IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0577/063/003
Case No: 2051903

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

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, **Grange Road**, **Dublin 13**, **Ireland**

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

Pergolide 1000 micrograms 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 **31/03/2009** until **24/02/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pergolide 1000 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1mg (1000 micrograms) of pergolide (as pergolide mesilate).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Mottled pink, capsule shaped tablet, with a breakline on one side and debossed with '9' on the left side of the line and '3' on the right side of the line. The other side is debossed with '7161'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Pergolide is indicated as second line treatment for the signs and symptoms of Parkinson’s disease in patients who are intolerant or unsuccessful with the use of a non-ergotamine derivative dopamine agonist as monotherapy.

It is also indicated as adjunctive treatment to levodopa (l-dopa) in the management of the signs and symptoms of Parkinson's disease.

4.2 Posology and method of administration

For oral use in adults only.

For the different dosage regimens pergolide is available in strengths of 0.05 mg (50 micrograms), 0.25 mg (250 micrograms) and 1 mg (1000 micrograms).
0.05 mg (50 micrograms) tablets should be taken whole.

The use of doses above 5 mg/day (5000 micrograms/day) is not recommended either as monotherapy or with levodopa.

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

Day	Morning	Midday	Evening	Total dose
1	-	-	0.05 mg	0.05 mg
2-4	-	0.05 mg	0.05 mg	0.1 mg
5-7	0.05 mg	0.05 mg	0.1 mg	0.2 mg
8-10	0.1 mg	0.1 mg	0.1 mg	0.3 mg
11-13	0.1 mg	0.15 mg	0.15 mg	0.4 mg
14-17	0.2 mg	0.2 mg	0.2 mg	0.6 mg
18-21	0.25 mg	0.25 mg	0.25 mg	0.75 mg
22-24	0.5 mg	0.25 mg	0.25 mg	1 mg
25-27	0.5 mg	0.5 mg	0.25 mg	1.25 mg
28-30	0.5 mg	0.5 mg	0.5 mg	1.5 mg

After day 30, the daily dose should be increased by at most 0.25 mg (250 micrograms) twice a week until an optimal therapeutic response is achieved. Pergolide is usually administered in divided doses 3 times per day.

In clinical studies of pergolide as monotherapy, the mean dose was 2.1 mg per day at 3 months and 2.51 mg per day at 1 year of treatment.

Adjunctive treatment:
Administration of pergolide should be initiated with a daily dosage of 0.05 mg (50 micrograms) for the first 2 days. The dosage should then be gradually increased by 0.1 mg/day (100 micrograms/day) or 0.15 mg/day (150 micrograms/day) every third day over the next 12 days of therapy. The dosage may then be increased by 0.25 mg/day (250 micrograms/day) every third day until an optimal therapeutic dosage is achieved.

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

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

The efficacy of pergolide at doses above 5 mg/day (5000 micrograms/day) has not been systemically evaluated, either as monotherapy or with l-dopa.

Domperidone may be used at recommended doses at initiation of treatment to minimise any gastrointestinal symptoms experienced.
As with other dopamine agonists, pergolide should be discontinued gradually.

Children and adolescents: Pergolide should not be used in this paediatric group since safety and effectiveness have not been established.

4.3 Contraindications

Hypersensitivity to pergolide, other ergot derivatives or to any of the excipients.

History of fibrotic disorders (see Section 4.4)

Anatomical evidence of cardiac valvulopathy of any valve (e.g. Echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis).

Pregnancy (see section 4.6)

Severe peripheral vascular insufficiency and coronary insufficiency: serious vascular undesirable effects have been observed with ergot alkaloids.

Based on the extensive hepatic metabolism and renal excretion of pergolide, use in patients with severe hepatic and/or renal insufficiency is not recommended.

4.4 Special warnings and precautions for use

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 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) to minimise the risk of symptomatic postural and/or sustained hypotension. With gradual dosage titration, tolerance to the hypotension usually develops.

Hallucinations:
In controlled trials, pergolide with l-dopa caused hallucinosis in about 14% of patients, as opposed to 3% taking placebo with l-dopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled. Tolerance to this undesirable effect was not observed.

Use in patients on l-dopa may cause and/or exacerbate pre-existing states of dyskinesia, confusion and hallucinations. Abrupt discontinuation of pergolide, 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.

