Boehringer Ingelheim

Sifrol® Tablets

1. NAME OF THE MEDICINAL PRODUCT

Sifrol® tablet 0.125mg
Sifrol® tablet 1.00mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sifrol® tablet 0.125mg
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
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).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Sifrol® tablet 0.125mg
Flat, round, white tablets with marking 'P6'.

Sifrol® tablet 1.00mg
Flat, round, white tablets with marking 'P9'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of 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	Dosage (mg)	Total Daily Dose (mg)
1	3 x 0.125	0.375
2	3 x 0.25	0.75
3	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.

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 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 for use)

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.

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, ie. 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 reduction is not considered necessary in patients with hepatic impairment.

Paediatric Use
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. 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	

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 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.

4.3 Contraindications
Hypersensitivity to pramipexole or any other component of the product.

4.4 Special warnings and precautions for use

Sudden onset of sleep during daily activities has been reported in rare cases. This can be life-threatening to the patient or others depending on the circumstances. These episodes have been reported in some cases without awareness of warning signs. If this occurs, reduction of dosage or termination of therapy should be considered. Patients being treated with pramipexole must be informed not to drive or engage in other activities where impaired alertness could put themselves or others at risk of serious injury or death (e.g. operating machines). Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole (see section on Effects on ability to drive and use machines and Undesirable effects).

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 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 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 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.

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 is not recommended, e.g. if dopamine-antagonistic effects can be expected (see section Interaction with other medicinal products and other forms of interaction).

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 (ie. 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.

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.

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.

Treatment discontinuation in Parkinson's disease
Symptoms suggestive of a neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. (see section Posology and method of administration)

Dopamine agonist withdrawal syndrome (DAWS)
DAWS has been reported with dopamine agonists, including pramipexole (see section Undesirable effects). To discontinue treatment with patients with Parkinson's disease, pramipexole should be tapered off (see section Posology and method of administration). Limited data suggests that patients with impulse control disorders and those receiving high daily dose and/or high cumulative doses of dopamine agonists may be at higher risk for developing DAWS. Withdrawal symptoms may include apathy, anxiety, depression, fatigue, sweating and pain and do not respond to levodopa. Prior to tapering off and discontinuing pramipexole, patients should be informed about potential withdrawal symptoms. Patients should be closely monitored during tapering and discontinuation. In case of severe and/or persistent withdrawal symptoms, temporary readministration of pramipexole at the lowest effective dose may be considered.

Rhabdomyolysis
A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with Sifrol® Tablet. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

Ophthalmologic monitoring
Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occurs.

Augmentation in Restless Legs Syndrome
Reports in the literature indicate that treatment of Restless Legs Syndrome 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.

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 Posology and method of 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Inhibitors or competitors of active renal elimination pathway
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 (including amantadine) attention should be paid to signs of dopamine overstimulation, such as dyskinesias, agitation or hallucinations. In such cases a dose reduction is necessary.

Pharmacokinetic interactions with selegiline or levodopa
Selegiline and levodopa do not influence the pharmacokinetics of pramipexole. The overall extent of absorption or elimination of levodopa is not changed by pramipexole.

Anticholinergic agents or amantadine
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. The interaction with anticholinergics and amantadine has not been examined.

Dopamine antagonists

Co-administration of pramipexole with antipsychotics (e.g. phenothiazines, butyrophenones, thioxanthenes) **or other centrally active dopamine antagonists such as metoclopramide** is not recommended, e.g. if dopamine-antagonistic effects can be expected (see section Special warnings and precautions for use).

Effect of pramipexole on levodopa or other antiparkinsonian medication
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 anti-parkinsonian medication kept constant.

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

4.6 Fertility, pregnancy and lactation

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. Animal studies did not indicate direct or indirect harmful effects with respect to male fertility.

4.7 Effects on ability to drive and use 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 for use)

4.8 Undesirable effects

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 behaviour (reflecting symptoms of impulse control disorders and compulsions) such as binge eating, compulsive shopping, hypersexuality 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** (see section Special warnings and precautions for use)
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**
Reproductive system and breast disorders	**Spontaneous penile erection**
General disorders and administration site conditions	**Fatigue** **Peripheral oedema** **Dopamine agonist withdrawal syndrome including apathy, anxiety, depression, fatigue, sweating and pain.**
Investigations	**Weight decrease including decreased appetite** **Weight increase**

Description of selected adverse reactions

Sudden onset 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 medications 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 (increase or decrease).

Dopamine agonist withdrawal syndrome

Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists including pramipexole. Symptoms include apathy, anxiety, depression, fatigue, sweating and pain (see section Special warnings and precautions for use).

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.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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 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. Pramipexole protects dopamine neurones from degeneration in response to ischemia or metamphetamine 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® prolonged-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.

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.

5.2 Pharmacokinetics properties

Absorption
Pramipexole is rapidly and completely absorbed following oral administration. The absolute bioavailability is greater than 90% and 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 shows linear kinetics and a relatively small inter-patient variation of plasma levels.

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.
Age - Pramipexole clearance decreases with the 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 (age less than 40 years). The 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.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Maize starch
Anhydrous colloidal silica
Povidone K 25
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to packaging for information on shelf-life

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

OPA/aluminium/PVC-aluminium blisters.
Each blister strip contains 10 tablets.
Tablets of 0.125mg and 1.0 mg in blister packs of 30's and 100's.
Note: Not all strengths are available in the market.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER/MANUFACTURER

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

8. MARKETING AUTHORISATION NUMBER(S)

Sifrol® tablet 0.125mg
MAL20000717AZ
BRU10060504P

Sifrol® tablet 1.00mg
MAL20000719AZ

9. DATE OF REVISION OF THE TEXT

27-Nov-2024