Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cabergoline 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg of cabergoline.

Excipient(s) with known effect:
Each tablet also contains 75 mg of anhydrous lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

7.5 × 4 mm, oval shaped, white coloured tablets, having scored on one side 'c' on left, '2' on right and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of Parkinson's disease
If treatment with a dopamine agonist is being considered, cabergoline 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 and 4.8).

4.2 Posology and method of administration

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

Cabergoline 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 cabergoline 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 mg to 3 mg/day for patients with signs and symptoms of Parkinson's disease. Cabergoline should be given as a single daily dose.

The maximum dose is 3 mg cabergoline per day.

The adjustment to the optimal dose should be an initial slow dosage titration starting with 0.5 mg cabergoline (*de novo* patients) or 1 mg cabergoline (patients on levodopa) daily.

Use in patients with liver or renal insufficiency
For use in patients with severe hepatic impairment or end-stage renal failure: see section 4.4.
In the presence of moderate to severe renal insufficiency, kinetics of cabergoline is not altered.

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

4.3 Contraindications

Hypersensitivity to cabergoline or to any of the excipients listed in section 6.1, or any ergot alkaloid.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders.

Preeclampsia, eclampsia.

Uncontrolled hypertension.

For long-term treatment: Evidence of cardiac valvulopathy as determined by pre-treatment echocardiography (see section 4.4).

4.4 Special warnings and precautions for use

General
As with other ergot derivatives, cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, peptic ulcer or gastrointestinal bleeding, or with a history of serious, particularly psychotic, mental disorders.

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

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

Renal Insufficiency:
No overall differences in the pharmacokinetics of cabergoline 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 cabergoline in these patients were similar to those of healthy volunteers as expected, since only a small fraction of cabergoline is eliminated renally. The pharmacokinetics of cabergoline 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
Lower doses of cabergoline should be considered in patients with severe hepatic insufficiency. Compared to normal volunteers and those with lesser degrees of hepatic insufficiency, an increase in AUC has been seen in patients with severe hepatic insufficiency (Child-Pugh Class C) who received a single 1 mg dose.

Postural Hypotension
Postural hypotension can occur following administration of cabergoline, particularly during the first days of administration of cabergoline. Care should be exercised when administering cabergoline concomitantly with other drugs known to lower blood pressure.

Fibrosis and cardiac valvulopathy and possibly related clinical phenomena
Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy involving one or more valves (aortic, mitral and tricuspid) or retroperitoneal fibrosis have occurred after prolonged usage of ergot derivatives with agonist activity at the serotonin $5HT_{2B}$ receptor, such as cabergoline.

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

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 creatinine measurements can also be used to help in the diagnosis of fibrotic disorder. Following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms (see section 4.3).

Valvulopathy has been associated with cumulative doses, therefore patients should be treated with the lowest effective dose. At each visit, the risk benefit profile of cabergoline treatment for the patient should be reassessed to determine the suitability of continued treatment with cabergoline.

Before initiating long-term treatment

All patients must undergo a cardiovascular evaluation, including echocardiogram, to assess the potential presence of asymptomatic valvular disease. 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.

In patients with valvular regurgitation, it is not known whether cabergoline treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with cabergoline (see section 4.3).

During long-term treatment

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

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

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

Clinical diagnostic monitoring for development of fibrotic disorders, as appropriate, is essential. 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 must occur at least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction, valve leaflet thickening or fibrotic valvular disease (see section 4.3).

The need for other clinical monitoring (e.g. physical examination including, cardiac auscultation, X-ray, CT scan) should be determined on an individual basis.

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

Symptomatic hypotension can occur following administration of cabergoline: particular attention should be paid when administering cabergoline 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.

Somnolence/Sudden Sleep Onset

Cabergoline has been associated with somnolence and episodes of sudden sleep onset in patients with Parkinson's disease. Sudden onset of sleep during activities, in some cases without awareness or warning signs, has been reported. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with cabergoline. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction in dosage or termination of therapy may be considered (see section 4.7).

Impulse control disorders

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

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of antiparkinson non-dopamine agonists (e.g. selegiline, amantadine, biperiden, trihexyphenidyl) was allowed in clinical studies for patients receiving cabergoline. In studies where the pharmacokinetic interactions of cabergoline with L-dopa or selegiline were evaluated, no interactions were observed.

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

Since cabergoline 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 cabergoline.

As with other ergot derivatives, cabergoline should not be used in association with macrolide antibiotics (e.g. erythromycin) due to increased systemic bioavailability.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies from the use of cabergoline in pregnant women. Animal studies have not demonstrated teratogenic effects, but reduced fertility and embryo-toxicity were observed in association with pharmacodynamic activity (see section 5.3).

