SIFROL® and SIFROL® ER

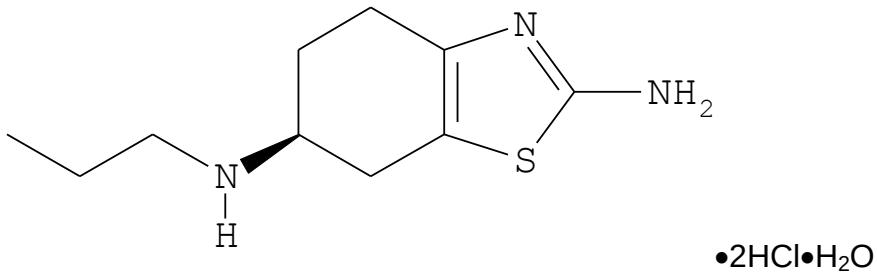
NAME OF THE MEDICINE

Pramipexole hydrochloride.

The chemical name of pramipexole is (*S*)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole, [$C_{10}H_{17}N_3S$], CAS registry number 104632-26-0, molecular weight 211.33.

SIFROL tablets and SIFROL ER tablets contain $C_{10}H_{17}N_3S.2HCl.H_2O$, molecular weight 302.3, CAS registry number 104632-25-9 for which the Australian Approved Name is pramipexole hydrochloride.

The structural formula is:



DESCRIPTION

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

SIFROL is available as immediate-release SIFROL tablets and extended-release SIFROL ER tablets.

SIFROL tablets also contain the following excipients: mannitol, starch-maize, silica-colloidal anhydrous, povidone and magnesium stearate.

SIFROL ER extended-release tablets also contain the following excipients: hypromellose, starch-maize, carbomer 941, silica-colloidal anhydrous and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics

SIFROL 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.

SIFROL 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 SIFROL 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.

