

**PRAMEXOL 0.125 mg Tablet**

**PRAMEXOL 0.25 mg Tablet**

**PRAMEXOL 1 mg Tablet**

Each tablet contains:

**Pramipexole dihydrochloride monohydrate 0.125 mg eq. to Pramipexole base 0.088 mg**

**Pramipexole dihydrochloride monohydrate 0.25 mg eq. to Pramipexole base 0.18 mg**

**Pramipexole dihydrochloride monohydrate 1 mg eq. to Pramipexole base 0.7 mg**

❁ **PRODUCT DESCRIPTION:**

**0.125 mg:**

White, flat, round tablet with engraved PM on one side and plain on the other

**0.25 mg:**

White, oval, flat-faced tablet with bevelled edge, engraved PM on one side and scored on the other

**1 mg:**

White, round, flat-faced tablet with bevelled edge, engraved PM 1 on one side and crossed-scored on the other

❁ **PHARMACOLOGICAL PROPERTIES:**

**Pharmacodynamic properties**

Pharmacotherapeutic group: dopamine agonist, ATC code: N04BC05

**Mode of Action**

Pramipexole, the active ingredient of Pramexol is a dopamine agonist and binds with high selectivity and specificity to the dopamine D2 subfamily receptors and has a preferential affinity to D3 receptors; it has full intrinsic activity.

Pramexol 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 neurones from degeneration in response to ischemia or Metamphetamine neurotoxicity.

The precise mechanism of action of Pramexol 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. Positron 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 neurones from Levodopa neurotoxicity.

**Pharmacodynamics**

In human volunteers a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where Pramexol prolonged-release tablets were titrated faster than recommended (every 3 days) up to 4.5 mg per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

**Clinical Trials**

**Parkinson's disease:** Efficacy of Pramexol in the controlled clinical trials was maintained for the duration of the trials, approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy.

**Restless Legs Syndrome:** The efficacy of Pramexol 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 Pramexol was maintained during open continuation trials lasting for up to 1 year. In a placebo controlled clinical trial over 26 weeks, the efficacy of Pramipexole was confirmed in patients with moderate to severe RLS.

**Pharmacokinetics**

**Absorption**

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.

**Distribution**

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 (approx. 8-fold compared to plasma).

**Biotransformation**

Pramipexole is metabolized in man only to a small extent.

**Elimination**

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

Age - Pramipexole clearance decreases with the age as the half-life and clearance are about 40% longer and 30% lower respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (age less than 40 years). The difference is most likely due to the well-known reduction in renal function with age, since Pramipexole clearance is correlated with renal function, as measured by creatinine clearance.

❁ **INDICATION:**

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

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

❁ **DOSAGE AND ADMINISTRATION:**

Oral

**Parkinson's disease**

**Initial treatment:**

As shown below dosages should be increased gradually from a starting-dose of 0.375 mg per day and then increased every 5-7 days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Ascending-Dose schedule of Pramexol		
Week	Dosage (mg)	Total Daily Dose (mg)
1	3 x 0.125	0.375
2	3 x 0.25	0.75
3	3 x 0.5	1.50

If a further dose increase is necessary the daily dose should be increased by 0.75 mg 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 0.375 mg to a maximum of 4.5 mg per day. During dose escalation in pivotal studies both in early and advanced disease, efficacy was observed starting at a daily dose of 1.5 mg. This does not preclude that in individual patients doses higher than 1.5 mg per day can result in additional therapeutic benefit.

This applies particularly to patients with advanced disease where a reduction of the Levodopa therapy is intended.

**Treatment discontinuation**

Pramexol tablets should be tapered off at a rate of 0.75 mg per day until the daily dose has been reduced to 0.75 mg. Thereafter the dose should be reduced by 0.375 mg per day.

### **Dosing in patients with concomitant Levodopa therapy**

In patients with concomitant Levodopa therapy, it is recommended that the dosage of Levodopa is reduced during both dose escalation and maintenance treatment with Pramexol. 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 schedule is suggested for initiation of therapy: Patients with a creatinine clearance above 50 mL/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 20 and 50 mL/min, the initial daily dose of Pramexol tablets should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg Pramipexole should not be exceeded. In patients with a creatinine clearance less than 20 mL/min, the daily dose of Pramexol tablets should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg Pramipexole should not be exceeded.

If renal function declines during maintenance therapy, reduce Pramexol daily dose by same percentage as decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce Pramexol 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 reduction is not considered necessary in patients with hepatic impairment.

### **Pediatric Use**

The safety and efficacy use of Pramexol in pediatric patients has not been established.

### **Method of Administration**

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

The daily dosage is administered in equally divided doses 3 x per day.

