AUSTRALIAN PRODUCT INFORMATION

SIMPRAL®

(Pramipexole dihydrochloride monohydrate) tablets

1 NAME OF THE MEDICINE

Pramipexole dihydrochloride monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SIMPRAL tablets contain either 0.125 mg, 0.25 mg or 1 mg of pramipexole dihydrochloride monohydrate as the active ingredient.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

SIMPRAL 0.125 mg tablets	:	Each 0.125 mg tablet is presented as a white to off white, round, flat-faced tablet, debossed with PX1 on one side and M on the other side.
SIMPRAL 0.25 mg tablets	:	Each 0.25 mg tablet is presented as a white to off-white, biconvex oval shaped tablet, debossed with PX2 on one side and M on one side of breakline on other side.
SIMPRAL 1 mg tablets	:	Each 1 mg tablet is presented as a white to off white, round, flat-faced tablet, debossed with M over PX4 on one side and breakline on other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

SIMPRAL is indicated for the treatment of signs and symptoms of idiopathic Parkinson's disease. It may be used as monotherapy or in combination with levodopa. It is also indicated for the symptomatic treatment of primary Restless Legs Syndrome.

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of Administration

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

Restless Legs Syndrome

SIMPRAL tablets are usually taken 2 to 3 hours before bedtime each day.

Parkinson's disease

The daily dosage is administered in equally divided doses three times per day.

Dosage

Parkinson's disease

Initial treatment

Dosages should be increased gradually from a starting dose of 0.375 mg SIMPRAL per day and then increased every 5 to 7 days (see Table 1). Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Table 1: Ascending dosage schedule of SIMPRAL for Parkinson's disease

Week	Total Daily Dose of Pramipexole dihydrochloride monohydrate	SIMPRAL tablets
1	0.375 mg	0.125 mg three times a day
2	0.75 mg	0.25 mg three times a day
3	1.5 mg	0.5 mg three times a day

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

Maintenance treatment

The individual dose should be in the range of 0.375 mg to a maximum of 4.5 mg of SIMPRAL 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. 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.

Treatment discontinuation

SIMPRAL 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. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Withdrawal-emergent hyperpyrexia and confusion).

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 SIMPRAL. 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.

Initiation of therapy

The following dosage schedule (Table 2) is suggested for initiation of therapy in patients with renal impairment.

Table 2: Initial dosage schedule of SIMPRAL tablets for patients with renal impairment and Parkinson's disease

Creatinine clearance	SIMPRAL tablets initial dose and frequency	Maximum daily dose (it should not be exceeded)
< 20 mL/min	0.125 mg once daily	1.5 mg
20 -50 mL/min	0.125 mg twice daily (0.25 mg daily)	2.25 mg
> 50 mL/min	No reduction in daily dose or dosing frequency	4.5 mg

Maintenance therapy

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

Restless legs syndrome (RLS)

Initial treatment

The recommended starting dose of SIMPRAL is 0.125 mg taken once daily 2 to 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 to 7 days to a maximum of 0.75 mg per day (see Table 3). The lowest effective dose should be used (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Augmentation in Restless Legs Syndrome).

Table 3: Ascending dosage schedule of SIMPRAL immediate release tablet(s) for RLS

Titration step	Once daily evening dose (pramipexole dihydrochloride monohydrate)
1	0.125 mg
2*	0.25 mg
3*	0.5 mg
4*	0.75 mg

*if needed

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

Treatment discontinuation

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

Renal impairment

The elimination of SIMPRAL is dependent on renal function and closely related to the creatinine clearance. Based on a pharmacokinetic study in renally impaired subjects, patients with a creatinine clearance above 20 mL/min requires no reduction in daily dose. The use of SIMPRAL in RLS patients with renal impairment has not been studied.

Hepatic impairment

Dose reduction is not considered necessary in patients with hepatic impairment, as approximately 90% of absorbed drug is excreted through the kidneys.

Paediatric use

The safety and efficacy of SIMPRAL have not been established in children and adolescents below 18 years.

