Public Assessment Report

Decentralised Procedure

PRAMIPEXOLE 0.18MG, 0.35MG AND 0.7MG TABLETS

UK/H/4061/002-4/DC
UK Licence No: PL 14894/0668-70

RANBAXY (UK) LIMITED
LAY SUMMARY

On 28th September 2010, the UK granted Marketing Authorisations (licences) for Pramipexole 0.18mg, 0.35mg and 0.7mg tablets (PL 14894/0668-70; UK/H/4061/002-4/DC).

Pramipexole tablets belong to a group of medicines called dopamine agonists, which stimulate dopamine receptors in the brain.

Dopamine receptors on stimulation triggers nerve impulses in the brain that help to control body movement.

Pramipexole tablets are used to treat signs and symptoms of idiopathic Parkinson's disease, either alone or in combination with another medicine called levodopa.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Pramipexole tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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2 Quality aspects  
3 Non-clinical aspects  
4 Clinical aspects  
5 Overall conclusions

Module 6: Steps taken after initial procedure ........................................... Not applicable
Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Pramipexole 0.18mg, 0.35mg and 0.7mg tablets</th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Pramipexole dihydrochloride monohydrate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.18mg, 0.35mg and 0.7mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Ranbaxy (UK) Limited</td>
</tr>
<tr>
<td></td>
<td>Building 4, Chiswick Park,</td>
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<td></td>
<td>566 Chiswick High Road,</td>
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<td></td>
<td>London W4 5YE</td>
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<td>Day 210 – 22\textsuperscript{nd} July 2010</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Pramipexole 0.18 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pramipexole 0.18 mg tablets contain 0.18 mg of pramipexole base (as 0.25 mg of pramipexole dihydrochloride monohydrate).

Please note:
Pramipexole doses as published in the literature refer to the salt form. Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, Oblong 9mm x 4.5mm, uncoated tablets with score line on one side
The tablet can be divided into equal halves

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Pramipexole is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

4.2 Posology and method of administration
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 times a day.

Initial treatment:
Dosages 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 side-effects, the dosage should be titrated to achieve a maximal therapeutic effect.

<p>| Ascending dose schedule of pramipexole |
|------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Week</th>
<th>Dosage (mg of base)</th>
<th>Total Daily Dose (mg of base)</th>
<th>Dosage (mg of salt)</th>
<th>Total Daily Dose (mg of salt)</th>
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<tbody>
<tr>
<td>1</td>
<td>3 x 0.088</td>
<td>0.264</td>
<td>3 x 0.125</td>
<td>0.375</td>
</tr>
<tr>
<td>2</td>
<td>3 x 0.18</td>
<td>0.54</td>
<td>3 x 0.25</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>3 x 0.35</td>
<td>1.1</td>
<td>3 x 0.5</td>
<td>1.50</td>
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</tbody>
</table>

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg/ day (see section 4.8).

Maintenance treatment:
The individual dose should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in three pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of undesirable effects. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, doses higher than 1.1 mg (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced.
during both the dose escalation and the maintenance treatment with pramipexole, depending on reactions in individual patients.

_Treatment discontinuation:_
Abrupt discontinuation of dopaminergic therapy can lead to the development of aneuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4).

_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.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of pramipexole should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily).

In patients with a creatinine clearance less than 20 ml/min, the daily dose of pramipexole should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily.

If renal function declines during maintenance therapy, reduce pramipexole daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the pramipexole 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 failure is probably not necessary, as approximately 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been investigated.

_Dosing in children and adolescents:_
Pramipexole is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to the active substance or any one of the excipients

4.4 Special warnings and precautions for use
When prescribing pramipexole tablets in a patient with Parkinson's disease with renal impairment, a reduced dose is suggested in line with section 4.2.

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

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

Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with pramipexole. 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. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.7 and section 4.8).
Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Furthermore, patients and caregivers should be aware of the fact that behavioural changes can occur. Dose reduction/taper discontinuation should be considered.

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 4.5).

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

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.

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

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 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.

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 and amantadine, may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with pramipexole.

When pramipexole is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage 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.

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

4.6 Pregnancy and lactation

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 (see section 5.3). pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the fetus.

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 breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.
4.7 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) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5 and 4.8).

