PRODUCT INFORMATION

Pramipexole XR GP

pramipexole hydrochloride monohydrate

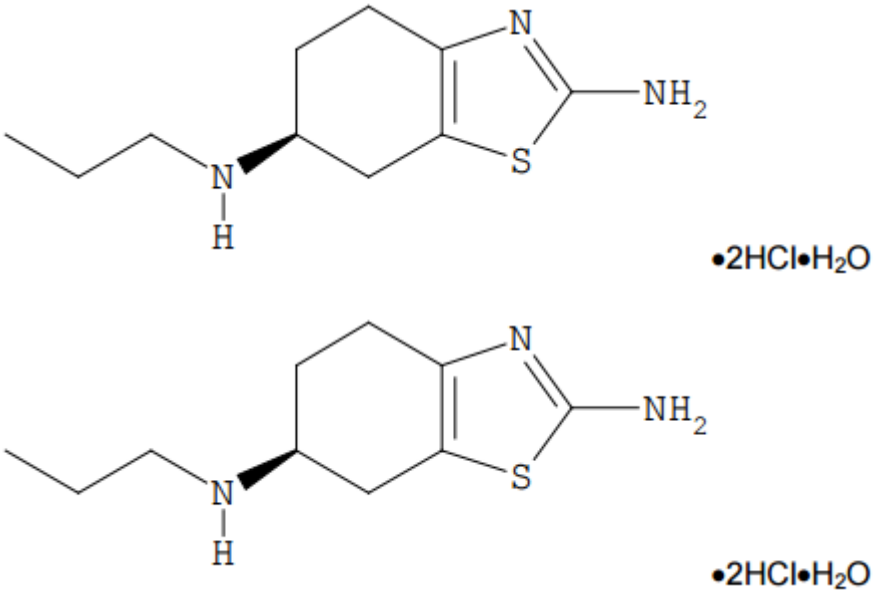
Mylan

NAME OF THE MEDICINE

Active ingredient: Pramipexole hydrochloride monohydrate.

Chemical name: (*S*)-2-amino-4,5,6,7-tetrahydro-6-propylamino- benzothiazole

Molecular formula: $C_{10}H_{17}N_3S.2HCl.H_2O$, Molecular weight: 311.33



Australian Approved

DESCRIPTION

Pramipexole hydrochloride monohydrate is a white to off-white crystalline powder, freely soluble (>20% w/v) in water.

Pramipexole hydrochloride monohydrate modified release tablets also contain the following excipients: hypromellose, calcium hydrogen phosphate anhydrous, magnesium stearate and silicon dioxide.

PHARMACOLOGY

Pharmacodynamics

Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the dopamine D_2 subfamily receptors and has a preferential affinity to D_3 receptors. It 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.

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

In a clinical trial with healthy volunteers, where pramipexole hydrochloride monohydrate modified release tablets were titrated faster than recommended (every 3 days) up to 4.5 mg per day, an increase in blood pressure and heart rate was observed. Such effects were not observed in clinical studies with Parkinson's disease (PD) patients, and are most likely due to the forced up-titration every 3 days.

Pharmacokinetics

Pramipexole displays linear pharmacokinetics over the clinical dosage range, irrespective of dosage form. Slow release of pramipexole from pramipexole hydrochloride monohydrate modified release tablets with once daily administration results in similar daily maximum and minimum pramipexole plasma concentrations (C_{max}, C_{min}) as three times daily administration of immediate-release pramipexole immediate release tablets. Peak to trough fluctuations of approximately 55% were seen with both the ER and immediate-release formulations and were highest with the fed ER formulation (mean 73%).

Absorption: Pramipexole is rapidly absorbed following oral administration. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Generally, concomitant administration with food does not affect the bioavailability of pramipexole.

Following administration of pramipexole immediate release tablets, maximum plasma concentrations (C_{max}) are reached in approximately 2 hours. Food does not affect the extent of pramipexole absorption, although the time to maximum plasma concentration (T_{max}) is delayed by about 1 hour when the drug is taken with a meal. Steady-state concentrations are achieved within 2 days of dosing.

Relative bioavailability of pramipexole hydrochloride monohydrate modified release tablets compared with immediate-release pramipexole tablets was approximately 100%. The maximum plasma concentrations occur at about 6 hours after administration of pramipexole hydrochloride monohydrate modified release once daily. In a repeat-dose study in healthy, male caucasian volunteers, pramipexole hydrochloride monohydrate modified release 4.5 mg tablets administered once daily in the fasted state was bioequivalent with regard to C_{max}, Concentration pre-dose (C_{pre}) and area under the plasma concentration-time curve (AUC) over 24 hours to immediate- release pramipexole tablets 1.5 mg administered three times daily every 8 hours. The half value duration (HVD), the time at which the concentration is above 50% of the maximum concentration, ranged between 20.8 and 22.2 hours for all dose strengths of pramipexole hydrochloride monohydrate modified release tablets.

Administration of pramipexole hydrochloride monohydrate modified release tablets with food (i.e. high-fat meal) did not affect AUC but increased C_{max} by approximately 20% and delayed T_{max} by approximately 2 hours compared with dosing under fasted conditions. The peak trough fluctuation of pramipexole hydrochloride monohydrate modified release and pramipexole immediate release tablets is comparable in the fasted state but is increased when pramipexole hydrochloride monohydrate modified release is given with food. Increase in systemic exposure of pramipexole following oral administration of 0.375 mg to 4.5 mg of pramipexole hydrochloride monohydrate modified release tablets was dose-proportional. For pramipexole hydrochloride monohydrate modified release tablets, steady state of exposure is reached within 5 days of continuous dosing.

Typical plasma concentration-time profiles after administration of modified-release pramipexole tablets once daily or immediate-release pramipexole tablets three times daily, either every 8 hours (8-8-8) or in a 6-6-12 hour posology are given in Figure 1.

