SIFROL® Tablets

COMPOSITION

SIFROL tablet 0.125mg
Flat, round, white tablets with marking 'P6'. 1 tablet contains 0.125mg of pramipexole dihydrochloride monohydrate, equivalent to 0.088mg (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (= pramipexole base).

SIFROL tablet 1.00mg
Flat, round, white tablets with marking 'P9'. 1 tablet contains 1.00mg of pramipexole dihydrochloride monohydrate equivalent to 0.7mg (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (= pramipexole base).

Excipients: mannitol, maize starch, anhydrous colloidal silica, povidone K25, magnesium stearate

SIFROL extended-release tablet 0.375mg
Biconvex, round, white tablets with marking 'P1'. 1 tablet contains 0.375mg of pramipexole dihydrochloride monohydrate equivalent to 0.26mg (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (= pramipexole base).

SIFROL extended-release tablet 1.5mg
Biconvex, oval, white tablets with marking 'P3'. 1 tablet contains 1.5mg of pramipexole dihydrochloride monohydrate equivalent to 1.05mg (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (= pramipexole base).

Excipients: hypromellose 2208, maize starch, carbomer 941, colloidal anhydrous silica, magnesium stearate

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: dopamine agonist, ATC code: N04BC05

Mode of Action

Pramipexole, the active ingredient of SIFROL, is a dopamine agonist and binds with high selectivity and specificity to the dopamine D2 subfamily receptors and has a preferential affinity to D3 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. Pramipexole protects dopamine neurones from degeneration in response to ischemia or methamphetamine neurotoxicity.
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 vitro studies demonstrate that pramipexole protects neurones from levodopa neurotoxicity.

Pharmacodynamics

In human volunteers a dose-dependent decrease in prolactin was observed. In a clinical trial with healthy volunteers, where SIFROL extended-release tablets were titrated faster than recommended (every 3 days) up to 4.5 mg per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Clinical Trials

Parkinson's disease:
Efficacy of SIFROL tablets in the controlled clinical trials was maintained for the duration of the trials, approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy.

The efficacy and tolerability of an overnight switch from SIFROL tablets to SIFROL extended-release tablets at the same daily dose was evaluated in a double-blind clinical study in patients with early Parkinson's disease.
Efficacy was maintained in 87 of 103 patients switched to SIFROL extended-release tablets. Out of these 87 patients, 82.8% did not change their dose, 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 UPDRS Part II+III score, the change from baseline was considered not clinically relevant.
One patient switched to SIFROL extended-release tablets experienced a drug-related adverse event leading to withdrawal.

Restless Legs Syndrome:
The efficacy of SIFROL was evaluated in four placebo controlled trials in approximately 1000 patients with moderate to very severe Restless Legs Syndrome. Efficacy was demonstrated in controlled trials in patients treated for up to 12 weeks and sustained efficacy was shown over a period of 9 months. The efficacy of SIFROL was maintained during open continuation trials lasting for up to 1 year. In a placebo controlled clinical trial over 26 weeks, the efficacy of pramipexole was confirmed in patients with moderate to severe RLS.

Pharmacokinetics

Absoption

Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90%.

Tablets

The maximum plasma concentrations occur between 1 and 3 hours. The rate of absorption is reduced by food intake but not the overall extent of absorption.

Extended-release tablets

The maximum plasma concentrations occur at about 6 hours. Generally, food does not affect the bioavailability of pramipexole. A slight increase of about 20% in peak concentration and a delay of about 2 hours in time to reach peak concentration after a high fat meal are not considered clinically relevant.

Pramipexole shows linear kinetics and a relatively small inter-patient variation of plasma levels irrespective of the pharmaceutical form.

Distribution

In humans the protein binding of pramipexole is very low (< 20 %) and the volume of distribution is large (400L). High brain tissue concentrations were observed in the rat (approx. 8-fold compared to plasma).

Biotransformation

Pramipexole is metabolised in man only to a small extent.

Elimination

Renal excretion of unchanged pramipexole is the major route of elimination and accounts for about 80% of dose. Approx. 90 % of a 14C-labelled dose is excreted through the kidneys while less than 2% is found in the feces. The total clearance of pramipexole is approx. 500 ml/min and the renal clearance is approx. 400 ml/min. The elimination half-life (t ½) varies from 8 hours in the young to 12 hours in the elderly.