4.8 Undesirable effects
Expected adverse reactions
The following adverse reactions are expected under the use of Pramipexole: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual disturbance including vision blurred and visual acuity reduced, vomiting, weight decrease, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on pramipexole and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. However, the majority of common adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was 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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Parkinson's disease, most common adverse reactions
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/day (see section 4.2). More frequent adverse drug reactions in combination with levodopa were dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Abnormal dreams, confusion, hallucinations, insomnia, behavioural symptoms of impulse control disorders and compulsions; restlessness.</td>
</tr>
<tr>
<td>Common</td>
<td>Delusion, libido disorder, paranoia; compulsive shopping, hypersexuality, pathological gambling.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>binge eating, hyperphagia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, dyskinesia, somnolence</td>
</tr>
<tr>
<td>Very common</td>
<td>Headache, amnesia</td>
</tr>
<tr>
<td>Common</td>
<td>Hyperkinesia, sudden onset of sleep, syncope</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>visual disturbance including vision blurred and</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>Infections and Infestions</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abnormal dreams, insomnia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusion, hallucinations, libido disorder, restlessness</td>
</tr>
<tr>
<td>Not known</td>
<td>behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality, and pathological gambling; delusion, hyperphagia, paranoia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Sudden onset of sleep, syncope</td>
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</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>visual disturbance including vision blurred and visual acuity reduced</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
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<td>Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
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</tr>
<tr>
<td>Uncommon</td>
<td>dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Common</td>
<td>Constipation, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypersensitivity, pruritus, rash</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
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</tr>
<tr>
<td>Common</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Common</td>
<td>Peripheral oedema</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Weight increase; weight decrease</td>
</tr>
<tr>
<td>Common</td>
<td></td>
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</tbody>
</table>

Restless Legs Syndrome, most common adverse reactions
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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
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</tr>
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<tbody>
<tr>
<td>Psychiatric disorders</td>
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<td></td>
</tr>
</tbody>
</table>

Somnolence
Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

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

Impulse control disorders and compulsive behaviours

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 (see also section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behavior (hypersexuality). 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 behaviors.

4.9 Overdose
There is no clinical experience with massive overdosage. The expected adverse events 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 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, administration of activated charcoal and electrocardiogram monitoring.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: dopamine agonists, ATC code: N04BC05

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.

The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

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

Clinical trials in Parkinson's disease
In patients, pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease.
Controlled clinical trials included approximately 2100 patients. Out of these, approximately 900 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, the efficacy of pramipexole in the controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole
However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.

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. 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.

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 8-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. Approximately 90% of 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 400 ml/min. The elimination half-life (t½) 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.

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

Mannitol E421
Maize starch
Povidone – K29/32
Silica Colloidal Anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PA-Al-PVC-Blisters
30 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0668

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/09/2010

10 DATE OF REVISION OF THE TEXT
28/09/2010
1 NAME OF THE MEDICINAL PRODUCT
Pramipexole 0.35 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pramipexole 0.35 mg tablets contain 0.35 mg of pramipexole base (as 0.5 mg of pramipexole dihydrochloride monohydrate).

Please note:
Pramipexole doses as published in the literature refer to the salt form. Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, circular, 9.5mm diameter, uncoated tablets with score line and embossed with “PM” in the both halves in one side and the other side.

The tablet can be divided into equal halves

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Pramipexole is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

4.2 Posology and method of administration
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 times a day.

Initial treatment:
Dosages 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 side-effects, the dosage should be titrated to achieve a maximal therapeutic effect.

<table>
<thead>
<tr>
<th>Ascending dose schedule of pramipexole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.8).

Maintenance treatment:
The individual dose should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in three pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of undesirable effects. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, doses higher than 1.1 mg (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with pramipexole, depending on reactions in individual patients.
Treatment discontinuation:
Abrupt discontinuation of dopaminergic therapy can lead to the development of aneuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4).

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.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of pramipexole should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily).

In patients with a creatinine clearance less than 20 ml/min, the daily dose of pramipexole should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily.

If renal function declines during maintenance therapy, reduce pramipexole daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the pramipexole 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 failure is probably not necessary, as approximately 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been investigated.

Dosing in children and adolescents:
Pramipexole is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to the active substance or any one of the excipients

4.4 Special warnings and precautions for use
When prescribing pramipexole tablets in a patient with Parkinson's disease with renal impairment, a reduced dose is suggested in line with section 4.2.

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

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

Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with pramipexole. 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. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.7 and section 4.8).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Furthermore, patients and caregivers...
should be aware of the fact that behavioural changes can occur. Dose reduction/taper discontinuation should be considered.

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 4.5).

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

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.

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

### 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 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.

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 and amantadine, may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with pramipexole.

