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LAY SUMMARY

The MHRA granted Fair-Med Healthcare GmbH Marketing Authorisations (licences) for the medicinal products Peroglide 0.05mg tablets (PL 20242/0001), Peroglide 0.25mg tablets (PL 20242/0002) and Peroglide 1.0mg tablets (PL 20242/0003). These are prescription only medicines (POM) for the treatment of symptoms of Parkinson’s disease.

Peroglide 0.05mg, 0.25mg and 1.0mg tablets contain the active ingredient peroglide which is a dopamine agonist.

The test product was considered to be equivalent to the original product Celance 50µg tablets (Eli Lilly and Company Ltd) based on the data submitted.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Peroglide 0.05mg, 0.25mg and 1.0mg tablets outweigh the risks, hence Marketing Authorisations have been granted.
PEROGLIDE 0.05MG TABLETS
PL 20242/0001

PEROGLIDE 0.25MG TABLETS
PL 20242/0002

PEROGLIDE 1.0MG TABLETS
PL 20242/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Peroglide 0.05mg, 0.25mg and 1.0mg tablets to Fair-Med Healthcare GmbH on 21 June 2007. The products are prescription only medicines.

Three strengths of peroglide were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC as amended, claiming to be generic products of Celance 50µg, 250µg and 1000µg tablets (Eli Lilly and Company Ltd). The reference products have been authorised in the UK since November 1990 and so the 10-year period of data exclusivity has expired.

The products contain the active ingredient peroglide and are indicated for the management of the signs and symptoms of Parkinson’s disease as a second line therapy for patients who are intolerant to or fail treatment with a non-ergot compound, as a monotherapy or as an adjunctive treatment to levodopa. Treatment should be initiated under specialist supervision and regularly reassessed.

Peroglide is a dopamine receptor agonist at D1, D2 and D3 receptor sites. It is believed to exert its therapeutic effect by directly stimulating post-synaptic dopamine receptors in the nigrostriatal system.

All applications were submitted at the same time and depend on the bioequivalence study that compares the applicant’s product with the reference product Celance 50µg tablets (Eli Lilly and Company Ltd). Consequently, all sections of the Scientific Discussion refer to all applications.
PHARMACEUTICAL ASSESSMENT

COMPOSITION

The products are formulated as tablets containing 0.05mg, 0.25mg or 1.0mg of the active pharmaceutical ingredient peroglide, as peroglide mesilate. The excipients present are mannitol, microcrystalline cellulose, pregelatinised starch, magnesium stearate, titanium dioxide, iron oxide yellow (Peroglide 0.05mg tablets only) and iron oxide red (Peroglide 1.0mg tablets only).

Peroglide 0.05mg, 0.25mg and 1.0mg tablets are presented in aluminium-foil sealed PVC/ACLAR blisters in packs of 10, 20, 30, 50, 60, 100, 250 (5x50), 300 (5x60) and 1000 (10x100) tablets.

DRUG SUBSTANCE

Peroglide
Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification based on the European Pharmacopoeia monograph is provided for peroglide.

Analytical methods have been validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided for three batches and comply with the proposed specification.

Peroglide is stored in appropriate packaging.

Stability data have been generated supporting a retest period of 2 years when stored in the proposed packaging at 25°C.

DRUG PRODUCT

Other ingredients
All excipients used in the manufacture of the tablets are routinely tested for compliance with current relevant international standards.

Satisfactory certificates of analysis have been provided for all excipients.

No excipients used contain material of animal or human origin.
Impurity Profile
Impurity profiles of each strength of the test product were compared to Celance 50µg, 250µg and 1000µg tablets as well as brand leaders from Germany and France. The assay results were comparable and less of the major degradant, peroglide sulphoxide, was present in the test product than in the innovator products.

Dissolution profiles
Dissolution profiles for the drug product were found to be similar to the reference product.

Manufacture
A full description and a detailed flow-chart of the manufacturing method including in-process control steps has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification
The proposed finished product specification is acceptable and the analytical methods used have been suitably validated. Batch analysis data have demonstrated compliance with the proposed release specification. Suitable reference standards were used.

