

1. NAME OF THE MEDICINAL PRODUCT

Sifrol® extended-release tablet 0.375mg

Sifrol® extended-release tablet 1.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sifrol® extended-release tablet 0.375mg

Each prolonged-release tablet contains 0.375 mg pramipexole dihydrochloride monohydrate equivalent to 0.26 mg (S)-2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole (= pramipexole base).

Sifrol® extended-release tablet 1.5mg

Each prolonged-release tablet contains 1.5 mg pramipexole dihydrochloride monohydrate equivalent to 1.05 mg (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

Extended-release tablet

3.1 Product description

Sifrol® extended-release tablet 0.375mg

White to off-white, round, biconvex, bevel-edged tablets, one side debossed with the BI company symbol and the other side debossed with P1

Sifrol® extended-release tablet 1.5mg

White to off-white, oval, biconvex tablets, one side debossed with the BI company symbol and the other side debossed with P3

4. CLINICAL PARTICULARS**4.1 Therapeutic indications**

Sifrol® extended-release tablet 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.

4.2 Posology and method of administration

(all dose information refers to pramipexole salt form)

Parkinson's disease**Posology****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®			
<i>week</i>	<i>total daily dose (mg)</i>	<i>tablets (mg)</i>	<i>extended-release tablets (mg)</i>
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.

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 Special warnings and precautions for use)

Missed dose

When the intake of a dose is missed, Sifrol® extended-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.

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.

Paediatric Use

Safety and efficacy of Sifrol® have not been established in children and adolescents up to 18 years.

Method of Administration

The extended-release tablets should be taken once daily at about the same time each day. The extended-release tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The extended-release tablets may be taken 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® in a patient with renal impairment a reduced dose is suggested in line with section Dosage and Administration.

Hallucinations and abnormal behaviour

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.

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.

Remnants in stool

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

Rhabdomyolysis

In the clinical development program for immediate-release pramipexole tablets, a single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease. 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.

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 kind 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 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.

<i>MedDRA System Organ Class terminology</i>	<i>Pramipexole adverse reactions</i>
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
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 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 (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 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 metamphetamine neurotoxicity. 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® 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.

5.2 Pharmacokinetic properties

Absorption

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

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 ($t_{1/2}$) varies from 8 hours in the young to 12 hours in the elderly. Age - Pramipexole clearance is reduced by approximately 30% in the elderly (aged 65 years or older) compared with young healthy volunteers (age less than 40 years). This difference is most likely due to the 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

Hypromellose
Maize starch
Carbomer
Silica colloidal anhydrous
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.
Store in the original package.

6.5 Nature and contents of container

OPA/aluminium/PVC-aluminium blisters.
Each blister strip contains 10 tablets.
Extended-release tablets of 0.375mg, 1.5 mg in blister packs of 10's and 30's
Note: Not all strengths and pack sizes are available in the market.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER

Manufactured by:
Rottendorf Pharma GmbH
Ostenfelder Straße 51-61
59320 Ennigerloh
Germany
for
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Sifrol® extended-release tablet 0.375mg
MAL20102062ACZ
BRU16092069PS2

Sifrol® extended-release tablet 1.5mg
MAL20102064ACZ
BRU16092070PS2

9. DATE OF REVISION OF THE TEXT

26 November 2024