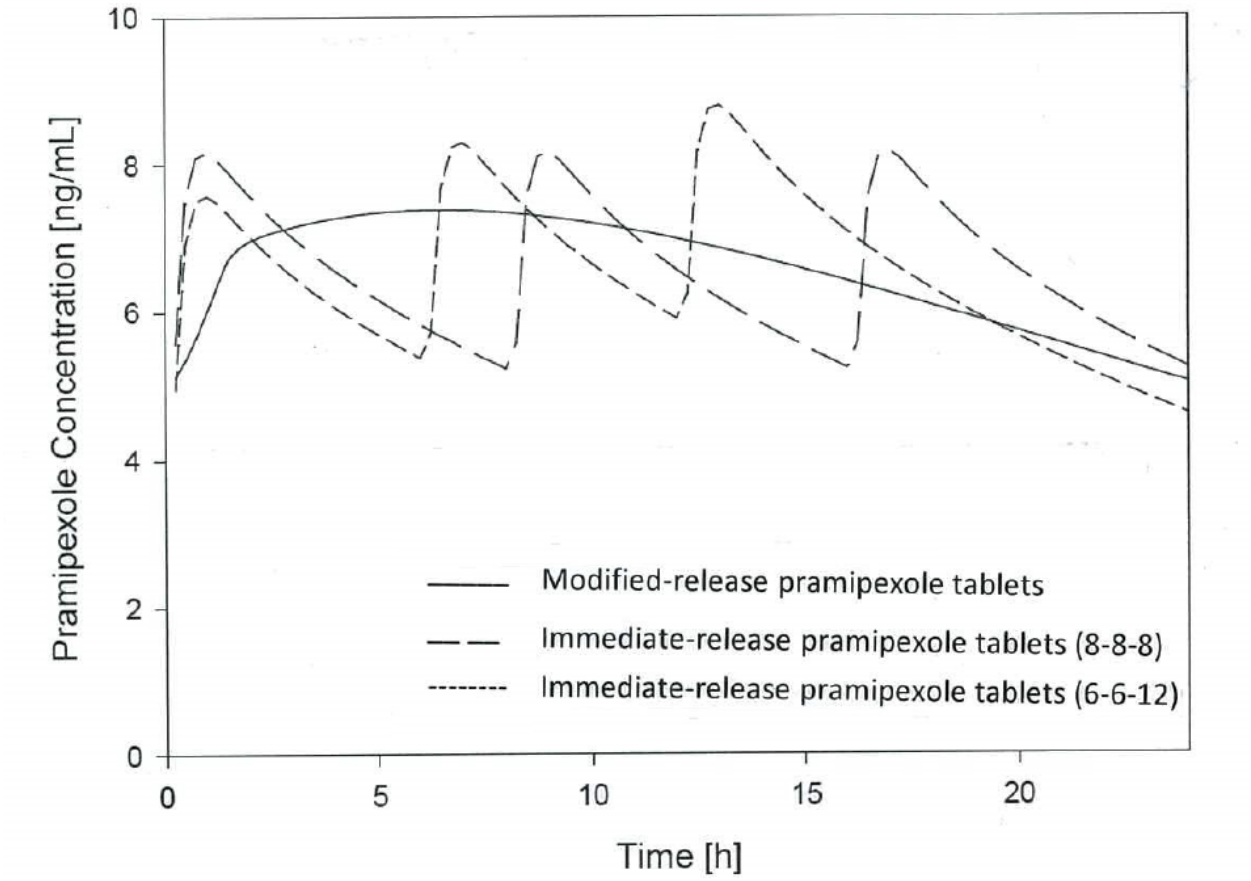


Figure 1: Plasma concentration-time profile of modified-release and immediate-release pramipexole tablets at steady state after dosing of 4.5 mg modified-release pramipexole tablets once a day (q.d.) or 1.5 mg immediate-release pramipexole tablets three times a day (t.i.d.) for typical PD patient with creatine clearance 78.5 mL/min and a body weight of 75 kg (median values)

Distribution: Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV] = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

Metabolism: Pramipexole is metabolised in humans only to a small extent. No specific active metabolite has been identified in human plasma or urine.

Elimination: Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. The renal clearance of pramipexole is approximately 400 mL/min (CV = 25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system. The terminal elimination half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers (see "*Special Populations"*).

Special Populations
Because therapy with pramipexole is initiated at a low dose and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment (see **DOSAGE AND ADMINISTRATION**).

Gender: Pramipexole clearance is about 30% lower in women than in men, but most of this difference can be accounted for by differences in body weight. There is no difference in half-life between males and females.

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

Parkinson's Disease Patients: A cross-study comparison of data suggests that the clearance of pramipexole may be reduced by about 30% in Parkinson's disease patients compared with healthy elderly volunteers. The reason for this difference appears to be reduced renal function in Parkinson's disease patients, which may be related to their poorer general health. The pharmacokinetics of pramipexole were comparable between early and advanced Parkinson's disease patients.

Restless Legs Syndrome (RLS): Pramipexole XR GP is not indicated to treat RLS and should not be used in the treatment of RLS. However, in relation to other pramipexole containing products, a cross-study comparison of data suggests that the pharmacokinetic profile of pramipexole administered once daily in patients with RLS is generally consistent with the pharmacokinetic profile of pramipexole in healthy volunteers.

Paediatric: The pharmacokinetics of pramipexole in the paediatric population have not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see **Dosage and Administration**). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis. Caution should be exercised when administering pramipexole to patients with renal disease.

CLINICAL TRIALS

Parkinson's disease
The clinical programme for pramipexole was designed to evaluate its efficacy in the treatment of both early and advanced Parkinson's disease.

In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subparts, served as the primary outcome assessment measure. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor performance (Part III), and complications of therapy (Part IV).

Part II of the UPDRS contains 13 questions related to activities of daily living, which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g. tremor, rigidity, bradykinesia, postural instability, etc.), scored for different body regions and has a maximum (worst) score of 108.

The Hoehn and Yahr scale is used to rate the severity of Parkinson's disease, and has six stages – Stage 0 (no signs of disease) to Stage V (wheelchair bound or bedridden unless aided).

Studies in patients with early Parkinson's disease:

Immediate-release Pramipexole tablets

Patients evaluated in these studies were diagnosed with idiopathic Parkinson's disease, characterised by Hoehn and Yahr Stages I to III. In two studies (protocols M/2730/0005 and M/2730/0072) the presence of 2 cardinal symptoms (resting tremor, bradykinesia, or rigidity) was required. In trials M/2730/0004 and M/2730/0072 the duration of Parkinson's disease was limited to seven years.

One study (M/2730/0001, n=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomised to pramipexole or placebo. Patients treated with pramipexole had a starting dose of 0.375 mg and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS Part II total score was 1.9 in the group receiving pramipexole and –0.4 in the placebo group, a difference that was statistically significant (p□0.0001). The mean improvement from baseline on the UPDRS Part III total score was 5.0 in the group receiving pramipexole and –0.8 in the placebo group, a difference that was also statistically significant (p□0.0001). A statistically significant difference between groups in favour of pramipexole was seen beginning at week 2 of the UPDRS Part II (maximum dose 0.75 mg/day) and at week 3 of the UPDRS Part III (maximum dose 1.5 mg/day).

