IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1562/007/002
Case No: 2063283

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

LTT Pharma Limited

Unit 18, **Oxleasow Road**, **East Moon Moat**, **Redditch, Worcestershire B98 0RE**, **United Kingdom**

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

Prempak-C 1.25mg Coated Tablets

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 **03/07/2009**.

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

Prempak-C 1.25mg Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prempak-C 1.25mg consists of 28 tablets containing 1.25mg conjugated estrogens, and 12 tablets containing 0.15mg norgestrel.

Excipients-Contains Lactose Monohydrate, Sucrose, Sunset Yellow (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet
Product imported from the UK:
28 Oval yellow sugar coated tablets marked with “1.25mg” in black ink: each tablet containing conjugated estrogens 1.25mg.
12 Round light brown sugar coated tablets containing norgestrel 0.15mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prempak-C 1.25mg is indicated for hormone replacement therapy (HRT) for estrogen-deficiency symptoms in menopausal and postmenopausal women with an intact uterus.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

(See also section 4.4)

4.2 Posology and method of administration

Adults:
Prempak-C is taken orally in a continuous sequential 28-day regimen of conjugated estrogen tablets, with 12 days of Norgestrel tablets taken with the estrogen tablets on days 17 to 28 of the woman's cycle with no breaks between packs. For treatment of postmenopausal symptoms, the lowest effective dose should be administered. Patients should be re-evaluated periodically to determine if treatment for symptoms is still necessary. 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.

For treatment of vasomotor symptoms, atrophic vaginitis, kraurosis vulvae, atrophic urethritis:
0.625-1.25mg conjugated estrogens daily depending on the response of the individual. One norgestrel tablet should be taken daily from day 17 to day 28 of estrogen therapy.

Prophylaxis of osteoporosis: The minimum effective dose is 0.625mg daily for most patients. One norgestrel tablet should be taken daily from day 17 to day 28 of estrogen therapy.

Concomitant progestogen use:
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women (see 4.4 – Special Warnings and Precautions for Use).

Since Norgestrel is administered to reduce the risk of endometrial hyperplasia and endometrial carcinoma, patients without a uterus do not require Prempak-C 1.25mg.
For most postmenopausal women therapy may be commenced at any convenient time although if the patient is still menstruating, commencement on first day of bleeding is recommended. Withdrawal bleeding usually occurs within three to seven days after the last norgestrel tablet. In women transferring from another sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen.

Breakthrough bleeding may occasionally occur in the first few weeks after initiating treatment and will usually settle. It can also be the result of poor compliance, or concurrent antibiotic use. It may, however, indicate endometrial pathology and therefore any doubt as to the cause of breakthrough bleeding is an indication for endometrial evaluation including endometrial biopsy.

Forgotten tablet: If a tablet is forgotten, it should be taken as soon as the patient remembers; therapy should then be continued as before. If more than one tablet has been forgotten, only the most recent tablet should be taken.
Missed pills may cause breakthrough bleeding in women with a uterus.

Elderly:
There are no special dosage requirements for elderly patients, but as with all medicines, the lowest effective dose should be used.

Children:
Not recommended.

4.3 Contraindications

1. Known, past or suspected breast cancer
2. Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer)
3. Undiagnosed abnormal genital bleeding.
4. Untreated endometrial hyperplasia
5. Previous or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)
6. Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
7. Acute liver disease or history of liver disease where the liver function tests have failed to return to normal.
8. Known hypersensitivity to the active substances or to any of the excipients of Prempak-C tablets.
9. 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 the 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.

1. Medical examination/Follow up
Before initiating or reinstituting HRT, a complete personal and family medical history should be taken.
Physical (including pelvic and breast) examination should be guided by the contraindications and warnings for use.
During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual women.
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.

