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# INSTRUCTION
## for medical use

## PIRITAN®

***Composition:***
*active substance:* pramipexole dihydrochloride monohydrate;
each tablet contains pramipexole dihydrochloride monohydrate 0.25 mg equivalent to pramipexole 0.18 mg or pramipexole dihydrochloride monohydrate 1.0 mg equivalent to pramipexole 0.7 mg;
*excipients:* mannitol (E 421), corn starch, povidone (PVPK30), povidone K90 (PVPK90), magnesium stearate, colloidal silicon dioxide.

**Pharmaceutical form.** Tablets.
*Basic physical and chemical properties*:
0.25 mg tablets: white to off white colour, oval shape, bevelled edge, biconvex tablet with deep breakline on one side and normal breakline on other side;
1.0 mg tablets: white to off white colour, round shape, bevelled edge, biconvex tablet with deep breakline on one side and plain on other side.

**Pharmacotherapeutic group.** Antiparkinsonian drugs. Dopaminergic drugs. Dopamine agonists.
ATC code: N04BC05.

***Pharmacological properties.***
*Pharmacodynamics.*
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 (striate body). Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.
The mechanism of action of pramipexole as treatment for restless legs syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.
During the investigation in human volunteers, a dose-dependent decrease in prolactin was observed.
*Pharmacokinetic properties.*
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 decreases with food intake, but the degree of absorption does not decrease. 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).
Metabolism.
Pramipexole is metabolised in man only to a small extent.
Elimination.
Renal excretion of unchanged pramipexole is the major route of elimination. Approximately 90% of $^{14}C$-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 400 ml/min. The elimination half-life varies from 8 hours in the young to 12 hours in the elderly.

**Clinical characteristics.**
***Indications.***
Treatment of signs and symptoms of idiopathic Parkinson's disease in adults as monotherapy (without levodopa) or in combination with levodopa during the course of the disease to late stages, when the effect of levodopa decreases or becomes unstable and there is a fluctuation of therapeutic effect (phenomenon of "inclusion-exclusion").
Symptomatic treatment of idiopathic restless legs syndrome from moderate to severe in adults, doses not exceeding 0.75 mg (as pramipexole dihydrochloride).

***Contraindications.***
Hypersensitivity to the active substance or to any of the drug excipients.

***Interaction with other medicinal products and other forms of 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. 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 increasing the dose of pramipexole in patients with Parkinson's disease, it is recommended to reduce the dose of levodopa, and the doses of other antiparkinsonian drugs are left unchanged.
Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections "Special

warnings and precautions for use", "Effects on ability to drive and use machines" and "Undesirable effects").
*Antipsychotic medicinal products.*
Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section "Special warnings and precautions for use"), e.g. if antagonistic effects can be expected.

***Special warnings and precautions for use.***
*Renal impairment.*
Patients with Parkinson's disease and impaired renal function are advised to prescribe pramipexole in reduced doses in accordance with the section "Dosage and administration".
*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 combination therapy with levodopa in progressive Parkinson's disease, dyskinesia may develop at the beginning of pramipexole titration. In this case, the dose of levodopa should be reduced.
*Dystonia.*
Cases of axial dystonia, including antecolis, camptocormia, and pleurototonus (Pisa syndrome), have been reported in patients with Parkinson's disease after an initial dose or a gradual increase in pramipexole. Although dystonia may be a symptom of Parkinson's disease, symptoms in these patients decrease after dose reduction or discontinuation 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.*
Pramipexole has been associated with drowsiness and episodes of sudden sleep onset, especially in patients with Parkinson's disease. There have been rare reports of a sudden onset of sleep during daytime activity, in some cases without awareness or warning signs. Therefore, patients should be advised to exercise caution when driving or operating machinery during treatment with pramipexole. Patients who experience drowsiness and/or episodes of sudden sleep onset should refrain from driving or operating machinery. In addition, dose reduction or shortening of treatment should be considered. Due to possible additive effects, caution should be exercised if the patient uses other sedative drugs in combination with pramipexole or consumes alcohol (see sections "Interaction with other medicinal products and other forms of interaction", "Effects on ability to drive and use machines" and "Undesirable Reactions").
*Impulse control disorders.*
Patients should be closely monitored for the development of impulse control disorders. Patients and caregivers should be aware that treatment with dopamine agonists, including pramipexole, may cause symptoms of urge control, including abnormal gambling, increased libido, hypersexuality, compulsive wasteful spending or purchasing, overeating and compulsive food consumption.
With the development of such symptoms, it is necessary to consider the possibility of reducing the dose or gradual discontinuing the drug.
*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 (see section “Interaction with other medicinal products and other forms of interaction”).
*Ophthalmologic monitoring.*
Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur.
*Severe cardiovascular disease*
In case of severe cardiovascular disease, it is necessary to prescribe pramipexole especially carefully. 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 (see section “Posology and method of administration”).
*Dopamine agonist withdrawal syndrome (DAWS).*
Withdrawal syndrome has been reported after discontinuation of dopamine agonists, including pramipexole (see section “Undesirable Reactions”). To discontinue treatment in patients with Parkinson’s disease, pramipexole should be tapered off (see section “Posology and method of administration”). There is limited evidence that patients with impulse control disorders and patients receiving high daily and/or cumulative doses of dopamine agonists may be at higher risk of developing withdrawal syndrome. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating, and pain and do not change with levodopa. Patients should be warned about these symptoms before dose reduction/discontinuation of dopamine agonists. Patients should be closely monitored during dose reduction/withdrawal of dopamine agonists. In case of severe or persistent withdrawal symptoms, temporary resumption of pramipexole at the lowest effective dose is possible.
*Augmentation (worsening of symptoms).*
Treatment of restless legs syndrome with dopaminergic drugs can cause 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. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Augmentation was observed in 11.8% of patients in the Pramipexole group (N = 152) and 9.4% of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between Pramipexole and placebo groups.