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

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

Pharmacokinetics

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

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

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

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

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

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

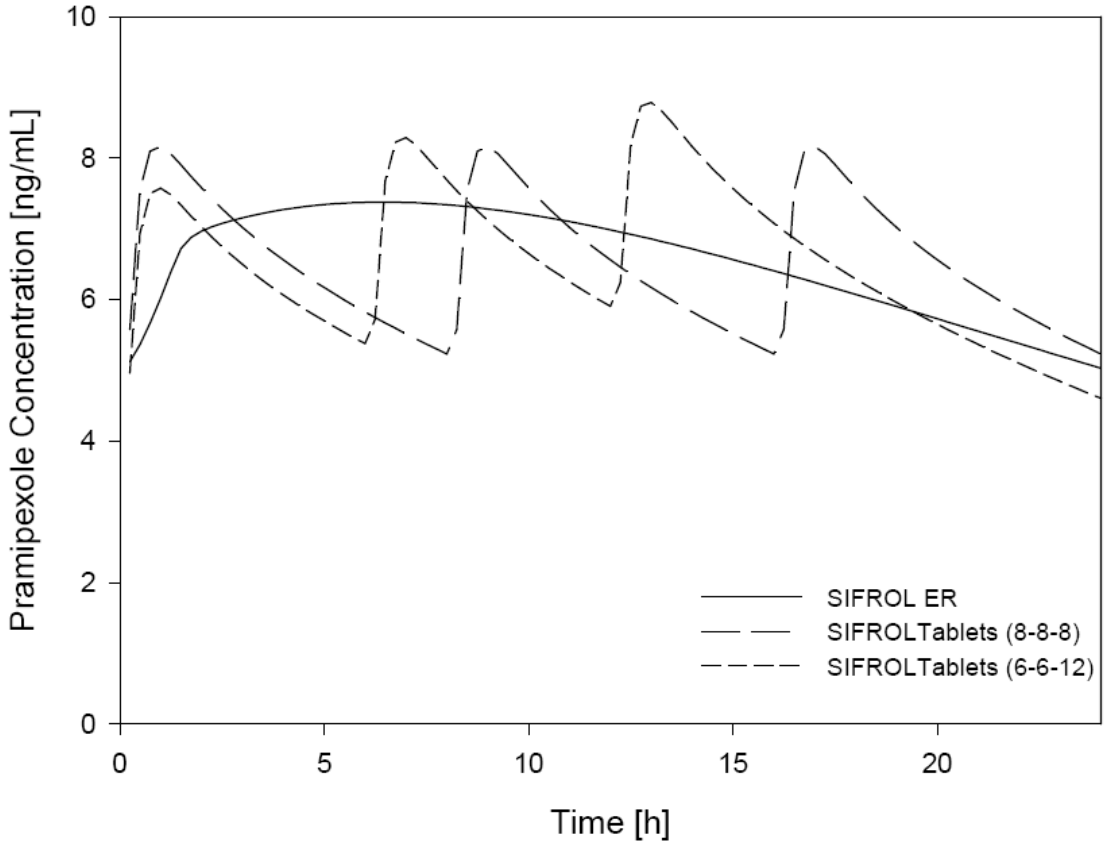


Figure 1: Plasma concentration-time profile of SIFROL ER and SIFROL tablets at steady state after dosing of 4.5 mg SIFROL ER once a day (q.d.) or 1.5 mg SIFROL tablets three times a day (t.i.d.) for typical PD patient with creatine clearance 78.5 mL/min and a body weight of 75 kg (median values) *Distribution:* Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV] = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.

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

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

Special Populations

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

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

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

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

Restless Legs Syndrome (RLS) Patients: A cross-study comparison of data suggests that the pharmacokinetic profile of pramipexole administered once daily in RLS patients is generally consistent with the pharmacokinetic profile of pramipexole in healthy volunteers.

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

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

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

CLINICAL TRIALS

Parkinson's disease

The clinical programme for SIFROL 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:

SIFROL tablets

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

One study (M/2730/0001, n=335) was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients could be on selegiline, anticholinergics, or both, but could not be on levodopa products or amantadine. Patients were randomised to SIFROL or placebo. Patients treated with SIFROL 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 SIFROL 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 SIFROL 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 SIFROL was seen beginning at week 2 of the UPDRS Part II (maximum dose 0.75 mg/day) and at week 3 of the UPDRS Part III (maximum dose 1.5 mg/day).

The second study (M/2730/0004, n=264) was a double-blind, placebo-controlled, parallel trial consisting of a 6-week dose-escalation period and a 4-week maintenance period. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but could not be on levodopa products. Patients were randomised to one of four fixed doses of SIFROL (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 SIFROL, 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 SIFROL 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 SIFROL for all doses.

The third study (M/2730/0005, n=290) was a double-blind, placebo-controlled, parallel design consisting of a 7-week dose-escalation period and a 24-week maintenance period (same as M/2730/0001). Again, patients were allowed use of selegiline, anticholinergics, amantadine, or any combination of these, but not levodopa products. Patients treated with SIFROL 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. SIFROL 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 SIFROL exhibited clinical improvement throughout treatment.

There was a further study (M/2730/0072, n=301) which was a double-blind, parallel design comparison of SIFROL 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 SIFROL 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 SIFROL (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 SIFROL 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 SIFROL and carbidopa-levodopa groups were –4.7 and –9.3 respectively. The results show that SIFROL is more effective than carbidopa-levodopa in delaying the occurrence of dopaminergic motor complications. Monotherapy with SIFROL is effective in the treatment of patients with early Parkinson's disease and in the delay of motor complications. Long-term administration of SIFROL was well tolerated and the adverse event profile was consistent with that reported for other SIFROL and levodopa trials.