The second study (M/2730/0004, n=264) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period and a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomised to one of four fixed doses of pramipexole (1.5, 3.0, 4.5 or 6.0 mg per day) or placebo. At the end of the 4-week maintenance period, the mean improvement from baseline on the UPDRS Part II total score was 1.8 in the patients treated with pramipexole, regardless of dose, and 0.3 in placebo-treated patients. The mean improvement from baseline on the UPDRS Part III total score was 4.2 in patients treated with pramipexole and 0.6 in placebo-treated patients. No dose-response relationship was demonstrated. The between-treatment differences on both Parts of the UPDRS were statistically significant in favour of pramipexole for all doses.

The third study (M/2730/0005, n=290) was a double-blind, placebo-controlled, parallel design consisting of a 7-week dose-escalation period and a 24-week maintenance period (same as M/2730/0001). Again, patients were allowed use of selegiline, anticholinergics, amantadine, or any combination of these, but not levodopa products. Patients treated with pramipexole had a starting dose of 0.375 mg/day and were titrated to a maximally-tolerated dose, but no higher than 4.5 mg/day. Pramipexole significantly ($p<0.0022$) reduced the severity of disease as measured by a decrease in the primary efficacy endpoints (change from baseline to the last visit prior to dose reduction) of both Parts II and III of the UPDRS. This significant difference ($p<0.021$ for UPDRS Parts II and III) was also seen at maintenance weeks 8, 12 and 16. Based on their steadily decreasing UPDRS total scores for Parts II and III, patients on pramipexole exhibited clinical improvement throughout treatment.

There was a further study (M/2730/0072, n=301) which was a double-blind, parallel design comparison of pramipexole and carbidopa-levodopa for initial treatment in early symptomatic Parkinson's disease. The primary objective was to compare the treatments with regard to the development of dopaminergic motor complications. Results for the first 2 years (as described in the original protocol) are available. The efficacy results showed that initial treatment with pramipexole was superior to carbidopa-levodopa, as measured by the amount of time elapsed before the first occurrence of dopaminergic complications. At the end of the maintenance interval, fewer patients treated with pramipexole (27.8%) than carbidopa-levodopa (50.7%) experienced dopaminergic motor complications (wearing off, "on" and "off" fluctuations, and dyskinesias). Similar results were obtained when the occurrence of each dopaminergic motor complication was analysed separately. The incidence of other dopaminergic complications (freezing, confusion, hallucinations and dementia) were similar in both groups, with only hallucinations occurring more frequently in the pramipexole group (9.3%) than the carbidopa-levodopa group (3.3%). At the end of the maintenance interval (23.5 months), the mean total change of the UPDRS score for the pramipexole and carbidopa-levodopa groups were –4.7 and –9.3 respectively. The results show that pramipexole is more

effective than carbidopa-levodopa in delaying the occurrence of dopaminergic motor complications. Monotherapy with pramipexole is effective in the treatment of patients with early Parkinson's disease and in the delay of motor complications. Long-term administration of pramipexole was well tolerated and the adverse event profile was consistent with that reported for other pramipexole and levodopa trials.

Modified-release Pramipexole tablets

The safety and effectiveness of pramipexole hydrochloride monohydrate modified release tablets in the treatment of early Parkinson's disease was evaluated in two randomised, double-blind, multinational clinical studies. One study conducted in early Parkinson's disease patients compared pramipexole hydrochloride monohydrate modified release tablets with placebo. A second study evaluated the efficacy of an overnight switch from immediate-release pramipexole tablets to pramipexole hydrochloride monohydrate modified release tablets.

The effectiveness of pramipexole hydrochloride monohydrate modified release tablets in 539 patients with early Parkinson's disease (Hoehn and Yahr Stages I-III) who were not on levodopa therapy was established in a randomised, double-blind, placebo-controlled, 3-parallel group clinical study. Patients were treated with pramipexole hydrochloride monohydrate modified release tablets, immediate-release pramipexole tablets, or placebo; those treated with pramipexole hydrochloride monohydrate modified release tablets or immediate-release pramipexole tablets had a starting dose of 0.375 mg/day followed by a flexible up-titration, based on efficacy and tolerability, up to 4.5 mg/day. Levodopa was permitted during the study as rescue medication. The primary efficacy objective was to test for superiority of pramipexole hydrochloride monohydrate modified release tablets versus placebo following 18 weeks of treatment on the mean change from baseline in the UPDRS Parts II+III score (primary endpoint). The secondary efficacy objective was to test for noninferiority of pramipexole hydrochloride monohydrate modified release tablets versus immediate-release pramipexole tablets following 33 weeks of treatment on the mean change from baseline in the UPDRS Parts II+III score.

At 18 weeks of treatment, the mean improvement from baseline UPDRS Parts II+III score was –8.1 points in patients receiving pramipexole hydrochloride monohydrate modified release tablets (n=102) and –5.1 points in patients receiving placebo (n=50), a difference that was statistically significant ($p<0.03$). Levadopa was allowed as a rescue medication. Seven patients treated with placebo (14%) and 3 patients treated with pramipexole hydrochloride monohydrate modified release tablets (3%) received levodopa rescue medication. For patients receiving immediate-release pramipexole tablets (n=101), the mean improvement from baseline was –8.4 points.

At 33 weeks, pramipexole hydrochloride monohydrate modified release tablets were non-inferior to pramipexole immediate-release tablets, with a mean improvement from baseline UPDRS Parts II+III score of -8.6 points in patients receiving pramipexole hydrochloride monohydrate modified release tablets (n=213) and -8.8 points in patients receiving immediate-release pramipexole tablets (n=207). A greater proportion of patients given pramipexole hydrochloride monohydrate modified release than pramipexole immediate-release tablets received rescue levodopa (7.0% for pramipexole hydrochloride monohydrate modified release vs. 4.3% for pramipexole immediate-release tablets). In patients receiving placebo (n=103), the mean improvement from baseline UPDRS Parts II+III score was -3.8 points, and twenty-two patients treated with placebo (21.4%) received levodopa rescue medication. At 18 and 33 weeks, the mean dose of pramipexole hydrochloride monohydrate modified release tablets as well as of immediate-release pramipexole tablets was approximately 3 mg/day.

No differences in effectiveness based on age or gender were detected. Patients receiving monoamine oxidase B inhibitors (MAOB-I), anticholinergics, or amantadine had responses similar to patients not receiving these drugs.

