SIFROL®
PRAMIPEXOLE

Description

Sifrol 0.125 mg

Flat, round, white tablets with bevelled edges and markings: on face 'P6'; other face with Boehringer Ingelheim Company symbol.

Sifrol 0.25 mg

White, oval tablets, both face flat, with bevelled edges and markings: 'P7' / deep breakline / P7 on one face, Boehringer Ingelheim Company symbol / breakline / Boehringer Ingelheim Company symbol on other face.

Composition

1 tablet contains 0.125 mg ; 0.25 mg
(S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate equivalent to 0.088 mg ; 0.18 mg pramipexole base.
Excipients: ** mannitol, maize starch, anhydrous colloidal silica, polyvidone, magnesium stearate

INDICATION/USAGE

SIFROL tablets and Extended-release tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose "on off" fluctuations). It may be used alone (without levodopa) or in combination with levodopa.

SIFROL tablets are indicated for the symptomatic treatment of idiopathic Restless Legs Syndrome.

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 prolonged-release tablets overnight, at the same daily dose.

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.

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 1.1 mg (1.5 mg of salt). In advanced Parkinson's disease, doses higher than 1.1 mg (1.5 mg of salt) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with SIFROL®, depending on reactions in individual patients.

Treatment discontinuation:
Abrupt discontinuation of dopaminergic therapy can lead to development of aneuroleptic malignant syndrome. Therefore, Pramipexole dihydrochloride monohydrate should be tapered off at 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 Special Warnings and Precautions).

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 dihydrochloride monohydrate 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 dihydrochloride monohydrate 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 dihydrochloride monohydrate 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.

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

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.

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	

As long-term efficacy of SIFROL in the treatment of RLS has not been sufficiently tested, patient's response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Treatment discontinuation:
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 dihydrochloride monohydrate. 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 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.

INSTRUCTION FOR USE /HANDLING

N/A

CONTRAINDICATION

Hypersensitivity to Pramipexole dihydrochloride monohydrate or any other component of the product.

SPECIAL WARNING & PRECAUTIONS

Renal impairment
When prescribing SIFROL in a patient with renal impairment a reduced dose is suggested in line with section 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 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 made aware of the fact that hallucinations can occur and may adversely affect their

ability to drive.

Abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours)
Patients and caregivers should be made aware of the fact that abnormal behavior (reflecting symptoms of impulse control disorders and compulsive behaviors) 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.

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

Retinal changes in albino rats
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.

Sudden onset of sleep and somnolence
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. 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.

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.

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 dihydrochloride monohydrate or other dopaminergic drugs.

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.

Augmentation in Restless Legs Syndrome

Reports in the literature that indicate treatment of RLS with dopaminergic medications can result in augmentation.

Treatment with SIFROL should be started with the recommended dose of 0.125 mg and may only be increased to a maximum recommended daily dose of 0.75 mg, if additional symptom relief is required (see section DOSAGE AND ADMINISTRATION). Prior to treatment, patients should be informed that augmentation may occur. They should be regularly monitored for the occurrence of augmentation. If augmentation occurs, the adequacy of pramipexole treatment should be reviewed and dosage adjustment or discontinuation considered.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy, Lactation, and Fertility

Pregnancy
The effect on pregnancy and lactation has not been investigated in humans. Pramipexole dihydrochloride monohydrate 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. Animal 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).

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.

INTERACTIONS

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

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 dihydrochloride monohydrate (e.g. cimetidine).

Antipsychotic medicinal products
Co-administration of antipsychotic medicinal products with Pramipexole dihydrochloride monohydrate should be avoided, e.g. if dopamine-antagonistic effects can be expected. (see section Special Warnings and Precautions).