Container Closure System
Satisfactory specifications and certificates of analysis have been provided for the packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability data support the proposed shelf-life of 2 years with storage conditions “Do not store above 25°C.”

Bioequivalence
Refer to the clinical assessment report.

SPC, PIL and Labels
The SPC, PIL and labels are pharmaceutically acceptable.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 01 July 2008.
CONCLUSION

The proposed products have been shown to be generic products of the reference products and have met the requirements with respect to qualitative and quantitative content of the active substance. Similar dissolution and impurity profiles have been demonstrated for the proposed and reference products.

It is recommended that Marketing Authorisations should be granted for these applications.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for applications of this type.
CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are generic abridged applications for tablets containing 0.05mg, 0.25mg and 1.0mg peroglide.

The applications are submitted under the provisions of Directive 2001/83/EC Article 10.1 as amended, claiming that Peroglide 0.05mg, 0.25mg and 1.0mg tablets are generic products of Celance 50µg, 250µg and 1000µg tablets (Eli Lilly and Company Ltd) which were authorised in the UK in November 1990.

Pergolide is a potent ergot derivative dopamine receptor agonist at D₁, D₂ and D₃ receptor sites. Its efficacy in Parkinson’s disease is via direct stimulation of postsynaptic dopamine receptors in the nigrostriatal system.

INDICATIONS

The following indications have been approved:

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. Pergolide mesilate is a dopamine receptor agonist at D₁, D₂ and D₃ receptor sites.

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, 4.4, & 4.8).

DOSE AND DOSE SCHEDULE

The proposed posology is essentially identical to the SPC text of the reference products, including tabulation of the initial dose titration regimen, and is satisfactory.

CLINICAL PHARMACOLOGY

A single bioequivalence study, carried out in compliance with Good Clinical Practice (GCP), was presented. Due to the need for gradual dose titration in order to avoid problems with postural hypotension and nausea, the lowest strength (0.05mg) was chosen for the study which is acceptable. The applicant asserts that a further study is not required for the 0.25mg and 1mg preparations as pharmacokinetics over the therapeutic range are dose proportional, the excipients are qualitatively and quantitatively the same, all are manufactured in the same way at the same site and dissolution behaviour is similar. There are adequate published data to indicate that the absorption of pergolide is linear over the relevant dose range.
The reference product was Celance 50µg tablets, sourced from the UK market, manufactured by Eli Lilly and Company Ltd, and is therefore satisfactory.

The study was a conventional comparative, randomised, two-way, two-period, single dose crossover study. Sixty healthy fed male volunteers received 0.1mg (2 x 0.05mg) orally of either the applicant's test product (Peroglide 0.05mg tablets) or the reference product (Celance 50µg tablets). Serum levels of pergolide were followed for 36 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max}. The washout period of 7 days between phases was sufficiently long. Log-transformed data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA. T_{max} was analysed non-parametrically.

**Results**

There were two withdrawals and therefore 58 subjects were included in the analysis, as specified in the protocol. This is satisfactory.

Bioequivalence results for log-transformed test/reference ratios with 90% CIs:

\[
\begin{array}{l}
\text{AUC}_t & 1.06 (1.02 - 1.10) \\
\text{AUC}_{inf} & 1.06 (1.02 - 1.09) \\
C_{max} & 1.07 (1.02 - 1.11) \\
T_{max} & 4 \text{ hrs (test)} \quad 4 \text{ hrs (reference)}
\end{array}
\]

**Discussion**

Bioequivalence has been satisfactorily demonstrated in accordance with Committee for Proprietary Medicinal Products (CPMP) criteria. Further bioequivalence studies are not required for higher tablet strengths.

**CLINICAL EFFICACY**

No new data were submitted and none are required for these types of application.

**CLINICAL SAFETY**

No new data were submitted and none are required for these types of application.

**CLINICAL EXPERT REPORT**

The clinical expert report has been written by an appropriately qualified medical doctor. It is an adequate summary of the clinical data provided in the dossier.

