PRODUCT INFORMATION

Ovestin Ovula

NAME OF THE MEDICINE

Ovestin Ovula
Oestriol 0.5 mg pessary

Molecular formula: C₁₈H₂₄O₃
Molecular weight: 288.4
CAS No. 50-27-1

Chemical name:
Estra - 1, 3, 5 (10) - triene - 3,16α - 17β - triol

Pharmaceutical form:
Pessaries, each containing 0.5 mg oestriol.

DESCRIPTION

Oestriol, the active ingredient of Ovestin is a synthetic white odourless micronised powder. Like other oestrogenic substances it is practically insoluble in water but is soluble in ethanol, chloroform, dioxane, ether and vegetable oils.

Each Ovestin Ovula pessary contains 0.5 mg of oestriol.

Inactive ingredients: hard fat, cetomacrogol 1000 and glyceryl ricinoleate.

Pharmacotherapeutic group: natural and semisynthetic oestrogens
ATC code: G03C-A04

PHARMACOLOGY

Pharmacodynamic properties:
Ovestin contains the natural female hormone oestriol. Unlike other oestrogens, oestriol 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. Oestriol is particularly effective in the treatment of urogenital symptoms. In case of atrophy of the lower urogenital tract oestriol 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, micturition complaints and mild urinary incontinence.

Pharmacokinetic properties

Absorption:
Intravaginal administration of oestrilol ensures optimal availability at the site of action. Oestrilol is also absorbed into the general circulation, as is shown by a sharp rise in the plasma levels of unconjugated oestrilol. Systemic absorption of oestrilol from Ovestin Ovula can produce significant plasma levels. Furthermore the initial circulation through the liver, which reduces the effectiveness of oral oestrilol by conjugation, is bypassed. However, with the doses recommended, absorption has not been sufficient to produce endometrial proliferation or any untoward systemic effect.

Following vaginal administration of 0.5 mg of oestrilol, plasma levels of unconjugated and conjugated oestrilol reach a maximum within 1 to 2 hours. After vaginal administration of 0.5 mg oestrilol, C_max is approximately 100 picogram/mL, C_min is approximately 25 pg/mL and C_average is approximately 70 pg/mL of unconjugated, presumably biologically active oestrilol. The proportion of unconjugated hormone was similar to that reported during pregnancy about 10%. After 3 weeks of daily administration of 0.5 mg vaginal oestrilol, C_average had decreased to 40 pg/mL.

Distribution:
Nearly all (90%) oestrilol is bound to albumin in the plasma and in contrast with other oestrogens hardly any oestrilol is bound to sex hormone-binding globulin.

Metabolism:
In contrast to oestradiol and oestrone, apart from being conjugated, oestrilol is not metabolised before excretion. It is also less strongly protein-bound and thus more rapidly cleared from the plasma. The metabolism of oestrilol consists principally of conjugation and deconjugation during the enterohepatic circulation. Various conjugates of oestrilol are found in both the urine and the faeces. The half-life of oestrilol in plasma after vaginal administration has been estimated as approximately 5 to 7 hours.

Excretion:
Oestrilol, a metabolic end product, is mainly excreted via the urine in the conjugated form. Only a small fraction (2%) is excreted via the faeces, mainly as unconjugated oestrilol.

INDICATIONS

Vulvo-vaginal complaints due to oestrogen deficiency associated with the climacteric and the postmenopause or after ovariectomy:

- Atrophic vaginitis
- Pruritus vulvae
- Dyspareunia due to vulvo-vaginal atrophy
- As auxiliary therapy in the treatment of vaginal infections
- As pre-operative therapy for vulvo-vaginal surgery and during subsequent convalescence
- Ulcers in cases of prolapse of the uterus or vagina
- To avoid misinterpretation of a cytological smear
CONTRAINDICATIONS

- Pregnancy
- Known past, or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours such as carcinoma of the endometrium.
- Undiagnosed genital bleeding
- Previous or current active venous thromboembolism (deep venous thrombosis, pulmonary embolism).
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see PRECAUTIONS).
- A history of recurrent venous thromboembolism (VTE) or known thrombophilic disease in a patient who is not already on anticoagulant treatment (see PRECAUTIONS).
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
- Thrombophlebitis, or a past history of this condition.
- A history during pregnancy or previous use of steroids of a manifestation or deterioration of otosclerosis.
- Endometriosis
- Untreated endometrial hyperplasia
- Porphyria
- Severe liver dysfunction, or a history of liver disease as long as liver function tests failed to return to normal.
- Disturbed lipid metabolism, particularly in the presence of other risk factors which may indicate a predisposition to cardiovascular disorders.
- Known hypersensitivity to the active substances or to any of the excipients.

