SCHEDULING STATUS: **S4**

PROPRIETARY NAME (and dosage form):

DOSTINEX® (Tablet)

COMPOSITION:

Each DOSTINEX tablet contains 0,5 mg cabergoline.

The inactive ingredients are leucine and lactose anhydrous.

PHARMACOLOGICAL CLASSIFICATION:

A 21.12 Hormone inhibitors

PHARMACOLOGICAL ACTION:

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 selectively 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).

Pharmacodynamics:

The pharmacodynamic effects of cabergoline have been studied in healthy volunteers, puerperal women and hyperprolactinemic 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 hyperprolactinemic 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 antiprolactinemic 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.

Pharmacokinetics:

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).

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.

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.

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 hyperprolactinemic disorders.

CONTRA-INDICATIONS:

Pregnancy and breast-feeding – refer to "PREGNANCY AND LACTATION".

Hypersensitivity to any ergot alkaloid.

By analogy with other ergot derivatives, DOSTINEX should not be used in women with **preeclampsia** or **post-partum hypertension**.

WARNINGS:

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

Since available data indicate that biliary excretion represents the main route of elimination of the drug, it is advisable not to administer the drug to subjects with severe liver insufficiency. Since hyperprolactinemia with amenorrhea/galactorrhea and infertility may be associated with pituitary tumours, a complete evaluation of the pituitary is indicated before treatment with DOSTINEX is initiated.

Pleural effusion/pulmonary fibrosis and valvulopathy have been reported following long-term administration of cabergoline. Therefore, DOSTINEX should be used with caution in patients with a history of, or current signs and/or clinical symptoms of, respiratory or cardiac disorders linked to fibrotic tissue. Following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms in small minority of affected patients.

INTERACTIONS:

Although there is no conclusive evidence of an interaction between DOSTINEX and other ergot alkaloids, the concomitant use of these medications 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 agents 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 cabergoline.

PREGNANCY AND LACTATION:

Pregnancy:

DOSTINEX is contra-indicated in confirmed or suspected pregnancy.

Before DOSTINEX is administered, pregnancy must be excluded and after treatment pregnancy must be prevented for at least a month. Pregnancy could occur in women treated for hyperprolactinemic 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 amenorrhea 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.

Breast-feeding:

Puerperal women should not breast-feed in case of failed lactation inhibition/suppression by DOSTINEX.

DOSAGE AND DIRECTIONS FOR USE:

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

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 hyperprolactinemic 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.

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.

Lower doses of DOSTINEX should be considered in patients with severe impairment of hepatic function.

Use in children

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

Use in the elderly

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

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 cabergoline.

The table below contains side-effects categorized as follows utilizing the incidence rates: Very common ≥ 1/10 (≥ 10%); Common ≥ 1/100 and < 1/10 (≥ 1% and < 10%); Uncommon ≥ 1/1000 and < 1/100 (≥ 0,1% and < 1%), Rare ≥ 1/10 000 and < 1/1000 (≥ 0,01% and < 0,1%); Very rare < 1/10 000 (< 0,01%).

Inhibition of Lactation		
MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
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***	Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic)

Suppression of Lactation		
MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
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

Hyperprolactinemic Disorders		
MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Psychiatric disorders	***Common***	Depression
Nervous system disorders	***Very common***	Dizziness/vertigo, headache

	Uncommon	Paresthesia
Vascular disorders	***Common***	Hot flushes
Gastrointestinal 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		
MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
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

Precautions:

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

Symptomatic hypotension can occur with DOSTINEX administration for any indication; monitoring of blood pressure is advised and care should be exercised when administering DOSTINEX concomitantly with other agents known to lower blood pressure.

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no experience in humans of overdosage with DOSTINEX used in the proposed indications. Overdosage is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension or thought/perception disturbances.

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

IDENTIFICATION:

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.

PRESENTATION:

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

STORAGE INSTRUCTIONS:

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

Keep out of reach of children.

REGISTRATION NUMBER: 28/21.12/0244

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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