A randomised, double-blind, parallel group trial was conducted in 156 patients with early Parkinson's disease (Hoehn and Yahr Stages I-III) to assess overnight switching of immediate-release pramipexole tablets to pramipexole hydrochloride monohydrate modified release tablets; stable doses of concomitant levodopa, MAOB-I, anticholinergics, or amantadine, individually or in combination, were allowed. Patients in this study had a mean disease duration of approximately 3.5 years. Patients at stable doses of immediate-release pramipexole tablets were randomised to receive the same

daily dose of blinded pramipexole hydrochloride monohydrate modified release tablets (n=104) or blinded immediate-release pramipexole tablets (n=52). Following 4 weeks of treatment, the study medication could be adjusted depending on efficacy and tolerability. The primary efficacy endpoint was the proportion of patients successfully switched to pramipexole hydrochloride monohydrate modified release tablets following 9 weeks of treatment; a patient was successfully switched if there was no worsening of the UPDRS Parts II+III score (by more than 15% from baseline), and the patient had no drug-related adverse events leading to discontinuation.

Efficacy was maintained in 87 of 103 patients switched to pramipexole hydrochloride monohydrate modified release tablets. Of these 87 patients, 82.8% (n=72) did not change the dose for the duration of the study, 13.8% increased and 3.4% decreased their dose. In half of the 16 patients who did not meet the criterion for maintained efficacy on the UPDRS Part II+III score, the change from baseline was considered not clinically relevant. One patient switched to pramipexole hydrochloride monohydrate modified release tablets experienced a drug–related adverse event leading to withdrawal. This study, as designed, cannot adequately assess non-inferiority of efficacy of immediate-release pramipexole tablets and pramipexole hydrochloride monohydrate modified release tablets.

Studies in patients with advanced Parkinson's disease:

Immediate-release Pramipexole tablets

Patients in these studies were in an advanced stage of disease (Hoehn and Yahr Stages II to IV) during "on" periods.

Patients in the first study (M/2730/0010, n=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods. The study was a double-blind, placebo- controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with pramipexole had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day in three divided doses. At selected times during the 6-month maintenance period, patients were asked to record the amount of "off", "on" or "on with dyskinesia" time per day for several sequential days. At the end of the 6-month maintenance period, the mean improvement from baseline on the UPDRS Part II total score was 2.7 in the group treated with pramipexole and 0.5 in the placebo group, a difference that was statistically significant (p□0.01). The mean improvement from baseline on the UPDRS Part III total score was 5.6 in the group treated with pramipexole and 2.8 in the placebo group, a difference that was statistically significant (p□0.01). A statistically significant difference between groups in favour of pramipexole was seen at week 3 of the UPDRS Part II (maximum dose 0.75 mg/day) and at week 2 of the UPDRS Part III (maximum dose 1.5 mg/day). Dose reduction of levodopa was allowed during this study if dyskinesia (or hallucinations) developed; levodopa dosage reduction occurred in 76% of patients treated with pramipexole versus 54% of placebo patients. On average, the levodopa dose was reduced by 27%. The mean number of "off" hours per day during baseline was 6 hours for both treatment groups. Throughout the trial, patients treated with pramipexole had a mean of 4 "off" hours per day, while placebo-treated patients continued to experience 6 "off" hours per day.

The second study (M/2730/0036, n=247) was a double-blind, placebo-controlled, parallel trial consisting of a 12-week titration, 6-month maintenance and 1-week dose reduction period. Pramipexole and bromocriptine were used as adjunctive treatment to levodopa. Patients with disturbances continuing individually optimised levodopa therapy were included. Primary endpoints were the UPDRS Parts II and III. At the end of the maintenance period, the median changes from baseline on the UPDRS Part II for pramipexole and placebo were –2.5 and –0.5, respectively (p=0.0002). In the UPDRS Part III, the changes for pramipexole and placebo were –6.0 and –2.0, respectively (p=0.0006). Pramipexole was superior to placebo for UPDRS Parts II and III from 4 and 6 weeks on, respectively. Superiority of pramipexole over placebo was also shown for UPDRS Part II during "on" periods. In the pramipexole group average percentage of "off" time decreased by 15.4% and in the placebo group by 2.3%. A reduction of 15% is approximately equal to a reduction of 2.5 hours per day, an important clinical improvement. Both pramipexole and bromocriptine were superior to placebo with respect to the primary endpoints (UPDRS Parts II and III). For percentage of "off" time and global assessment of efficacy pramipexole treatment tended to be superior to bromocriptine

treatment.

Modified-release Pramipexole tablets

The effectiveness of pramipexole hydrochloride monohydrate modified release tablets in advanced Parkinson's disease patients (Hoehn & Yahr Stages II-IV at "on" time) who were on concomitant levodopa therapy (at an optimised dose) and who had motor fluctuations (at least 2 cumulative hours of "off" time per day) was established in a randomised, double-blind, placebo-controlled, 3-parallel group clinical study. Patients were treated with pramipexole hydrochloride monohydrate modified release tablets, immediate-release pramipexole tablets, or placebo; those treated with pramipexole hydrochloride monohydrate modified release tablets or immediate-release pramipexole tablets had a starting dose of 0.375 mg/day followed by a flexible up-titration over 7 weeks, based on efficacy and tolerability, up to 4.5 mg/day, followed by a 26 week maintenance period. Levodopa dosage reduction was permitted only in the case of dopaminergic adverse events. The primary efficacy endpoint was the adjusted mean change from baseline in the UPDRS Parts II+III score for pramipexole hydrochloride monohydrate modified release tablets versus placebo following 18 weeks of treatment.

At 18 weeks of treatment, the adjusted mean improvement from baseline UPDRS Parts II+III score was -11.0 points in patients receiving pramipexole hydrochloride monohydrate modified release tablets (n=161) and -6.1 points in patients receiving placebo (n=174), (p=0.0001). The difference between pramipexole hydrochloride monohydrate modified release tablets and placebo was statistically significant by week 2. For patients receiving immediate-release pramipexole tablets (n=172), the adjusted mean improvement from baseline was –12.8 points (p<0.0001). The trial was not powered to test for non-inferiority between pramipexole hydrochloride monohydrate modified release tablets and immediate release pramipexole tablets. However, there was no clinically relevant difference between pramipexole hydrochloride monohydrate modified release and immediate release pramipexole groups in the mean change from baseline for week 18 in the UPDRAII+III score. At week 18, the adjusted mean improvement from baseline in "off" time was -2.1 hours for pramipexole hydrochloride monohydrate modified release and -1.4 hours for placebo (p=0.0199).

At 33-weeks the adjusted mean improvement from baseline UPDRS Parts II+III score was -11.1 points in patients receiving pramipexole hydrochloride monohydrate modified release tablets (n=117) and -6.8 points in patients receiving placebo (n=136) (p=0.0135). At week 33, the mean improvement from baseline in "off time" was -1.8 hours for pramipexole hydrochloride monohydrate modified release and -1.4 hours for placebo, which was not statistically significant.

