PRAMEXOL 1MG TABLET

Each tablet contains:
Pramipexole dihydrochloride monohydrate 1 mg eq. to Pramipexole base 0.7 mg

♦ PRODUCT DESCRIPTION:

1 mg:
White, round, flat-faced tablet with bevelled edge, engraved PM1 on one side and crossed-scored on the other

♦ MECHANISM OF ACTION:

Pharmacology
Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which 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.
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. Concomitant administration with food did not reduce the extent of Pramipexole absorption, but the rate of absorption was reduced. Pramipexole shows linear kinetics and a 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. Approximately 90% of 14C-labelled dose is excreted through the kidneys while less than 2% is found in the feces. The total clearance of Pramipexole is approximately 500 mL/min and the renal clearance is approximately 400 mL/min. The elimination half-life (t½) varies from 8 hours in the young to 12 hours in the elderly.

♦ 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
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.
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 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, ie. 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.
Paediatric Use
The safety and efficacy use of Pramexol in paediatric patients has not been established.
Restless Legs Syndrome
The tablets should be taken orally, swallowed with water, and can be taken either with or without food.

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)

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

* if needed

Treatment discontinuation:

Pramexol can be discontinued without tapered dose reduction.

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 n 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

♦ WARNING AND PRECAUTION[1]:

When prescribing Pramexol in a patient with Parkinson's disease with renal impairment a reduced dose is suggested.

Hallucinations

Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur.

Dyskinesia

In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of Pramexol. If they occur, the dose of levodopa should be decreased.

Dystonia

Axial dystonia including antecollis, camptocormia and pleurothotonus (Pisa Syndrome) has occasionally been reported in patients with Parkinson's disease following initiation or incremental dose increase of pramipexole. Although dystonia may be a symptom of Parkinson's disease, the symptoms in these patients have improved after reduction or withdrawal of pramipexole. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment in the dose of pramipexole considered.

Sudden onset of sleep and somnolence

Pramexol has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson’s diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Pramexol. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.

Impulse control disorders

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

Mania and delirium

Patients should be regularly monitored for the development of mania and delirium. Patients and carers should be made aware that mania and delirium can occur in patients treated with pramipexole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Patients with psychotic disorders

Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexole should be avoided.

Ophthalmologic monitoring

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

Severe cardiovascular disease

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.

Neuroleptic malignant syndrome

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

Dopamine agonist withdrawal syndrome

To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off. Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain which may be severe. Patients should be informed about this before tapering the dopamine agonist, and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the pramipexole dose temporarily.

Augmentation

Treatment of Restless Legs Syndrome with dopaminergic medicinal products 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.

This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.[1]

*Effects on Ability to Drive and Use Machine**

Patients being treated with Pramexol and presenting with somnolence and/or sudden sleep episodes 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) until such recurrent episodes and somnolence have resolved (see also section on special warnings and special precautions for use).

♦ 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. Pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the fetus.

Breastfeeding

As Pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of Pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma.

In the absence of human data, Pramipexole should not be used during breastfeeding. However, if its use is unavoidable, breastfeeding should be discontinued.

Fertility

No studies on the effect on human fertility have been conducted.

♦ **SIDE EFFECT:**

The majority of adverse drug reactions usually start early in therapy and most tend to disappear even as therapy is continued.

Within the system organ classes, adverse reactions are listed under headings of frequency, using the following categories: very common; common; uncommon; rare; very rare; not known.

