1. NAME OF THE MEDICINAL PRODUCT
For tablets:
Ovestin 1 mg or 2 mg tablets.

For cream:
Ovestin 1 mg cream.

For pessaries:
Ovestin 0.5 mg pessaries.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
For tablets:
Each tablet contains 1 mg or 2 mg estriol.

For cream:
Each gram of cream contains 1 mg estriol.

For pessaries:
Each pessary contains 0.5 mg estriol.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM
For tablets:
Tablet.
White, round, flat, scored tablets, with beveled edges. All tablets are marked with “Organon” on one side and a code on the other side. For 1 mg tablets: DG above and 7 below the score line. For 2 mg tablets: DG above and 8 below the score line.

For cream:
Cream.
Homogeneous, smooth, white to nearly white mass of creamy consistency.

For pessaries:
Pessary.
White, torpedo formed pessaries.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For tablets:
• Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.
• Infertility due to cervical hostility.

For cream and pessaries:
• Hormone replacement therapy (HRT) for the treatment of atrophy of the lower urogenital tract related to estrogen deficiency.

For all presentations:
• Pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery.
• A diagnostic aid in case of a doubtful atrophic cervical smear.

4.2 Posology and method of administration
For tablets:
• 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 (see also Section 4.4).
• For infertility due to cervical hostility:
In general 1-2 mg per day on days 6-15 of the menstrual cycle. However, for some patients dosages as low as 1 mg per day are sufficient, whereas others may need up to 8 mg per day. Therefore, the dosage should be increased each month until an optimal effect on the cervical mucus is obtained.
• As pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery: 4-8 mg per day in the 2 weeks before surgery; 1-2 mg per day in the 2 weeks after surgery.
• As a diagnostic aid in case of a doubtful atrophic cervical smear: 2-4 mg per day for 7 days before taking the next smear.
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.
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 (see Section 4.4).

For cream:

6. To apply cream, lie down, insert end of applicator deep into the vagina and slowly push plunger all the way in.

After use, pull plunger out of barrel and wash both in warm, soapy water.

Do not use detergents. Rinse well afterwards.

DO NOT PUT THE APPLICATOR IN HOT OR BOILING WATER.

A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be skipped and the regular dosing scheme continued.

Two doses must never be administered on the same day.

For pessaries:

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.

As pre- and postoperative therapy in postmenopausal women undergoing vaginal surgery:
1 application per day in the 2 weeks before surgery; 1 application twice a week in the 2 weeks after surgery.

As a diagnostic aid in case of a doubtful atrophic cervical smear:
1 application on alternate days in the week before taking the next smear.

Ovestin cream should be administered intravaginally by means of a calibrated applicator before retiring at night.

1 application (applicator filled to the ring mark) contains 0.5 g Ovestin cream which corresponds to 0.5 mg estriol.

Instructions for use for the patient

1. Apply the vaginal cream before retiring at night.
2. Remove cap from the tube, invert it, and use the sharp point to open the tube.
3. Screw the end of the applicator onto the tube.
4. Squeeze tube to fill the applicator with the cream until the plunger stops.
5. Unscrew applicator from tube and replace cap on tube.

Ovestin pessaries should be inserted intravaginally before retiring at night.

A missed dose should be administered as soon as remembered, unless the missed dose is noticed at the day of the next dose. In the latter case the missed dose should be skipped and the regular dosing scheme continued.
Two doses must never be administered on the same day.
For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration of time should be used (see Section 4.4).

In women not taking HRT or women who switch from a continuous combined HRT product, treatment with Ovestin may be started on any day. Women who switch from cyclic HRT regimen should start Ovestin treatment one week after completion of the cycle.

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 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 failed to return to normal
- Known hypersensitivity to the active substance or to any of the excipients
- Porphyria

For tablets:
- Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption (see Section 6.1).

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 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 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 Ovestin, in particular:
  - Leiomyoma (uterine fibroids) or endometriosis
  - A history of, or 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

**Endometrial hyperplasia**

*For tablets:*
- Clinical studies showed that the use of divided daily doses and long-term use of high doses of estriol (more than 8 mg daily) may lead to endometrium stimulation. In addition, one 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 the cycle.

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.

*For cream and pessaries:*
- 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**

HRT may increase mammographic density. This may complicate 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.

A randomized 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 estrogens, estrogen-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 estrogens (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 estrogen 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.

It is unknown whether Ovestin carries the same risk. In a recent 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.  

**Venous thromboembolism**

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomized controlled trial and epidemiological studies found a 2-3 fold higher risk for users compared with non-users. For nonusers 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 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 an 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. These studies did not include Ovestin and, in the absence of data, it is unknown whether Ovestin carries the same risk. Generally recognized risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index >30 kg/m²) and systemic lupus erythematosus (SLE). There is no consensus about the role of varicose veins in VTE. Patients with a history of recurrent 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 immobilization, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilization is liable to follow elective surgery, particularly abdominal surgery or orthopedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. If Ovestin is used for the indication ‘pre-and post operative therapy...’ consideration should be given to prophylactic treatment against thrombosis.1) If VTE develops after initiating Ovestin 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).

