IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0047/073/002
Case No: 2085192

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

Eli Lilly and Company Limited

Lilly House, Priestley Road, **Basingstoke**, **Hampshire**, **RG24 9NL**, **United Kingdom**

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

Celance 250 microgram tablets

the particulars of which are set out in 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 **07/07/2010**.

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

Celance 250 microgram tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pergolide mesilate equivalent to 250 micrograms of pergolide.

Excipient: Contains 286mg of lactose monohydrate per tablet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Green, modified rectangle shaped, scored, marked “Lilly 4133”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pergolide mesilate is an ergot derivative dopamine receptor agonist at D_1, D_2 and D_3 receptor sites.

If treatment with a dopamine agonist is being considered, pergolide mesilate is indicated as second line therapy in patients who are intolerant or fail treatment with a non-ergot compound, as monotherapy, or as adjunctive treatment to levodopa in the management of the signs and symptoms of Parkinson's disease.

Treatment should be initiated under specialist supervision. The benefit of continued treatment should be regularly reassessed taking into account the risk of fibrotic reactions and valvulopathy *(see sections 4.3, Contraindications 4.4, Special warnings and precautions for use and 4.8, Undesirable effects).*

4.2 Posology and method of administration

For oral administration to adults only.

Doses of pergolide mesilate above 3mg/day (3000 micrograms/day) are not to be used either as monotherapy or with levodopa due to the risk of fibrotic cardiac valvulopathy *(see section 4.4, Special warnings and Precautions for use)* that might increase in frequency with greater daily doses and or cumulative exposure. However valvulopathy and fibrotic reactions have been reported during treatment with pergolide at a variety of doses less than 3mg/day.

Adjunctive treatment
Administration of pergolide mesilate should be initiated with a daily dosage of 50 micrograms for the first 2 days. The dosage should then be gradually increased by 100 or 150 micrograms/day every third day over the next 12 days of therapy. The dosage may then be increased by 250 micrograms/day every third day until an optimal therapeutic dosage is achieved but not to exceed 3mg/day.

Pergolide mesilate is usually administered in divided doses 3 times per day. During dosage titration, the dosage of concurrent 1-dopa may be cautiously decreased.

In clinical studies, the mean therapeutic daily dosage of pergolide mesilate was 3mg/day (3000 micrograms/day). The average concurrent daily dosage of 1-dopa/carbidopa (expressed as 1-dopa) was approximately 650mg/day.

Monotherapy
The following titration should be used for initiation of pergolide as monotherapy:

Day	Morning	Noon	Evening	Total Dosage
1			50 micrograms	50 micrograms
2-4		50 micrograms	50 micrograms	100 micrograms
5-7	50 micrograms	50 micrograms	100 micrograms	200 micrograms
8-10	100 micrograms	100 micrograms	100 micrograms	300 micrograms
11-13	100 micrograms	150 micrograms	150 micrograms	400 micrograms
14-17	200 micrograms	200 micrograms	200 micrograms	600 micrograms
18-21	250 micrograms	250 micrograms	250 micrograms	750 micrograms
22-24	500 micrograms	250 micrograms	250 micrograms	1000 micrograms
25-27	500 micrograms	500 micrograms	250 micrograms	1250 micrograms
28-30	500 micrograms	500 micrograms	500 micrograms	1500 micrograms

After day 30, the daily dose should be increased by at most 250 micrograms twice a week until an optimal therapeutic response is achieved but not to exceed 3mg/day. Pergolide mesilate is usually administered in divided doses 3 times per day.

In clinical studies of pergolide as monotherapy, the mean dose was 2100 micrograms per day at 3 months and 2510 micrograms per day at 1 year of treatment.

Domperidone may be used at recommended doses at initiation of treatment to minimise any gastro-intestinal symptoms experienced.

As with other dopamine agonists, pergolide should be discontinued gradually.

Children: Safety and effectiveness have not been established.

4.3 Contraindications

Hypersensitivity to this drug or other ergot derivatives.

History of fibrotic disorders.

Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography.

4.4 Special warnings and precautions for use

Fibrosis and Cardiac Valvulopathy and possibly related clinical phenomena
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin 5HT2B receptor, such as pergolide.

In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.