4.3 CONTRAINDICATIONS

SIMPRAL is contraindicated in patients with known hypersensitivity to pramipexole or any excipients in the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 SIMPRAL tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with SIMPRAL tablets, 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.

Use in Renal Impairment

When prescribing pramipexole in a patient with renal impairment a reduced dose is suggested (see Section 4.2 DOSE AND METHOD OF 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. Within the clinical development program for registration of the *Restless Legs Syndrome* indication, one case of hallucinations has been reported. 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.

Patients with psychotic disorders

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

Postural hypotension

In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy.

Dystonia

Patients with Parkinson's disease may present with axial dystonia such as antecollis, camptocormia or pleurothotonus (Pisa Syndrome). Dystonia has been reported following initiation of dopamine agonists including pramipexole. Dystonia may also occur several months following medication initiation or dose adjustment. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment considered.

Compulsive Behaviour

Abnormal behaviours (reflecting symptoms of impulse control disorders and compulsive behaviours) such as pathological gambling, hypersexuality, compulsive shopping, binge eating, medication use, and punding (repetitive purposeless activity) have 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 behaviours, which may have serious financial and social consequences.

Dose reduction/tapered discontinuation should be considered.

Augmentation in Restless Legs Syndrome (RLS)

Treatment of Restless Legs Syndrome (RLS) with pramipexole can result in augmentation. Augmentation refers to the earlier onset of symptoms (in the evening or even in the afternoon), increase in symptoms, and spread of symptoms to involve other extremities.

The risk of augmentation may increase with higher dose. Treatment with pramipexole should be started with the recommended dose of 0.125 mg and may only be increased to a maximum recommended daily dose of 0.75 mg, if additional symptom relief is required (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). Prior to treatment, patients should be informed that augmentation may occur and should be advised to contact their physician if they experience symptoms of augmentation. They should be regularly monitored for the occurrence of augmentation. If augmentation is suspected, the adequacy of pramipexole treatment should be reviewed and dosage adjustment or discontinuation considered (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Treatment discontinuation for RLS

In RLS clinical trials, some patients 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. For RLS treatment, pramipexole can be discontinued without tapered dose reduction (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Drug withdrawal syndrome

A drug withdrawal syndrome has been reported during or after discontinuation of dopamine agonists including pramipexole. Risk factors may include high cumulative dopaminergic exposure. Withdrawal symptoms do not respond to levodopa, and may include apathy, anxiety, depression, fatigue, sweating and pain may occur when tapering or discontinuing dopamine agonists, including pramipexole, which may be severe (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Patients should be informed about potential drug withdrawal symptoms before tapering pramipexole and be closely monitored during and after discontinuation. In case of persistent or severe withdrawal symptoms, it

may be necessary to consider the temporary re-administration or increase of a dopamine agonist at the lowest effective dose.

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 creatine phosphokinase (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.

Melanoma

In patients with Parkinson's disease there are uncertain results regarding a potential increased risk of developing melanoma. Epidemiological studies have shown that patients with Parkinson's disease have a higher risk of developing melanoma than the general population.

Patients and their doctors should be aware of this potential additional risk for developing melanoma and monitor the 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 (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

Dopamine Dysregulation Syndrome

Dopamine Dysregulation Syndrome (DDS) is an addictive disorder resulting in excessive use of dopaminergic agonists, including SIMPRAL. Before initiation of treatment, patients and caregivers should be warned of the potential risk of developing DDS.

Use in the 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.

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Plasma protein binding

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 *t.i.d.*).

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.

Levodopa

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.

Antipsychotic medicinal products

Co-administration of antipsychotic medicinal products with pramipexole is not recommended, e.g. if dopamine-antagonistic effects can be expected (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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, indometacin, 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 t.i.d. 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 t.i.d. 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 t.i.d.).

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 (see Section 5.1 PHARMACODYNAMIC PROPERTIES – PHARMACODYNAMIC EFFECTS). 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.

4.7 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Somnolence and sudden onset of sleep). 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 4.

