

NEW ZEALAND DATA SHEET

1. NAME OF THE MEDICINAL PRODUCT

RAMIPEX 0.25 mg & 1 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance

Each 0.25 mg tablet contains 0.25 mg pramipexole dihydrochloride monohydrate equal to 0.18 mg pramipexole.

Each 1.0 mg tablet contains 1.0 mg pramipexole dihydrochloride monohydrate equal to 0.70 mg pramipexole.

Please note:

Pramipexole doses as published in the literature refer to the salt form. Therefore, doses will be expressed in terms of pramipexole salt.

Excipients:

	0.25 mg	1.0 mg
Mannitol	60.0 mg or	119.50 mg

For full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Tablets.

RAMIPEX 0.25 mg Tablets are white, oblong tablets with break line in one side and the other side plain.

RAMIPEX 1 mg Tablets are white, round tablets with break line in one side and the other side plain.

All tablets can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RAMIPEX is indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa.

RAMIPEX is indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome.

4.2 Posology and method of administration

Posology

Parkinson's disease

The daily dosage is administered in equally divided doses three times per day.

Initial Treatment

Dosages should be increased gradually from a starting dose of 375 µg per day and increased every 5 to 7 days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Ascending Dose Schedule of RAMIPEX.		
Week	Dosage	Total Daily Dose
1	3 x 125 µg	375 µg
2	3 x 250 µg	750 µg
3	3 x 500 µg	1.50 mg

If further dose increase is necessary, the daily dose should be increased by 750 µg at weekly intervals up to a maximum dose of 4.5 mg per day.

Maintenance Treatment

The individual dose should be in the range of 375 µg to a maximum of 4.5 mg of RAMIPEX per day. During dose escalation in three pivotal studies, both in early and advanced disease, efficacy was observed starting at a daily dose of 1.5 mg per day can result in additional therapeutic benefit. This applies particularly in patients with advanced disease where a reduction of the levodopa therapy is intended.

Treatment discontinuation

RAMIPEX should be tapered off over several days.

Additional information on special populations

Dosing patients with concomitant levodopa therapy

It is recommended that the dosage of levodopa is reduced during both, the dose escalation and the maintenance treatment with RAMIPEX. This may be necessary in order to avoid excessive dopaminergic stimulation.

Dosing in patients with renal impairment

The elimination of pramipexole is dependent on renal function. The following dosage scheme is suggested for initiation of therapy:-

Patients with creatinine clearance above 50 ml/min require no reduction in daily dose.

In patients with creatinine clearance between 20 and 50 ml/min, the initial daily dose of RAMIPEX should be administered in two divided doses, starting at 125 µg twice a day. In patients with a creatinine clearance of less than 20 ml/min, the daily dose of RAMIPEX should be administered in a single dose, starting at 125 µg daily.

If renal function declines during maintenance therapy, reduce the RAMIPEX daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the RAMIPEX daily dose by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min and as a single daily dose if creatinine clearance is less than 20 ml/min.

Dosing in patients with hepatic impairment

Dose adjustment in patients with hepatic impairment is not considered necessary.

Restless Legs Syndrome

The recommended starting dose RAMIPEX is 0.125 mg taken once daily 2 – 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 – 7 days to a maximum of 0.75 mg per day (as shown in the table below).

Ascending-Dose Schedule of RAMIPEX	
Titration Step	Once Daily Evening Dose (mg)
1	0.125
2*	0.25
3*	0.50
4*	0.75
* if needed	

Treatment discontinuation

RAMIPEX can be discontinued without tapered dose reduction.

Additional information on special populations

Dosing in patients with renal impairment

The elimination of RAMIPEX is dependent on renal function and closely related to the creatinine clearance. Based on a pharmacokinetic study in renally impaired subjects, patients with a creatinine clearance above 20 ml/min require no reduction in daily dose. The use of RAMIPEX in RLS patients with renal impairment has not been studied.

Dosing in patients with hepatic impairment

Dose reduction is not considered necessary in patients with hepatic impairment, as approximately 90% of absorbed drug is excreted through the kidneys.

Method of administration

The tablets should be taken orally, swallowed with water and can be taken either with or without food.

