Summary of Product Characteristics
CABERLIN 0.5
(Cabergoline 0.5 mg tablets)

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1. Name of the medicinal product

Caberlin 0.5 (Cabergoline 0.5 mg Tablet)

2. Qualitative and quantitative composition

Each film-coated tablet contains 0.5 mg of cabergoline.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet.

4. Clinical particulars

4.1 Therapeutic indications

Inhibition/suppression of physiological lactation

Cabergoline is indicated for the inhibition of physiological lactation soon after delivery, and for the suppression of established lactation, when the mother elects not to breast-feed or breast-feeding is contraindicated, and after stillbirth or abortion.

Hyperprolactinaemic disorders

Cabergoline is indicated for the treatment of dysfunctions associated with hyperprolactinaemia, including amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea, and in patients with prolactin-secreting pituitary adenomas (micro- and macroprolactinomas), idiopathic hyperprolactinaemia or empty sella syndrome with associated hyperprolactinaemia.

4.2 Posology and method of administration

Inhibition/suppression of physiological lactation

For inhibition of lactation, cabergoline should be administered during the first day post-partum; the recommended dose is 1 mg (two 0.5 mg tablets) as a single dose. For suppression of established lactation, the recommended regimen is 0.25 mg (half a tablet) every 12 hours for two days (1 mg total). A single dose of 0.25 mg should not be exceeded in nursing women to avoid potential postural hypotension.

Hyperprolactinaemic disorders

The recommended initial dose is 0.5 mg per week, given in one or two doses. The weekly dose should be increased gradually, preferably by 0.5 mg per week at monthly intervals, until an optimal response is achieved. The therapeutic dose is usually 1 mg per week (range 0.25 mg to 2 mg per week). The weekly dose may be given as a single administration or divided; division is advised for doses above 1 mg per week. Serum prolactin should be monitored monthly.

Paediatric population

The safety and efficacy of cabergoline have not been established in subjects less than 16 years of age.

Elderly

Experience in the elderly is limited; available data do not indicate a special risk.

Method of administration

For oral use, preferably taken with meals.

4.3 Contraindications

- Hypersensitivity to cabergoline, to any of the excipients, or to any ergot alkaloid.
- History of pulmonary, pericardial or retroperitoneal fibrotic disorders.
- Hepatic insufficiency and toxaemia of pregnancy.
- Concomitant use with antipsychotic medicines, or use in women with a history of puerperal psychosis.
- For long-term treatment: evidence of cardiac valvulopathy on pre-treatment echocardiography (see section 4.4).

4.4 Special warnings and precautions for use

Cabergoline should be given with caution to patients with severe cardiovascular disease, Raynaud's syndrome, renal insufficiency, peptic ulcer or gastrointestinal bleeding, or a history of serious (particularly psychotic) mental disorders. Symptomatic and postural hypotension can occur; care is needed with concomitant antihypertensives. Before administration, pregnancy should be excluded, and pregnancy prevented for at least one month after treatment.

Fibrosis and cardiac valvulopathy

Fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion and fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy (involving one or more valves) and retroperitoneal fibrosis have occurred after prolonged use of ergot derivatives with agonist activity at the serotonin 5-HT2B receptor, such as cabergoline. Valvulopathy has been associated with cumulative doses; patients should be treated with the lowest effective dose. Before initiating long-term treatment, all patients must undergo cardiovascular evaluation including echocardiography, with baseline erythrocyte sedimentation rate, lung function/chest X-ray and renal function. If fibrotic valvular disease is detected, the patient should not be treated. During long-term treatment, patients should be monitored for signs of fibrosis; the first echocardiogram should occur within 3–6 months of initiation and thereafter at least every 6 to 12 months. Cabergoline should be discontinued if new or worsened valvular regurgitation, valvular restriction or valve-leaflet thickening is detected.

Somnolence / sudden sleep onset

Cabergoline has been associated with somnolence and, uncommonly, with sudden sleep onset. Patients must be informed and advised to exercise caution while driving or operating machines; those who experience somnolence or sudden sleep onset must refrain from these activities.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, and binge or compulsive eating; dose reduction or tapered discontinuation should be considered if these develop.

Postpartum use

Serious adverse events, including hypertension, myocardial infarction, seizures, stroke and psychiatric disorders, have been reported in postpartum women treated with cabergoline for inhibition of lactation. Blood pressure should be carefully monitored, particularly during the first few days. Cabergoline should not be used in women with pregnancy-induced hypertension (e.g. pre-eclampsia) unless the benefit outweighs the risk.

