IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0022/068/002
Case No: 2026843

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

John Wyeth & Brother Limited

Huntercombe Lane South, **Taplow, Maidenhead**, **Berkshire SL6 0PH**, **United Kingdom**

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

Cathate 1.25 Milligram 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 **24/11/2006** until **18/09/2010**.

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

Cathate* Tablets 1.25mg Coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Cathate tablets contain 1.25 mg Conjugated Estrogens.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

A white coloured, oval coated tablet printed '1.25' in black.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cathate is indicated for hormone replacement therapy (HRT) for estrogen deficiency symptoms in menopausal and postmenopausal women.

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

Cathate tablets are an estrogen only HRT for oral use.

Posology:

Adults:

Cathate 0.625–1.25mg daily is the usual starting dose for women without a uterus. Cyclic administration is recommended (three weeks on followed by one week off).

For treatment of postmenopausal symptoms the lowest effective dose should be used. 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.

Vasomotor symptoms:

0.625–1.25 mg daily depending on the response of the individual.

Atrophic vaginitis, kraurosis vulvae, atrophic urethritis:

0.625–1.25mg daily depending on the response of the individual.

Prophylaxis of osteoporosis:

The minimum effective dose is 0.625mg for most patients.

Concomitant progestogen use for women with a uterus:

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 special precautions for use).

For most postmenopausal women, therapy may be commenced at any convenient time.

In women who are not taking hormone replacement therapy or women who switch from a continuous combined hormone replacement therapy product, treatment may be started on any convenient day. In women transferring from a sequential hormone replacement therapy regimen, treatment should begin the day following completion of the prior regimen.

Before therapy commences it is recommended that the patient is fully informed of all the relative risks and benefits, and the question of continued need for treatment should be reviewed periodically. She should have a complete physical and gynaecological examination with special emphasis on blood pressure, breasts, abdomen and pelvic organs and an endometrial assessment carried out if appropriate. Follow-up examinations are recommended every 6-12 months.

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 uterus.

Elderly:

There are no special dosage requirements for elderly patients, but as with all medicine 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 venous 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 Cathate 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 breast should be reported to their doctor or nurse (see 'Breast Cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

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 Cathate, 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.

For oral doses of estradiol >2mg, conjugated equine estrogens >1.25mg and patches >50 μg/day the endometrial safety of added progestogen have not been studied.

Breakthrough bleeding and spotting may occur during the first months of treatment. If break-through 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.

Endometriosis may be exacerbated with administration of estrogen therapy. Unopposed estrogen stimulation may lead to pre-malignant or malignant transformation it the residual foci of endometriosis. Therefore, the addition of progestogens to estrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

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 use 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 history of 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 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 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 VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors 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 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 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 use (at least 5-10 years) of estrogen-only HRT products in hysterectomised woman 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 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 Cathate 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 to biological 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 patients taking estrogens and therefore diabetic patients should be carefully observed while receiving hormone replacement therapy

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.

17. At present there is no established screening programme for determining women at risk of developing osteoporotic fractures. Epidemiological studies suggest a number of individual risk factors which contribute to the development of postmenopausal osteoporosis. These include: early menopause; family history of osteoporosis; thin, small frame; cigarette use; recent prolonged systemic corticosteroid use.

If several of these risk factors are present in a patient consideration should be given to treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Data from a drug-drug interaction study involving conjugated estrogens and medroxyprogesterone acetate indicated that the pharmacokinetic disposition of both drugs was not altered when the drugs were co-administered. Other clinical drug-drug interaction studies have not been conducted with conjugated estrogens.

The metabolism of estrogens 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 nelafinavir, 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. Johns wort (Hypericum perforatum). 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:

Cathate is not indicated for use during pregnancy.

For women with a uterus:

If pregnancy occurs during medication with Cathate, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Lactation:

Cathate 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 adverse reactions listed in the table are based on post-marketing spontaneous reporting rates, clinical trials and class-effects.