Additional information on special populations

Safety and efficacy of RAMIPEX have not been established in children and adolescents up to 18 years.

4.3 Contraindications

Hypersensitivity to pramipexole or to any of the excipients.

4.4 Special warnings and precautions for use

When prescribing RAMIPEX tablets in a patient with renal impairment a reduced dose is suggested (see Section 4.1).

Hallucinations and confusion are known side effects of treatment with dopamine agonists and levodopa in Parkinson's disease patients. Hallucinations were more frequent when pramipexole was given in combination with levodopa in Parkinson's disease patients with early disease. Within the RLS clinical development program for registration, one case of hallucinations has been reported. Patients should be informed that (mostly visual) hallucinations could occur.

Patients and caregivers should be aware of the fact that behavioural changes can occur (e.g. pathological gambling, hypersexuality, increased libido, binge eating). Health care professionals should inform patients to seek help from their doctor if they, their family or their carer notice that their behaviour is unusual. Dose reduction/taper discontinuation should be considered.

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. Evaluation of the retinas of albino mice, pigmented rats, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e. disk shedding) may be involved.

In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure,

especially at the beginning of treatment due to the general risk of postural hypotension associated with dopaminergic therapy.

Patients should be alerted to the potential sedating effects associated with pramipexole, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor operate other complex machinery until they have gained sufficient experience with pramipexole to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g. conversations, eating etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their physician.

Epidermiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanoma when using pramipexole or other dopaminergic drugs.

Parkinson's disease

Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy.

Augmentation in RLS

Reports in the literature indicate treatment of RLS with dopaminergic medications can result in augmentation.

Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of pramipexole in patients with RLS were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of pramipexole and the appropriate management of these events have not been evaluated in controlled clinical trials.

4.5 Interaction with other medicinal products and other forms of interaction

Pramipexole is bound to plasma proteins to a very low (<20%) extent and little biotransformation is seen in man. Therefore, interactions with other medications affecting plasma protein binding or elimination by biotransformation are unlikely.

Medications that inhibit the active renal tubular secretion of basic (cationic) drugs, such as cimetidine, or are themselves eliminated by active renal tubular secretions, may interact with RAMIPEX resulting in reduced clearance of either or both medications. In case of concomitant treatment with these kinds of drugs (including amantadine) attention should be paid to signs of dopamine overstimulation, such as dysknesias, agitation or hallucinations. Reduction of the RAMIPEX dose should be considered when these drugs are administered concomitantly with RAMIPEX.

Selegiline and levodopa do not influence the pharmacokinetics of pramipexole. The overall extent of absorption or elimination of levodopa is not changed by concomitant administration with RAMIPEX. The interaction with anticholinergics and amantadine has not been examined. As anticholinergics are mainly eliminated by hepatic metabolism, pharmacokinetic drug-drug interactions with pramipexole are rather unlikely. With amantadine, an interaction is possible via the same system of excretion in the kidney.

While increasing the dose of RAMIPEX, it is recommended that the dosage of levodopa is reduced and the dosage of other anti-parkinsonian medication kept constant.

Because of possible additive effects, caution should be advised when patients are taking other sedating

medication or alcohol in combination with RAMIPEX and when taking concomitant medication that increase plasma levels of pramipexole (e.g. cimetidine).

Additional information on special populations

Data is not available.

4.6 Pregnancy and lactation

General Recommendation

Pregnancy category is C

Pregnancy

The effect of pregnancy and lactation has not been investigated in humans. Animal studies in rodents and rabbits did not show any teratogenic effects but pramipexole was embryotoxic in the rat at maternotoxic doses. Pramipexole should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

The excretion of pramipexole into the breast milk has not been studied in women. In rats, the concentration of drug was higher in the breast milk than in plasma. As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. In consequence, pramipexole should not be used during breast feeding.

Fertility

No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected estrous cycles and reduced female fertility as expected for a dopamine agonist. However, these studies did not indicate direct or indirect harmful effects with respect to male fertility.

4.7 Effects on ability to drive and use machines

Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.

Patients should be alerted to the potential sedating effects associated with pramipexole including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor operate other complex machinery until they have gained sufficient experience with pramipexole to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g. conversations, eating etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their physician.