When pramipexole is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage 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.

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

### 4.6 Pregnancy and lactation

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 (see section 5.3). pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the fetus.

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 breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

### 4.7 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) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5 and 4.8).

4.8 Undesirable effects

Expected adverse reactions

The following adverse reactions are expected under the use of Pramipexole: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual disturbance including vision blurred and visual acuity reduced, vomiting, weight decrease, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on pramipexole and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. However, the majority of common adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was 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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Parkinson's disease, most common adverse reactions

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/day (see section 4.2). More frequent adverse drug reactions in combination with levodopa were dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Table 1: Parkinson’s disease

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Abnormal dreams, confusion, hallucinations, insomnia, behavioural symptoms of impulse control disorders and compulsions; restlessness.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Delusion, libido disorder, paranoia; compulsive shopping, hypersexuality, pathological gambling.</td>
</tr>
<tr>
<td>Not known</td>
<td>binge eating, hyperphagia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Dizziness, dyskinesia, somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Headache, amnesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperkinesia, sudden onset of sleep, syncope</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>visual disturbance including vision blurred and visual acuity reduced</td>
</tr>
</tbody>
</table>
Vascular disorders
- Very common: Hypotension

Respiratory, thoracic, and mediastinal disorders
- Uncommon: dyspnoea

Gastrointestinal disorders
- Very common: Nausea
- Common: Constipation, vomiting

Skin and subcutaneous tissue disorders
- Uncommon: Hypersensitivity, pruritis, rash

General disorders and administration site conditions
- Common: Fatigue, peripheral oedema

Investigations
- Uncommon: Weight increase
- Common: Weight decrease

Restless Legs Syndrome, most common adverse reactions
- 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).

Table 2: Restless Legs Syndrome

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infections</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abnormal dreams, insomnia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusion, hallucinations, libido disorder, restlessness</td>
</tr>
<tr>
<td>Not known</td>
<td>Behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality, and pathological gambling; delusion, hyperphagia, paranoia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Sudden onset of sleep, syncope</td>
</tr>
<tr>
<td>Not known</td>
<td>Dyskinesia, hyperkinesia, amnesia</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Visual disturbance including vision blurred and visual acuity reduced</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Common</td>
<td>Constipation, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<tr>
<td>Uncommon</td>
<td>Hypersensitivity, pruritis, rash</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Common</td>
<td>Peripheral oedema</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Weight increase; weight decrease</td>
</tr>
</tbody>
</table>

Somnolence
- Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).
Libido disorders

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

Impulse control disorders and compulsive behaviours

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 (see also section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behavior (hypersexuality). 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 behaviors.

4.9 Overdose

There is no clinical experience with massive overdosage. The expected adverse events 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 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, administration of activated charcoal and electrocardiogram monitoring.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

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

Clinical trials in Parkinson's disease

In patients, pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Controlled clinical trials included approximately 2100 patients. Out of these, approximately 900 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, the efficacy of pramipexole in the controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.
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. 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.

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 8-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. Approximately 90% of 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 400 ml/min. The elimination half-life (t½) 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.

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

Mannitol E421
Maize starch
Povidone – K29/32
Silica Colloidal Anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PA-Al-PVC-Blisters
30 and 100 tablets.

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London W4 5YE
United Kingdom

8 MARKETING AUTHORITY NUMBER(S)
PL 14894/0669

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/09/2010

10 DATE OF REVISION OF THE TEXT
28/09/2010
1 NAME OF THE MEDICINAL PRODUCT
Pramipexole 0.7 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Pramipexole 0.7 mg tablets contain 0.7 mg of pramipexole base (as 1.0 mg of pramipexole dihydrochloride monohydrate).

Please note:
Pramipexole doses as published in the literature refer to the salt form. Therefore, doses will be expressed in terms of both pramipexole base and pramipexole salt (in brackets).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.
White, circular, 9.5mm diameter, uncoated tablets with score line and embossed with “PA” in the both halves in one side and the other side plain.

The tablet can be divided into equal halves

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Pramipexole is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

4.2 Posology and method of administration
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 times a day.

Initial treatment:
Dosages 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 side-effects, the dosage should be titrated to achieve a maximal therapeutic effect.

