SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cabergoline 1mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1 mg cabergoline.

Excipient(s) with known effect:
Each tablet contains 75.3 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

The tablet can be divided into equal doses.

White, oval-shaped boconvex, tablets with scores on both sides. One side is debossed with 'CBG' and '1' on either side of the score.

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

Posology

Cabergoline is intended for chronic, long term treatment.

Adults and older people:
As expected for dopamine agonists, dose response for both efficacy and undesirable effects appears to be linked to individual sensitivity. Optimization of dose should be obtained through slow initial dose titration, from starting doses of 0.5mg cabergoline (de novo patients) and 1 mg cabergoline (patients on L dopa) 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 cabergoline should be done at weekly (initial weeks) or bi-weekly intervals, up to optimal doses.
The recommended therapeutic dosage is 2 to 3 mg cabergoline /day for patients with signs and symptoms of Parkinson's disease. The maximum dose of 3mg/day of cabergoline must not be exceeded. Cabergoline should be given as a single daily dose.

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

Patients with hepatic or renal impairment
For patients with severe hepatic dysfunction or end stage renal failure see section 4.3 and 4.4.

Method of administration
Cabergoline is to be administered by the oral route. In order to reduce the risk of gastrointestinal undesirable effects it is recommended that cabergoline is taken with meals for all therapeutic indications.

4.3 Contraindications

Pre-eclampsia, eclampsia
Uncontrolled hypertension.
Hypersensitivity to the active substance, any ergot alkaloid or to any excipient listed in section 6.1
History of pulmonary, pericardial and retroperitoneal fibrotic disorders or adverse pulmonary reactions.

For long term treatment: evidence of cardiac valvulopathy of any valve as determined by pre-treatment echocardiography (See section 4.4 Special warnings and precautions for use – Fibrosis and cardiac valvulopathy and possibly related clinical phenomena).

4.4 Special warnings and precautions for use

General

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

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

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

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 creatine 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 Contraindications).

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 should 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 Contraindications).

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 obstructions that may occur with pain in the loin/flank, and lower limb oedema, as well as any possible abdominal masses or tenderness that may indicate retroperitoneal fibrosis.
- Cardiac failure; cases of valvular and pericardial fibrosis have often manifested as cardiac failure. Therefore, valvular fibrosis (and constrictive pericarditis) should be excluded if such symptoms occur.

Clinical diagnostic monitoring for development of valvular disease or fibrotic disease as appropriate, is essential. Following treatment initiation, the first echocardiogram must occur within 3-6 months, thereafter, the frequency of echocardiographic monitoring should be determined by appropriate individual clinical assessment with particular emphasis on the above-mentioned signs and symptoms, but must occur at a least every 6 to 12 months.

Cabergoline should be discontinued if an echocardiogram reveals new or worsened valvular regurgitation, valvular restriction or valve leaflet thickening (See Section 4.3 Contraindications).

The need for other clinical monitoring (e.g. physical examination including careful 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 fibrotic disorder.

Somnolence/sudden sleep onset:
Cabergoline has been associated with somnolence and episodes of sudden sleep onsetin 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. A reduction of dosage or termination of therapy may be considered (See section 4.7 Effects on ability to drive and use machines).

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.

Renal insufficiency:
No overall differences in the pharmacokinetics of cabergoline were observed in moderate to severe renal disease. 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.

Serious adverse reactions in postpartum women:
Serious adverse events including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with cabergoline for

inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances. Blood pressure should be carefully monitored during the treatment. If hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of central nervous system toxicity develop, cabergoline should be discontinued and the patient evaluated promptly.

4.5 Interactions with other medicinal products and other forms of interactions

The concomitant use of antiparkinson non-dopamine agonists (eg, 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 that 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 (eg, erythromycin) due to increased systemic bioavailability.

4.6 Fertility, pregnancy and lactation

Pregnancy

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).

Before cabergoline administration, pregnancy should be excluded and after treatment should be prevented for at least one month.

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 abormality (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.

Contraception should be continued for at least 4 weeks after stopping cabergoline.