There is evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology. However, valvulopathy and fibrotic reactions have been reported during treatment with pergolide at doses less than 0.5 mg/day.

Before initiating treatment:
All patients must undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. In patients with valvular regurgitation, it is not known whether pergolide treatment might worsen the underlying disease.
If fibrotic valvular disease is detected, the patient should not be treated with pergolide *(see Section 4.3, Contraindications)*

It is also appropriate to perform baseline investigations of erythrocyte sedimentation rate or other inflammatory markers, lung function/chest X-ray and renal function prior to initiation of therapy.

During treatment:
Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations of progressive fibrosis.

Therefore, during treatment attention should be paid to the signs and symptoms of:

- Pleuro-pulmonary disease, such as dyspnoea, shortness of breath, persistent cough or chest pain.
- Renal insufficiency or ureteral/abdominal vascular obstruction that may occur with pain in the loin/flank and lower limb oedema as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis
- Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is essential. Following treatment initiation, the first echocardiogram should occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring must be determined by appropriate individual clinical assessment, with particular emphasis on the above-mentioned signs and symptoms, but must occur at least every 6 to 12 months.

Pergolide should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening. *(See Section 4.3, Contraindications)* The need for other clinical monitoring (e.g., physical examination, including cardiac auscultation, x-ray, CT scan) should be determined on an individual basis.

Additional appropriate investigations such as erythrocyte sedimentation rate and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder.

Endocrine Effects
A symptom complex resembling the neuroleptic malignant syndrome (NMS) (characterised by elevated temperature, muscular rigidity, altered consciousness and autonomic instability), with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinson therapy, including pergolide.

Hypotension
Patients and their families should be informed of the common adverse consequences of the use of pergolide mesilate and the risk of hypotension.
Patients should be warned to begin therapy with low doses and to increase dosage in carefully adjusted increments over a period of 3 to 4 weeks *(see section 4.2, Posology and method of administration)* to minimise the risk of symptomatic orthostatic or postural hypotension and/or sustained hypotension. With gradual dosage titration, tolerance to the hypotension usually develops *(see section 4.5, Interactions with other medicinal products and other forms of interaction).*

Hallucinations and Psychosis and related events
Hallucinations are known to be associated with dopamine agonists and levodopa treatment. In controlled trials, pergolide mesilate with l-dopa caused hallucinosis in about 14 percent of patients, as opposed to 3 percent taking placebo with l -dopa. This was of sufficient severity to cause discontinuation of treatment in about 3 percent of those enrolled. Tolerance to this untoward effect was not observed. Pergolide should only be administered with caution in patients with a history of psychosis, since pre-existing states of confusion and hallucination may be exacerbated.

Study Findings in the Elderly
In the placebo-controlled trial, 2 of 187 patients treated with placebo died, as compared with 1 of 189 patients treated with pergolide mesilate. Of the 2,299 patients treated with pergolide mesilate in pre-marketing studies evaluated in October 1988, 6.2 percent died while on the drug or shortly after discontinuation. The patient population under evaluation was elderly, ill and at high risk for death. A case-by-case review of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused these deaths.

Cardiac Disease/Arrhythmia
Caution should be exercised when administering pergolide to patients prone to cardiac dysrhythmias or with significant underlying cardiac disease.

In a placebo-controlled study, patients taking pergolide mesilate had significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia

Somnolence
Pergolide has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson’s disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with pergolide.
Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

Patients should be advised to tell their doctor if they become pregnant or intend to become pregnant during therapy. They should also tell their doctor if they are breast feeding.

Pathological gambling, increased libido and hypersexuality
Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson’s disease, including pergolide.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Use in patients on *l*-dopa may cause and/or exacerbate pre-existing states of dyskinesia, confusion and hallucinations *(see section 4.4, Special warnings and special precautions for use).* Abrupt discontinuation of pergolide mesilate, in patients receiving it chronically as an adjunct to *l*-dopa, may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually, even if the patient is to remain on *l*-dopa.

Drug interactions: Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with pergolide mesilate (a dopamine agonist); these agents may diminish the effectiveness of pergolide mesilate.

Because pergolide mesilate is approximately 90 percent associated with plasma proteins, caution should be exercised if it is co-administered with other drugs known to affect protein binding.