<table>
<thead>
<tr>
<th>Week</th>
<th>Dosage (mg of base)</th>
<th>Total Daily Dose (mg of base)</th>
<th>Dosage (mg of salt)</th>
<th>Total Daily Dose (mg of salt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 x 0.088</td>
<td>0.264</td>
<td>3 x 0.125</td>
<td>0.375</td>
</tr>
<tr>
<td>2</td>
<td>3 x 0.18</td>
<td>0.54</td>
<td>3 x 0.25</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>3 x 0.35</td>
<td>1.1</td>
<td>3 x 0.5</td>
<td>1.50</td>
</tr>
</tbody>
</table>

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.

However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg/day (see section 4.8).

Maintenance treatment:
The individual dose should be in the range of 0.264 mg of base (0.375 mg of salt) to a maximum of 3.3 mg of base (4.5 mg of salt) per day. During dose escalation in three pivotal studies, efficacy was observed starting at a daily dose of 1.1 mg of base (1.5 mg of salt). Further dose adjustments should be done based on the clinical response and the occurrence of undesirable effects. In clinical trials approximately 5% of patients were treated at doses below 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, doses higher than 1.1 mg (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with pramipexole, depending on reactions in individual patients.
Treatment discontinuation:
Abrupt discontinuation of dopaminergic therapy can lead to the development of aneuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.54 mg of base (0.75 mg of salt) per day until the daily dose has been reduced to 0.54 mg of base (0.75 mg of salt). Thereafter the dose should be reduced by 0.264 mg of base (0.375 mg of salt) per day (see section 4.4).

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.

In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of pramipexole should be administered in two divided doses, starting at 0.088 mg of base (0.125 mg of salt) twice a day (0.176 mg of base/0.25 mg of salt daily).

In patients with a creatinine clearance less than 20 ml/min, the daily dose of pramipexole should be administered in a single dose, starting at 0.088 mg of base (0.125 mg of salt) daily.

If renal function declines during maintenance therapy, reduce pramipexole daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the pramipexole 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 failure is probably not necessary, as approximately 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been investigated.

Dosing in children and adolescents:
Pramipexole is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to the active substance or any one of the excipients

4.4 Special warnings and precautions for use
When prescribing pramipexole tablets in a patient with Parkinson's disease with renal impairment, a reduced dose is suggested in line with section 4.2.

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

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

Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with pramipexole. 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. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see section 4.7 and section 4.8).

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including pramipexole. Furthermore, patients and
caregivers should be aware of the fact that behavioural changes can occur. Dose reduction/taper discontinuation should be considered.

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 4.4).

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

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.

Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

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 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.

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 and amantadine, may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with pramipexole.

When pramipexole is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage 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.

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

4.6 Pregnancy and lactation

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 (see section 5.3). pramipexole should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the fetus.

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 breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

4.7 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) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5 and 4.8).

4.8 Undesirable effects

Expected adverse reactions

The following adverse reactions are expected under the use of Pramipexole: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual disturbance including vision blurred and visual acuity reduced, vomiting, weight decrease, weight increase.

Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on pramipexole and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.

Tables 1 and 2 display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. However, the majority of common adverse drug reactions were mild to moderate, they usually start early in therapy, and most tended to disappear even as therapy was 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, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Parkinson's disease, most common adverse reactions

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/day (see section 4.2). More frequent adverse drug reactions in combination with levodopa were dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>pneumonia</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abnormal dreams, confusion, hallucinations, insomnia, behavioural symptoms of impulse control disorders and compulsions; restlessness.</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Delusion, libido disorder, paranoia; compulsive shopping, hypersexuality, pathological gambling.</td>
</tr>
<tr>
<td>Not known</td>
<td>binge eating, hyperphagia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Dizziness, dyskinesia, somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Headache, amnesia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hyperkinesia, sudden onset of sleep, syncope</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td>visual disturbance including vision blurred and visual acuity reduced</td>
</tr>
</tbody>
</table>
Restless Legs Syndrome, most common adverse reactions

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).

Table 2: Restless Legs Syndrome

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Drug Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestions</td>
<td>pneumonia</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abnormal dreams, insomnia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Confusion, hallucinations, libido disorder, restlessness</td>
</tr>
<tr>
<td>Not known</td>
<td>behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality, and pathological gambling; delusion, hyperphagia, paranoia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness, headache, somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Sudden onset of sleep, syncope</td>
</tr>
<tr>
<td>Not known</td>
<td>Dyskinesia, hyperkinesia, amnesia</td>
</tr>
<tr>
<td><strong>Eye Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>visual disturbance including vision blurred and visual acuity reduced</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).
Libido disorders
Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

Impulse control disorders and compulsive behaviours

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 (see also section 4.4).