**SPC, PIL and LABELS**

The SPC, PIL and labels are acceptable.
CONCLUSIONS

The clinical efficacy and safety of peroglide is well known from its use in clinical practice. No new data were submitted and this is acceptable. Bioequivalence of the product has been shown. Considering the relative composition of the 0.05mg, 0.25mg and 1.0mg products, dissolution profiles and pharmacokinetics, extrapolation of the outcome of the bioequivalence study to the higher strength products is justified. Marketing Authorisations should be granted for these applications.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Peroglide 0.05mg, 0.25mg and 1.0mg tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Peroglide 0.05mg tablets and Celance 50µg tablets (Eli Lilly and Company Ltd).

No new or unexpected safety concerns arose from these applications.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the reference products are interchangeable. The risk benefit is, therefore, considered to be positive.
PEROGLIDE 0.05MG TABLETS
PL 20242/0001

PEROGLIDE 0.25MG TABLETS
PL 20242/0002

PEROGLIDE 1.0MG TABLETS
PL 20242/0003

STEPS TAKEN FOR ASSESMENT

1  The MHRA received the Marketing Authorisation applications on 28 August 2003.

2  Following standard checks and communication with the applicant, the MHRA considered the applications valid on 21 October 2003.

3  Following assessment of the applications, the MHRA requested further information relating to the quality dossiers on 05 January 2004 and 14 December 2004 and further information relating to the clinical dossiers on 05 January 2004.

4  The applicant responded to the MHRA’s requests, providing further information on 17 February 2004 and 16 February 2006 for the quality sections, and again on 17 February 2004 for the clinical sections.

5  The applications were determined on 21 June 2007.
PEROGLIDE 0.05MG TABLETS  
PL 20242/0001

PEROGLIDE 0.25MG TABLETS  
PL 20242/0002

PEROGLIDE 1.0MG TABLETS  
PL 20242/0003

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
</table>

STEPS TAKEN AFTER AUTHORITY – SUMMARY
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pergolide 0.05 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each buff tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide.

3 PHARMACEUTICAL FORM
Tablets (buff, round, biconvex) containing 0.05 mg pergolide base.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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. Pergolide mesilate is a dopamine receptor agonist at D₁, D₂ and D₃ receptor sites.

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, 4.4, & 4.8).

4.2 Posology and method of administration
For oral administration to adults only.

The use of pergolide mesilate in doses above 5mg/day (5000 micrograms/day) is not recommended either as monotherapy or with levodopa (see Section 4.4).

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 3mg/day (3000 micrograms/day). The average concurrent daily dosage of l-dopa/carbidopa (expressed as l-dopa) was approximately 650mg/day.
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>50 micrograms</td>
<td>50 micrograms</td>
<td>50 micrograms</td>
</tr>
<tr>
<td>2-4</td>
<td>-</td>
<td>50 micrograms</td>
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<td>100 micrograms</td>
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<td>5-7</td>
<td>50 micrograms</td>
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<td>8-10</td>
<td>100 micrograms</td>
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<td>750 micrograms</td>
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<tr>
<td>22-24</td>
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<td>25-27</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
<td>250 micrograms</td>
<td>1250 micrograms</td>
</tr>
<tr>
<td>28-30</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
<td>500 micrograms</td>
<td>1500 micrograms</td>
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</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.

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.

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

4.4 Special warnings and precautions for use

Fibrosis and Cardiac Valvulopathy

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 such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.
Before initiating treatment:

All patients should 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).

There is some evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology.

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 as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear
- cardiac failure as cases of valvular fibrosis have often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear

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.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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 (e.g. physical examination, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

**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 ‘Posology and method of administration’) to minimise the risk of symptomatic postural and/or sustained
hypotension. With gradual dosage titration, tolerance to the hypotension usually develops (but see ‘Interactions with other medicaments and other forms of interaction’).

Hallucinations

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.

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 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 experience 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.

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 ‘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.

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 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.