### **Restless Legs Syndrome**

The recommended starting dose of Pramexol 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):

<b>Ascending-Dose schedule of Pramexol</b>	
<b>Titration Step</b>	<b>Once Daily Evening Dose (mg)</b>
1	0.125
2*	0.25
3*	0.50
4*	0.75

\*if needed

### **Treatment discontinuation**

Pramexol can be discontinued without tapered dose reduction. In a 26-week placebo controlled clinical trial, rebound of RLS symptoms (worsening of symptom severity as compared to baseline) was observed in 10% of patients (14 out of 135) after abrupt discontinuation of Pramipexole. This effect was found to be similar across all doses.

### **Dosing in patients with renal impairment**

The elimination of Pramexol 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 Pramexol 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 approx. 90% of absorbed drug is excreted through the kidneys.

### **Dosing in children and adolescents:**

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

### **Method of Administration**

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

## **⊗ WARNING AND PRECAUTION:**

Sudden onset of sleep during daily activities has been reported in rare cases. This can be life-threatening to the patient or others depending on the circumstances. These episodes have been reported in some cases without awareness of warning signs. If this occurs, reduction of dosage or termination of therapy should be considered. Patients being treated with Pramipexole must be informed not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines). Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with Pramipexole (see section on Effects on ability to drive and use machines and Side effect).

### **Renal impairment**

When prescribing Pramexol tablets in a patient with renal impairment a reduced dose is suggested in line with section Dosage and administration.

### **Hallucinations and confusions**

Hallucinations and confusion are known side effects of treatment with dopamine agonists and Levodopa in Parkinson's disease patients. Hallucinations were more frequent when Pramexol was given in combination with Levodopa in Parkinson's disease patients with advanced disease than in monotherapy 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 can occur. Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.

### **Abnormal behavior (reflecting symptoms of impulse control disorders and compulsive behaviors)**

Patients and caregivers should be made aware of the fact that abnormal behavior (reflecting symptoms of impulse control disorders and compulsive behaviors) such as binge eating, compulsive shopping, hypersexuality and pathological gambling, have been reported in patients treated with dopaminergic drugs. Dose reduction/tapered discontinuation should be considered.

### **Patients with psychotic disorders**

Patients with psychotic disorders should be treated with dopamine agonists only if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with Pramipexole is not recommended, e.g. if dopamine-antagonistic effects can be expected.

### **Retinal changes in albino rats**

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-years 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.

### **Postural hypotension**

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.

### **Dystonia**

Patients with Parkinson's disease may present with axial dystonia such as antecollis, camptocormia or pleurothotonus (Pisa Syndrome). Dystonia has occasionally been reported following initiation of dopamine agonists including pramipexole, although a clear causal relationship has not been established. Dystonia may also occur several months following medication initiation or adjustment. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment considered.

### **Sudden onset of sleep and somnolence**

Patients should be alerted to the potential sedating effects associated with Pramexol, 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 Pramexol 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.

### **Melanoma**

Epidemiological 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.

### **Treatment discontinuation in Parkinson's disease**

Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. (See section Dosage and administration and Method of administration)

### **Dopamine agonist withdrawal syndrome (DAWS)**

DAWS has been reported with dopamine agonists, including Pramipexole (see section Side effect). To discontinue treatment with patients with Parkinson's disease, Pramipexole should be tapered off (see section Dosage and administration and Method of administration). Limited data suggests that patients with impulse control disorders and those receiving high daily dose and/or high cumulative doses of dopamine agonists may be at higher risk for developing DAWS. Withdrawal symptoms may include apathy, anxiety, depression,

fatigue, sweating and pain and do not respond to Levodopa. Prior to tapering off and discontinuing Pramipexole, patients should be informed about potential withdrawal symptoms. Patients should be closely monitored during tapering and discontinuation. In case of severe and/or persistent withdrawal symptoms, temporary re-administration of Pramipexole at the lowest effective dose may be considered.

**Rhabdomyolysis**

A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with Pramexol Tablet. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

**Ophthalmologic monitoring**

Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occurs.

**Augmentation in Restless Legs Syndrome**

Reports in the literature indicate that treatment of Restless Legs Syndrome 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. Treatment with Pramexol should be started with the recommended dose of 0.125 mg and may only be increased to a maximum recommended daily dose of 0.75 mg, if additional symptom relief is required (see section Dosage and administration and Method of administration). Prior to treatment, patients should be informed that augmentation may occur. They should be regularly monitored for the occurrence of augmentation. If augmentation occurs, the adequacy of pramipexole treatment should be reviewed and dosage adjustment or discontinuation considered.

☛ **PREGNANCY AND LACTATION:**

**Pregnancy**

The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses. Pramexol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Breastfeeding**

The excretion of Pramexol 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 Pramexol treatment inhibits secretion of prolactin in humans inhibition of lactation is expected. In consequence, Pramexol should not be used during breastfeeding.