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behavior (hypersexuality). 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 behaviors.

4.9 Overdose
There is no clinical experience with massive overdosage. The expected adverse events 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 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, administration of activated charcoal and electrocardiogram monitoring.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: dopamine agonists, ATC code: N04BC05

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.

The mechanism of action of pramipexole as treatment for Restless Legs Syndrome is unknown. Neuropharmacological evidence suggests primary dopaminergic system involvement.

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

Clinical trials in Parkinson's disease
In patients, pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Controlled clinical trials included approximately 2100 patients. Out of these, approximately 900 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, the efficacy of pramipexole in the controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy. In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally higher in the escalation phase with the pramipexole group. However there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.
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. 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.

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 8-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. Approximately 90% of 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 400 ml/min. The elimination half-life (t½) 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.

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
Mannitol E421
Maize starch
Povidone – K29/32
Silica Colloidal Anhydrous
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
PA-Al-PVC-Blisters
30 and 100 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4, Chiswick Park,
566 Chiswick High Road,
London W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894/0670

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28/09/2010

10 DATE OF REVISION OF THE TEXT
28/09/2010
Module 3
Product Information Leaflet

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them,
even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this
leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Pramipexole is and what they are used for
2. Before you take Pramipexole
3. How to take Pramipexole
4. Possible side effects
5. How to store Pramipexole
6. Further information

1. WHAT PRAMIPEXOLE IS AND WHAT THEY ARE USED FOR
Pramipexole belong to a class of medicines known as dopamine agonists, which stimulate
dopamine receptors in the brain.

Dopamine receptors on stimulation triggers nerve impulses in the brain that help to control
body movement.

Pramipexole is used to treat:
• Signs and symptoms of idiopathic Parkinson's disease, either alone or in combination with
levodopa.

2. BEFORE YOU TAKE PRAMIPEXOLE
Do not take Pramipexole tablets
• If you are allergic to pramipexole or to any of the other ingredients (see section 6) of the tablets.

Take special care with Pramipexole tablets
Speak to your doctor before taking Pramipexole if you:
• have kidney problems.
• are suffering from psychosis.
• are taking sedatives or alcohol.
• are suffering from severe disease of the heart and its blood vessels.

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Speak with your doctor if you are concerned about or experience any of the following
side effects which may occur while taking Pramipexole:
• hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are
visual.
• dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have advanced
Parkinson’s disease and are also taking levodopa, you might develop dyskinesia during the
up titration of pramipexole.
• excessive daytime sleepiness and episodes of suddenly falling asleep
• behavioural changes (e.g. pathological gambling), increased libido (e.g. increased sexual
desire), binge eating.
• vision abnormalities. You should have regular eye examinations during treatment with
pramipexole.
• muscle rigidity, fever, unstable blood pressure, tachycardia (increased heart rate),
confusion, depressed level of consciousness (e.g. coma).
You will need to have your blood pressure checked regularly, especially at the beginning of treatment. This is to avoid a fall in blood pressure on standing up (postural hypotension).

**Taking other medicines**
Tell your doctor or pharmacist if you are taking or have previously taken any of the following:
- Cimetidine (used to treat excess stomach acid and stomach ulcers)
- Amantadine (which can be used to treat Parkinson’s disease)
- Levodopa (used in the treatment of Parkinson’s disease), the dose of levodopa is recommended to be reduced when you start treatment with pramipexole.
- Antipsychotic medicines (used in the treatment of psychosis).

Please tell your doctor or pharmacist, if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Taking with food and drink**
You should be cautious while drinking alcohol during treatment with Pramipexole. Pramipexole can be taken with or without food. Swallow the tablets with water.

**Pregnancy and breast-feeding**
Tell your doctor if you are pregnant, think you might be pregnant or if you intend to become pregnant. Your doctor will then discuss with you if you should continue to take Pramipexole.

The effect of Pramipexole on the unborn child is not known. Therefore, do not take Pramipexole if you are pregnant unless your doctor tells you to do so.

Pramipexole should not be used during breast-feeding. Pramipexole can reduce the production of breast milk. If use of Pramipexole is unavoidable, breast-feeding should be stopped.

*Ask your doctor or pharmacist for advice before taking any medicine*

**Driving and using machines**
Pramipexole can cause hallucinations (seeing, hearing or feeling things that are not there) and excessive daytime sleepiness and episodes of suddenly falling asleep. If affected, do not drive or use machinery. You should tell your doctor if this occurs.