INDICATION

Tablets

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

SIFROL tablet is indicated for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.

Extended-release tablets

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

DOSAGE AND ADMINISTRATION

(all dose information refers to pramipexole salt form)

Parkinson's disease

Dosage

Initial treatment:

As shown below dosages should be increased gradually from a starting dose of 0.375 mg per day and then increased every 5 - 7 days. Providing patients do not experience intolerable side effects, the dosage should be titrated to achieve a maximal therapeutic effect.

Ascending-Dose Schedule of SIFROL			
week	total daily dose (mg)	tablets (mg)	extended-release tablets (mg)
1	0.375	3 x 0.125	0.375
2	0.75	3 x 0.25	0.75
3	1.50	3 x 0.5	1.50

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 may be switched to SIFROL extended-release tablets overnight, at the same daily dose. Dosage adjustment may be necessary for some patients according to response.

Maintenance treatment:

The individual dose should be in the range of 0.375 mg to a maximum of 4.5 mg 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. This does not preclude that in individual patients doses higher than 1.5 mg per day can result in additional therapeutic benefit.

This applies particularly to patients with advanced disease where a reduction of the levodopa therapy is intended.

Treatment discontinuation:

SIFROL tablets and extended-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. (see section Special Warnings and Precautions)

Missed dose

When the intake of a dose is missed, SIFROL prolonged-release tablets should be taken up to 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time.

Dosing in patients with concomitant levodopa therapy:

In patients with concomitant levodopa therapy it is recommended that the dosage of levodopa is reduced during both dose escalation and maintenance treatment with SIFROL. This may be necessary in order to avoid excessive dopaminergic stimulation.

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.

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 same percentage as decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce 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.**

Extended-release tablets

In patients with a creatinine clearance between 30 and 50 ml/min, treatment should be started with 0.375 mg SIFROL extended-release tablets every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week. If a further dose increase is necessary, daily doses should be increased by 0.375 mg pramipexole at weekly intervals up to a maximum dose of 2.25 mg pramipexole per day.

No data are available for the treatment of patients with a creatinine clearance below 30 ml/min with SIFROL extended-release tablets. The use of SIFROL tablets should be considered.

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

Dosing in patients with hepatic impairment:

Dose reduction is not considered necessary in patients with hepatic impairment.

Method of Administration

Tablets
The tablets should be taken orally, swallowed with water, and can be taken either with or without food. **The daily dosage is administered in equally divided doses 3x per day.**

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

Restless Legs Syndrome

Dosage
The recommended starting dose of SIFROL is 0.125 mg taken once daily 2 - 3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4 - 7 days to a maximum of 0.75 mg per day (as shown in the table below).

Ascending-Dose Schedule of SIFROL	
Titration Step	Once Daily Evening Dose (mg)
1	0.125
2*	0.25
3*	0.50
4*	0.75
* if needed	

Treatment discontinuation:
Since daily dose for the treatment of Restless Legs Syndrome will not exceed 0.54 mg of base (0.75 mg of salt).**SIFROL can be discontinued without tapering off.**
Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded.
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 approx. 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 up to 18 years.

Method of Administration

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

INTRUCTIONS FOR USE / HANDLING
N/A

CONTRAINDICATIONS
Hypersensitivity to pramipexole or any other component of the product.

SPECIAL WARNINGS AND PRECAUTIONS

Renal impairment
When prescribing SIFROL tablets in a patient with renal impairment a reduced dose is suggested in line with section Dosage and administration.

Hallucinations
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 in monotherapy in Parkinson's disease patients with early disease. Within the RLS clinical development program for registration, one case of hallucinations has been reported. **Patients should be informed that (mostly visual) hallucinations can occur.**

Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.

Abnormal Behaviour
Patients and caregivers should be made aware of the fact that abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours) such as binge eating, compulsive shopping, hypersexuality and pathological gambling have been reported in patients treated with dopaminergic drugs. Dose reduction/tapered discontinuation should be considered.