At both 18 and 33 weeks the mean daily dose of pramipexole hydrochloride monohydrate modified release was 2.7 mg/day and the mean daily dose of immediate release pramipexole was 2.8 mg/day. At week 18, 4 patients (3%) in the placebo group, 14 patients (11%) in the pramipexole hydrochloride monohydrate modified release group, and 12 patients (8%) in the pramipexole immediate-release group had decreased their levodopa daily dose compared to baseline due to dopaminergic adverse events. The mean change from baseline to week 18 in L-dopa dose was -2.6mg/day in the pramipexole hydrochloride monohydrate modified release group compared to +9.4 mg/day in the immediate release pramipexole group.

No clinically relevant difference in effectiveness was observed in the sub-group analyses based on gender, age, race (White vs. Asian), or concomitant use of antiparkinsonian treatment (MAOB-I, amantadine or anticholinergics).

INDICATIONS

Modified-release pramipexole tablets are indicated for:

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

CONTRAINDICATIONS

Hypersensitivity to pramipexole or any excipients of the product.

PRECAUTIONS

Somnolence and Sudden Onset of Sleep

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 such as excessive drowsiness, has been reported. Some of these events have been reported as late as one year after the initiation of treatment. Before initiating treatment with pramipexole, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with pramipexole, such as concomitant sedation medications, the presence of sleep disorders and concomitant medications that increase pramipexole plasma levels (e.g. cimetidine). Patients must be informed of the potential sedating effects associated with pramipexole, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor operate other complex machinery until they have gained sufficient experience with pramipexole to gauge whether or not it affects their mental and/or motor performance adversely. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of these events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their physician. Furthermore, a reduction of dosage or termination of therapy may be considered. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living. Patients must also be advised to exercise caution when taking other sedating medication or alcohol in combination with pramipexole because of possible additive somnolent effects.

Renal impairment

When prescribing pramipexole in a patient with renal impairment a reduced dose is suggested (refer to **DOSAGE AND ADMINISTRATION**).

Hallucinations and confusion

Hallucinations and confusion are known side effects of treatment with dopamine agonists and levodopa in Parkinson's disease patients. Hallucinations were more frequent when pramipexole was given in combination with levodopa in Parkinson's disease patients with advanced disease than monotherapy in patients with early disease. Patients should be informed that hallucinations (mostly visual) can occur and may adversely affect their ability to drive.

Dyskinesias

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

Co-existing psychotic disorders

Patients with psychotic disorders should only be treated with a dopamine agonist if the potential benefits outweigh the risks.

Postural hypotension

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

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

Retinal changes

Animal Studies - Long term treatment of albino rats with pramipexole resulted in retinal degeneration, characterised by loss of photoreceptor cells. In short term studies, this was also produced in albino rats by continuous exposure to light, and was potentiated by pramipexole. Similar changes were not induced by higher intensity continuous light exposure in pigmented rats, with or without pramipexole treatment. Pramipexole has been shown to inhibit the naturally-occurring photoreceptor cell disk-shedding process in albino rats.

Human Studies - The long term ophthalmic safety of pramipexole in patients with Parkinson's disease was assessed in an open label cross-sectional, assessor blinded, matched pair design study. The average treatment duration was approximately four years and exceeded 2.5 years in all patients. This study showed that there was no evidence that prolonged treatment with pramipexole induced more signs of retinal degeneration in patients with Parkinson's disease than other dopamine agonists.

Fibro-osseous proliferative lesions in mice

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for two years with pramipexole at doses 0.5 times the highest clinical dose (based on body surface area) and above. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The potential significance in humans is not known.

Rhabdomyolysis

A single case of rhabdomyolysis occurred in a patient with advanced Parkinson's disease treated with pramipexole. The patient was hospitalised with an elevated CPK. The symptoms resolved with discontinuation of the medication.

Events reported with dopaminergic therapy

Although the events enumerated below have not been reported in association with the use of pramipexole in the development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

In patients with Parkinson's disease there are uncertain results regarding a potential increased risk of developing melanoma.

Patients and their doctors should be aware of this potential additional risk for developing melanoma, and monitor their skin accordingly.

Withdrawal-emergent hyperpyrexia and confusion

Although not reported with pramipexole in the development program, a symptom complex resembling the neuroleptic malignant syndrome (characterised by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious aetiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-parkinsonian therapy.

Fibrotic complications

Although not reported with pramipexole in the development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, non-ergot derived dopamine agonists (such as pramipexole) can cause them is unknown.

Compulsive Behaviour

Compulsive behaviour such as gambling, hypersexuality, shopping, eating, medication use and punding (repetitive purposeless activity) has been reported in patients taking dopamine agonists for the treatment of Parkinson's disease, especially at high doses. Prescribers, patients and caregivers should be alert to the possibility of such behaviour, which may have serious financial and social consequences.

Dose reduction/ tapered discontinuation should be considered.

Augmentation in Patients with Restless Legs Syndrome (RLS)

Pramipexole XR GP is not indicated to treat RLS and should not be used in the treatment of RLS. However, in relation to other pramipexole containing products, reports in the literature indicate administration of dopaminergic medications to patients with RLS can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Kaplan-Meier analysis of time to augmentation showed no statistically significant difference between pramipexole (N=152) and placebo groups (N=149). The frequency and severity of augmentation after longer-term use of pramipexole and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.

Treatment discontinuation

Pramipexole XR GP is not indicated to treat RLS and should not be used in the treatment of RLS. However, in relation to other pramipexole containing products, in RLS clinical trials, some patients have reported worsening of the RLS symptoms following abrupt discontinuation of pramipexole treatment. The worsening of symptoms was independent of pramipexole dosage and generally resolved within one week.

Effects on fertility

In rat fertility studies, doses of 2.5 mg/kg/day (approximately five times human exposure at the maximum recommended clinical dose of 4.5 mg/day, based on AUC) pramipexole prolonged oestrus cycles and inhibited nidation. These effects were associated with reductions of serum prolactin, a hormone necessary for implantation and maintenance of pregnancy in rats. Treatment of male rats with pramipexole had no effect on fertility. The effects of pramipexole on the fertility of a species in which implantation and maintenance of early pregnancy is not dependent on prolactin have not been investigated. No studies on the effect on human fertility have been conducted.

Use in pregnancy

Pregnancy Category B3.

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 maternotoxic doses.