### 3. HOW TO TAKE PRAMIPEXOLE

Always use your medicine exactly as your doctor has told you. Do not take more than the doctor told you to. You should check with your doctors or pharmacist if you are not sure.

**Parkinson’s disease**
The daily dose is to be taken divided into 3 equal doses.

*Initial treatment:*
During the first week, the usual dose is Pramipexole 0.088 mg three times a day (equivalent to 0.264 mg daily).

Depending upon the tolerability your doctor will increase the dose every 5 - 7 days until your symptoms are controlled.

In the second week, Pramipexole 0.18 mg three times a day is recommended. This makes a total daily dose of 0.54 mg.

In the third week, pramipexole 0.35 mg three times a day is recommended. This makes a total daily dose of 1.1 mg.

If a further dose increase is necessary the daily dose should be increased by 0.54 mg base (0.75 mg salt) at weekly intervals up to a maximum dose of 3.3 mg of base (4.5 mg of salt) per day.
Maintenance treatment:
The usual maintenance dose is in the range of 0.264 mg of base to a maximum of 3.3 mg of base per day. Your doctor may reduce the dosage of levodopa if you are taking it during treatment with pramipexole.

Patients with renal impairment:
Your doctor will prescribe you the suitable dose depending on your kidney function. If you have moderate or severe kidney disease, your doctor will prescribe a lower dose. In this case, you will have to take the tablets only once or twice a day. If you have moderate kidney disease, the usual starting dose is pramipexole 0.088 mg twice a day. In severe kidney disease, the usual starting dose is Pramipexole 0.088 mg daily.

Dosing in children and adolescents
Pramipexole is not recommended for use in children and adolescents below 18 years.

Swallow the tablets with water. You can take Pramipexole with or without food.

If you take more Pramipexole than you should
Consult your doctor or go to the nearest hospital casualty department immediately. Take this leaflet or some tablets with you so your doctor will know what you have taken. You may experience nausea, vomiting, restlessness, seeing, hearing or feeling things that are not there, increased movements and inability to keep still, fainting, light headedness, dizziness.

If you forget to take Pramipexole
Take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take a double dose to make up for forgotten individual doses.

If you stop taking your tablets for more than a few days and want to restart the treatment, you must start again at the lower dose. You can then build up the dose again, as you did the first time. Ask your doctor for advice.

If you stop taking Pramipexole
If you suffer from Parkinson’s disease you should not stop treatment with pramipexole abruptly. A sudden stop could cause you to develop a medical condition called neuroleptic malignant syndrome which may represent a major health risk. The symptoms include:
- Muscle rigidity
- Fever
- Unstable blood pressure
- Tachycardia (increased heart rate)
- Confusion
- Depressed level of consciousness (e.g. coma)

It is important that the course of treatment your doctor has prescribed is taken. You may start to feel better but it is important not to stop taking this medicine, until the doctor advises, otherwise your condition may get worse again.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pramipexole can have side effects, although not everybody gets them.

If any of the following happen, stop taking Pramipexole and tell your doctor immediately or go to the casualty department at your nearest hospital.
- Rashes, hives, itching, chest constriction, shortness of breath, fever or swelling of the face, lips, neck, hands/feet, fainting (allergic reaction)

These are all uncommon and very serious side effects. If you have them you may need urgent medical attention or hospitalization.
Based upon frequency of occurrence, side effects can be classified as:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>affects more than 1 user in 10</td>
</tr>
<tr>
<td>Common</td>
<td>affects 1 to 10 users in 100</td>
</tr>
<tr>
<td>Uncommon</td>
<td>affects 1 to 10 users in 1,000</td>
</tr>
<tr>
<td>Rare</td>
<td>affects 1 to 10 users in 10,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>affects less than 1 user in 10,000</td>
</tr>
<tr>
<td>Not known</td>
<td>frequency cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

**Very common**
- Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- Sleepiness
- Dizziness
- Nausea (sickness)
- Hypotension (low blood pressure)

**Common**
- Urge to behave in an unusual way
- Hallucinations (seeing, hearing or feeling things that are not there)
- Confusion
- Tiredness (fatigue)
- Sleeplessness (insomnia)
- Excess of fluid, usually in the legs (peripheral oedema)
- Headache
- Abnormal dreams
- Constipation
- Restlessness
- Amnesia (memory disturbance)
- Visual disturbance
- Vomiting (being sick)
- Weight loss

