AUSTRALIAN PI – APO-PRAMIPEXOLE TABLETS (PRAMIPEXOLE)

1 NAME OF THE MEDICINE

Pramipexole Hydrochloride monohydrate

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each tablet contains pramipexole hydrochloride monohydrate, as the active ingredient.

Pramipexole hydrochloride monohydrate is a white to off white crystalline powder. Freely soluble in water, soluble in methanol, sparingly soluble to slightly soluble in ethanol (96%) and practically insoluble in methylene chloride.

In addition to pramipexole, each tablet contains the following inactive ingredients: Mannitol, pregelatinised maize starch, microcrystalline cellulose, Povidone, purified talc and magnesium stearate.

APO-PRAMIPEXOLE tablets are round and white for each strength.

0.125 mg Tablets:

APO-PRAMIPEXOLE 0.125 mg tablets contain 0.125 mg pramipexole hydrochloride monohydrate and are marked with an “A” on one side of the tablet.

0.25 mg Tablets:

APO-PRAMIPEXOLE 0.25 mg tablets contain 0.25 mg pramipexole hydrochloride monohydrate and are marked with a “B” on one side of the tablet.

1 mg Tablets:

APO-PRAMIPEXOLE 1 mg tablets contain 1 mg pramipexole hydrochloride monohydrate and are marked with a “D” on one side of the tablet.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Parkinson's disease.

The tablets should be taken orally, swallowed with water. Pramipexole hydrochloride can be taken either with or without food.

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

Dosages should be increased gradually from a starting dose of pramipexole hydrochloride 0.375 mg/day and then increased every five to seven days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Pramipexole hydrochloride **Table 1**

Ascending dosage schedule of pramipexole hydrochloride for Parkinson's disease

Week	Pramipexole hydrochloride Dosage	Total Daily Dose of pramipexole hydrochloride
1	0.125 mg three times a day	0.375 mg
2	0.25 mg three times a day	0.75 mg
3	0.5 mg three times a day	1.5 mg

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/day.

Maintenance treatment. The individual dose should be in the range of 0.375 mg to a maximum of pramipexole hydrochloride 4.5 mg/day. During dose escalation in three pivotal studies, both in early and advanced disease, efficacy was observed starting at a daily dose of pramipexole hydrochloride 1.5 mg. 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, doses higher than 1.5 mg/day can be useful in patients where a reduction of the levodopa therapy is intended.

Treatment discontinuation. Pramipexole hydrochloride 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 hydrochloride. 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/minute require no reduction in daily dose.

In patients with a creatinine clearance between 20 and 50 mL/minute, the initial daily dose of pramipexole hydrochloride 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 should not be exceeded. In patients with a creatinine clearance less than 20 mL/minute, the daily dose of pramipexole hydrochloride should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg should not be exceeded.

If renal function declines during maintenance therapy, reduce pramipexole hydrochloride daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the pramipexole hydrochloride daily dose by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 mL/minute, and as a single daily dose if creatinine clearance is less than 20 mL/minute.

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 hydrochloride pharmacokinetics has not been investigated.

Dosing in children and adolescents. Safety and efficacy of pramipexole hydrochloride have not been established in children and adolescents below 18 years.

4.3 CONTRAINDICATIONS

Hypersensitivity to pramipexole or any excipients of PRAMIPEXOLE CH.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

A Somnolence and sudden onset of sleep

Pramipexole hydrochloride has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported. Some of these events have been reported as late as one year after the initiation of treatment. Before initiating treatment with pramipexole hydrochloride tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with pramipexole hydrochloride tablets, such as concomitant sedation medications, the presence of sleep disorders and concomitant medications that increase pramipexole plasma levels (eg cimetidine). Patients must be informed of the potential sedating effects associated with pramipexole hydrochloride, 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 hydrochloride 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) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their doctor. 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 hydrochloride because of possible additive somnolent effects.

Use in renal impairment

When prescribing pramipexole hydrochloride in a patient with renal impairment a reduced dose is suggested (see **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 hydrochloride 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 hydrochloride. If dyskinesias occur, the dose of levodopa should be decreased.

Coexisting 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 hydrochloride. 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.

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 antiparkinsonian 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, nonergot 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/ taper discontinuation should be considered.

Paediatric use

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

Use in the elderly

When prescribing pramipexole hydrochloride, 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 hydrochloride.

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 hydrochloride was increased in the elderly.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

The toxicological consequences (long-term, reproduction, carcinogenicity/ mutagenicity) 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 microM, 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 Tmax from 2.5 to 0.5 hours. When pramipexole hydrochloride is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage of other antiparkinsonian medication is kept constant while increasing the dose of pramipexole hydrochloride.

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 hydrochloride.