2. Conditions that 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 Prempak-C, in particular:

− Leiomyoma (uterine fibroids) or endometriosis
− A family history of, or risk factors for, thromboembolic disorders (see below)
− Risk factors for estrogen dependent tumours (e.g. first degree heredity for breast cancer)
− Hypertension
− Liver disorders (e.g. liver adenoma)
− Diabetes mellitus with or without vascular involvement
− Cholelithiasis
− Migraine or (severe) headaches
− Systemic lupus erythematosus (SLE)
− A history of endometrial hyperplasia (see below)
− Epilepsy
− Asthma
− Otosclerosis

3. Reasons for immediate withdrawal of therapy

Therapy should be discontinued if 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

4. Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

5. 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 estrogen, estrogen-progestogen 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 progestogen was added, either sequentially or continuously, and regardless of type of progestogen. 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.

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

6. Venous thromboembolism

Hormone replacement therapy (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 between 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 or family history and severe obesity (Body Mass Index >30kg/m_2) 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. Strong family history of thromboembolism or personal recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made, 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 immobilisation, major trauma or major surgery. As with 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 or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT 4-6 weeks earlier, if this is possible. Treatment should not be restarted until the woman is completely mobilised.If venous thromboembolism develops after initiating therapy the drug should be discontinued. Patients should be told to contact their doctor immediately when they are aware of potential thromboembolic symptoms (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

7. 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 an increased risk of cardiovascular morbidity particularly 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.

8. 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.

9. 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 different risk than estrogen-only products.

Other Conditions
10. Estrogens/progestogens 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 Prempak-C is increased.

11. The use of estrogens may influence the laboratory results of certain endocrine tests and liver enzymes.
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 by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are usually unaltered.

Patients dependent on thyroid hormone replacement therapy may require increased doses in order to maintain their free thyroid hormone levels in an acceptable range.

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 biologically active hormone concentrations are usually unchanged.
Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

12. A two- to four-fold increase in the risk of gallbladder disease requiring surgery in women receiving HRT has been reported.

13. A worsening of glucose tolerance may occur in some patients on estrogen/progestogen therapy and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy.
Patients with rare hereditary problems of galactose or fructose intolerance, the Lapp lactase deficiency, sucrose-isomaltase insufficiency or glucose-galactose malabsorption should not take this medicine, as the excipients in the tablet include lactose and sucrose.

14. Estrogens should be used with caution in individuals with severe hypocalcaemia.

15. Women with pre-existing hypertriglyceridemia 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.

16. 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 postmenopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).
Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
Hot flushes and vaginal bleeding have been reported in patients taking HRT and St. John's wort. St. John's wort may induce hepatic microsomal enzymes which theoretically may result in reduced efficacy of HRT.
CYP3A4 inhibitors such as cimetidine, erythromycin and ketoconazole may increase plasma concentrations of 17β-estradiol and may result in side effects.
Clinically, an increased metabolism of estrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.
The response to metyrapone may be reduced.

4.6 Pregnancy and lactation

Pregnancy*:*
Prempak-C is not indicated during pregnancy. If pregnancy occurs during medication with Prempak-C, treatment should be withdrawn immediately. Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of MPA on the foetus. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestogens
indicate no teratogenic or foetotoxic effect.

Lactation:
Prempak-C is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

See also 4.4 Special warnings and special precautions for use
Adverse drug reactions (ADRs) The following adverse reactions have been reported with Prempak-C or are undesirable effects associated with estrogens. It is not possible to calculate frequencies for these events based on sales data for patient exposure.

System Organ Class	**Adverse Reaction**
Infections and Infestations	Vaginitis, Vaginal candidiasis
Neoplasms benign and malignant (including cysts and polyps)	Breast cancer, fibrocystic breast changes, ovarian cancer; endometrial cancer; enlargements of hepatic hemangiomas
Immune system disorders	Anaphylactic/anaphylactoid reactions, including urticaria and angioedema
Metabolism and nutrition disorders	Glucose intolerance; hypocalcaemia; exacerbation of porphyria
Psychiatric disorders	Depression, changes in libido, mood disturbances, irritability, dementia
Nervous system disorders	Dizziness, headache (including migraine), anxiety, Exacerbation of epilepsy; Stroke; exacerbation of chorea
Eye Disorders	Intolerance of contact lenses; retinal vascular thrombosis
Cardiac disorders	Myocardial infarction
Vascular disorders	Venous thrombosis, superficial thrombophlebitis, pulmonary embolism
Respiratory, thoracic and mediastinal disorders	Exacerbation of asthma
Gastrointestinal disorders	Nausea, bloating, vomiting, abdominal pain; pancreatitis
Hepatobiliary disorder	Gallbladder disease; cholestatic jaundice
Skin and subcutaneous tissue disorders	Alopecia, pruritus, acne Chloasma/melasma, Hirsutism, rash; erythema multiforme; erythema nodosum
Musculoskeletal, connective tissue and bone disorders	Arthralgias, leg cramps
Reproductive system and breast disorders	Breakthrough bleeding/dysmenorrhoea, spotting; breast pain, tenderness; enlargement, discharge Changes in menstrual flow, change in cervical ectropion and secretion, Galactorrhoea, increased size of uterine leiomyomata; endometrial hyperplasia
General disorders and administration site conditions	Oedema
Investigations	Changes in weight (increase or decrease) Increased triglycerides; increase in blood pressure

