

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DOSTINEX[®]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DOSTINEX tablet contains 0.5 mg cabergoline.

Excipient(s) with known effect

- Lactose anhydrous

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Cabergoline 0.5 mg tablets are flat, capsule shaped tablets, 4 x 8 mm, scored, white tablets, engraved "PU" on one side and "700" on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of the onset of lactation in the puerperium only for clearly defined medical reasons: DOSTINEX is indicated for the inhibition of physiological lactation soon after delivery.

1. After parturition, when breast feeding is contraindicated due to medical reasons related to the mother or the new-born.
2. After stillbirth or abortion.

Treatment of hyperprolactinaemic disorders: DOSTINEX is indicated for the treatment of dysfunctions associated with hyperprolactinaemia, including amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea. DOSTINEX is indicated in patients with prolactin-secreting pituitary adenomas (micro- and macroprolactinomas), idiopathic hyperprolactinaemia, or empty sella syndrome with associated hyperprolactinaemia, which represent the basic underlying pathologies contributing to the above clinical manifestations.

4.2 Dose and method of administration

DOSTINEX is to be administered by the oral route. Since in clinical studies DOSTINEX has been mainly administered with food since the tolerability of this class of compound is improved with food, it is recommended that DOSTINEX be preferably taken with meals.

Inhibition of physiological lactation: DOSTINEX should be administered during the first day post-partum. The recommended therapeutic dose is 1 mg (two 0.5 mg tablets) as a single dose.

Treatment of hyperprolactinaemic disorders: The recommended initial dosage of DOSTINEX is 0.5 mg per week given in one or two (½ of a 0.5 mg tablet) doses (e.g. on Monday and Thursday) per week. The weekly dose should be increased gradually preferably by adding 0.5 mg per week at monthly intervals until the optimal therapeutic response is achieved. The therapeutic dosage is usually 1 mg per week and ranges from 0.25 to 2 mg per week. Doses of DOSTINEX up to 4.5 mg per week have been used in hyperprolactinaemic patients.

The weekly dose may be given as a single administration or divided into two or more doses per week according to patient tolerability. Division of the weekly dose into multiple administrations is advised when doses higher than 1 mg per week are to be given since the tolerability of doses greater than 1 mg given as a single weekly dose has been evaluated in only a few patients. Patients should be evaluated during dose escalation to determine the lowest dosage that produces the required therapeutic response. Monitoring of serum prolactin levels at monthly intervals is advised since; once the effective dosage regimen has been reached serum prolactin normalisation is usually observed within two to four weeks.

After DOSTINEX withdrawal, recurrence of hyperprolactinaemia is usually observed. However persistent suppression of prolactin levels has been observed for several months in some patients. In most women, ovulatory cycles persist for at least 6 months after DOSTINEX discontinuation.

Severe hepatic insufficiency: Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with DOSTINEX. (See section 4.4).

Children: The safety and efficacy of DOSTINEX has not been established in subjects less than 16 years of age.

Elderly: As a consequence of the indications for which DOSTINEX is presently proposed, the experience in the elderly is very limited. Available data do not indicate a special risk.

4.3 Contraindications

Hypersensitivity to cabergoline, any other component of the product, or any ergot alkaloid.

History of pulmonary, pericardial and retroperitoneal fibrotic disorders. (See section 4.4).

Anatomical evidence of cardiac valvulopathy of any valve 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

The safety and efficacy of DOSTINEX have not yet been established in patients with renal and hepatic disease. 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.

Lower doses should be considered in patients with severe hepatic insufficiency who receive prolonged treatment with DOSTINEX. 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 score >10) who received a single 1 mg dose.

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

Postural hypotension can occur following administration of cabergoline. Care should be exercised when administering DOSTINEX concomitantly with other drugs known to lower blood pressure.