4.5 Interaction with other medicinal products and other forms of interaction

No information is available on interactions between cabergoline and other ergot alkaloids; concomitant use during long-term treatment is not recommended. Cabergoline should not be concurrently administered with medicines that have dopamine-antagonist activity (phenothiazines, butyrophenones, thioxanthenes, metoclopramide), as these may reduce its prolactin-lowering effect. As with other ergot derivatives, cabergoline should not be used with macrolide antibiotics (e.g. erythromycin), owing to increased systemic bioavailability.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Owing to the long half-life and limited data on in-utero exposure, women planning pregnancy should discontinue cabergoline one month before intended conception; if conception occurs during therapy, treatment should be discontinued once pregnancy is confirmed. Women who become pregnant should be monitored for signs of pituitary enlargement.

Breast-feeding

As cabergoline prevents lactation, it should not be given to mothers with hyperprolactinaemic disorders who wish to breast-feed; mothers should be advised not to breast-feed in the case of failed lactation inhibition.

Fertility

Cabergoline restores ovulation and fertility in women with hyperprolactinaemic hypogonadism; a pregnancy test is recommended during the amenorrhoeic period and whenever a menstrual period is delayed.

4.7 Effects on ability to drive and use machines

Patients should be cautious during treatment initiation about activities requiring rapid and precise responses, such as driving or operating machinery. Patients presenting with somnolence or sudden sleep onset must refrain from driving or operating machines until such episodes have resolved.

4.8 Undesirable effects

Adverse events are generally dose-related. The adverse reactions are listed below by System Organ Class and frequency, defined as: 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) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Cardiac disorders	Very common	Valvulopathy (including regurgitation) and related disorders (pericarditis and pericardial effusion)
	Uncommon	Palpitations
	Not known	Angina pectoris
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, pleural effusion, fibrosis (including pulmonary fibrosis), epistaxis
	Very rare	Pleural fibrosis
	Not known	Respiratory disorder, respiratory failure, pleuritis, chest pain
Immune system disorders	Uncommon	Hypersensitivity reaction
Nervous system disorders	Very common	Headache, dizziness/vertigo
	Common	Somnolence
	Uncommon	Transient hemianopsia, syncope, paraesthesia
	Not known	Sudden sleep onset, tremor
Eye disorders	Not known	Visual impairment
Psychiatric disorders	Common	Depression
	Uncommon	Increased libido

System Organ Class	Frequency	Adverse reaction
	Not known	Aggression, delusions, hypersexuality, pathological gambling, psychotic disorder, hallucinations
Vascular disorders	Common	Postural hypotension, hot flushes
	Uncommon	Digital vasospasm, fainting
Gastrointestinal disorders	Very common	Nausea, dyspepsia, gastritis, abdominal pain
	Common	Constipation, vomiting
	Rare	Epigastric pain
General disorders and administration site conditions	Very common	Asthenia, fatigue
	Uncommon	Oedema, peripheral oedema
Hepatobiliary disorders	Not known	Hepatic function abnormal
Skin and subcutaneous tissue disorders	Uncommon	Rash, alopecia
Musculoskeletal and connective tissue disorders	Uncommon	Leg cramps
Reproductive system and breast disorders	Common	Breast pain
Investigations	Common	Asymptomatic decreases in blood pressure
	Uncommon	Decreased haemoglobin in amenorrhoeic women during the first months after resumption of menses
	Not known	Blood creatine phosphokinase increased, liver function tests abnormal

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 to the National Regulatory Authority.

4.9 Overdose

Symptoms of overdose would 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 any unabsorbed drug and to maintain blood pressure; administration of a dopamine-antagonist may be advisable.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Prolactin inhibitors, dopamine agonists. ATC code: G02CB03.

Cabergoline is a dopaminergic ergoline derivative with potent and long-lasting prolactin-lowering activity, acting by direct stimulation of D2 dopamine receptors on pituitary lactotrophs and thereby inhibiting prolactin secretion. The long-lasting effect is probably due to its long persistence in the target organ. After a single oral dose, a significant decrease in serum prolactin occurs within 3 hours and is dose-related in degree and duration.

5.2 Pharmacokinetic properties

Cabergoline is absorbed after oral administration and is subject to first-pass metabolism. It is extensively distributed, with a long elimination half-life (approximately 63–68 hours in hyperprolactinaemic patients) that supports once- or twice-weekly dosing. Metabolism is mainly by hydrolysis of the acylurea bond or the urea moiety; the CYP450 system plays a limited role. Excretion is mainly in the faeces, with a smaller amount in urine.

5.3 Preclinical safety data

Animal studies have not demonstrated teratogenic effects, but reduced fertility and embryotoxicity were observed in association with the pharmacodynamic activity of the compound. Cabergoline and/or its metabolites are excreted in the milk of rats.

6. Pharmaceutical particulars

6.1 List of excipients

- Microcrystalline cellulose
- L-Leucine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C. Protect from light and moisture. Keep out of the reach and sight of children.

6.5 Nature and contents of container

Blister pack of tablets, presented in a printed carton together with the package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder and Manufacturer

Sun Pharmaceutical Industries Limited, India.

8. Marketing Authorisation Number

H2009/19598/168

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text