Breast-feeding
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.

Fertility
Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism: since pregnancy might occur prior to reinitiation of menses, pregnancy testing is recommended as appropriate during the amenorrhoeic period and, once menses are reinitiated, every time a menstrual period is delayed by more than three days. Women not seeking pregnancy should be advised to use effective non-hormonal contraception during treatment and after cabergoline withdrawal. Because of limited experience on the safety of foetal exposure to cabergoline, it is advisable that women seeking pregnancy conceive at least one month after cabergoline discontinuation given that ovulatory cycles persist in some patients for 6 months after withdrawal. Should pregnancy occur during treatment, cabergoline is to be discontinued. As a precautionary measure, women who become pregnant should be monitored to detect signs of pituitary enlargement since expansion of pre-existing pituitary tumours may occur during gestation.

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 treated with cabergoline and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (eg, operating machines) until such episodes and somnolence have resolved (See section 4.4 Special warnings and precautions for use – Somnolence/sudden sleep onset).

4.8 Undesirable effects

About 1070 parkinsonian patients have received cabergoline 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.

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

MedDRA System Organ Class	Frequency	Undesirable Effects
	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 hemoglobin, hematocrit, 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 Special warnings and precautions for use).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose would likely be those of over-stimulation of dopamine receptors, eg, 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 agonist
ATC code: N04BC06

Cabergoline is a synthetic ergot alkaloid and an ergoline derivate with long-acting dopamine agonist and prolactin-inhibiting properties. A central dopaminergic effect via D2-receptor stimulation is achieved through higher doses than doses that reduce the levels of serum prolactin.

The prolactin-reducing effect is dose-dependent, starting within 3 hours and remaining for 2-3 weeks. The long-acting effect means that a single dose is generally sufficient to stop the initiation of milk secretion. In treatment of hyperprolactinaemia, the serum prolactin levels are generally normalised within two to four weeks of the optimal dose being attained. Prolactin can still be significantly reduced several months after withdrawal of the treatment.

With regard to the endocrine effects of cabergoline not related to the antiprolactinaemic effect, available data from humans confirm the experimental findings in animals indicating that the test compound is endowed with a very selective action with no effect on basal secretion of other pituitary hormones or cortisol.

The pharmacodynamic actions of cabergoline not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of cabergoline as single dose usually occurs during the first 6 hours after active substance 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.

Absorption

After oral administration cabergoline is rapidly absorbed from the gastrointestinal tract as the peak plasma concentration is received within 0.5 to 4 hours.

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

Distribution

"In-vitro" experiments showed that cabergoline at concentrations of 0.1 – 10 ng/ml is 41-42% bound to plasma proteins.

Biotransformation

In urine, the main metabolite identified is 6-allyl-8ß-carboxy-ergoline, which accounts for 4-6% of the dose. Three additional metabolites are identified in urine, which account overall for less than 3% of the dose. The metabolites have been found to be much less potent than cabergoline in inhibiting prolactin secretion "in-vitro".

Elimination

The elimination half-life of cabergoline, is long; (63-68 hours in healthy volunteers and 79-115 hours in hyperprolactinaemic patients).

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)–for 0.5mg cabergoline dose.

Ten days after administration about 18/20% and 55/72% of the dose is recovered in urine and faeces, respectively. Unchanged cabergoline in urine accounts for 2-3% of the dose.

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.

Linearity/Non-linearity
The pharmacokinetic profile is linear up to 7 mg per day.

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 (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture. The drying capsule or bag with silica gel must not be removed from the bottle.

6.5 Nature and contents of container

Brown glass bottles (type III) containing a dessication capsule with silica gel with an induction-sealed childproof aluminium membrane and childproof HDPE top.

Or

Brown glass bottles (type III) containing a dessication bag with silica gel with an induction-sealed childproof aluminium membrane and childproof PP top.

External box.
Packaging sizes: 2, 8, 14, 15, 16, 20, 28, 30, 32, 40, 48, 50, 60, 90, 98, 100.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirement.

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 00289/0989

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28/03/2023