Fibrosis and Cardiac Valvulopathy

As with other ergot derivatives, fibrotic and serosal inflammatory disorders such as pleuritis, pleural effusion, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy or retroperitoneal fibrosis have occurred after prolonged usage of cabergoline. The valvular effects were predominantly seen at doses exceeding the maximum recommended dose for treatment of hyperprolactinaemic disorders and maybe associated with cumulative dose. Some reports were in patients previously treated with ergotinic dopamine agonists. In some cases, following diagnosis of pleural effusion/pulmonary fibrosis or valvulopathy, the discontinuance of cabergoline has been reported to result in improvement of signs and symptoms. Progression of signs and symptoms may continue for a time before improvement occurs. 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.

Before initiating long-term treatment:

It is recommended that before initiating treatment with cabergoline all patients undergo a cardiovascular evaluation, including an echocardiogram, to assess potential presence of an occult 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.

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:

- Pleuropulmonary 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.

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.

DOSTINEX should be discontinued if fibrotic or serosal inflammatory disorders are diagnosed or an echocardiogram reveals valvular regurgitation, valvular restriction or valve leaflet thickening (See section 4.3 and section 4.8).

The need for other subsequent clinical monitoring (e.g. physical examination, careful cardiac auscultation, x-ray, additional echocardiogram, CT scan) should be determined on an individual basis.

Somnolence/Sudden Sleep Onset

Cabergoline 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.

Inhibition/Suppression of Physiologic Lactation

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

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.

Treatment of Hyperprolactinaemic Disorders

A complete evaluation of the pituitary is indicated before treatment with DOSTINEX is initiated.

DOSTINEX restores ovulation and fertility in women with hyperprolactinaemic hypogonadism. Because pregnancy might occur prior to reinitiation of menses, a pregnancy test is recommended at least every 4 weeks during the amenorrhoeic period and, once menses are reinitiated, every time a menstrual period is delayed by more than 3 days. Women who wish to avoid pregnancy should be advised to use mechanical contraception during treatment with DOSTINEX and after discontinuation of DOSTINEX until recurrence of anovulation. 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.

Psychiatric

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 DOSTINEX. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

4.5 Interaction with other medicines and other forms of interaction

The concomitant use of other drugs during early puerperium, particularly of methylergometrine maleate, has not been associated with detectable interactions modifying the efficacy and safety of DOSTINEX.

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

Since DOSTINEX 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 prolactin-lowering effect of DOSTINEX.

Mono-oxygenase activity was increased 1.5 to 3 fold in female rats treated with cabergoline 100 microgram/kg/day to 1.5 mg/kg/day orally. Concomitant administration of cabergoline with drugs metabolised by mono-oxygenases may result in altered exposure and activity.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Before DOSTINEX administration, pregnancy should be excluded.

Animal studies with cabergoline have not demonstrated teratogenic effects or effects on overall reproductive performance. However, there are no adequate and well-controlled studies in pregnant women. DOSTINEX should be used during pregnancy only if clearly needed. If conception occurs during therapy with DOSTINEX, discontinuation of treatment should be considered, after careful evaluation of the risks and benefits to mother and foetus. Pregnancy should be avoided for at least one month following discontinuation of treatment with DOSTINEX due to the long half-life of the drug and the limited data on *in utero* exposure, although the use of DOSTINEX at 0.5 to 2 mg/week for hyperprolactinaemic disorders does not appear to be associated with an increased risk of abortion, premature delivery, multiple pregnancy or congenital abnormalities.

Lactation

In rats, cabergoline and/or its metabolites are excreted in milk. No information is available on the excretion in breast milk in humans; however, mothers should be advised not to breast-feed 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 breast-feed their infants.

Fertility

No data available.

4.7 Effects on ability to drive and use machinery

Patients being treated with cabergoline 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) unless patients have overcome such experiences of somnolence.