*Renal failure*.
Pramipexole should be used with caution in patients with renal failure, as it is excreted by the kidneys.
*Rhabdomyolysis*.
The only case of rhabdomyolysis was reported in a 49-year-old man with progressive Parkinson’s disease during treatment with pramipexole. The patient was hospitalized with elevated creatine phosphokinase (CPK – 10,631 IU/l). The symptoms disappeared after discontinuation of treatment.

*Use during pregnancy and lactation.*
*Pregnancy.*
No studies on the effects of pramipexole on pregnancy and lactation in humans have been performed. Pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.
Breast-feeding.
As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. In the absence of human data, Pramipexole should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.
Fertility.

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

*Effects on ability to drive and use machines.*
Pramipexole can have a major influence on the ability to drive and use machines.
Hallucinations or somnolence can occur.
Patients being treated with Pramipexole 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).

***Posology and method of administration.***
*All dosing information applies to pramipexole as pramipexole dihydrochloride.*
Parkinson's disease
The daily dose is administered in equally divided doses 3 times a day.
*Initial treatment.*
As specified below, doses should be increased gradually from a starting dose of 0.264 mg of base (0.375 mg of salt) per day and then increased every 5–7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect (see Table. 1).

Table 1.

| Ascending dose schedule of pramipexole | | |
|---|---|---|
| Week | Dose (mg) | Total daily dose (mg) |
| 1 | 3 × 0.125 | 0.375 |
| 2 | 3 × 0.25 | 0.75 |
| 3 | 3 × 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. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg per day (see section "Undesirable Reactions").

*Maintenance treatment.*
The individual dose of Pramipexole should be in the range of 0.375 mg to a maximum of 4.5 mg per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.5 mg. Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In advanced Parkinson's disease, doses higher than 1.5 mg per day can be useful in patients where a reduction of the levodopa therapy is intended (in combination therapy with levodopa). It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with pramipexole, depending on reactions in individual patients (see section "Interaction with other medicinal products and other forms of interaction").
*Treatment discontinuation.*
Abrupt discontinuation of dopaminergic therapy may lead to the development of neuroleptic malignant syndrome or to the dopamine agonists withdrawal syndrome. The dose of pramipexole should be reduced gradually, by 0.75 mg per day, until the daily dose is reduced to 0.75 mg. After that, the dose should be reduced by 0.375 mg per day. With gradual dose reduction, dopamine agonist withdrawal syndrome may occur. In this case, it may be necessary to temporarily increase the dose of the drug with a subsequent return to its gradual withdrawal (see section "Special warnings and precautions for use").
*Renal impairment.*

The elimination of pramipexole is dependent on renal function. The following dose 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 the drug should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg per day). A maximum daily dose of pramipexole – 2.25 mg – should not be exceeded;
- in patients with a creatinine clearance less than 20 ml/min, the daily dose of the drug should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of pramipexole (1.5 mg) should not be exceeded.

If renal function declines during maintenance therapy, the pramipexole daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then the pramipexole daily dose should be reduced 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.

*Hepatic impairment.*

Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been investigated.

Restless legs syndrome.

The recommended starting dose of pramipexole 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 2 below).

Table 2.

| Dose schedule of pramipexole | |
|---|---|
| Titration step | Once daily evening dose (mg) |
| 1 | 0.125 |
| 2* | 0.25 |
| 3* | 0.50 |
| 4* | 0.75 |
| *if needed | |

Patient's response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

*Treatment discontinuation.*

Because the daily dose for the treatment of restless legs syndrome does not exceed 0.75 mg, pramipexole therapy can be discontinued without gradual dose reduction. There may be a resumption of restless legs syndrome symptoms (increased severity of symptoms compared to baseline) after abrupt discontinuation of pramipexole. This effect was found to be similar across all doses.

*Renal impairment.*

The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose.

The use of pramipexole has not been studied in haemodialysis patients, or in patients with severe renal impairment.
*Hepatic impairment.*
Dose reduction in patients with hepatic failure is not required, as approx. 90% of absorbed active substance 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.