**Uncommon**
- Paranoia (e.g. excessive fear for one’s own well-being)
- Delusion
- Excessive daytime sleepiness and suddenly falling asleep
- Hyperkinesia (increased movements and inability to keep still)
- Increased sexual desire (e.g. increased libido)
- Allergic reactions (e.g. rash, itching, hypersensitivity)
- Fainting
- Pathological gambling, especially when taking high doses of pramipexole
- Hypersexuality
- Compulsive shopping
- Dyspnoea (difficulties to breathe)
- Pneumonia (infection of the lungs)

**Unknown frequency**
Increased eating (binge eating, hyperphagia)

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE PRAMIPEXOLE

- Keep out of the reach and sight of children.
- Do not take pramipexole after the expiry date which is stated on the label.
- Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pramipexole tablets contain

- The active substance is pramipexole dihydrochloride monohydrate.
- The other ingredients are Mannitol, maize starch, silica colloidal anhydrous, povidone, magnesium stearate

What Pramipexole tablets look like and contents of the pack

- Pramipexole 0.18 mg tablets are white, oblong, 9 mm x 4.5 mm, uncoated tablets with score line on one side.
- Pramipexole 0.35 mg tablets are white, circular, 9.5 mm diameter, uncoated tablets with score line on one side and embossed with “PM” in the both halves in one side and the other side plain.
- Pramipexole 0.7 mg tablets are white, circular, 9.5 mm diameter, uncoated tablets with score line on one side and embossed with “PA” in the both halves in one side and the other side plain.

Pramipexole tablets are available in blister packs of 30 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Ranbaxy (UK) Limited, Building 4, Chiswick Park, 566 Chiswick High Road, London W4 5YE

Manufacturer
Ranbaxy Ireland Limited, Spafield, Cork Road, Cashel, Co-Tipperary, Ireland
Terapia S.A., 124 Fabricii Street, 400 632 Cluj Napoca, Romania
Ranbaxy Pharmacie Génériques, 11-15, quai de Dion Bouton, 92800 Puteaux, France
Basics GmbH., Hemmelrather Weg 201, D-51377 Leverkusen, Germany

This leaflet was last approved in August 2010.
Module 4
Labelling

Pramipexole 0.18mg Tablets

Each tablet contains 0.18 mg of pramipexole, as 0.25 mg pramipexole dihydrochloride monohydrate.

Oral use
Read the package leaflet before use.
Store in the original package in order to protect from light.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Marketing Authorisation Holder:
Ranbaxy UK Ltd
Building 4, Chiswick Park
566 Chiswick High Road, London W4 5YE
Marketing Authorisation Number:
PL 14894/0688

Affix pharmacy label here
Pramipexole 0.18mg, 0.35mg and 0.7mg Tablets

Each tablet contains 0.7 mg of pramipexole, as 1.0 mg pramipexole dihydrochloride monohydrate.

Oral use
Read the package leaflet before use.
Store in the original package in order to protect from light.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

Marketing Authorisation Holder:
Ranbaxy UK Ltd
Building 4, Chiswick Park
566 Chiswick High Road, London W4 5YE

Marketing Authorisation Number:
PL 14094/0670

Affix pharmacy label here

PACK CONTAINS
30 TABLETS
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, France, Germany, Italy, Romania and the UK considered that the applications for Pramipexole 0.18mg, 0.35mg and 0.7mg tablets could be approved. These products are prescription only medicines (POM) and are indicated in adults for the treatment of the signs and symptoms of idiopathic Parkinson’s disease; alone (without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or “on off” fluctuations).

The applications for Pramipexole 0.18mg, 0.35mg and 0.7mg tablets were submitted under Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products of Mirapexin 0.18mg, 0.35mg and 0.7mg tablets granted in the UK to Boehringer Ingelheim International GmbH in February 1998.

Pramipexole is a synthetic amino-benzothiazole derivative, which has been shown to act as a non-ergot dopamine agonist (DA) with high affinity and selectivity for the DA D2 receptor subfamily, and particularly the D3 receptor subtype.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of pramipexole dihydrochloride monohydrate is well-established.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP).
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Pramipexole 0.18mg, 0.35mg and 0.7mg tablets</th>
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<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Pramipexole dihydrochloride monohydrate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Dopamine agonists (N04BC05)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>0.18mg, 0.35mg and 0.7mg tablets</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<td>United Kingdom</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Pramipexole dihydrochloride monohydrate

Chemical name: (S)-2-amino-4,5,6,7-tetrahydro-N6-propyl-2,6-benzothiazolodiamine dihydrochloride monohydrate

(S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole dihydrochloride monohydrate

(6S)-N6-propyl-4,5,6,7-tetrahydro-1,3-benzthiazole-2,6-diamine dihydrochloride monohydrate.

