SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DOSTINEX® 0,5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DOSTINEX tablet contains 0,5 mg cabergoline.

Contains sugar (lactose anhydrous).

Excipients with known effect

Each DOSTINEX 0,5 mg tablet contains 75,9 mg lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Capsule-shaped, flat, white tablets. On the one surface the letter “P” appears on a side of the score and the letter “U” on the other. On the other surface the number “700” appears with a short score in the middle of the upper and lower extremity of the tablet surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Inhibition of lactation before the commencement of breastfeeding as well as inhibition of established lactation for medical reasons.
- Not recommended for the routine suppression of lactation or for the relief of symptoms of postpartum pain and engorgement, which can be adequately treated with simple analgesics and breast support.
- Treatment of hyperprolactinaemic disorders.

4.2 Posology and method of administration

Patients should be evaluated during dose escalation to determine the lowest dosage that produces the therapeutic response. Monitoring of serum prolactin levels at monthly intervals is advised.

Once the effective therapeutic dosage regimen has been reached, serum prolactin normalisation is usually observed within two to four weeks.

Posology

Adults

For inhibition of lactation

DOSTINEX should be administered during the first day post-partum. The recommended therapeutic dosage is 1 mg (two 0,5 mg tablets) given as a single dose.

For suppression of established lactation

The recommended therapeutic dosage regimen is 0,25 mg (one-half 0,5 mg tablet) every 12 hours for two days (1 mg total dose). DOSTINEX should not be administered as a single dose greater than 0,25 mg in this indication since this reduces tolerability.

For treatment of hyperprolactinaemic disorders

The recommended initial dosage is 0,5 mg given in one or two doses per week. The weekly dose should be increased gradually, preferably by adding 0,5 mg per week at monthly intervals until an optimal therapeutic response is achieved.

The therapeutic dosage is usually 1 mg per week and ranges from 0,25 mg to 2 mg per week. Doses up to 4,5 mg per week have been used.

The dosage should preferably be adjusted according to prolactin blood levels.

Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg per week are to be given.

Special populations

Use in the elderly

DOSTINEX has not been formally studied in elderly patients with hyperprolactinaemic disorders.

Paediatric population

Safety and efficacy have not been established in patients younger than 16 years.

Method of administration

DOSTINEX is to be administered by the oral route, preferably taken with meals.

4.3 Contraindications

- Hypersensitivity to cabergoline, any ergot alkaloid or to any of the excipients of DOSTINEX (listed in section 6.1)
- Pregnancy and breastfeeding (see section 4.6)
- By analogy with other ergot derivatives, DOSTINEX should not be used in women with pre-eclampsia or post-partum hypertension
- History of pulmonary, pericardial and retroperitoneal fibrotic disorders (see section 4.4)
- DOSTINEX is contraindicated in patients with hepatic insufficiency (see section 4.4)

Long-term treatment

Long term treatment is contraindicated in patients with cardiac valvulopathy as determined by pre-treatment echocardiogram showing valve leaflet thickening, valve restriction, valve mixed restriction-stenosis (see section 4.4).

4.4 Special warnings and precautions for use

General

DOSTINEX should be given with caution to patients with cardiovascular disease, Raynaud's syndrome, renal insufficiency, peptic ulcer or gastro-intestinal bleeding or with a history of serious, particularly psychotic, mental disorders.

Hepatic insufficiency

Biliary excretion represents the main route of elimination DOSTINEX, it is advisable not to administer DOSTINEX to subjects with severe liver insufficiency (see section 4.3).

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 DOSTINEX. Care should be exercised when administering DOSTINEX concomitantly with other medicines known to lower blood pressure.

Fibrosis/valvulopathy

Pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of DOSTINEX. Therefore, DOSTINEX should be not be used in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. 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 DOSTINEX has been reported to result in improvement of signs and symptoms (see section 4.3).

Long-term treatment

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 DOSTINEX treatment might worsen the underlying disease. If fibrotic valvular disease is detected, the patient should not be treated with DOSTINEX (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 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 least every 6 to 12 months.

DOSTINEX 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 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.

Somnolence/sudden sleep onset

DOSTINEX has been associated with somnolence. Dopamine agonists can be associated with sudden sleep onset episodes in patients with Parkinson's disease. A reduction of dosage or termination of therapy may be considered (see section 4.7).

Inhibition/suppression of physiologic lactation

DOSTINEX should not be used in women with certain pregnancy-induced hypertension, namely pre-eclampsia and post-partum hypertension (see section 4.3).

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 after 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 should be evaluated promptly.