See Use in Pregnancy and Use in Lactation under PRECAUTIONS below.

PRECAUTIONS

Special warnings and precautions for use:
For the treatment of postmenopausal symptoms, hormone replacement therapy (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, together with a thorough general and gynaecological examination. 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 current accepted practices, modified according 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 aggravated during pregnancy or previous hormone treatment, the benefits of treatment should be weighed against the possible risks. In these cases the patient should be closely supervised.
It should be taken into account that these conditions may, in rare cases, recur or be aggravated during treatment with Ovestin:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of thromboembolic disorders or the presence of risk factors (see below)
- Risk factors for oestrogen 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
- Epilepsy
- Asthma
- Otosclerosis
- Severe pruritus
- Cholestatic jaundice
- Herpes gestationis

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 headaches
- Pregnancy

Endometrial hyperplasia and carcinoma:
In order to prevent endometrial stimulation, the daily dose should not exceed 1 application (0.5 mg oestradiol) 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 oestradiol, but not vaginal oestradiol, may increase the risk for endometrial cancer. This risk increases with the duration of treatment and disappeared within one year after the treatment was terminated. The increase risk mainly concerned less invasive and highly differentiated tumours. 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 oestradiol than in subjects treated with other oestrogens.

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 estrogens, estrogen-progestagen combinations or tibolone for HRT for several years (see ADVERSE EFFECTS). 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 oestradiol (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, oestriol was found not to be associated with an increased risk of breast cancer, in contrast to other estrogens. Another, large observational study, the Million Women Study, has shown that compared to never-users, use of oestrogen-progestogen combined HRT is associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88-2.12). In the small number of women using vaginal or other topical HRT preparations, no increased risk of breast cancer was observed (RR = 0.67, 95% CI 0.30-1.49). For all HRT, including Ovestin, the benefits and risks of treatment should be carefully considered. It is recommended that women are encouraged to report any changes in their breasts to their doctor. Regular breast examinations and, where appropriate, mammography should be carried out, particularly in women with risk factors for 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 randomized controlled trial and epidemiological studies found a 2-3 fold 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 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.

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 (see CONTRAINDICATIONS).

Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilization, a personal history or family history, obesity (Body Mass Index > 30 kg/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and breast cancer. There is no consensus about the role of varicose veins in VTE. The risk of VTE may be temporarily increased with prolonged immobilisation, 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 immobilisation is liable to follow elective surgery, particularly abdominal surgery or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible.
Use of HRT in patients with a history of recurrent VTE or known thrombophilic states already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT (see also CONTRAINDICATIONS). The presence of a personal or strong family history of recurrent thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a definitive diagnosis has been made or anticoagulant treatment initiated use of HRT in such patients should be viewed as contra-indicated. Women already on anticoagulant treatment requires careful consideration of the benefit-risk of use of HRT.

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.

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).

**Coronary artery disease (CAD):**
There is no evidence from randomised 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.

It is suspected that oestrogen replacement therapy in post-menopausal women may increase the risk of myocardial infarction. Women who use oestrogens should therefore be strongly advised against smoking as it may further increase the risk of adverse cardiovascular effects.

Combined hormone replacement therapy should not be used for long term maintenance of general health, including primary prevention of cardiovascular disease. Ovestin does not fall in to this category. The concurrent use of Ovestin and other oestrogenic agents or partial oestrogenic agents has not been studied and is therefore not recommended as its use with other oestrogenic agents or partial oestrogenic agonists may contribute to long term risk.

**Ischaemic 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 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 or low potency estrogens (such as Ovestin) confers a different risk than estrogen-only products.

Other conditions:
- Oestrogens 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 Ovestin is increased.
- Oestriol is a weak gonadotrophin inhibitor without other significant effects on the endocrine system.
- Benign hepatic adenoma and hepato-cellular carcinoma appear to be associated with the use of oral contraceptives but such lesions have not been reported with the use of other oestrogen preparations.
- A two fold increase has been reported in the risk of gall bladder disease in women receiving oral oestrogen preparations (including oral contraceptives). However, there have been no reports of gall bladder disease in association with oestriol tablets, cream or pessaries.
- Susceptible women may experience a rise in blood pressure. Care should be exercised in prescribing oestrogens for patients with hypertension; regular measurement of blood pressure and careful observation for progressive hypertension is recommended.
- Because oestrogens may increase the size of uterine fibroids, the pathologist should be advised of oestrogen therapy when relevant specimens are submitted.
- Patients with diabetes, severe migraine, epilepsy, asthma, fibrocystic mastopathy, significant cardiac or renal dysfunction should be observed carefully during administration of oestrogens.
- Patients with metabolic bone disease or renal insufficiency should be treated with caution because of the effect of oestrogens on the metabolism of calcium and phosphorus.
- 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.