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

Body system/ Adverse Event	Early Therapy		Advanced Therapy	
	Pramipexole N = 388 % occurrence	Placebo N = 235 % occurrence	Pramipexole† 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	-	-	1	0
Cardiovascular system				
Postural hypotension	-	-	53	48
Nervous system				
Dizziness	25	24	26	25
Somnolence	22	9	9	6
Insomnia	17	12	27	22

Body system/ Adverse Event	Early Therapy		Advanced Therapy	
	Pramipexole N = 388 % occurrence	**Placebo N = 235 % occurrence**	**Pramipexole† N = 260 % occurrence**	**Placebo† N = 264 % occurrence**
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 abnormalities	-	-	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
Pneumonia	-	-	2	0

Body system/ Adverse Event	Early Therapy		Advanced Therapy	
	Pramipexole N = 388 % occurrence	**Placebo N = 235 % occurrence**	**Pramipexole† N = 260 % occurrence**	**Placebo† N = 264 % occurrence**
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 pramipexole 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.

Restless legs syndrome clinical trials

In the treatment of RLS, pramipexole 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 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 of RLS patients in controlled clinical studies is presented in Table 5.

Table 5: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Restless Legs Syndrome (Events ≥ 1% of patients treated with pramipexole and numerically more frequent than in the placebo group)

Body System/Adverse Event	**Pramipexole 0.125 – 0.75 mg/day (N = 575) %**	**Placebo (N = 223) %**
Ear and labyrinth 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

Body System/Adverse Event	Pramipexole 0.125 – 0.75 mg/day (N = 575) %	Placebo (N = 223) %
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
Augmentation in Restless Legs Syndrome	11.8	9.4
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
Pruritis	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 pramipexole.

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, antecollis, augmentation (in Restless Legs Syndrome), 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, spontaneous penile erection (both indications), 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.

Description of selected adverse reactions

Libido disorders

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

Sudden onset of sleep and somnolence

Patients treated with pramipexole 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Somnolence and sudden onset of sleep). Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole and which, according to the current knowledge of sleep physiology, always precedes falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other 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.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Compulsive Behaviour).

Cardiac failure

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

Drug withdrawal syndrome (Dopamine agonist withdrawal syndrome)

Withdrawal symptoms including apathy, anxiety, depression, fatigue, sweating, and pain may occur when tapering or discontinuing dopamine agonists, which may be severe (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Drug withdrawal syndrome).

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: dopamine agonist.

ATC code: N04BC05

Mechanism of Action

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.

The precise mechanism of action of pramipexole as a treatment for Restless Legs Syndrome is not known. Although the pathophysiology of Restless Legs Syndrome is largely unknown, neuropharmacological evidence suggests primary dopaminergic system involvement. Positron emission tomographic (PET) studies suggest that a mild striatal presynaptic dopaminergic dysfunction may be involved in the pathogenesis of Restless Legs Syndrome.

Pharmacodynamic Effects

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

Clinical Trials

Parkinson's disease

The clinical program 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

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.

Study M/2730/0001

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 ($p \leq 0.0001$). 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 ($p \leq 0.0001$). 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).

Study M/2730/0004

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.

Study M/2730/0005

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 ($p \leq 0.0022$) 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 ($p \leq 0.021$ 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.

Study M/2730/0072

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.

Studies in patients with advanced Parkinson's disease

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

Study M/2730/0010

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 ($p \leq 0.01$). 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 ($p \leq 0.01$). 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.

Study M/2730/0036

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.

Restless Legs Syndrome

The efficacy of pramipexole tablets in the treatment of Restless Legs Syndrome (RLS) was evaluated in a multinational drug development program consisting of four randomised, double-blind, placebo-controlled trials. This program included approximately 1000 patients with moderate to very severe primary (idiopathic) RLS; patients with RLS secondary to other conditions (e.g., pregnancy, renal failure and anaemia) were excluded. Patients were diagnosed with RLS based on standard criteria of the International RLS Study Group and were required to have a score of >15 on the International RLS (IRLS) Rating Scale. The mean age was 55.1 years in the placebo group and 54.6 years in the pramipexole group. About three quarter of patients were below 65 years of age and about two thirds were female. The baseline mean IRLS Rating Scale score was 25.4 in placebo and 24.3 in the pramipexole treated patients. The majority of patients in both treatment groups (55.7% [placebo] vs. 60.3% [pramipexole]) had a mean IRLS Rating Scale score between 21 and 30 indicative of a patient population with severe RLS. All patients were administered pramipexole (0.125 mg, 0.25 mg, 0.5 mg, or 0.75 mg) or placebo once daily 2-3 hours before going to bed.