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.
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 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 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.

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking pergolide (see ‘Special warnings and special 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% 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, and sinus tachycardia, rash, fever and neuroleptic malignant syndrome (with rapid detitration of pergolide), Raynauds phenomenon, compulsive self-rewarding behaviour (e.g., pathological gambling); libido increased.

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

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

Pharmacotherapeutic group: dopamine agonist
ATC code: 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 decrease 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 ¹⁴C 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 CO₂, 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 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 (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 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 (5.6mg or 5600 micrograms/kg/day). This may be related to depressed prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Microcrystalline Cellulose
Pregelatinised Starch
Magnesium Stearate
Titanium Dioxide
Iron oxide yellow

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25 °C

Store in original packaging

6.5 Nature and contents of container
Blister packs with forming material of 51 micron ACLAR/250 microns PVC and lidding material of 20 micron aluminium/6-8gms heat-sealing coating (blisters of 10 tablets).

Packages containing 10, 20, 30, 50, 60, 100, 250 (5x50), 300 (5x60) and 1000 (10x100) tablets.

6.6 Special precautions for disposal
For oral use.
7 MARKETING AUTHORISATION HOLDER
Fair-Med Healthcare GmbH
Cuxhavener Straße 249
D-21149 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 20242/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/06/2007

10 DATE OF REVISION OF THE TEXT
21/06/2007
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pergolide 0.25 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each white tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.25 mg of pergolide.

3 PHARMACEUTICAL FORM
Tablets (white, round, biconvex) containing 0.25 mg pergolide base.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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. Pergolide mesilate is a dopamine receptor agonist at D₁, D₂ and D₃ receptor sites.

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, 4.4, & 4.8).

4.2 Posology and method of administration
For oral administration to adults only.

The use of pergolide mesilate in doses above 5mg/day (5000 micrograms/day) is not recommended either as monotherapy or with levodopa (see Section 4.4).

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 3mg/day (3000 micrograms/day). The average concurrent daily dosage of l-dopa/carbidopa (expressed as l-dopa) was approximately 650mg/day.
**Monotherapy**

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

<table>
<thead>
<tr>
<th>Day</th>
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<th>Total Dosage</th>
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<td>1</td>
<td>-</td>
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<td>50 micrograms</td>
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<td>2-4</td>
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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.

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.

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

### 4.4 Special warnings and precautions for use

**Fibrosis and Cardiac Valvulopathy**

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 such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.
Before initiating treatment:

All patients should 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).

There is some evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology.

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 as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear
- cardiac failure as cases of valvular fibrosis have often manifested as cardiac failure; valvular fibrosis should be excluded if such symptoms appear

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.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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 (e.g. physical examination, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

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 ‘Posology and method of administration’) to minimise the risk of symptomatic postural and/or sustained
hypotension. With gradual dosage titration, tolerance to the hypotension usually develops (but see ‘Interactions with other medicaments and other forms of interaction’).

**Hallucinations**

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.

**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 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 experience 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.

**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 ‘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.

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 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.

**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.
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 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 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.

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking pergolide (see ‘Special warnings and special 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% 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, and sinus tachycardia, rash, fever and neuroleptic malignant syndrome (with rapid detitration of pergolide), Raynauds phenomenon, compulsive self-rewarding behaviour (e.g., pathological gambling); libido increased.

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

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
Pharmacotherapeutic group: dopamine agonist
ATC code: 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 decrease 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 ¹⁴C 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 CO₂, 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 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 (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 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 (5.6mg or 5600 micrograms/kg/day). This may be related to depressed prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Microcrystalline Cellulose
Pregelatinised Starch
Magnesium Stearate
Titanium Dioxide

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25 °C
Store in original packaging

6.5 Nature and contents of container
Blister packs with forming material of 51 micron ACLAR/250 microns PVC and lidding material of 20 micron aluminium/6-8gms heat-sealing coating (blisters of 10 tablets).

Packages containing 10, 20, 30, 50, 60, 100, 250 (5x50), 300 (5x60) and 1000 (10x100) tablets.

