

**IRISH MEDICINES BOARD ACT 1995**

**MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998**

**(S.I. No.142 of 1998)**

**PA0187/061/003**

Case No: 2036103

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

**Pharmacia Laboratories Limited**

**Ramsgate Road, Sandwich, Kent, CT13 9NJ, England**

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

**Cabaser 4mg Tablets**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/05/2007** until **28/10/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

## Part II

### Summary of Product Characteristics

#### 1 NAME OF THE MEDICINAL PRODUCT

Cabaser 4 mg Tablet

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg cabergoline as the active substance.

Each tablet also contains 301.6 mg of anhydrous lactose.

For full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Tablet

White, oval, both sides concave tablets, one side scored and engraved “7” on the left of the breakline and “03” on the right of it.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic Indications

###### Treatment of Parkinson's disease

If treatment with a dopamine agonist is being considered. Cabaser 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 plus dopa-decarboxylase inhibitor, in the management of the signs and symptoms of Parkinson's disease.

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

##### 4.2 Posology and method of administration

Cabaser is for oral administration. Since the tolerability of dopaminergic agents is improved when administered with food, it is recommended that Cabaser be taken with meals.

Cabaser is intended for chronic, long term treatment.

###### Adults and elderly patients

As expected for dopamine agonists, dose response for both efficacy and side effects appears to be linked to individual sensitivity. Optimization of dose should be obtained through slow initial dose titration, from starting doses of 1 mg daily. The dosage of concurrent levodopa may be gradually decreased, while the dosage of Cabaser is increased, until the optimum balance is determined. In view of the long half-life of the compound, increments of the daily dose of 0.5-1 mg should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.

The recommended therapeutic dosage is 2 to 6 mg/day as adjuvant therapy to levodopa/carbidopa. Cabaser should be given as a single daily dose.

Controlled clinical studies have demonstrated that Cabaser administered once daily at an average dose of 4mg/day following titration (up to 5-6 mg/day in the different studies) is effective.

**Use in children**

The safety and efficacy of Cabaser have not been investigated in children as Parkinson's disease does not affect this population.

**4.3 Contraindications**

Hypersensitivity to Cabaser, other ergot alkaloids or to any of the excipients.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders.

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

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

**4.4 Special warnings and precautions for use**

*Renal Insufficiency:* No overall differences in the pharmacokinetics of Cabaser were observed in 12 patients having moderate (creatinine clearance 31-60 ml/min) to severe (creatinine clearance 8-26 ml/min) renal disease. The pharmacokinetics of Cabaser in these patients were similar to those of healthy volunteers as expected, since only a small fraction of Cabaser is eliminated renally. The pharmacokinetics of Cabaser has not been studied in patients having end-stage renal failure, or in patients on haemodialysis; these patients should be treated with caution.

*Hepatic Insufficiency:* The pharmacokinetics of Cabaser was studied in 12 patients having varying degree of hepatic dysfunction (Child-Pugh score 5-11). Following single 1mg dose administration, Cabaser pharmacokinetics in patients with mild-moderate dysfunction (Child-Pugh score <10) were similar to those determined in previous studies in subjects with normal hepatic function. However, patients with the most severe dysfunction (Child-Pugh score > 10) showed AUC values 2-fold or more greater than patients with lesser dysfunction. No indication of prolonged half-life was found. These results suggest patients with severe hepatic insufficiency may require lower dose of Cabaser. These patients should be dosed with caution, and it is recommended that daily dose should be limited to no more than 1mg.

*Respiratory:* Pleural effusion/ pulmonary fibrosis has been reported in approximately 0.8% of patients following long term administration of Cabaser, and usually when given to patients previously treated with ergolinic DA agonists. Pleuritis and pleural fibrosis have also been reported after prolonged use of ergot derivatives. Therefore Cabaser should be given with caution to patients with a history or clinical symptoms of respiratory disorders linked to fibrotic tissue degeneration. A chest x-ray examination is recommended if clinical symptoms of respiratory disorders are observed. Where x-ray examination indicates pleural effusion/fibrosis, discontinuation of Cabaser is recommended and is expected to lead to an improvement of symptoms.

Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in case of unexplained ESR increases to abnormal values. Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorder. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy.

Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorder. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy.

*Cardiac:***Fibrotic 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 Cabaser. Therefore, Cabaser should be given with caution to patients with a history or clinical symptoms of cardiac disorders linked to fibrotic tissue

degeneration.

In some cases, symptoms or manifestations of cardiac valvulopathy improved after discontinuation of cabaser. Erythrocyte sedimentation rate (ESR) has been found to be abnormally increased in association with pleural effusion/fibrosis. Chest x-ray examination is recommended in cases of unexplained ESR increases to abnormal values.

Serum creatine measurements can also be used to help in the diagnosis of fibrotic disorders.

Valvulopathy was associated with cumulative doses.

Before initiating treatment:

All patients should undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. It may be appropriate to perform baseline investigations of ESR or other inflammatory markers, lung function/chest x-ray and renal function prior to initiation of therapy. If fibrotic valvular disease is detected, the patient should not be treated with Cabaser (See section 4.3).

During treatment:

Fibrotic disorders can have an insidious onset and patients should be regularly monitored for possible manifestations to progressive fibrosis. Therefore during treatment, attention should be paid to the signs and symptoms of:

- Pleuropulmonary 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.

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 appropriate

individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but should occur at a least every 6 to 12

months.

Cabaser 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.

Symptomatic hypotension can occur following administration of Cabaser: particular attention should be paid when administering Cabaser concomitantly with other drugs known to lower blood pressure. Because of its elimination half-life hypotensive effects may persist for a few days after cessation of therapy.

**CNS:** Cabaser has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Cabaser. 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.

In addition, by analogy with other ergot derivatives, Cabaser should be given with caution to patients suffering from severe cardiovascular disease, Raynaud's syndrome peptic ulcer, gastrointestinal bleeding or a history of serious,

particularly psychotic mental disease.

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

The effects of alcohol on overall tolerability of Cabaser are currently unknown.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

No pharmacokinetic interaction with L-dopa or selegiline was observed in the studies carried out in parkinsonian patients. The concomitant use of other drugs, particularly other antiparkinsonian non-dopamine-agonist agents, was not associated with detectable interactions modifying the efficacy and safety of Cabaser.

No other information is available about possible interaction between Cabaser and other ergot alkaloids: therefore the concomitant use of these medications during long term treatment with Cabaser is not recommended.

Since Cabaser exerts its therapeutic effect by direct stimulation of dopamine receptors, it should not be concurrently administered with drugs which have dopamine antagonist activity (such as phenothiazines, butyrophenones, thioxanthenes, metoclopramide) since these might reduce the therapeutic effect of Cabaser.

By analogy with other ergot derivatives, Cabaser should not be used in association with macrolide antibiotics (e.g. erythromycin) since the systemic bioavailability of Cabaser is increased and adverse effects could increase.

#### **4.6 Pregnancy and lactation**

Cabaser has been shown to cross the placenta in rats: it is unknown whether this occurs also in humans.

Animal studies in rats and mice have not demonstrated any teratogenic effect or any effect of the compound on global reproductive performance. In clinical studies there have been over 100 pregnancies in women treated with Cabaser for hyperprolactinaemic disorders. The compound was generally taken during the first 8 weeks after conception.

Among the pregnancies evaluable so far, there were approximately 85% live births and about 10% spontaneous abortions. Three cases of congenital abnormalities (Down's syndrome, hydrocephalus, malformation of lower limbs) which led to therapeutic abortion and three cases of minor abnormalities in live births were observed.

These incidence rates are comparable with those quoted for normal populations and for women exposed to other ovulation-inducing drugs. Based on the above data, the use of the product does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities.