Administration of 0.1, 0.5 or 1.5 mg/kg of pramipexole (approximately 0.3, 1.7 and 5 times human exposure at the maximum recommended human dose of 1.5 mg tid and based on AUC) to pregnant rats during the period of organogenesis resulted in a high incidence of total resorption of embryos at 1.5 mg/kg. No teratogenic effects were observed, however, because of the pregnancy impairment and embryolethality, limited teratogenicity data from the highest test dose were obtained. These finding are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not in rabbits or humans). Administration of oral doses of up to 10 mg/kg/day to rabbits during organogenesis (approximately 80 times human exposure at the maximum recommended human dose, 1.5 mg tid and based on AUC) did not result in any embryotoxic, fetotoxic or teratogenic effects.

Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day or greater during the latter part of pregnancy and throughout lactation (the plasma AUC was 1.7 times the AUC in

humans dosed at 1.5 mg tid).

There are no adequate and well-controlled studies in pregnant women. Pramipexole should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

The effect on lactation has not been investigated in humans. 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 drug-related material was higher in breast milk than in plasma. In the absence of human data, pramipexole should not be used during breast-feeding, if possible. However, if its use is unavoidable, breast-feeding should be discontinued.

Paediatric Use

The safety and efficacy of pramipexole in children has not been established.

Use in Elderly: When prescribing pramipexole, age-related reduction in renal function, which can result in a decline in renal clearance, should be considered, as this may cause an increase in the elimination half-life of pramipexole.

There are no apparent differences in the efficacy or safety between older and younger patients, except the relative risk of hallucination associated with the use of pramipexole was increased in the elderly.

Carcinogenicity

Two year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to mice at doses of 0.3, 2 and 10 mg/kg/day (the plasma levels were at least 0.2, 1.2, and 5.7 times the observed C_{max} in humans dosed 1.5 mg tid). Pramipexole was administered in the diet to rats at 0.3, 2 and 8 mg/kg/day (0.8, 5 and 20 times the highest clinical dose on a mg/m^2 basis).

Increased incidences of testicular Leydig cell adenomas were found in all groups of treated male rats. In contrast to the findings in rats, examination of the testes from mice after 2 years of treatment did not exhibit evidence of a drug-related increase in Leydig cell adenomas. These findings are of questionable significance in humans because of their high background incidence in rats, the absence of similar changes in mice treated with pramipexole for 2 years, and the probable involvement of endocrine mechanisms that are not relevant to humans.

Genotoxicity

Pramipexole was not mutagenic in *in vitro* assays for gene mutation, or cause chromosomal damage in *in vitro* and *in vivo* tests for clastogenic activity. Pramipexole was negative in an *in vitro* test for cell transformation.

Effects on ability to drive and use machines

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

INTERACTIONS WITH OTHER MEDICINES

Pramipexole is bound to plasma proteins to a very low extent (about 15%), and little biotransformation is seen in man. Therefore, metabolic interactions with other medications affecting plasma protein binding or elimination by biotransformation are unlikely.

The toxicological consequences (long-term, reproduction, carcinogenicity/ genotoxicity) of using pramipexole in combination with other Parkinson's disease medications have not been evaluated in animals.

CYP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolised by these enzymes *in vivo* or *in vitro*. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid). *Anticholinergics:* As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated.

Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa C_{max} by about 40% and a decrease in T_{max} from 2.5 to 0.5 hours. 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 medication is kept constant while increasing the dose of pramipexole.

Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole.

Drugs eliminated via renal secretion and renal tubular secretion inhibitors: Drugs that inhibit the active renal tubular secretion of basic (cationic) drugs or are eliminated by this pathway may interact with pramipexole, resulting in reduced clearance of either or both drugs. Drugs included in this category are cimetidine, diltiazem, quinidine, quinine, ranitidine, triamterene, verapamil, digoxin, procainamide and trimethoprim. Amantadine is also eliminated by this renal pathway. In case of concomitant treatment with this type of drug, attention should be paid to signs of dopamine overstimulation, such as dyskinesias, agitation or hallucinations. Reduction of the pramipexole dose should be considered when these drugs are administered concomitantly with pramipexole.

Drugs secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the clearance of pramipexole. Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12).

Alcohol and other sedating medications: Because of possible additive effects, caution should be advised when patients are taking alcohol or other sedating medications in combination with pramipexole and when taking concomitant medicines that increase plasma levels of pramipexole.

Dopamine antagonists: Since pramipexole is a dopamine agonist, dopamine antagonists such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide may diminish the effectiveness of pramipexole and should not be administered concurrently.

ADVERSE EFFECTS

Parkinson's Disease Clinical Trials

The following adverse events have been reported more frequently during the use of pramipexole than under placebo: nausea, constipation, somnolence, hallucinations, confusion, dizziness and peripheral oedema. More frequent adverse reactions in early disease were somnolence and constipation

and in advanced disease, and in combination with levodopa treatment, dyskinesia and hallucinations. These adverse events decreased with continued therapy; constipation, nausea and dyskinesia tended to even disappear.

Falling asleep while engaged in activities of daily living has been reported in patients with or without the perception of prior warning signs, such as excessive drowsiness.

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

A summary of adverse events reported in 1% or more of Parkinson's disease patients in controlled clinical studies is presented in Table 2.

Table 2: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Studies in Early (3 studies) and Advanced (4 studies) Disease (Events ≥ 1% of Patients Treated With Immediate-Release Pramipexole Tablets and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	Early Therapy		Advanced Therapy	
	Immediate release Pramipexole tablets N = 388 % occurrence	Placebo N = 235 % occurrence	Immediate release Pramipexole tablets † N = 260 % occurrence	Placebo† N = 264 % occurrence
Body as a whole				
Asthenia	14	12	10	8
General oedema	5	3	4	3
Malaise	2	1	3	2
Reaction unevaluable	2	1	-	-
Fever	1	0	-	-
Chest pain	-	-	3	2
Accidental injury	-	-	17	15
Digestive System				
Nausea	28	18	-	-
Constipation	14	6	10	9
Anorexia	4	2	-	-
Dysphagia	2	0	-	-
Dry mouth	-	-	7	3
Metabolic & Nutritional System				
Peripheral oedema	5	4	2	1
Decreased weight	2	0	-	-
Increased creatine PK	-	-	-	0
Cardiovascular System				
Postural hypotension	-	-	53	48