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For oral use.

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Cuxhavener Straße 249
D-21149 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)
PL 20242/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/06/2007

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Pergolide 1.0 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each pink tablet contains, as the active ingredient, pergolide mesilate equivalent to 1.0 mg of pergolide.

3 PHARMACEUTICAL FORM
Tablets (pink, round, biconvex) containing 1.0 mg pergolide base.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
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. Pergolide mesilate is a dopamine receptor agonist at D₁, D₂ and D₃ receptor sites.

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, 4.4, & 4.8).

4.2 Posology and method of administration
For oral administration to adults only.

The use of pergolide mesilate in doses above 5mg/day (5000 micrograms/day) is not recommended either as monotherapy or with levodopa (see Section 4.4).

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 3mg/day (3000 micrograms/day). The average concurrent daily dosage of l-dopa/carbidopa (expressed as l-dopa) was approximately 650mg/day.
**Monotherapy**

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

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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.

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

**4.4 Special warnings and precautions for use**

*Fibrosis and Cardiac Valvulopathy*

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 such as pergolide. In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of pergolide.
Before initiating treatment:
All patients should 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).

There is some evidence that higher dose and/or cumulative exposure are risk factors for development of valvular pathology.

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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
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- cardiac failure as cases of pericardial fibrosis have often manifested as cardiac failure; constrictive pericarditis should be excluded if such symptoms appear
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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.

Clinical diagnostic monitoring for development of valvular disease or fibrosis, as appropriate, is recommended. Following treatment initiation, the first echocardiogram should 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 should 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 (e.g. physical examination, careful cardiac auscultation, X-ray, echocardiogram, CT scan) should be determined on an individual basis.

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.

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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 ‘Posology and method of administration’) to minimise the risk of symptomatic postural and/or sustained
hypotension. With gradual dosage titration, tolerance to the hypotension usually develops (but see ‘Interactions with other medicaments and other forms of interaction’).

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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.

_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 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 experience 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.

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 ‘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.

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 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.

_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.
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 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 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.

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis, in patients taking pergolide (see 'Special warnings and special 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% 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, and sinus tachycardia, rash, fever and neuroleptic malignant syndrome (with rapid detitration of pergolide), Raynaud's phenomenon, compulsive self-rewarding behaviour (e.g., pathological gambling); libido increased.

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

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
Pharmacotherapeutic group: dopamine agonist
ATC code: 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 decrease 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 14C 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 CO₂, 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 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 (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 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 (5.6mg or 5600 micrograms/kg/day). This may be related to depressed prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Mannitol
Microcrystalline Cellulose
Pregelatinised Starch
Magnesium Stearate
Titanium Dioxide
Iron oxide red

6.2 Incompatibilities
None known.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Do not store above 25 °C

Store in original packaging

6.5 Nature and contents of container
Blister packs with forming material of 51 micron ACLAR/250 microns PVC and lidding material of 20 micron aluminium/6-8gms heat-sealing coating (blisters of 10 tablets).

Packages containing 10, 20, 30, 50, 60, 100, 250 (5x50), 300 (5x60) and 1000 (10x100) tablets.

6.6 Special precautions for disposal
For oral use.
7 MARKETING AUTHORIZATION HOLDER
Fair-Med Healthcare GmbH
Cuxhaven Straße 249
D-21149 Hamburg
Germany

8 MARKETING AUTHORIZATION NUMBER(S)
PL 20242/0003

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
21/06/2007

10 DATE OF REVISION OF THE TEXT
21/06/2007
UKPAR Peroglide 0.05mg, 0.25mg and 1.0mg tablets PL 20242/0001-3

PATIENT INFORMATION LEAFLET

Pergolide 0.05 mg, 0.25 mg and 1 mg tablets
(pergolide mesylate)

What you should know about Pergolide tablets

Please read this leaflet carefully before you start to take your medicine. It does not contain all the information you may need to know, so please ask your doctor or pharmacist if you have any questions. This leaflet only applies to Pergolide tablets.

