Ovestin Tablets

NAME OF THE MEDICINE

Ovestin® Tablets 1 mg

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:
Tablets, each containing 1 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.

Inactive ingredients: amylopectin, magnesium stearate, potato starch, lactose monohydrate.

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 oestrogen 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:
After oral administration oestriol is rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma levels of unconjugated oestriol are reached within 1 hour of administration. After oral administration of 8 mg oestriol, \( C_{\text{max}} \) is approximately 200 ng/mL; \( C_{\text{min}} \) is approximately 20 ng/mL and \( C_{\text{average}} \) approximately 40 ng/mL.

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

Metabolism:
The metabolism of oestriol consists principally of conjugation and deconjugation during the enterohepatic circulation.

Excretion:
Oestriol, being a metabolic end product, is mainly excreted via the urine in the conjugated form. Only a small part (± 2%) is excreted via the faeces, mainly as unconjugated oestriol.

INDICATIONS
- Short-term treatment of menopausal syndrome.

Review the need for continuation of treatment after 6 months treatment, taking into account the risk-benefit ratio for the individual user at that moment (including cardiovascular disease and breast cancer, refer to PRECAUTIONS). Ovestin tablets should only be continued for as long as the benefit outweighs the risks.

CONTRAINDICATIONS
- Known, past or suspected breast cancer.
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- Untreated endometrial hyperplasia.
- Pregnancy.
- Undiagnosed genital bleeding.
- Previous or current 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).
- Known hypersensitivity to the active substances or to any of the excipients.
- 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.
- Porphyria.
- Thrombophlebitis, or with a past history of this condition.
- A history during pregnancy or previous use of steroids of a manifestation or deterioration of otosclerosis.
- Endometriosis.
• Hyperlipoproteinaemia, particularly in the presence of other risk factors which may indicate a predisposition to cardiovascular disorders.
• Rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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

PRECAUTIONS

Special warnings and precaution 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. The benefits and risks of hormone treatment, including Ovestin tablets must always be carefully weighed, including consideration of the emergence of risks as therapy continues. Ovestin tablets should be used for the shortest duration consistent with treatment goals. The need for continued treatment should be reviewed after 6 months or earlier. Ovestin Tablets should only be continued for as long as the benefit outweighs the risks.

If prescribing HRT for long-term purposes (please note that Ovestin tablets are not indicated for the prevention or treatment of bone loss), the potential for increased cardiovascular, thrombotic and neoplastic adverse events and an increased incidence of probable dementia in older women, must also be considered as part of the risk-benefit assessment. Breast cancer can be fatal. Hormone treatments should not be used for the long-term maintenance of general health, including the primary prevention of cardiovascular disease.

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 recur or be aggravated during treatment with Ovestin, in particular:

• A history of, or the presence of risk factors for thromboembolic disorders (see below).
• Liver disorders (e.g. liver adenoma).
• Porphyria
• Diabetes mellitus with or without vascular involvement.
• Hypertension
• Leiomyoma (uterine fibroids) or endometriosis.
• Cholelithiasis
• Severe pruritus
- Migraine (or severe) headache
- Cholestatic jaundice
- Systemic lupus erythematosus
- Herpes gestationis
- Otosclerosis
- A history of endometrial hyperplasia (see below).
- Epilepsy
- Asthma
- Risk factors for oestrogen dependent tumours, e.g. first degree heredity for breast cancer.

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:
Clinical studies showed that the use of divided daily doses and long-term use of high doses of oestriol (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 oestriol 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 tumours. In women with an intact uterus, the following precautions should be taken:
- The total daily dose should be taken at one time.
- The patient should be informed to contact a doctor if vaginal bleeding occurs. Vaginal bleeding during medication should always be investigated.
- During long-term treatment, the endometrium should be monitored at least annually. Alternatively, a progestagen should be added, for at least 12-14 days of each calendar month.

The increased breast cancer risk associated with combined oestrogen-progestagen treatment should be considered, when making decisions to either monitor the endometrium or add a progestagen. There are no indications that treatment with oral oestriol alone increases the risk for breast cancer.

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 oestriol than in subjects treated with other oestrogens.

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 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 oestrogens (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 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.

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 oestrogens. 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 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/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and breast cancer. There is no consensus about the possible role of varicose veins in VTE. The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major elective or post-traumatic 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.

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 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 contraindicated. 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, Ovestin tablets should be discontinued and/or adequate anticoagulant treatment should be given. 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, dyspepsia).