1) Sentence to be deleted if not relevant for a specific country.

**Coronary artery disease (CAD)**

There is no evidence from randomized controlled trials of cardiovascular benefit with continuous combined conjugated estrogens 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 randomized 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 randomized clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischemic 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
drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. hydantoins, barbiturates, carbamazepin), anti-infectives (e.g. griseofulvin, rifamycins, the antiretroviral agents nevirapine and efavirenz) and herbal preparations containing St John’s wort (Hypericum Perforatum).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Clinically, an increased metabolism of estrogens may lead to decreased effectiveness of Ovestin and changes in uterine bleeding profile.

Estriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophyllines and troleandomycin.

4.6 Pregnancy and lactation
Ovestin is not indicated during pregnancy. If pregnancy occurs during medication with Ovestin, 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.

Ovestin 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
As far as is known Ovestin has no effect on alertness and concentration.

4.8 Undesirable effects
For tablets:
From literature and safety surveillance monitoring, the following adverse reactions have been reported:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse reactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast discomfort and pain</td>
</tr>
<tr>
<td></td>
<td>Postmenopausal spotting</td>
</tr>
<tr>
<td></td>
<td>Cervical discharge</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Fluid retention</td>
</tr>
</tbody>
</table>

*MedDRA version 9.1

These adverse reactions are usually transient, but
Breast cancer
According to evidence from a large number of epidemiological studies and one randomized 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.

Other adverse reactions have been reported in association with estrogenprogestagen treatment. In the absence of data, it is unknown whether Ovestin is distinct in this regard.

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer and breast cancer. For further information see Sections “4.3 Contraindications” and “4.4 Special warnings and precautions for use”
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than among non-users. In the absence of data, it is unknown whether Ovestin is distinct in this regard. For further information see Sections “4.3 Contraindications” and “4.4 Special warnings and precautions for use”
- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia (see Section 4.4)

For cream and for pessaries:
From literature and safety surveillance monitoring, the following adverse reactions have been reported:

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Adverse reactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Application site irritation and pruritus</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Breast discomfort and pain</td>
</tr>
</tbody>
</table>

*MedDRA version 9.1

These adverse reactions are usually transient, but may also be indicative of too high a dosage.
Ovestin 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.

Clinical trial information
- Relief of menopausal symptoms was achieved during the first weeks of treatment.
- Vaginal bleeding after treatment with Ovestin has only rarely been reported.

5.2 Pharmacokinetic properties
For tablets:
After oral administration estriol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma levels of unconjugated estriol are reached within 1 hour of administration. After oral administration of 8 mg estriol, $C_{\text{max}}$ is approximately 200 ng/ml, $C_{\text{min}}$ is approximately 20 ng/ml and $C_{\text{average}}$ approximately 40 ng/ml.

For cream and pessaries:
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. Peak plasma levels are reached 1-2 hours after application. After vaginal application of 500 microgram estriol, $C_{\text{max}}$ is approximately 100 pg/ml, $C_{\text{min}}$ is approximately 25 pg/ml and $C_{\text{average}}$ is approximately 70 pg/ml. After 3 weeks of daily administration of 0,5 mg vaginal estriol, Caverage has decreased to 40 pg/ml.
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. 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.

5.3 Preclinical safety data
No special particulars.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
For tablets:
1 mg tablets:
Amylopectin
Magnesium stearate
Potato starch
Lactose monohydrate
2 mg tablets:
Potato starch
Povidone
Silica colloidal anhydrous
Magnesium stearate
Lactose monohydrate

For cream:
Octyldodecanol
Cetyl palmitate
Glycerol
Cetyl alcohol
Stearyl alcohol
Polysorbate 60
Sorbitan stearate
Lactic acid
Chlorhexidine dihydrochloride
Sodium hydroxide
Purified water

For pessaries:
Hard fat

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
For tablets:
5 years.

For cream and pessaries:
3 years.

6.4 Special precautions for storage
For tablets:
Store at 2 - 30°C. Store in original package to protect from light and moisture.

For cream:
Store at 2 - 30°C. Do not freeze.

For pessaries:
Store at 2 - 25°C. Store in original package to protect from light and moisture.

6.5 Nature and contents of container
For tablets:
Ovestin 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 pushthrough strip contains 30 tablets. The strips are packed in cardboard boxes.

For cream:
Ovestin 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 applicator consists of a styrene acrylonitril barrel and a polyethylene plunger. Each tube is packed together with an applicator in a cardboard box.

For pessaries:
Ovestin pessaries are packed in blisters of polyvinylchloride (PVC-PE). Each blister contains 5 pessaries. The blisters are packed in cardboard boxes.

6.6 Special precautions for disposal
No special requirements.

10. DATE OF REVISION OF THE TEXT
August 2007