

IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0748/034/001

Case No: 2061894

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

Janssen-Cilag Ltd

50-100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG, United Kingdom

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

Ortho-Gynest 0.5mg Pessaries.

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

This authorisation, unless previously revoked, shall continue in force from **05/05/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ortho-Gynest 0.5mg Pessaries.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pessary contains estriol 0.5 mg.

Also contains the excipients: 0.8 mg benzoic acid (E210) and 0.5mg butylated hydroxytoluene (E321).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Pessary.

Description of the product

Ortho-Gynest Pessaries are yellowish-white, egg-shaped vaginal Pessaries. Their consistency is that of soft paraffin.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the management of atrophic vaginitis and kraurosis vulvae in post-menopausal women and pruritus vulvae and dyspareunia when associated with atrophic vaginal epithelium.

4.2 Posology and method of administration

Route of administration: Intravaginal.

No added progestagen needed.

Administration

The pessary should be inserted high into the vagina, preferably in the evening.

Guidance on how to start therapy and maintenance

Ortho-Gynest Pessaries can be started any time after the manifestation of atrophic vaginitis or associated symptoms (eg dyspareunia, pruritus). The recommended initial dose is one pessary per day. A maintenance dose of one pessary every three or four days (twice a week) may be used after restoration of the vaginal mucosa has been achieved.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

Attempts to taper and discontinue medication should be made at three to six month intervals following physical examination.

Advice when a dose is forgotten

If a dose is forgotten, a pessary should be inserted as soon as it is remembered.

4.3 Contraindications

- Known, past or suspected breast cancer.
- Known or suspected estrogen-dependent malignant tumours (eg 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 (eg angina, myocardial infarction).
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.
- Known hypersensitivity to the active substance or to any of the excipients.
- Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical examination/follow-up

Before initiating or re-instituting 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 contra-indications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Ortho-Gynest Pessaries, in particular:

- Leiomyoma (uterine fibroids) or endometriosis.
- A history of, or risk factors for, thromboembolic disorders (see below).
- Risk factors for estrogen dependent tumours, e.g. 1st degree heredity for breast cancer.

- Hypertension.
- Liver disorders (eg 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 if a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function.
- Significant increase in blood pressure.
- New onset of migraine-type headache.
- Pregnancy.

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when systemic estrogens are administered alone for prolonged periods (see Section 4.8). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces, but may not eliminate this risk.

Even with a weak estrogen like estriol, the endometrial safety of long-term or repeated use of topical vaginal estrogens is uncertain. Therefore, if repeated, treatment should be reviewed at least annually, with special consideration given to symptoms of endometrial hyperplasia or carcinoma.

If break-through bleeding or spotting appears at any time on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast Cancer

A randomised placebo- controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS) have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years (see Section 4.8, Undesirable Effects). For all HRT, an excess risk becomes apparent within a few years of use and increases duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

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

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

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

Venous Thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate =4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate =9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m²) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contra-indicated. The women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4 to 6 weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg, painful swelling of a leg, sudden pain in the chest, dyspnoea).

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 randomised controlled trials examining effect in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

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

Ovarian cancer

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

Other conditions

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Ortho-Gynest Pessaries is increased.

Women with pre-existing hypertriglyceridaemia should be followed closely during estrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with estrogen therapy in this condition.

Oral estrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). With vaginal administration, stimulation of the liver by the first-pass effect is avoided and thus, transvaginal estrogens might affect hormone binding proteins and other serum proteins produced by the liver less than oral hormones.

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 combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

The serum concentration and efficacy of estrogens could be reduced and its metabolism increased by concomitant administration of drugs known to induce drug metabolising enzymes, specifically CYP 450 enzymes, such as anticonvulsants (eg, phenobarbital, phenytoin, carbamazepine) and anti-infectives (eg, rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's Wort (*Hypericum perforatum*) may raise the metabolism of estrogens and progestagens. With intravaginal administration, the first-pass effect in the liver is avoided and thus, estriol given intravaginally might be less affected by enzyme inducers than oral hormones.

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

Contact between contraceptive diaphragm or condoms and Ortho-Gynest Pessaries must be avoided since the rubber may be damaged by this preparation.

Estrogen-containing oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between estrogen-containing hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both drugs together. Therefore, dose adjustment of lamotrigine may be necessary.

4.6 Pregnancy and lactation

Pregnancy

Ortho-Gynest Pessaries are not indicated during pregnancy. If pregnancy occurs during use of Ortho-Gynest Pessaries, treatment should be withdrawn immediately.

There are no clinical data on exposed pregnancies.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestagens indicate no teratogenic or foetotoxic effect.

Lactation

Ortho-Gynest Pessaries are not indicated during lactation.

4.7 Effects on ability to drive and use machines

There is no information on effects of Ortho-Gynest Pessaries on the ability to drive and use machines.