**Coronary Artery Disease (CAD):**
Hormone treatment should not be initiated or continued to prevent or treat cardiovascular disease. There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and 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.

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 randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a five 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 CCE and MPA for five 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 women 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 oestrogen-only HRT products in hysterectomized 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 oestrogens (such as Ovestin) confers a different risk than oestrogen-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.

- Vaginal bleeding during medication should always be investigated. The patient should be informed to contact a doctor if vaginal bleeding occurs.

- Treatment of long duration (exceeding 6 months) should be discontinued from time to time for a period of 2 to 3 weeks to see whether the patient remains symptom free, in which case treatment should be suspended.

- Patients with myocardial or renal disease, or epilepsy or migraine should be followed carefully, since fluid retention has been observed during continued use of large doses of oestrogens.

- The following warnings are common to all oestrogen preparations:
  - in women receiving post menopausal oestrogens there may be a two to three fold increased risk of gall bladder disease similar to that noted after use of oral contraceptives for 2 years or more;
  - an increase in blood pressure has been reported during oestrogen replacement therapy in the menopause. Blood pressure should therefore be monitored especially if high doses are used.

- Oestrogens may increase the size of uterine fibroids. The pathologist should be advised of oestrogen therapy when relevant specimens are submitted.

- Diabetic patients should be observed carefully during administration of oestrogens.

- Oestrogens may be poorly metabolised in patients with impaired liver function and they should be administered with caution in such patients.

- Patients with metabolic bone diseases or renal insufficiency should be treated with caution because of the effect of oestrogens on calcium and phosphorus metabolism.

- 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 on 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):
Ovestin Tablets are contraindicated 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 oestrogens indicate no teratogenic or fetotoxic effects.

Use in Lactation:
Ovestin is contraindicated during lactation. There are insufficient data on the use of this medicine during breastfeeding to assess the 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 estrogens 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 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 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:
Large doses of oestrogens may interfere with certain liver function tests and blood coagulation and endocrine tests including thyroid function and glucose tolerance (as for oestrogen-containing oral contraceptives). If results are abnormal, tests should be repeated after withdrawing exogenous oestrogens for one month.

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>Reproductive system and breast disorders</td>
<td>Breast discomfort and pain</td>
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<td>Postmenopausal spotting</td>
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<td>Cervical discharge</td>
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<td>Gastrointestinal disorders</td>
<td>Nausea</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Fluid retention</td>
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* MedDRA version 9.1

These adverse effects are usually transient, but may also be indicative of too high a dose.
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.

For oestrogen-only HRT, estimates of relative risk (RR) from a re-analysis of original from 51 epidemiological studies (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 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 is 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 Special warnings and precautions for use].

**DOSAGE AND ADMINISTRATION**

- Ovestin tablets should be taken orally and swallowed with some water or other drink, preferably at the same time every day.

- When initiating therapy, depending on the severity of the symptoms, a daily dosage of up to 4 mg (4 tablets) will usually be required. This dosage should be given in the first 5 to 7 days and can then be reduced to the maintenance level (1 to 2 mg daily, i.e. 1 to 2 tablets) in the course of the following 1 to 3 weeks depending on the degree of patient response. The lowest dose which will control the symptoms should be used.

- Oestriol tablets should be prescribed for the shortest duration consistent with treatment goals. Review the need for continuation of treatment at least every 6 months, taking into account the risk-benefit ratio for the individual user at that moment (refer to PRECAUTIONS and INDICATIONS). Treatment should not be continued for more than 12 months.

- Ovestin can be administered either continuously or intermittently. If preference is given to the latter treatment, a tablet free period of 5 to 7 days may be introduced after about each three weeks of treatment.

- 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.

- In women not taking HRT or women who switch from a continuous combined HRT product, treatment with Ovestin Tablets may be started on any day. Women who switch from cyclic HRT regimen should start Ovestin treatment 1 week after completion of the cycle.

**Monitoring Advice:**
As for all steroids with hormonal activity, yearly medical examination particularly of the breasts and pelvic areas is advisable.

**OVERDOSAGE**

Contact the Poisons Information Centre for advice on management.

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

Ovestin Tablets 1 mg are white, round, flat, scored tablets, with bevelled edges. All tablets are marked with "Organon" on one side and coded "DG" above "7" on the reverse.

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.

The following package is available: 1 push-through strip with 30 tablets.

Store in original package to protect from light. Store below 30°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

Date of TGA Approval or amendment: 16 July 2009

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