Nervous System				
Dizziness	25	24	26	25
Somnolence	22	9	9	6
Insomnia	17	12	27	22
Hallucinations	9	3	17	4
Confusion	4	1	10	7
Amnesia	4	2	6	4
Hyperesthesia	3	1	-	-
Dystonia	2	1	8	7
Thinking abnormalities	2	0	3	2
Decreased libido	1	0	-	-
Myoclonus	1	0	-	-
Hypertonia	-	-	7	6
Paranoid reaction	-	-	2	0
Delusions	-	-	1	0
Sleep disorders	-	-	1	0
Dyskinesia	-	-	47	31
Gait abnormalities	-	-	7	5
Dream abnormalities	-	-	11	10
Special Senses				
Vision abnormalities	3	0	3	1
Accommodation abnormaltieis	-	-	4	2
Diplopia	-	-	1	0
Urogenital System				
Impotence	2	1	-	-
Urinary frequency	-	-	6	3
Urinary tract infection	-	-	4	3
Urinary incontinence	-	-	2	1
Musculoskeletal System				
Arthritis	-	-	3	1
Twitching	-	-	2	0
Bursitis	-	-	2	0
Myasthenia	-	-	1	0
Respiratory System				
Dyspnoea	-	-	4	3
Rhinitis	-	-	3	1
Penumonia	-	-	2	0
Skin & Appendages				
Skin disorders	-	-	2	1

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus,

patients may be included in more than one category.
† Patients received concomitant levodopa.

Other events reported by 1% or more of patients treated with pramipexole but reported equally or more frequently in the placebo group were as follows:

Early Parkinson's disease - infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, diarrhoea, rash, ataxia, dry mouth, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnoea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

Advanced Parkinson's disease - nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhoea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hyperesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

The events listed below occurred in less than 1% of patients exposed to immediate-release pramipexole tablets during premarketing development. All reported events, except those already listed above, are included without regard to determination of a causal relationship to pramipexole.
Events are listed within the body-system categories in order of decreasing frequency.

Body as a whole: fever, enlarged abdomen, rigid neck, no drug effect.

Cardiovascular system: palpitations, angina pectoris, atrial arrhythmia, peripheral vascular disease.

Digestive system: tongue discolouration, GI haemorrhage, faecal incontinence.

Endocrine system: diabetes mellitus.

Haemic & lymphatic system: ecchymosis.

Metabolic & nutritional system: gout.

Musculoskeletal system: bursitis, myasthenia.

Nervous system: apathy, libido decrease, paranoid reaction, akinesia, coordination abnormalities, speech disorder, hyperkinesia, neuralgia.

Respiratory system: voice alteration, asthma, haemoptysis.

Skin & appendages: skin disorder, herpes simplex.

Special senses: tinnitus, taste perversion, otitis media, dry eye, ear disorder, hemianopia.

Urogenital system: urinary incontinence, dysuria, prostate disorder, kidney calculus.

The safety profile of the immediate-release pramipexole tablets and modified-release pramipexole tablets was comparable, in both the early and advanced Parkinson's disease clinical studies, at comparable daily doses and duration of treatment. The use of modified-release pramipexole tablets in Parkinson's disease patients is generally well tolerated. No new or unexpected safety or tolerability risks were identified during the clinical development program of modified-release pramipexole tablets.

Adverse Effects Reported with Pramipexole-containing Products in Other Patient Groups

Immediate-release pramipexole tablets has been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year. The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients were treated with pramipexole for up to 12 weeks. The most commonly observed adverse events with pramipexole (observed in > 5% of pramipexole treated patients and at a rate at least twice that observed in placebo-treated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and transient.

Approximately 7% of 575 patients treated with pramipexole immediate release tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

A summary of adverse events reported in 1% or more patients in controlled clinical studies is presented in Table 3.

Table 3: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo- Controlled Trials in other Patient Groups (Events ≥ 1% of patients treated with Immediate-release Pramipexole tablets and numerically more frequent than in the placebo group):

Body System/Adverse Event	Immediate-release Pramipexole 0.125 - 0.75 mg /day (N=575) %	Placebo (N=223) %
Ear and labryrinth disorders		
Vertigo	1.2	0.4
Gastrointestinal disorders		
Nausea	15.7	5.4
Constipation	3.5	0.9
Diarrhoea	3.3	1.3
Dry mouth	3	1.3
Vomiting	2.4	1.8
Gastro-oesophageal reflux disease	1.7	0.9
Flatulence	1	0
General disorders and administration site conditions		
Fatigue	8.7	7.2
Peripheral oedema	1.6	1.3
Pain	1.4	0
Asthenia	1.2	0
Infections and infestations		
Influenza	3.3	1.3
Upper respiratory tract infection	1.9	0.9
Sinusitis	1.2	0.9
Urinary tract infection	1.2	0.4
Gastroenteritis	1	0.9

Investigations		
Weight increased	1	0.4
Musculoskeletal and connective tissue disorders		
Back pain	2.3	2.2
Pain in extremity	2.1	1.8
Arthralgia	1.9	1.3
Muscle cramp	1.7	0.9
Myalgia	1.6	0.9
Nervous system disorders		
Headache	16.2	14.8
Somnolence	6.1	3.1
Dizziness	5.9	5.8
Paraesthesia	1.4	0.9
Sinus headache	1	0.4
Psychiatric disorders		
Abnormal dreams	1.9	0.9
Respiratory, thoracic and mediastinal disorders		
Cough	1.6	1.3
Dyspnoea	1.2	0
Nasal congestion	1.2	0.4
Skin and subcutaneous tissue disorders		
hyperhidrosis	1.6	0.4
Pruritus	1.4	0.4
Vascular disorders		
Flushing	1	0.4

*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

In general, the prevalence of nausea and fatigue was reduced with continued pramipexole therapy. Adverse reactions reported in less than 1% of 575 patients treated with pramipexole (and numerically more frequent than in the placebo group) in the controlled studies are listed by system organ class below:

Blood and lymphatic system disorders: leukopenia

Cardiac disorders: palpitations

Ear and labyrinth disorders: deafness, tinnitus

Eye disorders: abnormal sensation in eye, diplopia, eye oedema, vision blurred, visual impairment

Gastrointestinal disorders: abdominal distension, abdominal pain, gastritis, gastrointestinal pain, intestinal spasm, salivary hypersecretion, stomach discomfort

General disorders and administration site conditions: chest pain, feeling abnormal, feeling drunk, irritability, pitting oedema

Investigations: blood triglycerides increased, body temperature increased, heart rate increased, lipase increased, weight increased

Metabolism and nutrition disorders: increased appetite

Musculoskeletal and connective tissue disorders: joint stiffness, muscle tightness
Nervous system disorders: dizziness postural, dysgeusia, lethargy, loss of consciousness, sedation, syncope, tremor

Psychiatric disorders: agitation, cognitive deterioration, confusional state, disorientation, dysphoria, excitability, flight of ideas, initial insomnia, libido decreased, middle insomnia, restlessness, sleep disorder

Renal and urinary disorders: nocturia, pollakiuria

Reproductive system and breast disorders: breast discomfort

Respiratory, thoracic and mediastinal disorders: hiccups, nasal disorder, pharyngeal oedema, yawning

Skin and subcutaneous system disorders: night sweats, purpura, rash, skin hyperpigmentation

Vascular disorders: hot flush, hypertension

Post-Marketing experience

In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified (essentially in Parkinson's disease patients) during post-approval use of immediate-release pramipexole tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: abnormal dreams, amnesia, cardiac failure, accidents (including fall), blackouts, fatigue, hallucinations, headache, hiccups, hypotension (including postural hypotension), inappropriate antidiuretic hormone secretion, increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders, hypersexuality, compulsive shopping and other abnormal behaviour (reflecting symptoms of impulse control disorders and compulsions); restlessness, paranoia, syncope, visual disturbance including blurred vision and reduced visual acuity, vomiting, weight decrease including decreased appetite, weight increase, pneumonia, dyspnoea and hypersensitivity.