Because clinical experience is still limited and the drug has a long half-life, as a precautionary measure it is recommended that women seeking pregnancy discontinue Cabaser one month before intended conception, in order to prevent possible foetal exposure to the drug. If conception occurs during therapy, treatment is to be discontinued as soon as pregnancy is confirmed, to limit foetal exposure to the drug.

In rats Cabaser and/or its metabolites are excreted in milk. Lactation is expected to be inhibited/suppressed by Cabaser, in view of its dopamine-agonist properties. Therefore, while no information on the excretion of Cabaser in maternal milk in humans is available, puerperal women should be advised not to breast-feed in case of failed lactation inhibition/suppression by the product.

#### **4.7 Effects on ability to drive and use machines**

During treatment with Cabaser, patients should be cautioned about engaging in activities requiring rapid and precise responses, such as driving or operating machinery.

Patients being treated with Cabaser and presenting with somnolence and/or sudden sleep onset 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 episodes and somnolence have resolved.

#### 4.8 Undesirable effects

About 1070 parkinsonian patients have received Cabaser as adjuvant therapy to L-dopa in clinical studies; of these 74% had at least one adverse event, mainly of mild to moderate severity and transient in nature, and requiring discontinuation in a small proportion of cases.

In the majority of cases (51%), events were related to the nervous system: most frequently reported events were dyskinesia, hyperkinesia, hallucinations or confusion. The gastrointestinal system was involved in 33% of cases: events most frequently reported were nausea, vomiting, dyspepsia and gastritis. The cardiovascular system was involved in 27% of cases, most frequently reported events being dizziness and hypotension. The respiratory system was involved in 13% of cases, symptomatic pleural effusion/fibrosis being reported with a frequency <2%.

Other adverse events expected for the pharmacological class, in view of the vasoconstrictive properties, include angina (reported in about 1% of the patients on Cabaser) and erythromelalgia (observed in 0.4% of the patients).

Similarly expected for the pharmacological class, peripheral oedema occurred in 6% of patients.

Gastric upset was more frequent in female than in male patients, while CNS events were more frequent in the elderly.

A blood pressure decrease of clinical relevance was observed mainly on standing in a minority of patients. The effect was mainly evident in the first weeks of therapy. Neither modification of heart rate nor consistent changes of ECG tracing were observed during Cabaser treatment.

Alterations in standard laboratory tests are uncommon during long term therapy with Cabaser. In clinical studies, increase of triglycerides greater than 30% above the upper limit of the laboratory reference range were observed in 6.8% of the Cabaser-treated patients who had values within the normal range at baseline. In most cases the increases were transient. No clear indications of increases over time or significant shifts from normal to abnormal values were observed in the overall group of patients treated with Cabaser. A clinically relevant decrease in haemoglobin, haematocrit and/or red blood cell count (>15% Vs baseline) was observed at least once in 6.8% of clinical study patients with normal values at entry; normalization was observed in one third of these patients.

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 Cabaser (See 'Special warnings and special precautions for use'). The incidence of valvulopathy with Cabaser 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 Cabaser may be in the range of 20% or greater.

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

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

**Post-marketing Surveillance:** The following events have been reported in association with Cabaser: somnolence, sudden sleep onset.

#### 4.9 Overdose

The acute toxicity studies carried out in animals indicate very low toxicity, with a wide safety margin with respect to pharmacologically active doses. Clinical signs and cause of death, if any, were related to CNS stimulation.

There is no experience in humans of overdosage with Cabaser in the proposed indication: it is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, confusion/psychosis or hallucinations. The vomiting stimulating properties of dopamine agonists are expected to favour removal of unabsorbed drug. Supportive measures should be taken to remove unabsorbed drug and to maintain blood pressure, if necessary. In addition, in case of pronounced central nervous system effects (hallucinations) the administration of dopamine antagonist drugs may be advisable.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Cabaser is a dopaminergic ergoline derivative endowed with potent and long-lasting dopamine D<sub>2</sub> receptor agonist properties.

Cabaser has showed to be effective in decreasing daily fluctuations in motor performance in Parkinsonian patients receiving levodopa/carbidopa therapy. Improvement of motor deficit has been demonstrated, while substantially decreasing the levodopa/carbidopa dose.