4.8 Undesirable effects

In a double-blind, placebo controlled clinical trial of 30 women treated with Ortho-Gynest, the following undesirable effects were reported in the estriol pessary treatment group more frequently than in the placebo group: Breast pain, micturition frequency increased, vaginal discharge, cystitis, leg pain, pre-menstrual tension, lower abdominal pain, palpitations and depression.

Breast Cancer

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

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

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

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95% CI: 1.88-2.12) than use oestrogens alone (RR = 1.0, 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 year's use.
- Between 3 and 7 (best estimate = 5) for 10 year's use.

For users of oestrogen plus progestagen combined HRT:

- Between 5 and 7 (best estimate = 6) for 5 year's 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 70 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 year's use.

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

Endometrial Cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2 – to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

Other adverse events which have been reported in association with estrogen/progestagen treatment are:

- Estrogen-dependent neoplasms benign and malignant; e.g. endometrial cancer; breast cancer.
- Venous thromboembolism. Deep leg or pelvic venous thrombosis and pulmonary embolism are more frequent among HRT users than among non-users. For further information, see section 4.3 Contra-indications and 4.4 Special Warnings and Precautions for Use.
- Myocardial infarction and stroke.
- Gall bladder disease.

- Skin and subcutaneous tissue disorders: chloasma; erythema multiforme; erythema nodosum; vascular purpura.
- Probable dementia (see section 4.4).

4.9 Overdose

Symptoms of overdose of estrogen therapy may include breast pain or tenderness, nausea, break-through bleeding, abdominal cramps and/or bloating. Vaginal lavage should be considered. If accidental ingestion of large quantities of the product occurs, an appropriate method of gastric emptying may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Estriol, a weak estrogen, is a natural metabolite of estradiol, the predominant estrogen. Estriol exerts estrogenicity by binding to estrogen receptors, present in the female genital tract. However, the final outcomes in different tissues may differ from those of estradiol, as the intracellular signalling processes seem distinct.

Oral or vaginal estriol, similar to estradiol, corrects lowered proliferation and abnormal physiology in the atrophic vaginal epithelium seen in estrogen deficient states, such as after natural or surgical menopause. Studies of the endometrium after using Ortho-Gynest Pessaries rarely show minor signs of proliferation in previously atrophic endometria.

Clinical trial information

Improvement of vaginal epithelial cytology was noted in 50 subjects with vaginal atrophy already after 7 days of daily treatment with Ortho-Gynest Pessaries. Improvement was sustained over 7 or more weeks in a total of 70 patients studied in two clinical trials. Alleviation of associated symptoms (eg dyspareunia, urethral symptoms) was first observed after 4 weeks of daily treatment with Ortho-Gynest Pessaries in a total of 110 women in four clinical trials and further improvement was seen over subsequent months.

5.2 Pharmacokinetic properties

Estriol is readily absorbed following intravaginal application. Peak serum estriol concentrations are generally observed within 2 hours following intravaginal application and remain elevated for 6 hours. Systemic bioavailability on vaginal administration is better than after oral administration. Intravaginal application of 1 mg estriol in women with senile atrophy of the vaginal epithelium results in serum levels similar to those seen after oral administration of 10 mg estriol.

Upon first use of an Ortho-Gynest Pessary, plasma levels of estriol rise within 2 hours to 450 +/-113 pmol/L (156+/-39 pg/mL) (mean+/- SD), and remain elevated for at least 6 hours in supine subjects, while levels decline to baseline within 4 hours in active subjects. Upon continuous use, little if any accumulation occurs, as plasma estriol levels 8-10 hours after last administration were detectable only in one third of subjects.

Estriol circulates with the blood, about 14% free, 8% bound to SHBG and the rest bound to albumin.

Primary metabolites of estriol include the 16- α -glucuronide, 3-glucuronide, 3-sulfate and 3-sulfate 16- α -glucuronide. More than 95% of estriol is excreted in the urine, predominantly in the form of glucuronides.

5.3 Preclinical safety data

Preclinical effects are reported at exposures considered sufficiently in excess of the maximum human exposure, or were related to an exaggerated pharmacological effect, or were related to differences between species regarding hormonal regulation/metabolism and indicate little relevance to the proposed clinical use of this product.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzoic acid (E210)
Butylated hydroxytoluene (E321)
Macrogol 400
Macrogol 1000
Sorbitan stearate
Hard fat

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC or PVC/PE moulds.

Packs of 5 or 15 pessaries in an outer cardboard carton are available.

Not all pack sizes may be marketed.

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

Empty blisters may be disposed of in household waste. Return unused drug to your pharmacy for destruction. Do not dispose of unused drug in household waste or flush it down the toilet.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 2nd July 2006

10 DATE OF REVISION OF THE TEXT

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