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 hydrochloride 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 hydrochloride and should not be administered concurrently.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effect 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 (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 pramipexole 0.1, 0.5 or 1.5 mg/kg (approximately 0.3, 1.7 and 5 times human exposure at the maximum recommended human dose of 1.5 mg tid and based on area under the curve (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 hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

The effect on lactation has not been investigated in humans. As pramipexole hydrochloride treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole hydrochloride 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 hydrochloride should not be used during breastfeeding, if possible. However, if its use is unavoidable, breastfeeding 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 hydrochloride, 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 hydrochloride 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) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their doctor.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Parkinson's disease clinical trials.

The following adverse events have been reported more frequently during the use of pramipexole hydrochloride 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 hydrochloride, compared to placebo treatment, was not increased. However, in individual patients, hypotension may occur at the beginning of treatment, especially if pramipexole hydrochloride 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.

Pramipexole hydrochloride **Table 2**

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 hydrochloride and numerically more frequent than in the placebo group)

Body System/Adverse Event	**Early Therapy**		**Advanced Therapy**	
	Pramipexole hydrochloride **N = 388** **% occurrence**	**Placebo** **N = 235** **% occurrence**	**Pramipexole hydrochloride†** **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 and 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
Hallucinations	9	3	17	4
Confusion	4	1	10	7
Amnesia	4	2	6	4
Hyperaesthesia	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
Bursistis	-	-	2	0
Myasthenia		-	1	0
Respiratory System				
Dyspoenea	-	-	4	3
Rhinitis	-	-	3	1
Pneumonia	-	-	2	0
Skin and 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 hydrochloride 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 CPK, nervousness, dream abnormalities, chest pain, neck pain, paraesthesia, 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, paraesthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hyperaesthesia, 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 hydrochloride during premarketing development. All reported events, except those already listed above, are included without regard to determination of a causal relationship to pramipexole hydrochloride. 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, gastrointestinal (GI) haemorrhage, faecal incontinence.

Endocrine system. Diabetes mellitus.

Haemic and lymphatic system. Ecchymosis.

Metabolic and 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 and 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.

Pramipexole hydrochloride **Table 3** Treatment-emergent adverse-event* incidence in double-blind, placebo-controlled studies in different indications (events ≥ 1% of patients treated with different brands and numerically more frequent than in the placebo group)		
Body System/Adverse Event	**Different brands of Pramipexole hydrochloride** **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 hydrochloride therapy.

Adverse reactions reported in less than 1% of 575 patients treated with other brands of pramipexole hydrochloride (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. Leucopenia.

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, GI 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. Postural dizziness, 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.

Postmarketing 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 postapproval use of pramipexole hydrochloride. 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), increased eating (including binge eating, compulsive eating and hyperphagia), libido disorders (including increased and decreased libido), 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.

Patients treated with pramipexole hydrochloride 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 **4.4 Special Warnings and Precautions for use**). Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole hydrochloride 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 hydrochloride, 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.

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 http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

Treatment

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 hydrochloride 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.

Clinical trials

Parkinson's disease. The clinical program for pramipexole hydrochloride 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 (eg 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 stage I to III. In two studies (protocols M/2730/0005 and M/2730/0072) the presence of two 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 seven week dose escalation period and a six 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 hydrochloride or placebo. Patients treated with pramipexole hydrochloride 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 six month maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.9 in the group receiving pramipexole hydrochloride and -0.4 in the placebo group, a difference that was statistically significant (p less than or equal to 0.0001). The mean improvement from baseline on the UPDRS part III total score was 5.0 in the group receiving pramipexole hydrochloride and -0.8 in the placebo group, a difference that was also statistically significant (p less than or equal to 0.0001). A statistically significant difference between groups in favour of pramipexole hydrochloride 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 six week dose escalation period and a four 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 hydrochloride (1.5, 3.0, 4.5 or 6.0 mg/day) or placebo. At the end of the four week maintenance period, the mean improvement from baseline on the UPDRS part II total score was 1.8 in the patients treated with pramipexole hydrochloride, 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 hydrochloride 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 hydrochloride for all doses.