ADVERSE REACTIONS

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	*Pramipexole adverse reactions*
Infections and infestations	Pneumonia
Endocrine disorders	Inappropriate antidiuretic hormone secretion
Psychiatric disorders	Abnormal behavior (reflecting symptoms of impulse control disorders and compulsions) such as binge eating, compulsive shopping, hyper sexuality and pathological gambling Abnormal dreams Confusion Delusion Hallucinations Hyperphagia Insomnia Libido disorders Paranoia Restlessness

Nervous system disorders	Amnesia Antecollis Dizziness Dyskinesia Headache Hyperkinesia Somnolence Sudden onset of sleep Syncope Augmentation in Restless Legs Syndrome
Eye disorders	Visual impairment including diplopia, vision blurred and visual acuity reduced.
Cardiac disorders	Cardiac failure
Vascular disorders	Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnoea Hiccups
Gastrointestinal disorders	Constipation Nausea 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) (see section Special Warnings and Precautions)
Investigations	Weight decrease including decreased appetite Weight increase

Description of selected adverse reactions

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 (increase or decrease).

Sudden onset of sleep and somnolence

Patients treated with Pramipexole dihydrochloride monohydrate 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 dihydrochloride 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.

Cardiac failure

In clinical studies and post-marketing experience cardiac failure has been reported in patients with Pramipexole dihydrochloride monohydrate. In a pharmacoepidemiological study Pramipexole dihydrochloride monohydrate use was associated with an increased risk of cardiac failure compared with non-use of Pramipexole dihydrochloride monohydrate. A causal relationship between Pramipexole dihydrochloride monohydrate and cardiac failure has not been demonstrated.

OVERDOSE

Symptoms

There is no clinical experience with massive overdose. 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 overdose 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.

PHARMACOLOGICAL PROPERTIES

Mode of Action

Pramipexole dihydrochloride monohydrate, 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 dihydrochloride monohydrate inhibits dopamine synthesis, release, and turnover.Pramipexole dihydrochloride monohydrate 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 dihydrochloride monohydrate 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 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 prolonged-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 prolonged-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 dihydrochloride monohydrate was confirmed in patients with moderate to severe RLS.

Pharmacokinetics

Pharmacotherapeutic group: dopamine agonist, ATC code: N04BC05

Absorption

Pramipexole dihydrochloride monohydrate 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.

Pramipexole dihydrochloride monohydrate 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 dihydrochloride monohydrate 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 dihydrochloride monohydrate is metabolised in man only to a small extent.

Elimination

Renal excretion of unchanged Pramipexole dihydrochloride monohydrate 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 faeces. The total clearance of Pramipexole dihydrochloride monohydrate 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.

TOXICOLOGY

Repeated-dose toxicity

Repeated dose toxicity studies showed that Pramipexole dihydrochloride monohydrate exerted functional effects, mainly involving the CNS and, in the rat, the female reproductive system, probably resulting from an exaggerated pharmacodynamic effect of Pramipexole dihydrochloride monohydrate.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

Reproductive and developmental toxicity

The potential effects of Pramipexole dihydrochloride monohydrate on reproductive function have been investigated in rats and rabbits. Pramipexole dihydrochloride monohydrate was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the hypoprolactinaemic effect of the compound and the special role of prolactin in reproductive function in the female rat, the effects of Pramipexole dihydrochloride monohydrate on pregnancy and female fertility were not fully elucidated.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

Genotoxicity and carcinogenicity

Pramipexole dihydrochloride monohydrate was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of Pramipexole dihydrochloride monohydrate. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of the salt form) and higher, Pramipexole dihydrochloride monohydrate was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study, or in any other species investigated.

Availability

Tablets of 0.125 mg — Reg. No: XXXXXXXXXXXXXXX
Box, contains 3 alublister @ 10 tablets

Tablets of 0.25 mg — Reg. No: XXXXXXXXXXXXXXX
Box, contains 3 alublister @ 10 tablets

Sensitive to light. Store below 30°C. Store in the original package.
Store in a safe place out of the reach of children!

Only on doctor's prescription
Harus dengan resep dokter

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

For:
Boehringer Ingelheim International GmbH.
Germany

Imported by:
PT. Tunggal Idaman Abdi
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