In healthy volunteers the administration of Cabaser at single oral doses of 0.3-2.5 mg was associated with a significant decrease in serum PRL levels. The effect is prompt (within 3 hours of administration) and persistent (up to 7-28 days). The PRL-lowering effect is dose-related both in terms of degree of effect and duration of action.

The pharmacodynamic actions of Cabaser not linked to the therapeutic effect relate only to blood pressure decrease. The maximal hypotensive effect of Cabaser as a single dose usually occurs during the first 6 hours after drug intake and is dose-dependent both in terms of maximal decrease and frequency.

### 5.2 Pharmacokinetic properties

The pharmacokinetic and metabolic profiles of Cabaser have been studied in healthy volunteers of both sexes, in female hyperprolactinaemic patients and in parkinsonian patients. After oral administration of the labelled compound, radioactivity was rapidly absorbed from the gastrointestinal tract as the peak of radioactivity in plasma was between 0.5 and 4 hours. Ten days after administration about 18/20% and 55/72% of the radioactive dose (<sup>3</sup>H-cabergoline/<sup>14</sup>C-cabergoline) was recovered in urine and faeces, respectively. Unchanged drug in urine accounted for 2-3% of the dose.

In urine, the main metabolite identified was 6-allyl-8b-carboxy-ergoline, which accounted for 4-6% of the dose. Three additional metabolites were identified in urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than Cabaser as D<sub>2</sub> dopamine receptor agonists "*in vitro*".

The low urinary excretion of unchanged Cabaser has been confirmed also in studies with non-radioactive product. The elimination half-life of Cabaser, estimated from urinary excretion rates, is long (63-68 hours in healthy volunteers, 79-115 hours in hyperprolactinaemic patients).

The pharmacokinetics of Cabaser seems to be dose-independent both in healthy volunteers (doses of 0.5-1.5 mg) and parkinsonian patients (steady state of daily doses up to 7 mg/day).

On the basis of the elimination half-life, steady state conditions should be achieved after 4 weeks, as confirmed by the mean peak plasma levels of Cabaser obtained after a single dose (37±8 pg/ml) and after a 4 week multiple-regimen (101±43 pg/ml). "*In vitro*" experiments showed that the drug at concentrations of 0.1-10 ng/ml is 41-42% bound to plasma proteins.

Food does not appear to affect absorption and disposition of Cabaser.

While renal insufficiency has been shown not to modify Cabaser kinetics, hepatic insufficiency of severe degree (> 10 Child-Pugh score, maximum score 12) has been shown to be associated with an increase of AUC.

### 5.3 Preclinical safety data

Almost all the findings noted throughout the series of preclinical safety studies are a consequence of the central dopaminergic effects or the long-lasting inhibition of PRL in rodents with a specific hormonal physiology different to man.

Preclinical safety studies of Cabaser indicate a consistent safety margin for this compound in rodents and in monkeys, as well as a lack of teratogenic, genotoxic or carcinogenic potential.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose anhydrous  
Leucine

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf Life

2 years.

### 6.4 Special precautions for storage

Do not store above 25°C. Containers should be kept tightly closed.

### 6.5 Nature and contents of container

Amber glass bottles with aluminium tamper resistant screw cap equipped with a low density polyethylene / thermoplastic elastomer plastic undercap acting as a container holding silica gel, closed by a plastic cap with porous paper at the lower extremity.

Each bottle contains 15 or 16 tablets of 4 mg strength and is enclosed in an outer cardboard carton.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Bottles of Cabaser are supplied with desiccant in the caps. This desiccant must not be removed.

## 7 MARKETING AUTHORISATION HOLDER

Pharmacia Laboratories Limited  
Ramsgate Road  
Sandwich  
Kent CT13 9NJ  
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER



PA 187/61/3

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 29 October 1999

Date of last renewal: 29 October 2004

**10 DATE OF REVISION OF THE TEXT**

May 2007