A single dose of 0,25 mg of DOSTINEX should not be exceeded in nursing women treated for suppression of established lactation to avoid potential postural hypotension (see Postural hypotension and-section 4.3).

Treatment of hyperprolactinaemic disorders

Since hyperprolactinaemia with amenorrhoea/galactorrhoea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary is indicated before treatment with DOSTINEX is initiated.

Psychiatric

Impulse control disorders such as pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists including DOSTINEX. This has been generally reversible upon reduction of the dose or treatment discontinuation.

Special populations

The safety and efficacy of DOSTINEX have not been established in patients with renal and hepatic disease or in patients younger than 16 years.

Excipients with known effect

DOSTINEX contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

No information is available about interactions between DOSTINEX and other ergot alkaloids, therefore the concomitant use of these medicines during therapy with DOSTINEX is not recommended.

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

DOSTINEX should not be used with macrolide antibiotics (e.g. erythromycin) due to the increased systemic bioavailability of DOSTINEX.

4.6 Fertility, pregnancy and lactation

Pregnancy

DOSTINEX is contraindicated in confirmed or suspected pregnancy.

If conception occurs during therapy with DOSTINEX, treatment should be discontinued. Before DOSTINEX is administered, pregnancy must be excluded.

Pregnancy should be avoided for at least one month following discontinuation of treatment with DOSTINEX due to the long half-life of the medicine and the limited data on in utero exposure (see section 4.3).

Pregnancy could occur in women treated for hyperprolactinaemic hypogonadism before restoration of the menstrual cycle; it is advisable to carry out a pregnancy test at least every four weeks during the period of amenorrhoea and afterwards every time the menstrual period is delayed by more than three days.

Women who do not wish to become pregnant should use a mechanical contraceptive during the treatment and after discontinuation until the ovulatory cycles cease.

When pregnancy is confirmed during the treatment, the use of DOSTINEX should be suspended, and as a precautionary measure, pituitary size should be monitored since expansion of pre-existent tumours could occur during pregnancy.

Breastfeeding

In rats, DOSTINEX and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however mothers should not breastfeed their infants in case of failed lactation inhibition/suppression by DOSTINEX. Since it prevents lactation, DOSTINEX should not be administered to mothers with hyperprolactinaemic disorders who wish to breastfeed their infants.

4.7 Effects on ability to drive and use machines

Patients being treated with DOSTINEX and presenting with somnolence 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) (see section 4.4, Somnolence/sudden sleep onset).

During the first days of DOSTINEX administration, patients should be cautioned about re-engaging in activities requiring rapid and precise responses such as driving an automobile or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

DOSTINEX generally exerts a hypotensive effect in patients. Symptoms mainly appear during the first two weeks of therapy and disappear despite continued therapy.

Being an ergot derivative, DOSTINEX may also act in some patients as a vasoconstrictor.

Valvulopathy and fibrosis have been reported in association with DOSTINEX (see section 4.4).

Tabulated summary of adverse reactions

The table below contains side effects categorised as follows utilising the incidence rates: 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.

Adverse events have been observed in nursing women treated with 0,25 mg of DOSTINEX every 12 hours for 2 days for suppression of lactation.

Table 1 includes side effects reported when DOSTINEX was used for the inhibition of lactation.

Table 1: Inhibition of lactation

System organ class	**Frequency**	**Side effect**
Nervous system disorders	Common	Dizziness, vertigo, headache
	Uncommon	Transient hemianopsia
	Rare	Somnolence
Cardiac disorders	Uncommon	Palpitations

Respiratory, thoracic and mediastinal disorders	Uncommon	Epistaxis
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Rare	Epigastric pain
Investigations	Common	Decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic)

Table 2 includes events reported when DOSTINEX was used for the suppression of lactation.

Table 2: Suppression of lactation

System organ class	**Frequency**	**Side effect**
Nervous system disorders	Common	Dizziness, vertigo, headache, somnolence
	Uncommon	Syncope
Vascular disorders	Uncommon	Hot flushes
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting
General disorders and administration site conditions	Uncommon	Asthenia

Hyperprolactinaemic disorders

Data obtained in a controlled clinical trial of 6 months therapy, with doses ranging between 1 and 2 mg per week given in two weekly administrations, indicate a 68 % incidence of adverse events during therapy with DOSTINEX. Most disappeared with continued therapy. Severe adverse events were reported at least once

during therapy by 14 % of patients. Therapy was discontinued because of adverse events in approximately 3 % of patients. Adverse events subsided upon discontinuation of DOSTINEX, usually within a few days.

Table 3 includes events reported when DOSTINEX was used for the treatment of hyperprolactinaemic disorders.