**Fertility**

No studies on the effect on human fertility have been conducted. Animal studies did not indicate direct or indirect harmful effects with respect to male fertility.

☛ **SIDE EFFECT:**

**Tabulated summary of adverse reactions**

The following adverse reactions have been reported during use of Pramexol in the clinical trials and in the post-marketing experience.

MedDRA System Organ Class terminology	Pramipexole adverse reactions
Infections and infestations	Pneumonia
Endocrine disorders	Inappropriate antidiuretic hormone secretion
Psychiatric disorders	Abnormal behavior (reflecting symptoms of impulse control disorders and compulsions) such as binge eating, compulsive shopping, hypersexuality and pathological gambling Abnormal dreams Confusion Delusion Hallucinations Hyperphagia Insomnia Libido disorders Paranoia Restlessness
Nervous system disorders	Amnesia Antecollis Dizziness Dyskinesia Headache Hyperkinesia Somnolence Sudden onset of sleep Syncope Augmentation in Restless Legs Syndrome (see section Warning and precaution)
Eye disorders	Visual impairment including diplopia, vision blurred and visual acuity reduced
Cardiac disorders	Cardiac failure
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnea Hiccups
Gastrointestinal disorders	Constipation Nausea Vomiting
Skin and subcutaneous tissue disorders	Hypersensitivity Pruritus Rash
General disorders and administration site conditions	Fatigue Peripheral edema Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain
Investigations	Weight decrease including decreased appetite Weight increase

**Description of selected adverse reactions**

**Sudden onset of sleep and somnolence**

Patients treated with Pramipexole 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, and which, according to the current knowledge of sleep physiology, always precedes falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medications with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy.

**Hypotension**

The incidence of hypotension under Pramexol, compared to placebo treatment, was not increased. However, in individual patients, hypotension may occur at the beginning of treatment, especially if Pramexol is titrated too rapidly.

**Libido disorders**

Pramexol may be associated with disorders of libido (increase or decrease).

**Dopamine agonist withdrawal syndrome**

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including Pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain (see section Warning and precaution).

**Cardiac Failure**

In clinical studies and post-marketing experience cardiac failure has been reported in patients with Pramipexole. In a pharmacoepidemiological study Pramipexole use was associated with an increased risk of cardiac failure compared with non-use of Pramipexole. A causal relationship between Pramipexole and cardiac failure has not been demonstrated.

☛ **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 Pramexol, including somnolence and the possibility of falling asleep while engaged in activities of daily living. (See section Warning and precaution)

❁ **CONTRAINDICATION:**

Hypersensitivity to the active substance or to any of the excipients.

❁ **DRUG 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. Medication that inhibit the active renal tubular secretion of basic (cationic) drugs, such as Cimetidine, or are themselves eliminated by active renal tubular secretion, may interact with Pramexol resulting in reduced clearance of either or both medication. In case of concomitant treatment with these kinds of drugs (including Amantadine) attention should be paid to signs of dopamine overstimulation, such as dyskinesias, agitation or hallucinations. In such cases a dose reduction is necessary. Selegiline and Levodopa do not influence the pharmacokinetics of Pramipexole. The overall extent of absorption or elimination of Levodopa is not changed by Pramipexole. 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.

Antipsychotic medicinal products

Co-administration of antipsychotic medicinal products with Pramipexole is not recommended, e.g. if dopamine-antagonistic effects can be expected. (See section Warning and precaution). While increasing the dose of Pramexol in Parkinson's disease patients it is recommended that the dosage of Levodopa is reduced, and the dosage of other antiparkinsonian medication kept constant.

Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with Pramexol and when taking concomitant medications that increase plasma levels of Pramipexole (e.g. Cimetidine).

❁ **OVERDOSE AND TREATMENT:**

Symptoms

There is no clinical experience with massive overdose. The expected adverse reactions would 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 overdose 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, administration of activated charcoal and electrocardiogram monitoring. Hemodialysis has not been shown to be helpful.

❁ **LIST OF EXCIPIENTS:**

Microcrystalline cellulose (Avicel PH 101), Corn starch, Croscarmellose sodium Calcium carbonate (Heavy), Mannitol, Povidone (PVP K-30), Edetate disodium, Sodium metabisulfite, Purified water, Colloidal silicon dioxide and Magnesium stearate

❁ **STORAGE:**

Store at temperature of not more than 30°C.

❁ **DOSAGE FORM AND PACKAGING AVAILABLE:**

0.125 mg Tablet, Blister 3x10's

0.25 mg Tablet, Blister 3x10's

1 mg Tablet, Blister 3x10's

❁ **DATE OF REVISION:**

May 06, 2024

Manufactured by:  
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