The third study (M/2730/0005, n = 290) was a double blind, placebo controlled, parallel design consisting of a seven 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 hydrochloride 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 hydrochloride significantly (p less than or equal to 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 less than or equal to 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 hydrochloride 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 hydrochloride 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 two years (as described in the original protocol) are available. The efficacy results showed that initial treatment with pramipexole hydrochloride 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 hydrochloride (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 hydrochloride 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 hydrochloride and carbidopa/ levodopa groups were -4.7 and -9.3, respectively. The results show that pramipexole hydrochloride is more effective than carbidopa/ levodopa in delaying the occurrence of dopaminergic motor complications. Monotherapy with pramipexole hydrochloride is effective in the treatment of patients with early Parkinson's disease and in the delay of motor complications. Long-term administration of pramipexole hydrochloride was well tolerated and the adverse event profile was consistent with that reported for other pramipexole hydrochloride 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 stage II to IV) during 'on' periods. Patients in the first study (M/2730/0010, n = 360) had a mean disease duration of nine years, had been exposed to levodopa for long periods of time (mean eight 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 seven week dose escalation period and a six 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 hydrochloride 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 six month maintenance period, patients were asked to record the amount of 'off', 'on' or 'on with dyskinesia' time/day for several sequential days. At the end of the six month maintenance period, the mean improvement from baseline on the UPDRS part II total score was 2.7 in the group treated with pramipexole hydrochloride and 0.5 in the placebo group, a difference that was statistically significant (p less than or equal to 0.01). The mean improvement from baseline on the UPDRS part III total score was 5.6 in the group treated with pramipexole hydrochloride and 2.8 in the placebo group, a difference that was statistically significant (p less than or equal to 0.01). A statistically significant difference between groups in favour of pramipexole hydrochloride 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 hydrochloride versus 54% of placebo patients. On average, the levodopa dose was reduced by 27%. The mean number of 'off' hours/day during baseline was six hours for both treatment groups. Throughout the trial, patients treated with pramipexole hydrochloride had a mean of four 'off' hours/day, while placebo treated patients continued to experience six 'off' hours/day.

The second study (M/2730/0036, n = 247) was a double blind, placebo controlled, parallel trial consisting of a 12 week titration, six month maintenance and one week dose reduction period. Pramipexole hydrochloride 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 hydrochloride and placebo were -2.5 and -0.5, respectively (p = 0.0002). In the UPDRS part III, the changes for pramipexole hydrochloride and placebo were -6.0 and -2.0, respectively (p = 0.0006). Pramipexole hydrochloride was superior to placebo for UPDRS parts II and III from four and six weeks on, respectively. Superiority of pramipexole hydrochloride over placebo was also shown for UPDRS part II during 'on' periods. In the pramipexole hydrochloride 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/day, an important clinical improvement. Both pramipexole hydrochloride 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 hydrochloride treatment tended to be superior to bromocriptine treatment.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pramipexole is rapidly absorbed, reaching peak concentrations in approximately two hours. The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism. Food does not affect the extent of pramipexole absorption, although the time of maximum plasma concentration (Tmax) is increased by about one hour when the drug is taken with a meal.

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 two.

Metabolism

Pramipexole displays linear pharmacokinetics over the clinical dosage range. Its terminal half-life is about eight hours in young healthy volunteers and about 12 hours in elderly volunteers (see Special populations). Steady-state concentrations are achieved within two days of dosing.

Excretion

Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. Nonrenal routes may contribute to a small extent to pramipexole elimination, although no metabolites have been identified in plasma or urine. The renal clearance of pramipexole is approximately 400 mL/minute (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 **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 bodyweight. 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.

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/minute) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/minute) compared with healthy volunteers. A lower starting and maintenance dose is recommended in these patients (see **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 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.

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 three times daily (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 two 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 two years, and the probable involvement of endocrine mechanisms that are not relevant to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See Section 4.5-Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, the 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 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

0.125 mg Tablets

Blister pack (PA/Al/PVC/Al) of 30 tablets.

0.25 mg Tablets

Blister pack (PA/Al/PVC/Al) of 100 tablets.

1 mg Tablets

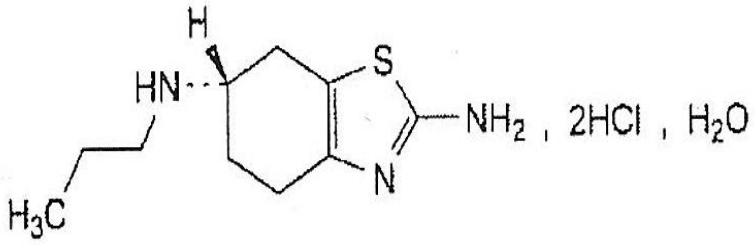
Blister pack (PA/Al/PVC/Al) of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical Name: (6*S*)-6-*N*-Propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine dihydrochloride monohydrate.

Chemical Formula: $C_{10}H_{19}Cl_2N_3S,2HCl.H_2O$

Molecular Weight: 302.3

CAS number

191217-81-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

Southern Cross Pharma Pty Ltd

Suite 5/118 Church Street,

Hawthorn, VIC, 3122.

9 DATE OF FIRST APPROVAL

25 October 2011

10 DATE OF REVISION

15 June 2018

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information
2,3	Trade name change
4.4	Minor editorial changes
8	Address update