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

Patients treated with immediate-release pramipexole tablets have rarely reported suddenly falling asleep (or sudden onset of sleep) while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see **PRECAUTIONS**). Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving immediate-release pramipexole tablets at doses above 1.5 mg/day, and which, according to the current knowledge of sleep physiology, always proceeds falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy.

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

In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole.

DOSAGE AND ADMINISTRATION

Modified-release pramipexole tablets should be taken once daily at about the same time each day. Modified-release pramipexole tablets should be swallowed whole with water and must not be chewed, divided or crushed. Modified-release pramipexole tablets may be taken with or without food.

Parkinson's disease

Initial treatment: Dosages should be increased gradually from a starting dose of 0.375 mg pramipexole hydrochloride monohydrate immediate release tablets* per day and then increased every 5 to 7 days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

*: Note that immediate-release pramipexole tablets can be available from other product/s.

Ascending Dosage Schedule of pramipexole hydrochloride for Parkinson's disease			
Week	Total Daily Dose of (pramipexole hydrochloride)	Immediate-release pramipexole tablets	Modified-release pramipexole tablets
1	0.375 mg	0.125 mg three times a day	0.375 mg once daily
2	0.75 mg	0.25 mg three times a day	0.75 mg once daily
3	1.5 mg	0.5 mg three times a day	1.5 mg once daily

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

Patients already taking immediate-release pramipexole tablets (with or without concomitant levodopa) may be switched to modified-release pramipexole tablets overnight, at the same daily dose without dose adjustment.

Maintenance treatment: The individual dose should be in the range of 0.375mg to a maximum of 4.5 mg of pramipexole immediate release tablets per day. During dose escalation in pivotal studies, both in early and advanced disease, efficacy was observed starting at a daily dose of 1.5 mg of pramipexole immediate release tablets. Further dose adjustments should be done based on the clinical response and tolerability. In clinical trials approximately 5% of patients were treated at doses below 1.5 mg. In advanced Parkinson's disease, pramipexole doses higher than 1.5 mg per day can be useful in patients where a reduction of the levodopa therapy is intended.

In case a dose is missed, modified-release pramipexole tablets should be taken up to 12 hours after the regular time. After 12 hours, the missed dose should be omitted and the next dose should be taken the following day at the regular time.

Treatment discontinuation: immediate-release and modified-release pramipexole tablets should be tapered off at a rate of 0.75 mg per day until the daily dose has been reduced to 0.75 mg. Thereafter the dose should be reduced by 0.375 mg per day.

Dosing in patients with concomitant levodopa therapy: It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with pramipexole immediate release tablets. Based on clinical trials in advanced patients a reduction of the levodopa dose by 25% or more can be justified. This should be considered also in order to avoid excessive dopaminergic stimulation resulting in dyskinesias, sleep disturbances or hallucinations.

Dosing in patients with renal impairment: The elimination of pramipexole is dependent on renal function. The following dosage schedule is suggested for initiation of therapy:

Patients with a creatinine clearance above 50 mL/min require no reduction in daily dose or dosing frequency.

For immediate-release pramipexole tablets, in patients with a creatinine clearance between 20 and 50 mL/min, the initial daily dose of pramipexole immediate release tablets should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg pramipexole should not be exceeded. In patients with a creatinine clearance less than 20 mL/min, the daily dose of pramipexole immediate release tablets should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg pramipexole should not be exceeded.
If renal function declines during maintenance therapy, reduce immediate-release pramipexole tablets daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the immediate-release pramipexole tablets 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.

For modified-release pramipexole tablets, the use of modified-release pramipexole in patients with a creatinine clearance < 50 mL/min (moderate and severe renal impairment) has not been fully assessed.
If renal function declines during maintenance therapy the recommendations given above should be followed.

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

OVERDOSAGE

In case of poisoning or overdose, advice should be obtained from the Poisons Information Centre (telephone 13 11 26).

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

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

PRESENTATION AND STORAGE CONDITIONS

Pramipexole hydrochloride monohydrate modified release tablets
Pramipexole hydrochloride monohydrate 0.375 mg modified release tablets are white or nearly white, cylindrical, plans and bevel tablets marked with 026 on one side. Each modified release tablet contains 0.375 mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate 0.75 mg modified release tablets are white or nearly white, cylindrical and biconvex tablets marked with 052 on one side. Each modified release tablet contains 0.75 mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate 1.5 mg modified release tablets are white or nearly white, cylindrical and biconvex tablets marked with 105 on one side. Each modified release tablet contains 1.5 mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate 2.25mg modified release tablets are white or nearly white, cylindrical and biconvex tablets marked with 157 on one side. Each modified release tablet contains

2.25mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate 3 mg modified release tablets are white or nearly white, cylindrical and biconvex tablets marked with 210 on one side. Each modified release tablet contains 3 mg pramipexole hydrochloride monohydrate.
Pramipexole hydrochloride monohydrate 3.75mg modified release tablets are white or nearly white, cylindrical and biconvex tablets marked with 262 on one side. Each modified release tablet contains 3.75mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate 4.5 mg modified release tablets are white or nearly white, cylindrical, plans and bevel tablets marked with 315 on one side. Each modified release tablet contains 4.5 mg pramipexole hydrochloride monohydrate.

Pramipexole hydrochloride monohydrate modified release tablets are available in blister packs containing 10 and 30 modified release tablets.

Storage: Store below 25°C.

Not all strengths and pack sizes of Pramipexole hydrochloride monohydrate modified release tablets are being distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited
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Millers Point NSW 2000
Australia

www.mylan.com.au

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

17/06/2015

DATE OF MOST RECENT AMENDMENT

24/11/2016