What is your medicine?

Your medicine is called Pergolide. Its active ingredient is pergolide as the mesylate. The tablets are round and are buff, white or pink.

Each buff tablet has 0.05 mg of pergolide as the mesylate in it. Each white tablet has 0.25 mg and each pink tablet has 1 mg. The tablets also contain the inactive ingredients mannitol, microcrystalline cellulose, pregelatinised starch and magnesium stearate. The buff tablets are coloured with iron oxide yellow (E 172) and titanium dioxide (E 171), the white ones with E 171, and the pink ones with iron oxide red (E 172) and E 171.

Pergolide comes in packs of 10, 20, 30, 50, 60, 100, 250 (5x50), 300 (5x60) or 1000 (10x100) tablets. They contain either 0.05 mg, 0.25 mg or 1 mg of pergolide as the mesylate in each tablet.

Pergolide is one of a group of medicines called dopamine agonists. It is used to treat Parkinson’s disease, sometimes with other medicines.

Pergolide is made by Pharmaxis S.A., Attikis, Greece and is released on to the market by Fair-Med Healthcare GmbH, D-21149 Hamburg, Germany. The marketing authorisation is held by Fair-Med Healthcare GmbH, D-21149 Hamburg, Germany.

Why Pergolide?

Pergolide is used to reduce the symptoms and problems of Parkinson’s disease after your doctor has tried an alternative medicine. It is sometimes used with other medicines that have developed in them, such as Sinemast and Madopar.

Before taking your medicine

Make sure it is safe for you to take Pergolide. Before you are given Pergolide your doctor will arrange for you to have tests to assess the condition of your heart. Your doctor will continue to monitor your medical condition while you are taking Pergolide tablets.

It should not be given to children.

If you answer YES to any of the following questions or you are not sure about the answer, tell your doctor or pharmacist and do not take any Pergolide tablets.

• Have you ever had a rash or other allergic reaction to Pergolide or to an ‘ergot’ medicine such as bromocriptine or lyseralide?
• Have you ever had heart trouble?
• Are you pregnant or could you be, or are you breast-feeding?
• Are you taking any medicine that thins the blood, such as warfarin?
• Are you taking any medicine for high blood pressure, nausea or a psychiatric condition?
• If you have ever been diagnosed in the past with a problem known as fibrosis which affects the lungs, lower back and kidneys or heart, you must tell your doctor as Pergolide may not be appropriate for you.

Tell your doctor about any other medicines you are taking and which other medical problems you are being treated for.

Pergolide can cause somnolence (feeling very tired) and cause you to suddenly go to sleep. You must not drive or carry out any activities where this could put you or others at risk of serious injury or death (for example, operating machines).

Taking your medicine

• Follow your doctor’s instructions. Check the label for how many tablets to take and how often to take them.
  • Your doctor will probably tell you to start on a low dose of one buff tablet (0.05 mg) for the first one or two days.
  • After that your doctor will usually tell you to step up the dose every third or fourth day over a period of several weeks.
- You will usually take the tablets 3 times per day, and at regular intervals. Swallow the tablets with water. It does not matter whether you take them with or without food.

- Do not take more than 5 pink tablets (5 x 1 mg tablets) per day.
- If you are not sure how many tablets to take, ask your doctor.
- If you miss a dose, take it as soon as you remember. If you miss several doses, ask your doctor what to do. Do not stop taking your medicine without telling your doctor first. If your doctor tells you to stop taking this medicine, you should not stop taking it suddenly because this may cause side effects. Your doctor will tell you how to reduce the dose gradually.
- Even though you are taking Pergolide, you should go on taking any other medicines that your doctor has told you to.
- During your treatment with Pergolide take special care when you drive or operate a machine. If you feel very tired or even suddenly go to sleep, do not drive or operate machines, and contact your doctor.
- If you ever take too many tablets, tell your doctor at once or go to your nearest hospital casualty department.