Retinal changes in albino rats
Opthalmological monitoring is recommended at regular interval or if vision abnormalities occur. **Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-years carcinogenicity study.** Evaluation of the retinas of albino mice, pigmented rats, monkeys, and minipigs did not reveal similar changes. **The potential significance of this effect in**

humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e. disk shedding) may be involved.

Postural hypotension

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

Dystonia

Patients with Parkinson's disease may present with axial dystonia such as antecollis, camptocormia or pleurothotonus (Pisa Syndrome). Dystonia has occasionally been reported following initiation of dopamine agonists including pramipexole, although a clear causal relationship has not been established. Dystonia may also occur several months following medication initiation or adjustment. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment considered.

Treatment discontinuation in Parkinson's disease

Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section Dosage and Administration).

Drug withdrawal syndrome

A drug withdrawal syndrome has been reported during or after discontinuation of dopamine agonists including pramipexole. Risk factors may include high cumulative dopaminergic exposure. Withdrawal symptoms do not respond to levodopa, and may include apathy, anxiety, depression, fatigue, sweating and pain. Prior to discontinuation, patients should be informed about potential withdrawal symptoms, and closely monitored during and after discontinuation. In case of severe withdrawal symptoms, temporary re-administration of a dopamine agonist at the lowest effective dose may be considered.

Melanoma

Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, **patients and providers are advised to monitor for melanoma when using pramipexole or other dopaminergic drugs.**

Patients with psychotic disorder

Patient with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risk. Co-administration of antipsychotic medications with SIFROL is not recommended, e.g. if dopamine-antagonistic effects can be expected.

Augmentation in 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 significant difference between pramipexole (N=152) and placebo groups (N=149).

Remnants in stool

Some patients have reported the occurrence of remnants in faeces which may resemble intact SIFROL prolonged-release tablets. If patients report such an observation, the physician should reassess patient's response to therapy.

Sudden onset of sleep and somnolence

Falling Asleep During Activities of Daily Living:

Patients treated with Pramipexole have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on Pramipexole, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving Pramipexole at doses above 1.5 mg/day. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. **For this reason, prescribers should continually reassess patents for drowsiness of sleepiness, especially since some of the 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.**

Before initiating treatment with Pramipexole, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Pramipexole such as concomitant sedating medications, the presence of sleep dis orders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine – see PRECAUTIONS, Drug Interactions). **If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), Pramipexole should ordinarily be discontinued. If a decision is made to continue Pramipexole, patients should be advised to not drive and to avoid other potentially dangerous activities. 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.**

USE IN SPECIFIC POPULATIONS

Pregnancy, Lactation and Fertility

Pregnancy

The effect on pregnancy and lactation has not been investigated in humans. **Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses.**
SIFROL should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

The excretion of SIFROL into the breast milk has not been studied in women. **In rats, the concentration of drug was higher in the breast milk than in plasma. As SIFROL treatment inhibits secretion of prolactin in humans inhibition of lactation is expected. In consequence, SIFROL should not be used during breast-feeding.**

Fertility

No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected oestrous cycles and reduced female fertility as expected for a dopamine agonist. However, **these studies did not indicate direct or indirect harmful effects with respect to male fertility.**

Driving and Using Machines Patients should be aware of the fact that hallucinations can occur and may adversely affect their ability to drive.
Patients 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. (see section Special Warnings and Precautions)

ADVERSE REACTIONS

SIFROL Tablets - Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.
SIFROL Extended-Release Tablets - Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,778 Parkinson's disease patients on pramipexole and 1,297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% of patients on placebo reported at least one adverse drug reaction.

The majority of adverse drug reactions usually start early in therapy and most tended to disappear even as therapy was continued.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ($\geqslant$ 1/10);

common (⩾ 1/100 to < 1/10); uncommon (⩾ 1/1,000 to < 1/100); rare (⩾ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Parkinson's disease, most common adverse reactions

The most commonly (⩾ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg pramipexole salt per day. A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

Tabulated summary of adverse reactions

The following adverse reactions have been reported during use of SIFROL in the clinical trials and in the post-marketing experience.