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 estrogen-only HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which>80% of HRT use was estrogen-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 estrogen plus progestogen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, compared to never users, the use of various types of estrogenprogestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of estrogens 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 estrogen-progestogen 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 estrogen-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 estrogen plus progestogen 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 estrogenprogestogen 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 estrogen plus progestogen 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 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 estrogens. According to data from epidemiological studies, the best estimate of 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 estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies form 2- to 12-fold greater compared with non-users. Adding a progestogen to estrogen-only therapy greatly reduces this increased risk.
Other adverse reactions reported in association with estrogen/progestogen treatment including Prempak-C:
− Estrogen-dependent neoplasms benign and malignant, e.g. endometrial hyperplasia, endometrial cancer

− Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among nonusers.

For further information, see section 4.3 Contraindications and 4.4 Special Warnings and special Precautions for Use.
− Retinal vascular thrombosis
− Myocardial infarction and stroke
− Increases in blood pressure
− Cholestatic jaundice
− Enlargement of hepatic haemangiomas
− Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura
− Probable dementia (see section 4.4)
− Exacerbation of chorea
− Exacerbation of porphyria
− Exacerbation of hypocalcaemia

4.9 Overdose

Numerous reports of ingestion of large doses of estrogen/progestogen-containing oral contraceptives by young children indicate that acute serious ill effects have not been observed. Overdosage of estrogens may cause nausea and vomiting, and withdrawal bleeding may occur in females. There is no specific antidote and further treatment should be symptomatic

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Conjugated estrogen tablets have identical pharmacological actions to endogenous estrogens. In this preparation the estrogen action is used to restore estrogen levels, and thus prevent symptoms of postmenopausal estrogen deficiency.

5.2 Pharmacokinetic properties

Both conjugated estrogens and DL-norgestrel are readily absorbed from the gastrointestinal tract and are excreted in the urine and faeces in the form of glucuronide or sulphate conjugates. Both drugs have elimination half lives sufficient to allow once daily dosing.

5.3 Preclinical safety data

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Conjugated estrogen tablets:
Lactose Monohydrate
Methylcellulose
Magnesium Stearate
Sucrose
Glyceryl mono-oleate
Macrogol
Carnauba Wax
Calcium Sulphate Anhydrous
Microcrystalline Cellulose
Pharmaceutical Glaze (Shellac)

Titanium Dioxide (E171)
Stearic Acid
Purified Water
Iron Black Oxide (E172)
Ethanol
n-butyl alcohol
Propylene Glyco (E1520)
Ammonia Solution
Sunset Yellow (E110)
Ethyl Acetate
Quinoline Yellow (E104)
Shellac (E904)

Norgestrel Tablets:
Lactose Monohydrate
Starch
Polyvinylpyrrolidine
Talc
Magnesium Stearate
Sucrose
Macrogol
Calcium Carbonate
Bleached Wax
Carnauba Wax
Titanium Dioxide (E171)
Iron Oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blisters containing 28 conjugated estrogen and 12 norgestrel tablets in an overlabelled container. Three calendar packs per carton

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

No special requirements

7 Parallel Product Authorisation Holder

LTT Pharma Limited
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8 Parallel Product Authorisation Number

PPA 1562/7/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd July 2009

10 DATE OF REVISION OF THE TEXT