*Children.*
Parkinson's disease.
Safety and efficacy of pramipexole in children (under 18 years of age) have not been established. There is no justification for the use of pramipexole in children with Parkinson's disease.
Restless legs syndrome.
Pramipexole is not recommended for use in children (below 18 years of age) due to a lack of data on safety and efficacy.
Tourette's syndrome.
Pramipexole should not be used in children (under 18 years of age) with Tourette's syndrome because of the negative benefit/risk ratio for this disease.

***Overdose.***
*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.
*Treatment.* 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.

***Undesirable reactions.***
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 (number of patients expected to experience the reaction), using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
*Parkinson's disease.*
The most commonly (≥ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo 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 per day (see section "Posology and method of administration"). The most 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.
*Infections and infestations.*
Uncommon: pneumonia.
*Endocrine system disorders.*
Uncommon: inappropriate antidiuretic hormone secretion[1].
*Psychiatric disorders.*

Common: insomnia, hallucinations, sleep disturbances, confusion, symptoms of impulse control disorder and compulsive behaviour.
Uncommon: pathological urge to go shopping, pathological urge to gamble, anxiety, hypersexuality, delusions, libido disorders, paranoia, delirium, overeating[1], hyperphagia[1].
Rare: mania.
*Nervous system disorders.*
Very common: somnolence, dizziness, dyskinesia.
Common: headache.
Uncommon: sudden onset of sleep, amnesia, hyperkinesia, syncope.
*Eye disorders.*
Common: visual impairment including diplopia, vision blurred, visual acuity reduced.
*Cardio-vascular disorders.*
Common: arterial hypotension.
Uncommon: cardiac failure[1].
*Respiratory, thoracic and mediastinal disorders.*
Uncommon: shortness of breath, hiccups.
*Gastrointestinal disorders*.
Very common: nausea.
Common: constipation, vomiting.
*Skin and subcutaneous tissue disorders.*
Uncommon: hypersensitivity, itching, rash.
*General disorders.*
Common: increased fatigue, peripheral oedema.
Not known: dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain).
*Investigations.*
Common: weight decrease including decreased appetite.
Uncommon: weight increase.

[1] This adverse reaction was observed in the post-marketing period. In 95% the frequency is not higher than "uncommon", but may be lower. It is not possible to establish the exact frequency, as no adverse reaction was observed in clinical trials among 2762 patients with Parkinson's disease treated with pramipexole.

*Restless legs syndrome.*
The most commonly (≥ 5%) 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 pramipexole (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively).
*Infections and infestations.*
Uncommon: pneumonia[2].
*Endocrine system disorders.*
Uncommon: inappropriate antidiuretic hormone secretion[2].
*Psychiatric disorders.*
Common: insomnia, sleep disorders.
Uncommon: anxiety, confusion, hallucinations, libido disorders, delusions[2], hyperphagia[2], paranoia[2], mania[2], delirium[2], symptoms of impulse control disorders and compulsive behavior[2] (such as pathological urge to go shopping, pathological urge to gambling, hypersexuality, overeating).
*Nervous system disorders.*
Common: headache, dizziness, somnolence.
Uncommon: sudden onset of sleep, syncope, dyskinesia, amnesia[2], hyperkinesia[2].
*Eye disorders.*
Uncommon: visual impairment including diplopia, vision blurred, visual acuity reduced.

*Cardio-vascular disorders.*
Uncommon: heart failure[2], arterial hypotension.
*Respiratory, thoracic and mediastinal disorders.*
Uncommon: shortness of breath, hiccups.
*Gastrointestinal disorders.*
Very common: nausea.
Common: constipation, vomiting.
*Skin and subcutaneous tissue disorders.*
Uncommon: hypersensitivity, itching, rash.
*General disorders.*
Common: increased fatigue.
Uncommon: peripheral oedema.
Not known: dopamine agonist withdrawal syndrome (including apathy, anxiety, depression, fatigue, sweating and pain).
*Investigations.*
Uncommon: weight decrease including decreased appetite, weight increase.
[2] This side effect has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 1,395 patients with Restless Legs Syndrome treated with pramipexole.
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 (see section "Special warnings and precautions for use").
*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 Pramipexole (see section "Special warnings and precautions for use").
*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 "Special warnings and precautions for use").
*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 (observed risk ratio 1.86; 95% CI, 1.21–2.85).
Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after drug registration is an important procedure. This allows you to continue to monitor the benefit/risk ratio for this medicine. Medical staff are asked to report all suspected adverse reactions to the State Expert Centre of the Ministry of Health of Ukraine and the applicant via the feedback form website: https://kusum.ua/pharmacovigilance/.

***Shelf life.***
3 years.

**Storage conditions.**
Store in the original package at the temperature not more than 25°C.
Keep out of reach of children.

**Package.**
10 tablets in a blister; 3 or 6 blisters in a carton package.

**Condition of supply.**
By prescription.

**Manufacturer.**
KUSUM HEALTHCARE PVT LTD.

**Manufacturer's location and address of the place of business.**
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

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