SIFROL ER tablets

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

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

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

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

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

A randomised, double-blind, parallel group trial was conducted in 156 patients with early Parkinson's disease (Hoehn and Yahr Stages I-III) to assess overnight switching of immediate-release pramipexole tablets to SIFROL ER tablets; stable doses of concomitant levodopa, MAOB-I, anticholinergics, or amantadine, individually or in combination, were

allowed. Patients in this study had a mean disease duration of approximately 3.5 years. Patients at stable doses of immediate-release pramipexole tablets were randomised to receive the same daily dose of blinded SIFROL ER tablets (n=104) or blinded immediate-release pramipexole tablets (n=52). Following 4 weeks of treatment, the study medication could be adjusted depending on efficacy and tolerability. The primary efficacy endpoint was the proportion of patients successfully switched to SIFROL ER tablets following 9 weeks of treatment; a patient was successfully switched if there was no worsening of the UPDRS Parts II+III score (by more than 15% from baseline), and the patient had no drug-related adverse events leading to discontinuation.

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

Studies in patients with advanced Parkinson's disease:

SIFROL tablets

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

Patients in the first study (M/2730/0010, n=360) had a mean disease duration of 9 years, had been exposed to levodopa for long periods of time (mean 8 years), used concomitant levodopa during the trial, and had "on-off" periods. The study was a double-blind, placebo-controlled, parallel trial consisting of a 7-week dose-escalation period and a 6-month maintenance period. Patients were treated with concomitant levodopa products and could additionally be on concomitant selegiline, anticholinergics, amantadine, or any combination. Patients treated with SIFROL 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 SIFROL 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 SIFROL 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 SIFROL 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 SIFROL 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 SIFROL had a mean of 4 "off" hours per day, while placebo-treated patients continued to experience 6 "off" hours per day.

The second study (M/2730/0036, n=247) was a double-blind, placebo-controlled, parallel trial consisting of a 12-week titration, 6-month maintenance and 1-week dose reduction period. SIFROL 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 SIFROL and placebo were –2.5 and –0.5, respectively (p=0.0002). In the UPDRS Part III, the changes for SIFROL and placebo were –6.0 and –2.0, respectively (p=0.0006). SIFROL was superior to placebo for UPDRS Parts II and III from 4 and 6 weeks on, respectively.

Superiority of SIFROL over placebo was also shown for UPDRS Part II during “on” periods. In the SIFROL 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 SIFROL 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 SIFROL treatment tended to be superior to bromocriptine treatment.

SIFROL ER tablets

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

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

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

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

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

Restless Legs Syndrome

The efficacy of SIFROL 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 SIFROL 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 SIFROL treated patients. The majority of patients in both treatment groups (55.7% [placebo] vs. 60.3% [SIFROL]) had a mean IRLS Rating Scale score between 21 and 30 indicative of a patient population with severe RLS. All patients were administered SIFROL (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.

In Study 1, fixed doses of SIFROL were compared to placebo in a study of 12 weeks duration. Patients treated with SIFROL (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 SIFROL treatment groups compared to placebo are summarised in Table 1. All treatment groups reached statistically significant superiority compared to placebo for both endpoints.

Table 1: Adjusted mean changes from baseline to Week 12 in IRLS Score and CGI-I

	SIFROL 0.25 mg	**SIFROL 0.5 mg**	**SIFROL 0.75 mg**	**SIFROL 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.”

These results confirm the significant benefits of SIFROL (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 SIFROL 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 [SIFROL] 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 SIFROL 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 demonstrated sustained efficacy of SIFROL for treatment of RLS over a period of nine months. RLS patients who responded to SIFROL 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.

In patients who had responded to 6-month open label treatment with SIFROL, the administration of placebo led to a rapid decline in their overall conditions and worsening of their RLS symptoms (Figure 2). 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).

