SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pergolide 250 microgram Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 250 micrograms of pergolide.

3. PHARMACEUTICAL FORM

Tablet: light green, rectangular shaped, scored, marked ‘G’.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Second-line therapy of Parkinson’s disease, or as adjunctive treatment to levodopa, when treatment with dopamine agonist is considered and when non-ergot alkaloids are contraindicated or are no longer adequate.

The treatment should be initiated under specialist supervision. The benefit of continuing treatment should be regularly reassessed taking into account the risk of fibrotic reactions and valvulopathy (see sections 4.3, 4.4 and 4.8).

4.2 Posology and method of administration

For oral administration to adults only.

Monotherapy

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Morning</th>
<th>Noon</th>
<th>Evening</th>
<th>Total Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>50 micrograms</td>
<td>50 micrograms</td>
</tr>
<tr>
<td>2 – 4</td>
<td>-</td>
<td>50 micrograms</td>
<td>50 micrograms</td>
<td>100 micrograms</td>
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</tbody>
</table>
After day 30, the daily dose should be increased by at most 250 micrograms twice a week until an optimal therapeutic response is achieved. 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.

**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.

Pergolide mesilate 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 mesilate 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.

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

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

**Paediatric population**
Safety and effectiveness have not been established.

<table>
<thead>
<tr>
<th>5 – 7</th>
<th>50 micrograms</th>
<th>50 micrograms</th>
<th>100 micrograms</th>
<th>200 micrograms</th>
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</thead>
<tbody>
<tr>
<td>8 – 10</td>
<td>100 micrograms</td>
<td>100 micrograms</td>
<td>100 micrograms</td>
<td>300 micrograms</td>
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<td>11 – 13</td>
<td>100 micrograms</td>
<td>150 micrograms</td>
<td>150 micrograms</td>
<td>400 micrograms</td>
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<td>14 – 17</td>
<td>200 micrograms</td>
<td>200 micrograms</td>
<td>200 micrograms</td>
<td>600 micrograms</td>
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<td>18 – 21</td>
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<td>22 – 24</td>
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<td>500 micrograms</td>
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<td>250 micrograms</td>
<td>1250 micrograms</td>
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<tr>
<td>28 – 30</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
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</tbody>
</table>

4.3 Contraindications
Hypersensitivity to pergolide and excipients (lactose monohydrate), hypersensitivity to other ergot derivatives.

Pregnancy, lactation.

Patients with a history of fibrotic disorders or who developed fibrotic and serosal inflammatory disorders after prolonged use of ergot derivatives.

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).

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 must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should 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). The need for other clinical monitoring (eg, 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.

Specific risk factors predisposing patients to developing fibrosis with ergot derivatives have not been identified.

Pergolide should be withdrawn if fibrotic or serosal inflammatory changes are diagnosed or suspected.

Before increasing the dose of pergolide, therapeutic benefits should be carefully weighed against potential risks, as there is a possible suggestion that valvulopathy and fibrotic reactions may be more frequently reported during treatment with higher doses within the recommended dose range.

**Dyskinesia**
Use in patients on levodopa may cause or exacerbate pre-existing states of dyskinesia.

**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) to minimise the risk of symptomatic orthostatic or postural hypotension and/or sustained hypotension. With gradual dosage titration, tolerance to the hypotension usually develops (but see section 4.5).

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.

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.

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 2,229 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.

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists, including Pergolide. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

**Neuroleptic Malignant Syndrome (NMS)**

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.

### 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). 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.

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.

**Drug Interactions**

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

Caution should be exercised with antipsychotic neuroleptics (except clozapine), rye ergot alkaloids (ergotamine, dihydroergotamine, methylergometrine), macrolides (except spiramycin), alpha sympathomimetics.

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 (INR) 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 Fertility, pregnancy and lactation

Pregnancy
Pergolide use in pregnancy is contraindicated.

In animal studies there was no evidence of harm of 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.

Breast-feeding
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, pergolide should not be used during breastfeeding. 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

Pergolide can influence the 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 (eg, operating machines) until such recurrent episodes and somnolence have resolved (see also 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 levodopa (see below).

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 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.

**Monotherapy Clinical Trials:**
Nervous System disorders:
Dizziness; insomnia

Gastrointestinal disorders:
Nausea; vomiting

**Adjunctive treatment clinical trials**

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, constipation, diarrhoea

Nervous System: Confusion, dizziness, dyskinesia, hallucinations, somnolence, insomnia.

Pergolide is associated with somnolence and has been associated rarely with excessive daytime somnolence and sudden sleep onset episodes.

Respiratory system: Rhinitis, dyspnoea.

**Cardiovascular:** Orthostatic hypotension, palpitation, syncope

**Skin:** Rash

**Other uncommon or rare undesirable effects:** Fever, liver function test abnormal

**Cardiac disorders:** very common:

cardiac valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion).

There is limited information available on the reversibility of these reactions.

Special Senses: Diplopia

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), retroperitoneal fibrosis, neuroleptic malignant syndrome (with rapid de-titration of pergolide); narcolepsy; sudden onset of sleep; Raynaud’s phenomenon; ); blood creatine phosphokinase increased (in the absence of NMS) in patients taking pergolide (see section “Special warnings and special precautions for
use”). Hiccups and erythromelalgia (warm, red, painful swelling of the extremities) have also been reported. There is limited information available on the reversibility of these reactions.

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

*Impulse control disorders*
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including pergolide (see section 4.4 “Special warnings and precautions for use”).

Nausea and postural hypotension occur most frequently during the initial titration phase.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the yellow card scheme, on Freephone 0808 100 3352 or via the website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is no clinical experience with massive overdosage. Overdosages of 60 mg on one day, 19 mg/day for 3 days, or 14 mg/day for 23 days have occurred. Symptoms and signs include vomiting, hypotension, agitation, severe hallucinations, severe involuntary movements and tingling sensations, palpitations and ventricular extrasystoles. Another patient who inadvertently received 7 mg, 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 30mg.

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 or 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: dopamine agonists, ATC group: N04BC02

Pergolide mesilate is a potent ergot derivative dopamine receptor agonist at D1, D2 and D3 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 decreased in serum concentrations of luteinizing hormone. In Parkinson’s disease, pergolide mesilate 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 50 micrograms may be complete and can last for at least 24 hours.

Following oral administration of $^{14}$C radio labelled 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.

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 percent bound to plasma proteins. This extent of protein binding may be important to consider when pergolide mesilate 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 (6 mg 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 oestrogen/progesterone ratio, which would occur in rodents as a result of the prolactin-inhibiting 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipient(s)

- Microcrystalline cellulose
- Glycerol dibehenate
- Magnesium stearate
- Mannitol
- Iron oxide yellow
- Indigo Carmine

6.2. Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in original package.

Do not store above 25°C.

6.5 Nature and contents of container

White 277μm PVC/PVdC and 28μm Aluminium blister strips.
Pergolide tablets are available in packs of 10, 20, 30, 50 and 100 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Do not crush tablets. Caution is advised to minimize 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 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

Norton Healthcare Limited
T/A IVAX Pharmaceuticals UK
Ridings Point, Whistler Drive,
Castleford, West Yorkshire,
WF10 5HX

8. MARKETING AUTHORISATION NUMBER

PL 00530/0652

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

15/11/2010

10 DATE OF REVISION OF THE TEXT

20/02/2014