4.8 Undesirable effects

Inhibition/Suppression of lactation: Approximately 14% of women treated with a single 1 mg dose of DOSTINEX for inhibition of physiological lactation complained of at least one side effect. All side effects were mild to moderate in severity and of a transient nature. The most frequently occurring adverse events were dizziness/vertigo, headache, nausea and abdominal pain. In addition rarely palpitations, epigastric pain, somnolence, epistaxis and transient hemianopsia, vomiting, syncope, asthenia, and hot flushes were reported.

Asymptomatic decreases in blood pressure (≥ 20 mmHg systolic and ≥ 10 mmHg diastolic) may occur usually once during the first 3-4 days postpartum.

Adverse effects have been observed in approximately 14% of nursing women treated with 0.25 mg of DOSTINEX every 12 hours for two days for suppression of lactation. The most frequent symptoms were dizziness/vertigo, headache, nausea, somnolence, abdominal pain. In addition, rarely vomiting, syncope, asthenia, and hot flushes were reported. Most side effects were transient and mild to moderate in severity.

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 effects during DOSTINEX therapy. However, the symptoms were generally mild to moderate in degree, mainly appearing during the first two weeks of therapy, and mostly disappearing despite continued therapy. Severe adverse events were reported at least once during therapy by 14% of patients but therapy was discontinued because of adverse events in only approximately 3% of patients. DOSTINEX withdrawal results in reversal of side effects, usually within a few days after discontinuation. The most common symptoms in decreasing rank of frequency were nausea, headache, dizziness/vertigo, abdominal pain/dyspepsia/gastritis, asthenia/fatigue, constipation, vomiting, breast pain, hot flushes, depression and paraesthesia.

General: DOSTINEX generally exerts a hypotensive effect in patients treated chronically; however, symptomatic hypotension or fainting has been reported rarely.

Being an ergot derivative, DOSTINEX may also act in some patients as a vasoconstrictor: digital vasospasm and leg cramps have occasionally been reported.

Side effects are generally dose-related. In patients known to be intolerant of dopaminergic drugs, side effects may be lessened by starting DOSTINEX therapy with reduced doses (e.g. 0.25 mg once a week) with subsequent gradual increase until the therapeutic range is reached. In case of persistent or severe adverse events, temporary reduction of dosage followed by a more gradual increase (e.g. in steps of 0.25 mg per week fortnightly) may result in reversal of side effects once they have occurred.

Alterations in standard laboratory tests are uncommon during long term therapy with DOSTINEX. A decrease in haemoglobin values have been observed in amenorrhoeic women during the first few months after menses resumption.

Post-marketing surveillance

There have been reports of fibrotic and serosal inflammatory conditions, such as pleuritis, pleural effusion, pleural fibrosis, pulmonary fibrosis, pericarditis, pericardial effusion, cardiac valvulopathy and retroperitoneal fibrosis in patients taking cabergoline. (See section 4.4).

The prevalence of asymptomatic valvular regurgitation is significantly greater than that of non-ergot dopamine agonists.

The following events have been reported in association with cabergoline: aggression, alopecia, blood creatinine phosphokinase increased, delusions, dyspnoea, oedema, hepatic function abnormal, hypersensitivity reaction, liver function tests abnormal, rash, psychotic disorder, respiratory disorder, respiratory failure, valvulopathy and fibrosis (see section 4.4 – Fibrosis/Valvulopathy).

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including DOSTINEX (see 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. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

There is no experience in humans of overdosage with DOSTINEX in the proposed indications. It is likely to lead to symptoms due to over-stimulation of dopamine receptors. These might include nausea, vomiting, gastric complaints, hypotension, nasal congestion, confusion hallucinations, psychosis or thought/perception disturbances. Treatment of overdose is symptomatic and supportive. Supportive measures should be directed to maintain blood pressure, if necessary.

Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within 1 hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

In addition, in case of pronounced central nervous system effects the administration of dopamine antagonist drugs may be advisable.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

DOSTINEX is a dopaminergic ergoline derivative with potent and long-lasting Prolactin-lowering activity. It acts by direct stimulation of the D2-dopamine receptors on pituitary lactotrophs, thus inhibiting Prolactin secretion. In rats the compound decreases prolactin secretion at oral doses of 3-25 µg/ml, and *in vitro* at a concentration of 45 pg/ml. In addition DOSTINEX exerts a central dopaminergic effect via D2 receptor stimulation at oral doses higher than those effective in lowering serum Prolactin levels. The long-lasting Prolactin-lowering effects of DOSTINEX is probably due to its long persistence in the target organ as suggested by the slow elimination of total radioactivity from the pituitary after a single oral dose in rats ($t_{1/2}$ of approximately 60 hours).

The pharmacodynamic effects of DOSTINEX have been studied in healthy women, puerperal women and hyperprolactinaemic patients. After a single oral administration of DOSTINEX (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 DOSTINEX not related to the antiprolactinaemic effect, data available 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 DOSTINEX not correlated with the therapeutic effect only relate to blood pressure decrease. The maximal hypotensive effect of DOSTINEX as a single dose usually occurs during the first 6 hours after medicine intake and is dose-dependent both in terms of maximal decrease and frequency.

Inhibition/suppression of physiological lactation: In controlled clinical trials DOSTINEX given as a single 1 mg administration during the first day post-partum was effective in inhibiting milk secretion, as well as breast engorgement and pain in 70-90% of the women. Less than 5% of women experienced rebound breast symptomatology during the third post-partum week (which was usually mild in severity).

Hyperprolactinaemic disorders: On chronic therapy, DOSTINEX at doses ranging between 1 and 2 mg per week was effective in normalising serum prolactin levels in approximately 84% of hyperprolactinaemic patients. Regular cycles were resumed in 83% of previously amenorrhoeic women. Restoration of ovulation was documented in 89% of women with progesterone levels monitored during the luteal phase. Galactorrhoea disappeared in 90% of cases showing this symptom before therapy. Reduction in tumour size was obtained in 50-90% of female and male patients with micro- or macro-prolactinoma.

5.2 Pharmacokinetic properties

The pharmacokinetic and metabolic profiles of DOSTINEX have been studied in healthy volunteers of both sexes and in female hyperprolactinaemic patients.

After oral administration of the labelled compound, radioactivity was rapidly absorbed from the gastrointestinal tract. The peak of the radioactivity in the 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 drug in urine accounted for 2-3% of the dose.

In urine the main metabolite identified was 6-allyl-8B-carboxyl-ergoline, which accounted for 4-6% of the dose. Three additional metabolites were identified in the urine, which accounted overall for less than 3% of the dose. The metabolites have been found to be much less potent than DOSTINEX in inhibiting prolactin secretion *in vitro*. DOSTINEX biotransformation was also studied in plasma of healthy male volunteers treated with [¹⁴C]-cabergoline. A rapid and extensive biotransformation of cabergoline was shown. The low urinary excretion of unchanged DOSTINEX has also been confirmed in studies with non-radioactive product. The elimination half life of DOSTINEX estimated from urinary excretion rates, is long (63-68 hours in healthy volunteers, 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 DOSTINEX obtained after a single dose (37 ± 8 pg/ml) after a 4 week multiple-regimen (101 ± 43 pg/ml).

In vitro experiments showed that the cabergoline 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 DOSTINEX.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose anhydrous
- Leucine.

6.2 Incompatibilities

No data available.

6.3 Shelf life

Two year shelf life.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

2 or 8 tablets packed in either glass bottles with aluminium caps or HDPE bottles with polypropylene caps.

Not all pack sizes may be marketed.

DOSTINEX tablets are supplied in bottles with desiccant in the caps. This desiccant must not be removed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

17 March 1994

10. DATE OF REVISION OF THE TEXT

21 May 2019

Summary table of changes

Section changed	Summary of new information
All	New Data Sheet format in accordance with Medsafe guidance.