While taking your medicine

You and your family should talk to your doctor or pharmacist about how Pergolide may affect you. Pergolide tablets can cause side-effects, such as:

- shaking and twitching
- stomach ache
- hallucinations
- somnolence (feeling very tired)
- pains
- feeling or being sick
- confusion
- suddenly going to sleep

You may also faint or feel faint, dizzy or light-headed when you get up or stand up. You may feel sick when you first start to take your medicine. This usually wears off but your doctor may give you something to help this.

Some patients have not been able to sleep, felt dizzy or fainted or have had constipation or diarrhoea. Some patients have had palpitations (when they are aware of their heart beat). Rarely, tests have shown changes in the way the patient’s liver works.

Some patients have had indigestion, a runny nose, difficulty in breathing, chest or back pain, swollen legs, a racing heart, double vision, rash or fever. (But these symptoms are rare.)

As with other dopamine agonists, pathological gambling, hypersexuality and increased sex-drive in patients receiving pergolide therapy has been reported rarely.

Some patients may experience fibrosis. The early symptoms may be one or more of the following: difficulty in breathing, shortness of breath, chest, back or pelvic pain and swollen legs.

If you begin to experience any one of these symptoms, you must tell your doctor immediately.

- Some of the symptoms may be caused by Parkinson’s disease, or by medicines you are already taking, or by other medical conditions. Tell your doctor if you have any side-effects when you are taking Pergolide tablets. Your doctor has more information about Pergolide and will tell you what to do. He or she may change the amount of any medicines that you are taking.
- Rarely, some patients have had unexplained fever probably with faster breathing, sweating, muscle stiffness or sleepiness when they have stopped taking this medicine suddenly. You should reduce the daily dose gradually when stopping.

How to store your medicine

- Do not take the tablets after the ‘Use before’ date.
- Store the tablets in the original packaging.
- Do not store above 25 °C.
- Keep all medicines where children cannot see or reach them. Your medicines could harm them.
- If your doctor tells you to stop taking the tablets, please take any you have left back to the pharmacist.

REMEMBER: This medicine is for you. Only a doctor can prescribe it for you. Never give it to others. It may harm them, even if their symptoms are the same as yours.

Date this leaflet was written: May 2007
# LABELLING

<table>
<thead>
<tr>
<th>PERGOLIDE 0.05 MG TABLETS</th>
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<td>D-21149 Hamburg, Germany</td>
<td>D-21149 Hamburg, Germany</td>
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**lot:** exp:

## PERGOLIDE 0.05 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide

10 tablets

for oral use

Pergolide 0.05 mg tablets

10 tablets

Keep out of the reach and sight of children.

Use as directed by a medicinal practitioner.

Store in the original package.

Do not store above 25 °C.

### Pergolide 0.05 mg tablets

Space for dispensing label

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PL: 20242/0001
PERGOLIDE 0.05 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide

20 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 0.05 mg tablets

20 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Space for dispensing label

Pergolide 0.05 mg tablets

20 tablets
PERGOLIDE 0.05 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide.

30 tablets for oral use.

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 0.05 mg tablets

30 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Pergolide 0.05 mg tablets

Space for dispensing label

POM

Bar code

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Fair-Med Healthcare GmbH, Coehavener Straße 249, D-21149 Hamburg, Germany

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PL: 20242/0001

| Bar code |
PERGOLIDE 0.05 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide

60 tablets
for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 0.05 mg tablets

60 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Pergolide 0.05 mg tablets

Space for dispensing label

PL: 20242/0001

Pergolide 0.05 mg tablets

60 tablets
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Fair-Med Healthcare GmbH, Cuxhaven Straße 249, D-21149 Hamburg, Germany

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**Pergolide 0.05 mg tablets**

100 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25°C.

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**Pergolide 0.05 mg tablets**

100 tablets

Space for dispensing label

POM

Bar code

PL: 20242/0001
**PERGOLIDE 0.25 MG TABLETS**

Fair-Med Healthcare GmbH  
D-21149 Hamburg, Germany

**PERGOLIDE 0.25 MG TABLETS**

Fair-Med Healthcare GmbH  
D-21149 Hamburg, Germany

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10 tablets

for oral use

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**Pergolide 0.25 mg tablets**

10 tablets

Keep out of the reach and sight of children.  
Use as directed by a medicinal practitioner.  
Store in the original package.  
Do not store above 25 °C.