Structural formula:

\[
\begin{array}{c}
-\text{H}_{\text{C}}-
\end{array}
\]

Molecular formula: C_{10}H_{17}N_{3}S *2HCl.H_{2}O

Appearance: White to off-white powder

Solubility: Soluble in methanol and water

Molecular weight: 302.26

Pramipexole dihydrochloride monohydrate complies with in-house specifications.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance pramipexole dihydrochloride monohydrate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Suitable Certificates of Analysis have been provided for all reference standards used. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.
Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

P. Medicinal Product
Other Ingredients
Other ingredients consist of pharmaceutical excipients mannitol E421, maize starch, Povidone – K29/32, silica colloidal anhydrous and magnesium stearate.

All excipients comply with their European Pharmacopoeia monographs

None of the excipients used contain material of human origin. The magnesium stearate contained in this product is sourced from vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development programme was to produce products that could be considered generic medicinal products of Mirapexin 0.18mg, 0.35mg and 0.7mg tablets.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative in vitro dissolution profiles and impurity profiles have been provided for the proposed and originator products.

Mirapexin 0.18mg tablets licensed in Spain was used as the reference product in the bioequivalence study. This reference product is centrally authorised.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Process validation data on pilot-scale batches of each strength have been provided and has shown satisfactory results. The applicant has committed to perform process validation on production-scale batches of each strength.

Finished Product Specification
The finished product specifications proposed for the products are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for working standards used.

Container-Closure System
The tablets are packaged in blisters composed of polyamide, aluminium and polyvinyl chloride (PVC) and come in pack sizes of 30 and 100 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with the storage instruction ‘Store in the original package in order to protect from light’.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK PIL and label mock-ups are included in modules 3 and 4 of this report.

User testing results of the PIL for these products have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

**MAA forms**
The MAA forms are pharmaceutically satisfactory.

**Expert report**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of pramipexole dihydrochloride monohydrate are well-known. As pramipexole dihydrochloride monohydrate is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA).
III.3 CLINICAL ASPECTS

Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Pharmacokinetics
To support these applications, the Marketing Authorisation Holder has submitted a single dose bioequivalence study:

A comparative, single-dose, randomised, two-period, cross-over bioequivalence study of the test product Pramipexole 0.18mg tablets versus the reference product Mirapexin 0.18mg tablets in healthy subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed at baseline and up to 48 hours post dose in each treatment period. The washout period between phases was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results from this study are presented below as log-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-4} (ng.h/mL)</th>
<th>AUC_{0-∞} (ng.h/mL)</th>
<th>C_{max} (ng/ml)</th>
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<tr>
<td>Test</td>
<td>5.122</td>
<td>5.552</td>
<td>0.400</td>
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<tr>
<td>Reference</td>
<td>4.964</td>
<td>5.341</td>
<td>0.405</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>(99.39 – 107.11)</td>
<td>(100.90 – 107.11)</td>
<td>(95.52 – 102.51)</td>
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</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-4} and C_{max} for lie within 80-125% boundaries. Thus, bioequivalence has been shown between the test and reference products in this study.

As the 0.35mg and 0.7mg strengths meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study with the 0.18mg strength can be extrapolated to the 0.35mg and 0.7mg tablet strengths.

Efficacy
No new data on the efficacy of pramipexole dihydrochloride monohydrate are submitted and none are required for these types of applications.

Safety
No new safety concerns were raised during the pharmacokinetic studies.
Post marketing experience
Pramipexole dihydrochloride monohydrate has a well-recognised efficacy and an acceptable level of safety in the indications approved for Mirapexin tablets and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

Benefit-Risk assessment
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with pramipexole dihydrochloride monohydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Conclusions
The grant of Marketing Authorisations for Pramipexole 0.18mg, 0.35mg and 0.7mg tablets is recommended from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Pramipexole 0.18mg, 0.35mg and 0.7mg tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Pramipexole 0.18mg tablets and the reference product Mirapexin 0.18mg tablets. As the 0.35mg and 0.7mg strengths of the product meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study with the 0.18mg strength can be extrapolated to the 0.35mg and 0.7mg tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the originator products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with pramipexole dihydrochloride monohydrate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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