of estradiol (17β-oestradiol); the active substance is delivered directly into the bloodstream (with no first-pass effect) and to the target organs. Estradiol, which in women is formed from the menarche to the menopause mainly by the ovarian follicle, is the most potent estrogen at the receptor level. Following the menopause, when ovarian function ceases, only a little estradiol is produced in the body, and this is formed in the liver and fatty tissue from estrone. The loss of ovarian estradiol induces vasomotor and thermoregulatory instability in many women (hot flushes), sleep disturbances and increasing atrophy of mucous membranes and other tissues in the urogenital system. After oral administration estradiol is metabolised in the intestine and particularly in the liver to estrone and its conjugates. With transdermal application using Estrogel® on the other hand estradiol - as there is no hepatic first-pass effect - is delivered in an unchanged form directly into the bloodstream and in physiological quantities; there is consequently less stress on the liver than with oral administration. Estradiol concentrations are raised by Estrogel® to values similar to those in the early to mid follicular phase. Transdermally administered estradiol has according to studies so far available no influence on blood coagulation factors fibrinopeptide A, high molecular fibrinogen, antithrombin III (content and activity). It also has no effect on the blood levels of circulating renin substrate or sex hormone-, thyroxine- and cortisol-binding globulin.

5.2. Pharmacokinetic properties:

After administration of 2 unit doses (2.5 g) Estrogel® (1.5 mg estradiol) relatively uniform plasma concentrations of between 65 and 85 pg/ml are found. When the dose is increased dose proportionality is largely uniform, and interindividual fluctuations are similar to those for other transdermal forms of administration. In steady-state the estradiol levels are between 50 and 200 pg/ml for dosages of 2.5 g to 5 g Estrogel® per day. The half-life for elimination of estradiol from plasma is about 1 hour. Estradiol is metabolised mainly in the liver. The most important metabolites are estriol and estrone and their conjugates (glucuronide, sulfate). They are much less potent than estradiol. Estrogen
metabolites undergo enterohepatic circulation. Excretion is mainly in the urine in the form of conjugates. At the end of replacement treatment plasma estradiol levels return rapidly to the baseline value, the excretion rate of urinary estradiol conjugates returns to baseline values on the 2nd day.

5.3.  Preclinical safety data:

Based on local tolerability studies of Estrogel® in the rabbit, the preparation with a skin irritation score of 0.4, can be regarded as non-irritant to the skin. In studies in mice and guinea pigs Estrogel® had neither antigenic nor phototoxic or photosensitising effects.

6.  PHARMACEUTICAL PARTICULARS

6.1.  Excipients:

Carbopol, triethanolamine, ethanol, purified water

6.2.  Incompatibilities:

None known

6.3.  Shelf-life:

36 months. Do not use for longer than 8 weeks after the first application.

6.4.  Special precautions for storage:

Do not store above 25° C. Protect from light.

6.5.  Nature and contents of the container:

80 g metered-dose pump (64 unit doses).
Pack size 1 unit.

6.6.  Instructions for use and handling:

The metered-dose pump does not contain aerosol propellant. When the pump is pressed 1.25 g of the gel is delivered (Fig. 1). The first unit dose may not be exact and should be discarded. After 64 individual doses the amount of gel dispensed is very small; the rest of the pack should then no longer be used and the metered-dose pump thrown away with the household refuse.
Each time it is used the small cap should be replaced on the tip of the dispenser (Fig. 2), and the cover put back over the top of the pump.
7. NAME OR COMPANY AND ADDRESS OF THE PHARMACEUTICAL COMPANY:

Marketing authorisation holder: VIATRIS Pharma GmbH, Liesinger-Flurgasse 2c, 1230 Vienna

Manufacturer: Laboratoires Besins International, Paris

8. MARKETING AUTHORISATION NUMBER(S): 1-22063

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION:

12 August 1997

10. DATE OF REVISION OF THE TEXT:

February 2004

11. LEGAL CATEGORY:

POM