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**Pergolide 0.25 mg tablets**

Space for dispensing label

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**Pergolide 0.25 mg tablets**

10 tablets

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Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

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<td>30 tablets</td>
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<td>for oral use</td>
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**Pergolide 0.25 mg tablets**

30 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

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**Pergolide 0.25 mg tablets**

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PL: 20242/0001-3

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**Pergolide 0.25 mg tablets**

30 tablets
PERGOLIDE 0.25 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.25 mg of pergolide

50 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 0.25 mg tablets

50 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Pergolide 0.25 mg tablets

Space for dispensing label

Bar code

PL: 20242/0002

Pergolide 0.25 mg tablets

50 tablets
PERGOLIDE 0.25 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.25 mg of pergolide.

60 tablets

for oral use

Pergolide 0.25 mg tablets

60 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Pergolide 0.25 mg tablets

Space for dispensing label

POM

Bar code

PL: 20242/0002

Pergolide 0.25 mg tablets

60 tablets
**PERGOLIDE 0.25 mg TABLETS**

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.25 mg of pergolide

100 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

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**Pergolide 0.25 mg tablets**

100 tablets

Keep out of the reach and sight of children.

Use as directed by a medicinal practitioner.

Store in the original package.

Do not store above 25 °C.

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**Pergolide 0.25 mg tablets**

100 tablets
PERGOLIDE 1.0 MG TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 1.0 mg of pergolide

10 tablets

for oral use

Pergolide 1.0 mg tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Pergolide 1.0 mg tablets

Space for dispensing label

POM

Bar code

PL: 20242/0003

Pergolide 1.0 mg tablets

10 tablets
UKPAR Peroglide 0.05mg, 0.25mg and 1.0mg tablets

PERGOLIDE 1.0 mg TABLETS
Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 1.0 mg of pergolide
20 tablets
for oral use

Perglide 1.0 mg tablets
20 tablets
Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Perglide 1.0 mg tablets

Space for dispensing label

Perglide 1.0 mg tablets
20 tablets

PL: 20242/0001-3
### PERGOLIDE 1.0 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 1.0 mg of pergolide

| 30 tablets | for oral use |

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

#### Pergolide 1.0 mg tablets

30 tablets

Keep out of the reach and sight of children.
Use as directed by a medicinal practitioner.
Store in the original package.
Do not store above 25 °C.

Space for dispensing label

#### Pergolide 1.0 mg tablets

30 tablets
UKPAR Peroglide 0.05mg, 0.25mg and 1.0mg tablets

PERGOLIDE 1.0 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 1.0 mg of pergolide

50 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 1.0 mg tablets

50 tablets

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Pergolide 1.0 mg tablets

Space for dispensing label

POM

Bar code

PL 20242/0001-3

Pergolide 1.0 mg tablets

50 tablets
<table>
<thead>
<tr>
<th>Pergolide 1.0 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 tablets</td>
</tr>
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<td>Keep out of the reach and sight of children.</td>
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<td>Do not store above 25 °C.</td>
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</tbody>
</table>

**PERGOLIDE 1.0 mg TABLETS**

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide

60 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhaven Strasse 249, D-21149 Hamburg, Germany
PERGOLIDE 1.0 mg TABLETS

Each tablet contains, as the active ingredient, pergolide mesilate equivalent to 0.05 mg of pergolide

100 tablets

for oral use

Fair-Med Healthcare GmbH, Cuxhavener Straße 249, D-21149 Hamburg, Germany

Pergolide 1.0 mg tablets

100 tablets

Keep out of the reach and sight of children.
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Do not store above 25 °C.

Pergolide 1.0 mg tablets

Space for dispensing label

Bar code

PL: 20242/0003

Pergolide 1.0 mg tablets

100 tablets