There are no studies involving the concomitant administration of pergolide and warfarin. When these two drugs are co-prescribed, careful monitoring of anticoagulation should be performed, with adjustments of dosage as necessary.

Because of the risk of postural and /or sustained hypotension in patients taking pergolide, caution should be exercised if it is co-administered with antihypertensive agents.

4.6 Pregnancy and lactation

Pregnancy: In animal studies there was no evidence of harm to the foetus due to pergolide mesilate. There are, however, no adequate and well-controlled studies in pregnant women. In pre-marketing studies of women who received pergolide for endocrine disorders, there were 33 pregnancies that resulted in healthy babies and 6 pregnancies that resulted in congenital abnormalities, although a causal relationship has not been established. This drug should be used during pregnancy only if clearly needed.

Nursing mothers: It is not known whether pergolide is excreted in human milk. The pharmacological action of pergolide suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Patients being treated with pergolide and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved *(see section 4.4, Special warnings and precautions for use).*

4.8 Undesirable effects

Monotherapy
The types of adverse events observed for pergolide as monotherapy generally reflect those seen when pergolide is used as adjunctive treatment to levodopa (see below).

In clinical trials of pergolide as monotherapy, the overall reported incidence of nausea was higher than was reported in trials of pergolide as adjunctive therapy. Overall, only 3.2 percent of patients discontinued due to nausea or nausea and vomiting. However, the incidence of dyskinesia, hallucinations and dizziness was lower in monotherapy trials in comparison to trials of pergolide as adjunctive therapy.

Adjunctive treatment
The following adverse events, which are listed in decreasing order of frequency under body system, were observed during placebo-controlled clinical trials at a frequency of one percent or greater and at a significantly higher incidence than placebo (*P* value ≤0.05):

Body as a whole: Pain, abdominal pain.

Digestive system: Nausea, vomiting, dyspepsia.

Nervous system: Dyskinesia, hallucinations, somnolence. Pergolide is associated with somnolence and has been associated rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory system: Rhinitis, dyspnoea.

Special senses: Diplopia.

Cardiac Disorders: Very common: cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion).

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy (including restrictive valvular heart disease and pulmonary hypertension) and retroperitoneal fibrosis, in patients taking pergolide *(see section 4.4, Special warnings and precautions for use).* The incidence of valvulopathy with pergolide is not known, however based on recent studies of the prevalence of valvular regurgitation (the most sensitive echocardiographic marker for restrictive valvulopathy), the prevalence of regurgitation (virtually all cases asymptomatic) potentially attributable to pergolide may be in range of 20 percent or greater.
There is limited information available on the reversibility of these reactions.

Other events that have been reported include insomnia, confusion, dizziness, constipation, diarrhoea, abnormal liver function tests, postural hypotension, syncope, palpitation, atrial premature contractions, sinus tachycardia, peripheral vasospasm, rash, fever, Raynauds phenomenon and neuroleptic malignant syndrome (with rapid detitration of pergolide), blood creatine phosphokinase increased (in the absence of NMS). Hiccups and erythromelalgia (warm, red, painful swelling of the extremities) have also been reported.

The more common events that caused discontinuation were related to the nervous system, primarily hallucinations and confusion.

Patients treated with dopamine agonists for treatment of Parkinson’s disease, including pergolide, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

4.9 Overdose

There is no clinical experience with massive overdosage. Overdoses of 60mg on one day, 19mg/day for 3 days, or 14mg/day for 23 days have occurred. Symptoms and signs included vomiting, hypotension, agitation, severe hallucinations, severe involuntary movements and tingling sensations.

Another patient who inadvertently received 7mg, instead of the prescribed 0.7mg (700 micrograms), experienced palpitations, hypotension and ventricular extrasystoles. The highest daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30mg.

In animals, manifestations of overdosage include nausea, vomiting, convulsions, decreased blood pressure and CNS stimulation.

Treatment: Symptomatic supportive therapy and cardiac monitoring is recommended.

Arterial blood pressure should be maintained. An antiarrhythmic agent may be necessary. If signs of CNS stimulation are present, a phenothiazine, or other butyrophenone neuroleptic agent, may be indicated.