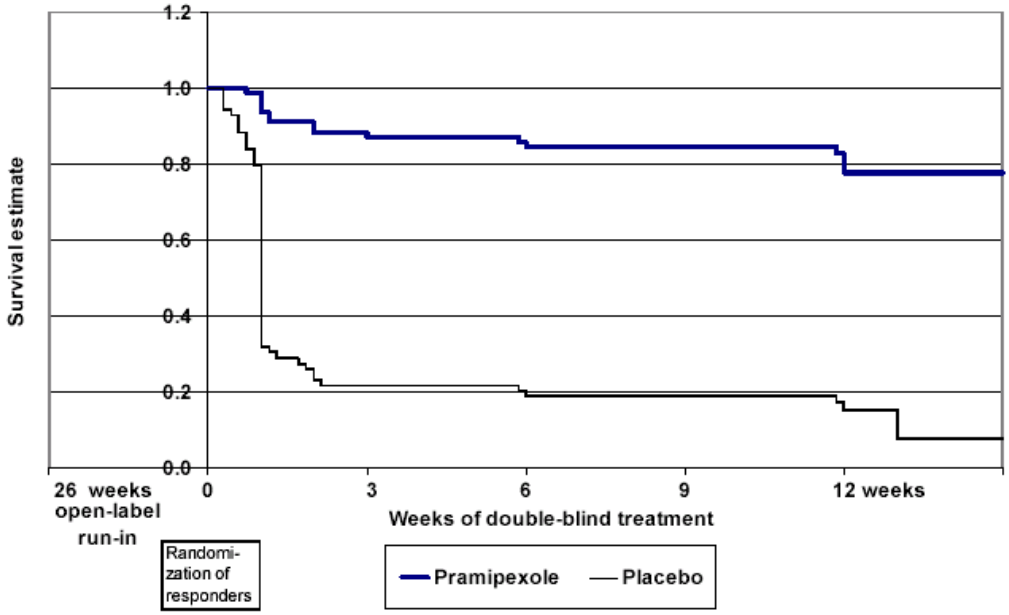


FIGURE 2: Kaplan-Meier estimates of time to treatment failure (CGI-I score of "minimally worse" to "very much worse" and IRLS Scale score above 15) in responders to 6-months open label SIFROL therapy after randomisation to placebo or blinded SIFROL:

In a separate 3-week study, fixed doses of 0.125 mg, 0.25 mg, 0.5 mg, and 0.75 mg SIFROL 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 SIFROL 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 SIFROL 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.

INDICATIONS

SIFROL tablets and SIFROL ER tablets are indicated for:

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

SIFROL tablets are also indicated for:

- the symptomatic treatment of primary Restless Legs Syndrome.

CONTRAINDICATIONS

Hypersensitivity to pramipexole or any excipients of SIFROL.

PRECAUTIONS

Somnolence and Sudden Onset of Sleep: SIFROL 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 SIFROL tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with SIFROL 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 SIFROL, 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 SIFROL 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 SIFROL because of possible additive somnolent effects.

Renal impairment: When prescribing SIFROL in a patient with renal impairment a reduced dose is suggested (refer to 'Dosage and Administration').

Hallucinations and confusion: Hallucinations and confusion are known side effects of treatment with dopamine agonists and levodopa in Parkinson's disease patients. Hallucinations were more frequent when SIFROL 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 SIFROL. If dyskinesias occur, the dose of levodopa should be decreased.

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

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

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

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

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

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

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

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

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

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

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

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

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

Dose reduction/ tapered discontinuation should be considered.

Augmentation in Restless Legs Syndrome (RLS): Reports in the literature indicate that treatment of RLS with dopaminergic medications can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Kaplan-Meier analysis of time to augmentation showed no statistically significant difference between pramipexole (N=152) and placebo groups (N=149). The frequency and severity of augmentation after longer-term use of SIFROL and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.

Treatment discontinuation for RLS: In RLS clinical trials, some patients have reported worsening of the RLS symptoms following abrupt discontinuation of SIFROL treatment. The worsening of symptoms was independent of SIFROL dosage and generally resolved within one week. For the RLS treatment, SIFROL can be discontinued without tapered dose reduction.

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

Use in pregnancy: Pregnancy Category B3.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternotoxic doses.

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

Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day or greater during the latter part of pregnancy and throughout lactation (the plasma AUC was 1.7 times the AUC in humans dosed at 1.5 mg tid).

There are no adequate and well-controlled studies in pregnant women. SIFROL 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 SIFROL treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of SIFROL 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, SIFROL should not be used during breast-feeding, if possible. However, if its use is unavoidable, breast-feeding should be discontinued.

Use in Children: The safety and efficacy of SIFROL in children has not been established.

Use in Elderly: When prescribing SIFROL, 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 SIFROL.