The primary outcome measures in the two key RLS trials were:

1. IRLS Rating Scale - contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms.

2. Clinical Global Impression-Improvement (CGI-I) assessment - a subset of CGI, which is designed to assess the severity of illness, clinical progress (global improvement), therapeutic effect, as well as side effects.

Study 1

In Study 1, fixed doses of pramipexole were compared to placebo in a study of 12 weeks duration. Patients treated with pramipexole (n=254) had a starting dose of 0.125 mg/day and were titrated to one of the three active treatment groups (0.25, 0.5, 0.75 mg/day) in the first three weeks of the study. The mean improvement from baseline on the IRLS Rating Scale score and the percentage of CGI-I responders for each of the pramipexole treatment groups compared to placebo are summarised in Table 6. All treatment groups reached statistically significant superiority compared to placebo for both endpoints.

These results confirm the significant benefits of pramipexole (over placebo) observed in an earlier randomised, double-blind, placebo-controlled, flexible-dose study of 6 weeks duration. In this flexible-dose study, the decrease in the IRLS Rating Scale score for the pramipexole group (n=224) (after 6 weeks of double-blind therapy) was statistically significant compared to the placebo group (adjusted mean change from baseline: –12.3 [pramipexole] vs. –5.7 [Placebo]; adjusted mean difference to placebo [95% CI]: –6.6 [–8.6, –4.5], p=0.0001). In addition, 62.9% of the pramipexole treated patients reached a CGI-Global improvement of at least 'much improved', compared to only 32.5% patients in the placebo group (adjusted treatment difference to placebo [95% CI]: 30.4% [19.8, 41.2]). This difference was also statistically significant (p<0.0001).

Study 2

Study 2 demonstrated sustained efficacy of pramipexole for treatment of RLS over a period of nine months. RLS patients who responded to pramipexole treatment in a preceding 6-month open label treatment phase (7 on 0.125 mg, 44 on 0.25 mg, 47 on 0.5 mg, 49 on 0.75 mg) were randomised to receive either blinded active treatment at an individually optimised dose (n=78) or placebo (n=69) for 12 weeks. Responders were defined as having a CGI-I rating of "very much improved" or "much improved" compared to baseline and an IRLS score of 15 or below. The primary endpoint of this study was time to treatment failure based on a CGI-I score of "minimally worse" to "very much worse" and an IRLS Scale score above 15.

Table 6: Adjusted mean changes from baseline to Week 12 in IRLS Score and CGI-I

	Pramipexole 0.25 mg	Pramipexole 0.5 mg	Pramipexole 0.75 mg	Pramipexole Total	Placebo
IRLS score					
Number of patients	n=88	n=79	n=87	n=254	n=85
Baseline mean (SD)	23.4 (4.9)	22.9 (5.1)	24.1 (5.2)	23.4 (5.1)	23.5 (5.2)
Change from baseline					
Adjusted mean (SE)	-12.8 (1.0)	-13.8 (1.0)	-14.0 (1.0)	-13.5 (0.6)	-9.3 (1.0)
Difference to Placebo					
Adjusted mean (SE)	-3.6 (1.3)	-4.6 (1.4)	-4.7 (1.3)	-4.3 (1.1)	
95% CI	-6.2, -0.9	-7.3, -1.8	-7.4, -2.1	-6.4, -2.1	
p-value	p=0.0086	p=0.0011	p=0.0005	p<0.0001	
CGI-Improvement					
Number of patients	n=87	n=78	n=85	n=250	n=84
Responders*	74.7%	67.9%	72.9%	72%	51.2%
Difference to Placebo	23.5%	16.7%	21.7%	20.8%	
95% CI	9.5, 37.6	1.9, 31.6	7.5, 36.0	8.8, 32.9	
p-value	p=0.0005	p=0.0484	p=0.0038	p=0.0005	

*CGI-I responder = "much improved" and "very much improved."