Study Findings in the Elderly:
In a placebo-controlled trial, 2 of 187 patients treated with placebo died, as compared with 1 of 189 patients treated with pergolide. Of the 2299 patients treated with pergolide in pre-marketing studies evaluated in October 1988, 6.2 % died while on the substance or shortly after discontinuation. The patient population under evaluation was elderly, ill and at high risk of 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 to patients prone to cardiac dysrhythmias or with significant underlying cardiac disease. In a placebo-controlled study, patients taking pergolide had significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

Fibrosis and Cardiac Valvulopathy:
Pergolide is an ergot derivative. Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves, and retroperitoneal fibrosis have been observed distinctly more frequently under treatment with ergot derivatives, including pergolide, than under non-ergot dopamine agonists (see also section 4.8). In some patients, similar events have occurred during use of the ergot derivative bromocriptine. Pergolide is not recommended for use in patients with a history of such events, especially patients in whom such events have occurred during use of other ergot derivatives. Before pergolide is used, the therapeutic benefit should be weighed up carefully against any risks. This evaluation should include a risk-benefit evaluation of ergot derivatives, including pergolide, compared to non-ergot derivatives. It is recommended that at the start of the treatment a cardiovascular examination, including echocardiogram, should be performed in all patients, to investigate the possibility of an occult heart valve disease. Further diagnostic measures in the course of treatment to monitor the development of heart valve changes or fibroses are recommended (e.g., physical examination, X-ray, echocardiogram, computer tomography). At these regular check-ups, a watch should be kept for symptoms of possible manifestations of fibrotic diseases in the following regions:

- in the examination of the heart, including auscultation for heart murmurs, or signs of heart failure induced by pericardial fibrosis/pericarditis.

- in the examination of the lungs and pleura for symptoms such as dyspnoea, shortness of breath, persistent cough, chest pain.

- in the abdominal examination for signs of kidney failure induced by a retroperitoneal fibrosis or stenosis of the urethral/abdominal vessels, such as pain the lumbar region, oedema of the legs or hardening of the abdominal tissue.

It has not so far been possible to identify specific factors, which predispose a patient to the development of a fibrosis during treatment with ergot derivatives. If a patient develops a fibrosis or heart valve change during the treatment with pergolide, the treatment should be withdrawn.

Before an increase in the dose of pergolide, the therapeutic benefit should be weighed up carefully against possible risks, since there are indications that heart valve changes or fibrotic reactions are reported more frequently when higher doses are used within the recommended dose range.

Appropriate investigations such as erythrocyte sedimentation rate, chest X-ray and serum creatinine measurements should be performed if necessary to support a diagnosis of a fibrotic disorder. 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.

These disorders can have an insidious onset and patients should be regularly and carefully monitored while taking pergolide for manifestations of progressive fibrotic disorders. Pergolide should be withdrawn if fibrotic or serosal inflammatory changes are diagnosed or suspected.

A periodical echocardiography should be performed during treatment (3 to 6 months after initiating treatment and thereafter at least every 6 to 12 months). Frequency is determined by individual clinical assessment.

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 and their families should be informed of the common undesirable effects of the use of pergolide and the risk of hypotension.

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.
No specific laboratory tests are essential for the management of patients. Periodic routine evaluation is appropriate.

There have been reports that pergolide exerts porphyrinogenic effects *in vitro.* Caution is therefore recommended when treating patients with acute porphyria.

The pharmacokinetics in elderly patients and patients with diminished function of the liver and/or kidney is not known, careful dosing should occur in these patient groups (see section 4.3).
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product since it contains lactose.

Gastric ulcer has occurred in occasional Parkinson patients taking bromocriptine. There are reports of epigastric pain developing or worsening after therapy with pergolide. The possibility of ulceration should be borne in mind.

Pergolide should only be used under the regular supervision of an appropriate medicinal practitioner having facilities for monitoring of response.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

There are no studies involving the concomitant administration of pergolide and warfarin. When these two substances 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:
Animal studies have shown no teratogenic potential of pergolide (see section 5.3). There are, however, no adequate and well-controlled clinical studies in pregnant women. There were 38 pregnant women who received pergolide that resulted in 5 babies with congenital abnormalities. Although a causal relationship has not been established, the rate of the defects is clearly above the expected rate from 2-4%. Therefore, the use of pergolide is contraindicated in pregnancy (see section 4.3).
In women of childbearing potential, pregnancy must be excluded before starting treatment with pergolide. During the treatment an effective contraception must be provided.

Lactation:
It is not known whether pergolide is excreted into human milk. Because pergolide reduces prolactin levels and interferes with lactation, the use of pergolide during lactation cannot be recommended. If treatment of the mother is unavoidable, breast-feeding has to be stopped.

4.7 Effects on ability to drive and use machines

Because pergolide may cause somnolence, patients should be cautioned about operating hazardous machinery, including motor vehicles, while taking pergolide.

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).

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 l-dopa.
In clinical trials of pergolide as monotherapy, the overall reported incidence of nausea was higher than was reported in the trials of pergolide as adjunctive therapy. Overall, only 3.2% 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 undesirable effects, which are listed in decreasing order of frequency under body system, were observed during placebo-controlled clinical trials at a frequency of 1 % or greater and at a significantly higher incidence than placebo (P value ≤ 0.05).