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 SIFROL was increased in the elderly.

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

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

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

Effects on ability to drive and use machines: Patients should be informed that hallucinations can occur and may adversely affect their ability to drive. Also, they should be alerted to the potential sedating effects associated with SIFROL, 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 SIFROL to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased somnolence or episodes of falling asleep during activities of daily living (e.g., conversations, eating, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities and should contact their physician.

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

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

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

Anticholinergics: As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated.

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

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 SIFROL.

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 SIFROL 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 SIFROL and should not be administered concurrently.

ADVERSE EFFECTS

Parkinson's Disease Clinical Trials

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

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

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

Body System/Adverse Event	Early Therapy		Advanced Therapy	
	SIFROL N = 388 % occurrence	Placebo N = 235 % occurrence	SIFROL† 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
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	-	-

Body System/Adverse Event	Early Therapy		Advanced Therapy	
	SIFROL N = 388 % occurrence	Placebo N = 235 % occurrence	SIFROL† N = 260 % occurrence	Placebo† N = 264 % occurrence
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
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 SIFROL 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 SIFROL during premarketing development. All reported events, except those already listed above, are included without regard to determination of a causal relationship to SIFROL.

Events are listed within the body-system categories in order of decreasing frequency.

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

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

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

Endocrine system: diabetes mellitus.

Haemic & lymphatic system: ecchymosis.

Metabolic & nutritional system: gout.

Musculoskeletal system: bursitis, myasthenia.

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

Respiratory system: voice alteration, asthma, haemoptysis.

Skin & appendages: skin disorder, herpes simplex.

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

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

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

Restless Legs Syndrome Clinical Trials

In the treatment of RLS, SIFROL 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 with RLS were treated with SIFROL for up to 12 weeks. The most commonly observed adverse events with SIFROL in the treatment of RLS (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 SIFROL 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 3.

Table 3: Treatment-Emergent Adverse-Event* Incidence in Double-Blind, Placebo-Controlled Trials in Restless Legs Syndrome (Events ≥ 1% of patients treated with SIFROL and numerically more frequent than in the placebo group):

Body System/ Adverse Event	**SIFROL 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

Body System/ Adverse Event	SIFROL 0.125 – 0.75 mg /day (N=575) %	Placebo (N=223) %
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 SIFROL therapy.

Adverse reactions reported in less than 1% of 575 patients treated with SIFROL (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 SIFROL. 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 SIFROL have rarely reported suddenly falling asleep (or sudden onset of sleep) while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see Precautions). Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving SIFROL 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 SIFROL, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

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

DOSAGE AND ADMINISTRATION

SIFROL tablets

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

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

SIFROL ER tablets

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

Parkinson's disease

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

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

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

Patients already taking SIFROL tablets (with or without concomitant levodopa) may be switched to SIFROL ER tablets overnight, at the same daily dose without dose adjustment.

Maintenance treatment: The individual dose should be in the range of 0.375mg to a maximum of 4.5 mg of SIFROL 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 SIFROL. Further dose adjustments should be done based on the clinical response and tolerability. In clinical trials approximately 5% of patients were treated at doses below 1.5 mg. In advanced Parkinson's disease, pramipexole doses higher than 1.5 mg per day can be useful in patients where a reduction of the levodopa therapy is intended.

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

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

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

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

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

For SIFROL tablets, in patients with a creatinine clearance between 20 and 50 mL/min, the initial daily dose of SIFROL tablets should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg pramipexole should not be exceeded. In patients with a creatinine clearance less than 20 mL/min, the

daily dose of SIFROL tablets should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg pramipexole should not be exceeded.

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

For SIFROL ER tablets, the use of SIFROL ER in patients with a creatinine clearance < 50 mL/min (moderate and severe renal impairment) has not been fully assessed.

If renal function declines during maintenance therapy the recommendations given above should be followed.

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

Restless Legs Syndrome

The immediate-release SIFROL tablets should be taken orally, swallowed with water. SIFROL tablets can be taken either with or without food.