CGI = Clinical Global Impression-Improvement; IRLS = International Restless Legs Syndrome;

SD = standard deviation; SE = standard error; CI = Confidence Interval

In patients who had responded to 6-month open label treatment with pramipexole, the administration of placebo led to a rapid decline in their overall conditions and worsening of their RLS symptoms (Figure 1). At the end of the 12-week observation period, 85% of patients treated with placebo had failed treatment, compared to 21% treated with blinded pramipexole; the difference between the treatment groups was highly statistically significant ($p < 0.0001$).

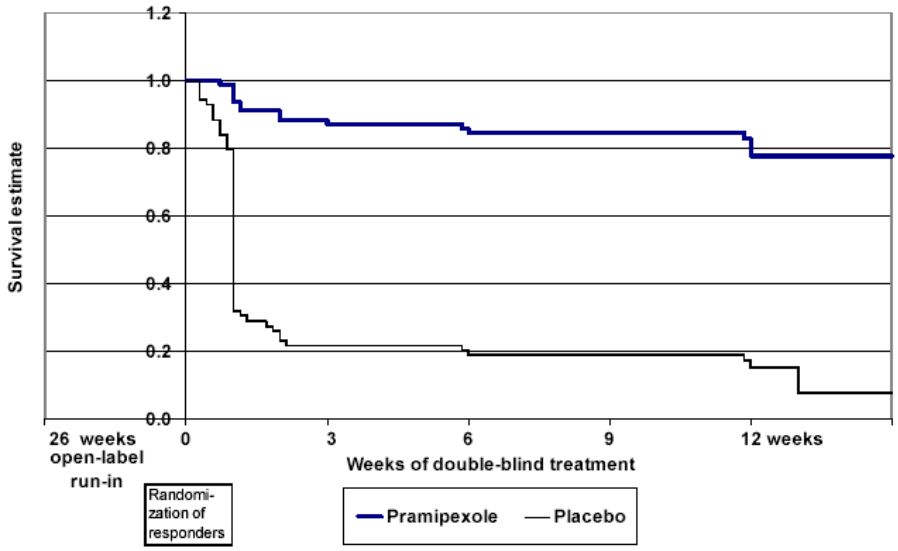


Figure 1: Kaplan-Meier estimates of time to treatment failure (CGI-I score of "minimally worse" to "very much worse" and IRLS Scale score above 15) in responders to 6-months open label pramipexole therapy after randomisation to placebo or blinded pramipexole

Study 3

In a separate 3-week study, fixed doses of 0.125 mg, 0.25 mg, 0.5 mg, and 0.75 mg pramipexole were all shown to significantly reduce the number of periodic limb movements during sleep as measured by the Periodic Limb Movement during time in bed Index (PLMI) compared to placebo. Upon initiation of treatment, 37% of 476 patients treated with pramipexole reported that they felt significantly better after one week of therapy, compared to 10% of 199 patients treated with placebo. During the long-term studies (without placebo control), the effect of pramipexole was maintained up to at least one year.

No differences in effectiveness based on age or gender were detected. There were too few non-Caucasian patients to evaluate the effect of race.

5.2 PHARMACOKINETIC PROPERTIES

Pramipexole displays linear pharmacokinetics over the clinical dosage range, irrespective of dosage form.

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 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.

Typical plasma concentration-time profiles after administration of pramipexole tablets three times daily, either every 8 hours (8-8-8) or in a 6-6-12 hour posology are given in Figure 2.