Carcinogenicity/Mutagenicity:
Long term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinoma of the breast, uterus, cervix, vagina, testis and liver. The relevance of these findings is uncertain.

Use in Pregnancy (Category B1):
Oestrogen must not be used during pregnancy (see CONTRAINDICATIONS). 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 oestrogens indicate no teratogenic or fetotoxic effects.
Use during Lactation:
There are insufficient data on the use of this medicine during breast-feeding to assess potential harm to the infant. Oestriol is excreted in breast milk and may decrease milk production.

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

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. hydantoins, barbiturates, carbamazepine), anti-infectives (e.g. griseofulvin, rifamycins, the antiretroviral agent's 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 oestrogens may lead to decreased effectiveness of Ovestin and changes in uterine bleeding profile.

Oestriol may possibly increase the pharmacological effects of corticosteroids, succinylcholine, theophyllines and troleandomycin. If necessary the dosage should be reduced. Oestriol may possibly change the effectiveness of oral anticoagulants.

Effects on laboratory tests:
Unknown.

Effects on ability to drive and use machines:
As far as is known Ovestin has no effect on alertness and concentration.

ADVERSE EFFECTS

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

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<tr>
<th>System organ class</th>
<th>Adverse reactions*</th>
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<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>
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*MedDRA version 9.1

As with any product that is to be applied to mucosal surfaces, Ovestin Ovula may cause local irritation or itching in very sensitive persons at the beginning of treatment. Breast tension or pain may occasionally occur (frequency 0.1-1%). In general, this is of a temporary nature, but may also be indicative of too high a dosage.

Other adverse effects have been reported in association with oestrogen-only and oestrogen-progestagen combined treatment. In the absence of data, it is unknown whether Ovestin is distinct in this regard.
- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer and breast cancer. For further information see CONTRAINDICATIONS and PRECAUTIONS.
- 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 CONTRAINDICATIONS and PRECAUTIONS.
- Myocardial infarction and stroke.
- Gall bladder disease
- Skin and subcutaneous disorders: Chloasma, erythema multiforme, erythema nodosum, vascular purpure.
- Probable dementia over the age of 65 (see PRECAUTIONS).

Breast cancer risk:
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. Topical (vaginally administered) products were not included in the WHI study and there are limited data in the Million Women Study. At present, there is uncertainty whether these data apply to oestriol.

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 trials 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 responding 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 Special warnings and precautions for use]

**DOSAGE AND ADMINISTRATION**

- Ovestin Ovula is intended for intravaginal administration, before retiring at night. Each pessary contains 0.5 mg oestriol.

- For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration of time should be used (see Special warnings and precautions for use).

- Usual dosage for vulvo-vaginal complaints associated with the menopause: one pessary per day for 2-3 weeks initially.

- As maintenance dosage, one pessary once or twice a week is recommended. Medication should be discontinued every 2 to 3 months for a period of 4 weeks to assess the necessity for further treatment.

- Pre-surgery therapy (one pessary per day) should begin 2 weeks before the operation (see PRECAUTIONS).

- In the case of a suspect cytological smear a daily application of 0.5 mg oestriol for 7 days is recommended before re-evaluating the cytology.

- 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.

- 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 regime should start Ovestin treatment 1 week after completion of the cycle.

**Administration - Patient Instructions:**
The pessary should be inserted before retiring at night.

- Remove one pessary from its wrapper.
- Either using a squatting position or lying on your back or side, insert the pessary deeply into the vagina.

**OVERDOSE**

Contact the Poisons Information Centre for advice on management.
The acute toxicity of oestriol in animals is very low. Overdose with Ovestin pessaries and cream after vaginal administration is unlikely. However, in cases where large quantities of pessaries or cream are ingested, nausea, vomiting and withdrawal bleeding in females may develop. No specific antidote is known. Symptomatic treatment can be given if necessary.

**PRESENTATION AND STORAGE CONDITIONS**

Ovestin Ovula are white, torpedo shaped pessaries packed in blisters of polyvinylchloride (PVC). Each blister contains 5 pessaries. Three blister strips are packed in a cardboard box.

Each Ovestin Ovula pessary contains 0.5 mg oestriol.

Store below 25°C. Protect from light and moisture.

Avoid excessive heat: pessaries will melt at temperatures above 32°C.

**NAME AND ADDRESS OF THE SPONSOR**

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street
South Granville NSW 2142
Australia

**POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

**DATE OF APPROVAL**

TGA approval date or amendment: 16 July 2009

Date of most recent amendment: 26 October 2011 (Safety-related Notification)