Activated charcoal may be considered instead of, or in addition to, gastric emptying.

Dialysis or haemoperfusion are unlikely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pergolide mesilate is a potent ergot derivative dopamine receptor agonist at D_1, D_2 and D_3 receptor sites. Pergolide is 10 to 1,000 times more potent than bromocriptine on a milligram per milligram basis in various *in vitro* and *in vivo* test systems. Pergolide mesilate inhibits the secretion of prolactin in humans and lowers serum prolactin concentrations; it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone.

In Parkinson's disease, pergolide mesilate is believed to exert its therapeutic effect by directly stimulating postsynaptic dopamine receptors in the nigrostriatal system.

5.2 Pharmacokinetic properties

Studies in male healthy volunteers have shown that pergolide appears to be active at the pituitary, as measured by attenuation of plasma prolactin levels, 2 hours post dosing. Suppression of prolactin following a dose of 50 micrograms may be complete and can last for at least 24 hours. In Parkinson’s disease patients, pergolide appears to be active at the pituitary within 30 minutes of oral dosing, as measured by time to attenuation of plasma prolactin levels. Complete suppression of prolactin occurs 2 hours post dose.

Following oral administration of ^{14}C radiolabelled pergolide mesilate to healthy subjects, approximately 55 percent of the administered radioactivity can be recovered as pergolide metabolites from the urine, 40 percent from the faeces and 5 percent from expired CO_2, suggesting that a significant fraction is absorbed. Nothing can be concluded about the extent of presystemic clearance, if any.

Data on post absorption distribution of pergolide are unavailable.

In humans, pergolide is metabolised extensively. At least 10 metabolites have been detected, including N-despropylpergolide, pergolide sulfoxide, and pergolide sulfone. Pergolide sulfoxide and pergolide sulfone are dopamine agonists in animals. The other detected metabolites have not been identified and it is not known whether any other metabolites are active pharmacologically.

The major route of excretion is via the kidney.

Because pergolide mesilate is approximately 90 percent associated with plasma proteins, caution should be exercised if it is co-administered with other drugs known to affect protein binding.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis and impairment of fertility: Two year carcinogenicity studies in mice and rats used doses up to 340 and 12 times the maximum human oral dose (6mg or 6000 micrograms/day equivalent to 120 micrograms/kg/day). A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats.

Endometrial sarcomas were observed in mice. These occurrences are probably attributable to the high oestrogen/progesterone ratio, which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesilate. These endocrine mechanisms are not present in humans. Furthermore, no increased risk of uterine malignancies has been identified among patients receiving pergolide.

Mutagenic potential was evaluated in a battery of tests. A weak response was noted in one test, a mammalian cell-point-mutation assay, only after metabolic activation with rat liver microsomes, but the other five tests were negative. The relevance to humans is unknown.

Impaired fertility was observed in mice at the highest dose (5.6mg or 5600 micrograms/kg/day). This may be related to depressed prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Croscarmellose sodium
Povidone
Magnesium stearate
Iron oxide yellow (E172)
Indigo carmine (E132)
Methionine

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the blister in the outer carton to protect from light.

6.5 Nature and contents of container

Blister packs of 100 tablets, with forming material of 25 micron nylon / 40 micron aluminium / 60 micron UPVC and lidding material of 20 micron aluminium / 5-6 gms clear heat-sealing coating.

Starter Pack (adjunctive treatment): 81 tablets containing 75 x 50 microgram tablets and 6 x 250 microgram tablets.

Starter Pack (monotherapy): 166 tablets containing 109 x 50 microgram tablets and 57 x 250 microgram 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

Do not crush tablets. Caution is advised to minimise exposure risks when splitting tablets. In spontaneous cases, reports of eye irritation, irritating smell, or headache when pergolide tablets were split or crushed have been identified. In animal studies, pergolide was found to cause eye irritation and inhalation toxicity. In the event of pergolide powder exposure to the the eye, the affected eye should be flushed immediately with water, and medical advice obtained.

For nasal irritation, move to fresh air.

7 MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Limited
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Basingstoke
Hampshire
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8 MARKETING AUTHORISATION NUMBER

PA 0047/073/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 18 October 2008

10 DATE OF REVISION OF THE TEXT

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