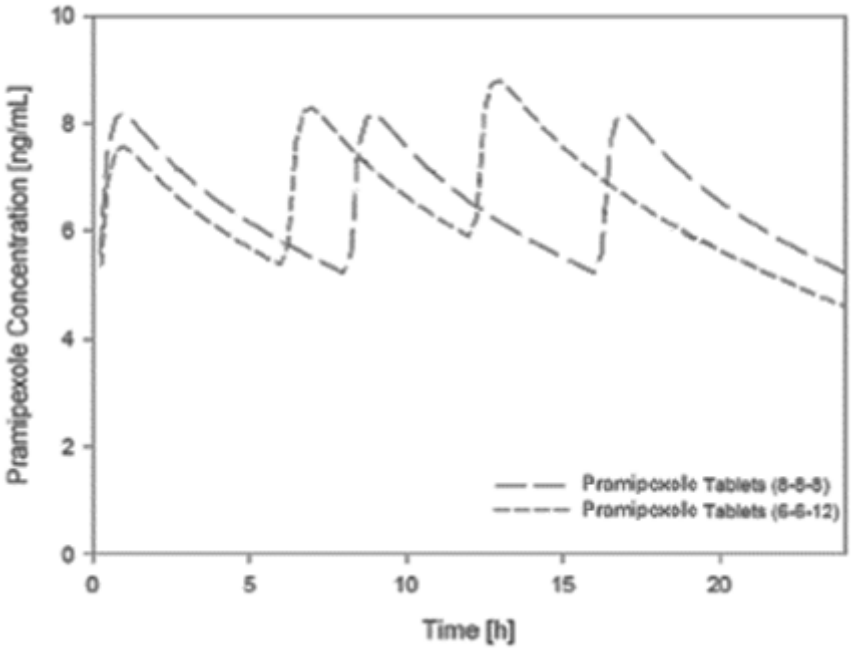


Figure 2: Plasma concentration-time profile of pramipexole tablets at steady state after dosing 1.5 mg pramipexole tablets three times a day (t.i.d.) for typical PD patient with creatinine clearance 78.5 mL/min and a body weight of 75 kg (median values)

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.

Excretion

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 Section 5.2 PHARMACOKINETIC PROPERTIES – 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 Section 4.2 DOSE AND METHOD OF 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) patients

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 use

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

Hepatic impairment

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

Renal impairment

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 Section 4.2 DOSE AND METHOD OF 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Two year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered into the diet of 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 *t.i.d.*). Pramipexole was administered into the diet of 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 the 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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

SIMPRAL tablets contain: mannitol, pregelatinised maize starch, hyprolose, crospovidone, sodium citrate, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Protect from light. Store in the original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PA/Al/PVC/Al

Pack sizes: 10, 100 tablets (for 0.125 mg, 0.25 mg and 1 mg strengths), 30 tablets (for 0.125 mg strength only).

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 173139 - SIMPRAL pramipexole dihydrochloride monohydrate 0.125 mg tablet blister pack

AUST R 173138 - SIMPRAL pramipexole dihydrochloride monohydrate 0.25 mg tablet blister pack

AUST R 173137 - SIMPRAL pramipexole dihydrochloride monohydrate 1 mg tablet blister pack

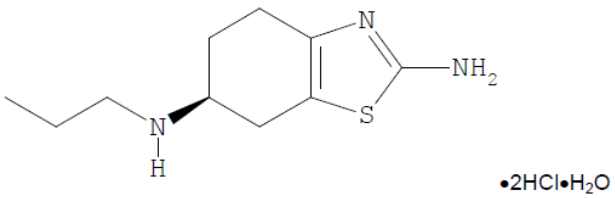
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical Structure



Chemical name : (S)-2-amino-4,5,6,7-tetrahydro-6-propylaminobenzothiazole

Molecular formula : $C_{10}H_{17}N_3S.2HCl.H_2O$ Molecular weight : 302.26 (monohydrate)

CAS Number

191217-81-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

09/04/2013

10 DATE OF REVISION

31/10/2025

Summary Table of Changes

Section Changed	Summary of New Information
4.4	Addition of Dopamine Dysregulation Syndrome to Warnings and Precautions for Use. Minor editorial changes.

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