Nervous system disorders:
Dyskinesia, hallucinations, somnolence, confusion.
Other events that have been reported include insomnia, and dizziness.
Pergolide is associated with somnolence and has been associated rarely with excessive daytime somnolence and sudden sleep onset episodes.

Eye disorders:
Diplopia.

Cardiac and vascular disorders:
Atrial premature contractions, arrhythmias including sinus tachycardia, myocardial infarction, Rarely (incidence greater than 1/10,000 and < 1/1000), valvular heart disease, vasodilatation, hypotension including orthostatic hypotension, syncope, hypertension. Raynaud's phenomenon has also been reported.

Respiratory thoracic and mediastinal disorders:
Rhinitis, dyspnoea. There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion and retroperitoneal fibrosis, in patients taking pergolide (see section 4.4).

Fibrosis and/or heart valve changes have been reported distinctly more frequently during treatment with ergot derivatives, including pergolide, than under non-ergot dopamine agonists (see section 4.4).

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 a range of 20 percent or greater. There is limited information available on the reversibility of these reactions.

The incidence of asymptomatic heart valve changes is age-dependent. In Parkinson's patients, knowledge of occult heart valve changes permits a better risk assessment. Therefore cardiovascular examinations, including an echocardiogram, should be performed in all patients at the start of and during treatment with pergolide. If a patient develops a fibrosis or heart valve change, the treatment should be withdrawn.

Gastrointestinal disorders:
Nausea, vomiting, dyspepsia, anorexia, dry mouth.
Other events that have been reported include constipation and diarrhoea

Hepato-biliary disorders:
Abnormal liver function tests.

Skin and subcutaneous tissue disorders:
Rash.

General disorders:
Pain, abdominal pain, fever and neuroleptic malignant syndrome (with rapid detitration of pergolide).

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

In a multicentre, double-blind trial, a total of 376 patients were treated with l-dopa/decarboxylase inhibitors, in addition to pergolide or placebo. The undesirable effects listed below were observed.

The following standard terms describe the frequencies of adverse events:
Very common: >1/10 (10%)
Common: >1/100 (1%) and <1/10 (10%)
Uncommon: >1/1000 (0.1%) and <1/100 (1%)
Rare: >1/10000 (0.01%) and <1/1000 (0.1%)
Very rare: <1/10000 (0.01%) including isolated cases

Body system/ Undesirable Effect[1]	**l-dopa+ decarboxylase inhibitors with Pergolide (n = 189) as %**	**Placebo (n = 187) as %**
Infections and Infestations		
Infection	1.1 [Common]	0
Blood and lymphatic system disorders		
Anaemia	1.1 [Common]	< 1 [Uncommon]
Nervous system disorders		
Dyskinesia*	62.4 [Very common]	24.6 [Very common]
Dizziness	19.1 [Very common]	13.9 [Very common]
Hallucinations*	13.8 [Very common]	3.2 [Common]
Dystonia	11.6 [Very common]	8.0 [Common]
Confusion	11.1 [Very common]	9.6 [Common]
Somnolence*	10.1 [Very common]	3.7 [Common]
Insomnia	7.9 [Common]	3.2 [Common]
Anxiety	6.4 [Common]	4.3 [Common]
Headache	5.3 [Common]	6.4 [Common]
Tremors	4.2 [Common]	7.5 [Common]
Depression	3.2 [Common]	5.4 [Common]
Abnormal dreams	2.7 [Common]	4.3 [Common]
Personality disorder	2.1 [Common]	< 1 [Uncommon]
Psychosis	2.1 [Common]	0
Impaired gait	1.6 [Common]	1.6 [Common]
Acathisia	1.6 [Common]	0
Extrapyramidal syndrome	1.6 [Common]	1.1 [Common]
Coordination disorders	1.6 [Common]	< 1 [Uncommon]
Paraesthesia	1.6 [Common]	3.2 [Common]
Akinesia	1.1 [Common]	1.1 [Common]
Increased muscular tone	1.1 [Common]	0
Neuralgia	1.1 [Common]	< 1 [Uncommon]
Impaired speech	1.1 [Common]	1.6 [Common]
Eye disorders		
Impaired vision	5.8 [Common]	5.4 [Common]
Diplopia*	2.1 [Common]	0
Sight disorders	1.1 [Common]	0
Cardiac disorders		
Postural hypotension	9.0 [Common]	7.0 [Common]
Peripheral oedema	7.4 [Common]	4.3 [Common]
Palpitations	2.1 [Common]	<1 [Uncommon]
Hypotension	2.1 [Common]	1 [Common]
Syncope	2.1 [Common]	1.1 [Common]
Hypertension	1.6 [Common]	1.1 [Common]
Arrhythmia	1.1 [Common]	< 1 [Uncommon]
Myocardial infarct	1.1 [Common]	<1 [Uncommon]
Oedema	1.6 [Common]	0
Vascular disorders		
Vasodilatation	3.2 [Common]	< 1 [Uncommon]