Parkinson's disease, most common adverse reactions

The most commonly reported adverse drug reactions in patients with Parkinson's disease were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg pramipexole salt per day. A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson's disease

Body System	Very common	Common	Uncommon	Rare	Not known
Infections and infestations			pneumonia		
Endocrine disorders			inappropriate antidiuretic hormone secretion		
Psychiatric disorders		Insomnia hallucinations abnormal dreams confusion behavioural symptoms of impulse control disorders and compulsions	compulsive shopping pathological gambling restlessness hypersexuality delusion libido disorder paranoia delirium binge eating hyperphagia	mania	
Nervous system disorders	somnolence dizziness dyskinesia	headache	sudden onset of sleep amnesia hyperkinesia syncope		
Eye disorders		visual impairment including diplopia vision blurred visual acuity reduced			
Cardiac disorders			cardiac failure		
Vascular disorders		hypotension			
Respiratory, thoracic, and mediastinal disorders			Dyspnoea hiccups		
Gastrointestinal disorders	nausea	constipation vomiting			
Skin and subcutaneous tissue disorders			hypersensitivity pruritus rash		
General disorders and administration site conditions		fatigue peripheral oedema			Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.
Investigations		weight decrease including decreased appetite	weight increase		

Restless Legs Syndrome, most common adverse reactions

The most commonly reported adverse drug reactions in patients with Restless Legs Syndrome treated with pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with Pramexol compared to males.

Table 2: Restless Legs Syndrome

Body System	Very common	Common	Uncommon	Not known
Infections and infestations			pneumonia	
Endocrine disorders			inappropriate antidiuretic hormone secretion	
Psychiatric disorders		insomnia abnormal dreams	restlessness confusion hallucinations libido disorder delusion hyperphagia paranoia mania delirium behavioural symptoms of impulse control disorders and compulsions[1] (such as: compulsive shopping, pathological gambling, hypersexuality, binge eating)	
Nervous system disorders		headache dizziness somnolance	sudden onset of sleep syncope dyskinesia amnesia hyperkinesia	
Eye disorders			visual impairment including visual acuity reduced diplopia	

			vision blurred	
Cardiac disorders			cardiac failure	
Vascular disorders			hypotension	
Respiratory, thoracic, and mediastinal disorders			dyspnoea hiccups	
Gastrointestinal disorders	nausea	constipation vomiting		
Skin and subcutaneous tissue disorders			hypersensitivity pruritus rash	
General disorders and administration site conditions		fatigue	peripheral oedema	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

Somnolence

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

Libido disorders

Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Pramexol.

Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤ 65 years), not being married and self-reported family history of gambling behaviours.

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.

Cardiac failure

Cardiac failure has been reported in patients with pramipexole.

♦ CONTRAINDICATION:

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

♦ DRUG INTERACTION:

Plasma protein binding

Pramipexole is bound to plasma proteins to a very low (< 20%) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with Selegiline and Levodopa.

Inhibitors/competitors of active renal elimination pathway

Cimetidine reduced the renal clearance of Pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as Cimetidine, Amantadine, Mexiletine, Zidovudine, Cisplatin, Quinine, and Procainamide, may interact with Pramipexole resulting in reduced clearance of Pramipexole. Reduction of the Pramipexole dose should be considered when these medicinal products are administered concomitantly with Pramipexole.

Combination with Levodopa

When Pramipexole is given in combination with Levodopa, it is recommended that the dose of Levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of Pramipexole.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with Pramipexole.

Antipsychotic medicinal products

Co-administration of antipsychotic medicinal products with Pramipexole should be avoided, e.g. if antagonistic effects can be expected.

♦ OVERDOSE AND TREATMENT:

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. 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.

♦ SHELF LIFE:

Two (2) years

♦ STORAGE:

Store at temperature of not more than 30°C.

♦ DOSAGE FORM AND PACKAGING AVAILABLE:

1 mg, Blister 3x10's

♦ DATE OF REVISION:

April 9, 2018

Manufactured by:
UNISON LABORATORIES CO., LTD.
39 Moo 4, Klong Udomcholjorn, Muang Chachoengsao,
Chachoengsao 24000 Thailand
Product Registration Holder/ Importer:
MEDISPEC (M) SDN. BHD.
No. 55 & 57, Lorong Sempadan 2, (Off Boundary Road)
11400 Ayer Itam, Penang Malaysia

MY/030417-01 (RA)_IRA Memo 17-012 (D) & 17-013 (D)_Apr 2017
(www.emc-medicines.org.uk;*www.pdr.net, [1]DRGD_MY)