The recommended starting dose of SIFROL is 0.125mg 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.

Ascending Dosage Schedule of SIFROL for RLS	
Titration Step	Once Daily Evening Dose (pramipexole hydrochloride)
1	0.125 mg
2*	0.25 mg
3*	0.5 mg
4*	0.75 mg

*if needed

Treatment discontinuation: SIFROL 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.

Dosing in patients with renal impairment: The elimination of SIFROL 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 require no reduction in daily dose. The use of SIFROL in RLS patients with renal impairment has not been studied.

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

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

OVERDOSAGE

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

Symptoms

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

Therapy

There is no established antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a neuroleptic agent may be indicated. Management of the overdose may require general supportive measures, intravenous fluids and electrocardiogram monitoring.

Haemodialysis has not been shown to be helpful.

PRESENTATION AND STORAGE CONDITIONS

SIFROL tablets

SIFROL 0.125 mg tablets are flat, round, white tablets, with 'P6' on one face and company symbol on the other face. Each tablet contains 0.125 mg pramipexole hydrochloride.

SIFROL 0.25 mg tablets are flat, oval, white, scored tablets, with 'P7' on both sides of the score of one face, and company symbol on both sides of the score of the other face. Each tablet contains 0.25 mg pramipexole hydrochloride.

SIFROL 1 mg tablets are flat, round, white, scored tablets, with 'P9' on both sides of the score of one face, and company symbol on both sides of the score of the other face. Each tablet contains 1 mg pramipexole hydrochloride.

SIFROL 1.5 mg tablets are flat, round, white, scored tablets, with 'P11' on both sides of the score of one face, and company symbol on both sides of the score of the other face. Each tablet contains 1.5 mg pramipexole hydrochloride.

SIFROL tablets are available in blister packs containing 10 and 100 tablets, except for SIFROL 0.125 mg which is also available in blister packs of 30 tablets.

Storage: Store below 30°C.Protect from light.

SIFROL ER tablets

SIFROL ER 0.375 mg extended-release tablets are white to off-white, round, biconvex, bevel-edged tablets, with 'P1' on one face and company symbol on the other face. Each extended-release tablet contains 0.375 mg pramipexole hydrochloride.

SIFROL ER 0.75 mg extended-release tablets are white to off-white, round, biconvex, bevel-edged tablets, with 'P2' on one face and company symbol on the other face. Each extended-release tablet contains 0.75 mg pramipexole hydrochloride.

SIFROL ER 1.5 mg extended-release tablets are white to off-white, oval, biconvex tablets, with 'P3' on one face and company symbol on the other face. Each extended-release tablet contains 1.5 mg pramipexole hydrochloride.

SIFROL ER 2.25mg extended-release tablets are white to off-white, oval, biconvex tablets with 'P12' on one face and company symbol on the other. Each extended-release tablet contains 2.25mg pramipexole hydrochloride.

SIFROL ER 3 mg extended-release tablets are white to off-white, oval, biconvex tablets, with 'P4' on one face and company symbol on the other face. Each extended-release tablet contains 3 mg pramipexole hydrochloride.

SIFROL ER 3.75mg extended-release tablets are white to off-white, oval, biconvex tablets with ‘P13’ on one face and company symbol on the other. Each extended-release tablet contains 3.75mg pramipexole hydrochloride.

SIFROL ER 4.5 mg extended-release tablets are white to off-white, oval, biconvex tablets, with ‘P5’ on one face and company symbol on the other face. Each extended-release tablet contains 4.5 mg pramipexole hydrochloride.

SIFROL ER extended-release tablets are available in blister packs containing 30 extended-release tablets, except for SIFROL ER 0.375 mg and 0.75 mg which are also available in blister packs of 10 extended-release tablets

The SIFROL ER STARTER PACK contains blister packs of 10 tablets of 0.375mg, 0.75 mg and 1.5mg extended release tablets.

Storage: Store below 30˚C.

Not all strengths and pack sizes of SIFROL and SIFROL ER are being distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 24 February 2011

Date of most recent amendment: 16 March 2011