Table 3: Hyperprolactinaemic disorders		
System organ class	**Frequency**	**Side effect**
Psychiatric disorders	Common	Depression
Nervous system disorders	Very common	Dizziness, vertigo, headache
	Uncommon	Paraesthesia
Vascular disorders	Common	Hot flushes
Gastro-intestinal disorders	Very common	Abdominal pain, dyspepsia, gastritis, nausea
	Common	Constipation, vomiting
Reproductive system and breast disorders	Common	Breast pain
General disorders and administration site conditions	Very common	Asthenia, fatigue

General

Table 4 includes general events.

Table 4: General		
System organ class	**Frequency**	**Side effect**
Vascular disorders	Common	DOSTINEX generally exerts a hypotensive effect in patients on long-term treatment, postural hypotension
	Uncommon	Digital vasospasm, fainting

Musculoskeletal and connective tissue disorders	Uncommon	Leg cramps
Investigations	Uncommon	Decrease in haemoglobin values in amenorrhoeic women during the first few months after menses resumption

Post-marketing studies

The following events (in Table 5) have been reported in association with DOSTINEX:

Table 5	
System organ class	**Side effect**
Psychiatric disorders	Aggression, delusions, impulse control disorders such as hypersexuality, increased libido and pathological gambling, psychotic disorder
Respiratory, thoracic and mediastinal disorders	Dyspnoea, respiratory disorder, respiratory failure, valvulopathy
Hepatobiliary disorders	Abnormal hepatic function
Skin and subcutaneous tissue disorders	Alopecia, rash
General disorders and administration site conditions	Oedema, fibrosis
Investigations	Abnormal liver function tests, increased blood creatinine phosphokinase

The prevalence of asymptomatic valvular regurgitation is significantly greater than that of non-ergot dopamine agonists (see section 4.3 and section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Report any suspected adverse drug reactions associated with the use of the medicine directly to Pfizer via ZAF.AEReporting@pfizer.com.

4.9 Overdose

Symptoms of overdosage 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 undertaken to remove any unabsorbed medicine and maintain blood pressure if necessary. In addition, the administration of dopamine antagonist medicines may be advisable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.12 Hormone inhibitors

Cabergoline is a dopaminergic ergoline derivative with prolactin lowering activity. It acts by direct stimulation of the D_2-dopamine receptors on pituitary lactotrophs, thus inhibiting prolactin secretion. In addition, cabergoline exerts a central dopaminergic effect via D_2-receptor stimulation at oral doses higher than those effective in lowering serum prolactin levels. The prolactin-lowering effect of cabergoline is probably due to its persistence in the target organ as suggested by the slow elimination of total radioactivity from the pituitary after a single oral dose in rats ($t_{½}$ of approximately 60 hours).

The pharmacodynamic effects of cabergoline have been studied in healthy volunteers, puerperal women and hyperprolactinaemic patients. After a single oral administration of cabergoline (0,3 - 1,5 mg) a significant decrease in serum prolactin levels was observed in each of the populations studied. The effect is prompt (within 3 hours from administration) and persistent (up to 7 - 28 days in healthy volunteers and hyperprolactinaemic patients and up to 14 - 21 days in puerperal women). The prolactin-lowering effect is dose-related, both in terms of degree of effect and duration of action.

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 has a 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 a single dose usually occurs during the first 6 hours after 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 and in female hyperprolactinaemic patients.

After oral administration of the labelled compound, radioactivity was absorbed from the gastrointestinal tract and the peak of radioactivity in plasma was between 0,5 and 4 hours.

Ten days after administration about 18 % and 72 % of the radioactive dose was recovered in urine and faeces, respectively. Unchanged medicine in urine accounted for 2 - 3 % of the dose.

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 hyperprolactinaemic patients) – using a HPLC method.

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 cabergoline at concentrations of 0,1 - 10 ng/mL is 41 – 42 % bound to plasma proteins. Food does not appear to affect the absorption and disposition of cabergoline.

Biliary excretion is the main route of elimination.

In rats cabergoline and/or its metabolites are excreted in milk; no information on its excretion in maternal milk in humans is available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous

Leucine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C in airtight containers and protect from light.

6.5 Nature and contents of container

Amber glass bottles with an aluminium tamper evident screw cap or high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) cap containing 2, 4 or 8 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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8. REGISTRATION NUMBER

28/21.12/0244

9. DATE OF FIRST AUTHORISATION

21 November 1995

10. DATE OF REVISION OF THE TEXT

18 November 2025

NAMIBIA: S2

Reg. No.: 04/21.12/0727