4.8 Undesirable effects

The following side effects are listed under the use of pramipexole: abnormal dreams, confusion, constipation, delusion, dizziness, dyskinesias, fatigue, hallucinations, headache, hyperkinesias, hypotension, increased eating (binge eating, hyperphagia), insomnia, libido disorders, nausea, peripheral oedema, paranoia, pathological gambling, hypersexuality and other abnormal behaviour, somnolence, weight increase, sudden onset of sleep; pruritus, rash and other hypersensitivity.

The incidence of hypotension under pramipexole, compared to placebo treatment, was not increased. However in individual patients, hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too rapidly. Pramipexole may be associated with disorders of libido (increase or decrease).

Patients treated with pramipexole tablets have reported falling asleep during activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole tablets at doses

above 1.5 mg/day, and which, according to the current knowledge of sleep physiology, always proceeds falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy.

Patients treated with dopamine agonists for Parkinson's disease, including pramipexole, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorization 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

Symptoms

There is no clinical experience with massive overdosage. The expected adverse events should be those related to the pharmacodynamic profile of a dopamine agonist including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension.

Therapy

There is no established antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures along with gastric lavage, intravenous fluids and electrocardiogram monitoring. Haemodialysis has not been shown to be helpful.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

Drug abuse and dependence

Drug dependency, addiction and recreational abuse have not been reported as a problem with this compound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-Parkinson drugs, dopamine agonists

ATC code: N04BC05

Mechanism of Action:

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the dopamine D2 subfamily receptors. It has a preferential affinity to D3 receptors and has full intrinsic activity.

PRAMIPEXOLE alleviates Parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release and turnover. Pramipexole protects dopamine neurons from degeneration in response to ischemia or amphetamine neurotoxicity.

The precise mechanism of action of pramipexole as a treatment for Restless Legs Syndrome is not known. Although the pathophysiology of Restless Legs Syndrome is largely unknown, neuropharmacological evidence suggests primary dopaminergic system involvement. Position emission tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of Restless Legs Syndrome.

In vitro studies demonstrate that pramipexole protects neurons from levodopa neurotoxicity.

In human volunteers a dose-dependent decrease in prolactin was observed.

Parkinson's disease

In the controlled clinical trials efficacy was maintained for approximately six months.

In open continuation trials lasting more than three years there were no signs of decreasing efficacy.

Restless Legs Syndrome

The efficacy of pramipexole was evaluated in four placebo controlled trials in approximately 1000 patients with moderate to very severe Restless Legs Syndrome.

Efficacy was demonstrated in controlled trials in patients treated for up to 12 weeks and sustained efficacy was shown over a period of 9 months. The efficacy of pramipexole was maintained during open continuation trials lasting for up to 1 year.

5.2 Pharmacokinetic properties

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and the maximum plasma concentrations occur between 1 and 3 hours. The rate of absorption is reduced by food intake but not the overall extent of absorption. Pramipexole shows linear kinetics and a relatively small inter-patient variation of plasma levels.

In humans the protein binding of pramipexole is very low (<20%) and the volume of distribution is large (400 L). High brain tissue concentrations were observed in the rat (approximately eight-fold compared to plasma).

Pramipexole is metabolised in man only to a small extent.

Renal excretion of unchanged pramipexole is the major route of elimination and accounts for about 80% of dose. Approximately 90% of a ¹⁴C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 ml/min and the renal clearance is approximately 400ml/min. The elimination half-life (t_{1/2}) varies from 8 hours in the young to 12 hours in the elderly.

5.3 Preclinical safety data

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

6. PHARMACEUTICAL PARTICULARS**6.1 List of Excipients**

Maize starch

Mannitol

Povidone

Colloidal anhydrous silica

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Store in the original package.
Keep out of the reach and sight of children.

6.5 Nature and contents of container

Opaque white polyvinyl chloride (PVC) and Aclar (PCTFE) Film – Aluminum blisters of 30 and 100 tablets

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

DEVATIS LIMITED
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9. DATE OF FIRST APPROVAL

Date of first authorization: 20/02/2014

10. DATE OF REVISION OF THE TEXT

December 2024