Respiratory, thoracic and mediastinal disorders		
Rhinitis*	12.2 [Very common]	5.4 [Common]
Dyspnoea*	4.8 [Common]	1.1 [Common]
Nose bleeds	1.6 [Common]	< 1 [Uncommon]
Hiccups	1.1 [Common]	0
Gastrointestinal disorders		
Nausea*	24.3 [Very common]	12.8 [Very common]
Constipation	10.6 [Very common]	5.9 [Common]
Diarrhoea	6.4 [Common]	2.7 [Common]
Dyspepsia*	6.4 [Common]	2.1 [Common]
Abdominal pain*	5.8 [Common]	2.1 [Common]
Loss of appetite	4.8 [Common]	2.7 [Common]
Dry mouth	3.7 [Common]	< 1 [Uncommon]
Vomiting	2.7 [Common]	1.6 [Common]
Impaired sense of taste	1.6 [Common]	0
Skin and subcutaneous tissue disorders		
Rash	3.2 [Common]	2.1 [Common]
Sweating	2.1 [Common]	2.7 [Common]
Musculoskeletal, connective tissue and bone disorders		
Neck pain	2.7 [Common]	1.6 [Common]
Back pain	1.6 [Common]	2.1 [Common]
Arthralgia	1.6 [Common]	2.1 [Common]
Bursitis	1.6 [Common]	< 1 [Uncommon]
Myalgia	1.1 [Common]	< 1 [Uncommon]
Muscular tremors	1.1 [Common]	0
Renal and urinary disorders		
Micturition difficulties	2.7 [Common]	6.4 [Common]
Urinary tract infection	2.7 [Common]	3.7 [Common]
Haematuria	1.1 [Common]	< 1 [Uncommon]
General disorders and administration site conditions		
Pain*	7.0 [Common]	2.1 [Common]
Asthenia	4.2 [Common]	4.8 [Common]
Chest pains	3.7 [Common]	2.1 [Common]
Flu-like symptoms	3.2 [Common]	2.1 [Common]
Shivering	1.1 [Common]	0
Facial oedema	1.1 [Common]	0
Weight loss	1.6 [Common]	0
Injury and poisoning		
Injury, accident	5.8 [Common]	7.0 [Common]
Surgical and medical procedures		
Surgery	1.6 [Common]	< 1 [Uncommon]

[1] Events with a frequency of at least 1%

* Significantly higher incidence than placebo ($p \leq 0.05$)

4.9 Overdose

There is no clinical experience with massive overdosage. Overdoses of 60 mg on one day, l9 mg/day for 3 days, or 14 mg/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 7 mg (7000 micrograms), instead of the prescribed 0.7 mg (700 micrograms), experienced palpitations, hypotension and ventricular extrasystoles. The highest daily dose (prescribed for several patients with refractory Parkinson's disease) has exceeded 30 mg.

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

Pharmacotherapeutic group: dopaminergic agent, dopamine agonist
ATC code: N04B C02

Pergolide 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 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 is believed to exert its therapeutic effect by directly stimulating post-synaptic 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 0.05 mg (50 micrograms) may be complete and can last for at least 24 hours.

Following oral administration of ^{14}C radiolabelled pergolide mesilate to healthy subjects, approximately 55% of the administered radioactivity can be recovered as pergolide metabolites from the urine, 40% from the faeces and 5% 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 sulphoxide, and pergolide sulfone. Pergolide sulphoxide 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.
Pergolide is approximately 90% bound to plasma proteins. This extent of protein binding may be important to consider when pergolide mesilate is co-administered with other substances 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 (6 mg or 6000 micrograms/day equivalent to 0.12 mg or 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 cases of uterine malignancies have been reported 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.

Reproduction studies have shown no toxic effects in the species investigated (mice and rabbits). Peri-/postnatal development in mice was not impaired. Mice exposed to high doses showed reduced fertility, probably because pergolide reduces prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Pregelatinised starch (maize)
Sodium starch glycollate (Type A)
Microcrystalline cellulose
Magnesium stearate
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months.

6.4 Special precautions for storage

Do not store above 25°C.
Store in the original package. Keep container in the outer carton.

6.5 Nature and contents of container

Aluminium-aluminium PVC blisters (aluminium 45/20.0 µm thick, polyamide 25 µm thick, PVC 60 µm thick). Blister packs containing 10, 20, 30, 40, 50 and 100 tablets. Hospital packs of 100 and 10 x 20 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

Mc Dermott Laboratories T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/63/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 2005

10 DATE OF REVISION OF THE TEXT

March 2006