MedDRA System Organ Class terminology	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to < 1/100)	Rare (≥1/10,000 to <1/1,000)	Not known
Infections and infestations			Pneumonia		
Endocrine disorders			inappropriate antidiuretic hormone secretion[1]		
Psychiatric disorders		Insomnia hallucinations abnormal dreams confusion behavioural symptoms of impulse control disorders and compulsions	compulsive shopping pathological gambling restlessness hypersexuality delusion libido disorder paranoia delirium binge eating[1] hyperphagia[1]	mania	
Nervous system disorders	somnolence dizziness dyskinesia	headache	sudden onset of sleep amnesia hyperkinesia		

			syncope Antecollis		
Eye disorders		visual impairment including diplopia vision blurred visual acuity reduced			
Cardiac disorders			cardiac failure[1]		
Vascular disorders		hypotension			
Respiratory, thoracic, and mediastinal disorders			Dyspnoea Hiccups		
Gastrointestinal disorders	nausea	constipation vomiting			
Skin and subcutaneous tissue disorders			hypersensitivity pruritus rash		
General disorders and administration site conditions		fatigue peripheral oedema			Drug withdrawal syndrome (Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.
Investigations		weight decrease including	weight increase		

		decreased appetite			

[1] This side effect has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 2,762 patients with Parkinson's Disease treated with pramipexole.

Description of selected adverse reactions

Sudden onsert of sleep and Somnolence

Patients treated with pramipexole have reported falling asleep during activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole, and which, according to the current knowledge of sleep physiology, always 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.

Hypotension

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

Libido disorders

SIFROL may be associated with disorders of libido (increased or decreased).

Impulse control disorders and compulsive behaviours

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 a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behavior (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age ($\leqslant$ 65 years), not being married and self-reported family history of gambling behaviours.

Cardiac failure

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. A causal relationship between pramipexole and cardiac failure has not been demonstrated.

DRUG INTERACTIONS

Pramipexole is bound to plasma proteins to a very low (< 20%) extent and little biotransformation is seen in man. Therefore, interactions with other medication affecting plasma protein binding or elimination by biotransformation are unlikely.

Medication that inhibit the active renal tubular secretion of basic (cationic) drugs, such as cimetidine, or are themselves eliminated by active renal tubular secretion, may interact with SIFROL resulting in reduced clearance of either or both medication. In case of concomitant treatment with these kinds of drugs (incl. amantadine) attention should be paid to signs of dopamine over stimulation, such as dyskinesias, agitation or hallucinations. In such cases a dose reduction is necessary.

Selegiline and levodopa do not influence the pharmacokinetics of pramipexole. The overall extent of absorption or elimination of levodopa is not changed by pramipexole. The interaction with anticholinergics and amantadine has not been examined.
As anticholinergics are mainly eliminated by hepatic metabolism, pharmacokinetic drug-drug interactions with pramipexole are rather unlikely. With amantadine, an interaction is possible via the same system of excretion in the kidney.

Antipsychotic medicinal products
Co-administration of antipsychotic medicinal products with pramipexole is not recommended, e.g. if dopamine-antagonistic effects can be expected. (see section Special Warnings and Precautions)

While increasing the dose of SIFROL in Parkinson's disease patients it is recommended that the dosage of levodopa is reduced and the dosage of other antiparkinsonian medication kept constant.

Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with SIFROL and when taking concomitant medication that increase plasma levels of pramipexole (e.g., cimetidine).

OVERDOSAGE

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 along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

Haemodialysis has not been shown to be helpful.

Availability

Tablets of 0.125, 1.0 mg in blister packs of 30's.
Extended-release tablets of 0.375, 1.5mg in blister packs of 30's.
(Note: Not all strengths are available in the market)

Container Closure System:
Sifrol Tab 0.125mg: Aluminium based lidding foil
Sifrol Tab 1mg: Aluminium based lidding foil
Sifrol Extended Release Tablet 0.375: Alu/Alu blister
Sifrol Extended Release Tablet 1.5mg: Alu/Alu blister

Store below 30°C.
Please refer to packaging for information on shelf-life.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein, Germany

or

Rottendorf Pharma GmBH (for extended-release tablets)
Ostenfelder Straße 51 – 61
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Germany

for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

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Store in a Safe Place Out of Reach of Children