In a twelve year observational study on pregnancy outcomes following cabergoline therapy, information is available on 256 pregnancies. Seventeen of these 256 pregnancies (6.6%) eventuated in major congenital malformations or abortion. Information is available on 23/258 infants who had a total of 27 neonatal abnormalities, both major and minor. Musculoskeletal malformations were the most common neonatal abnormality (10), followed by cardio-pulmonary abnormalities (5). There is no information on perinatal disorders or long-term development of infants exposed to intra-uterine cabergoline. Based on recent published literature, the prevalence of major congenital malformations in the general population has been reported to be 6.9% or greater. Rates of congenital abnormality vary between different populations. It is not possible to accurately determine if there is an increased risk as no control group was included.

It is recommended that contraception is used whilst on treatment with cabergoline.

Cabergoline should only be used during pregnancy if clearly indicated and after an accurate benefit/risk evaluation.

Due to the long half-life of the drug and limited data on in utero exposure, women planning to become pregnant should discontinue cabergoline one month before intended conception. If conception occurs during therapy, treatment should be discontinued as soon as pregnancy is confirmed to limit foetal exposure to the drug.

In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on excretion in breast milk in humans; however, lactation is expected to be inhibited/suppressed by cabergoline, in view of its dopamine agonist properties. Mothers should be advised not to breast-feed while being treated with cabergoline.

4.7 Effects on ability to drive and use machines

Patients should be careful when performing actions which require fast and accurate reaction during treatment initiation.

Patients being treated with cabergoline 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 (see section 4.4).

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with cabergoline with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
Cardiac disorders	Very Common	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
	Common*	Angina pectoris
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Pleural effusion, pulmonary fibrosis
	Very rare	Fibrosis (including pleural fibrosis)
	Not Known	Respiratory disorder, respiratory failure, pleuritis, chest pain
Immune system disorders	Uncommon	Hypersensitivity reaction
Nervous system disorders	Common	Headache, somnolence, dizziness/vertigo, dyskinesia
	Uncommon	Hyperkinesia
	Not Known	Sudden sleep onset, syncope, tremor
Eye disorders	Not Known	Visual impairment
Psychiatric disorders	Common	Hallucinations, sleep disturbances, increased libido, confusion
	Uncommon	Delusions, psychotic disorder
	Not Known	Aggression, hypersexuality, pathological gambling
Vascular disorders	Common	Cabergoline generally exerts a hypotensive effect in patients on long-term treatment; Postural hypotension
	Uncommon	Erythromelalgia
	Not Known	Digital vasospasm
Gastrointestinal disorders	Very common	Nausea
	Common	Constipation, dyspepsia, gastritis, vomiting
General disorders and administration site conditions	Very common	Peripheral oedema
	Common	Asthenia
	Uncommon	Oedema, fatigue
Hepato-biliary disorders	Uncommon	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Not Known	Alopecia
Musculoskeletal and connective tissue disorders	Not Known	Leg cramps
Investigations	Common	Liver function tests abnormal, decreased haemoglobin, haematocrit, and/or red blood cell (>15% vs baseline)
	Not Known	Blood creatinine phosphokinase increased

* When concomitant use with levodopa therapy

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including cabergoline (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors, e.g. nausea, vomiting, gastric complaints, postural hypotension, confusion/psychosis or hallucinations.

Supportive measures should be taken to remove unabsorbed drug and maintain blood pressure, if necessary. In addition, the administration of dopamine antagonist drugs may be advisable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopamine agonists, ATC code: N04BC06

Cabergoline is a dopaminergic ergoline derivative endowed with potent and long-lasting dopamine D_2 receptor agonist properties.

Cabergoline 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 cabergoline 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 cabergoline not linked to the therapeutic effect relate only to blood pressure decrease. The maximal hypotensive effect of cabergoline 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 cabergoline have been studied in healthy volunteers of both sexes**,** in female hyperprolactinemic 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 (^{3}H cabergoline/^{14}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 cabergoline as D_2 dopamine receptor agonists "in vitro".

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

The pharmacokinetics of cabergoline seem 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 cabergoline 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 cabergoline.

While renal insufficiency has been shown not to modify cabergoline 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 cabergoline 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
L-Leucine
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene bottles with a child-resistant polypropylene cap and silica gel pillow packs inside.

Each bottle contains 30 or 100 tablets and is enclosed in an outer cardboard carton.

6.6 Special precautions for disposal

Bottles of Cabergoline are supplied with silica gel pillow-packs inside. These pillow-packs must not be removed.

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
12 Crowe Street
Dundlak, Co Louth
Ireland, A91NN29

8 MARKETING AUTHORISATION NUMBER

PA22865/011/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th October 2023

10 DATE OF REVISION OF THE TEXT

May 2024