System Organ Class	Common ADRs (>1/100, < 1/10)	Uncommon ADRs (>1/1000, <1/100)	Rare ADRs (>1/10000, <1/1000)	Very Rare ADRs (<1/10000), isolated reports
Infections and infestations	**None**	Vaginitis, including vaginal candidiasis	None	None
Neoplasms benign and malignant (including cysts and polyps)	None	None	Breast cancer; Fibrocystic breast changes Ovarian cancer	Endometrial cancer; Enlargement of hepatic haemangiomas
Immune system disorders	None	None	Anaphylactic/ anaphylactoid reactions, including urticaria and angioedema	None
Metabolism and nutrition disorders	None	None	Glucose intolerance	Exacerbation of porphyria; hypocalcaemia
Psychiatric disorders	Depression	Changes in libido; Mood disturbances; dementia	Irritability	None
Nervous system disorders	**None**	Dizziness; Headache; Migraine; Anxiety	Stroke; Exacerbation of epilepsy;	Exacerbation of chorea
Eye disorders	None	Intolerance to contact lenses	None	Retinal vascular thrombosis
Cardiac disorders	None	None	Myocardial infarction	None
Vascular disorders	None	Venous thrombosis	Pulmonary embolism; Superficial thrombophlebitis	None
Respiratory, thoracic and mediastinal disorders	None	**None**	Exacerbation of asthma	None
Gastrointestinal disorders	None	Nausea; Bloating; Abdominal pain	Vomiting; Pancreatitis	None
Hepatobiliary disorders	None	Gallbladder disease	None	Cholestatic jaundice
Skin and subcutaneous tissue disorders	**Alopecia**	Chloasma/melasma; Hirsutism; Pruritus; Rash	None	Erythema multiforme; erythema nodosum
	Arthralgias; Leg			None

Musculoskeletal, connective tissue and bone disorders	**cramps**	None	None	
Reproductive system & breast disorders	Breakthrough bleeding/spotting; breast pain, tenderness, enlargement, discharge	Change in menstrual flow; Change in cervical ectropion and secretion	Dysmenorrhoea; Galactorrhoea; Increased size of uterine leiomyomata	Endometrial hyperplasia
General disorders and administration site conditions	None	Oedema	**None**	None
Investigations	Changes in weight (increase or decrease); Increased triglycerides	None	None	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 re-analysis 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 estrogen-progestogen 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 estrogen-progestogen 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 from 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 Premarin:

- 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 non-users. 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-containing oral contraceptives by young children indicate that acute serious ill effects do not occur. Overdosage of estrogen 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

Cathate is a mixture of equine conjugated estrogens.

Estrogens are important in the development and maintenance of the female urogenital system and secondary sex characteristics. During the female reproductive stage of life, the ovary is the chief source of estrogens although the amounts of circulating and excreted hormone vary greatly during the menstrual cycle. Estrogens also affect the release of pituitary gonadotrophins.

As women approach the menopause, the number of follicles in the ovaries diminishes and follicle stimulating hormone (FSH) levels rise. Estradiol levels diminish, and the predominant post-menopausal estrogen is estrone which is produced peripherally. Near the end of the peri-menopausal period luteinising hormone (LH) begins to increase. Finally the endometrium fails to proliferate, primarily because of the low average level of estrogens and permanent amenorrhoea occurs.

Initial changes that occur as a result of these diminished levels of circulating hormone are largely vasomotor and include hot flushes and night sweats (with insomnia)

Intermediate changes are represented by atrophy of the genitourinary systems leading to pruritus vulvae, vaginal dryness and urinary symptoms of bladder instability. A long-term effect of estrogen deficiency is osteoporosis (loss of bone mass).

The pharmacological effects of conjugated estrogens are similar to those of endogenous estrogens. In responsive tissues estrogens enter the cell and specific RNA and protein synthesis occurs.

5.2 Pharmacokinetic properties

Conjugated estrogens are soluble in water and are well absorbed from the gastrointestinal tract. Metabolism and inactivation occur primarily in the liver. Some estrogens are excreted in the bile: however, they are reabsorbed from the intestine and returned to the liver through the portal venous system. Water-soluble estrogen conjugates are strongly acidic and are ionised in body fluids, which favours excretion through the kidneys since tubular re-absorption is minimal.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Lactose Monohydrate
Methylcellulose

Magnesium stearate

Coating:
Sucrose
Glycerol mono-oleate
Macrogol 20000
Carnauba wax
Calcium sulphate
Shellac solution
Microcrystalline cellulose
Stearic acid
Titanium dioxide (E171)
Edible printing ink (containing iron oxide black (E172), shellac, ethanol, n-butyl alcohol, propylene glycol and ethyl acetate)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/Aluminium foil blister pack and polypropylene Securitainers.
Blister strips of 21 or 28 tablets and Securitainers of 100 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

John Wyeth and Brother Limited
Trading as: Wyeth Laboratories
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Taplow Maidenhead
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 22/68/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

January 2006