Product Information

Sifrol ER
pramipexole
Extended-release tablets

1. NAME OF THE MEDICINAL PRODUCT

SIFROL ER 0.375 mg extended-release tablets
SIFROL ER 0.75 mg extended-release tablets
SIFROL ER 1.5 mg extended-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Sifrol ER 0.375 mg extended-release tablet contains 0.375 mg pramipexole dihydrochloride monohydrate equivalent to 0.26 mg pramipexole.

Each Sifrol ER 0.75 mg extended-release tablet contains 0.75 mg pramipexole dihydrochloride monohydrate equivalent to 0.52 mg pramipexole.

Each Sifrol ER 1.5 mg extended-release tablet contains 1.5 mg pramipexole dihydrochloride monohydrate equivalent to 1.05 mg pramipexole.

Please note:
Pramipexole doses as published in the literature refer to the salt form.
Therefore, doses will be expressed in terms of both pramipexole salt and pramipexole base (in brackets).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-release tablets.

The tablets are white to off-white and have a code embossed.

Strength (mg salt)	**Appearance**
Sifrol ER 0.375 mg	round, with bevelled edges, code embossed (one side with code P1 and one side with the Boehringer Ingelheim company symbol).
Sifrol ER 0.75 mg	round, with bevelled edges, code embossed (one side with code P2 and one side with the Boehringer Ingelheim company symbol).
Sifrol ER 1.5 mg	oval, code embossed (one side with code P3 and one side with the Boehringer Ingelheim company symbol).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SIFROL is indicated for treatment of signs and symptoms of idiopathic Parkinson's disease, as monotherapy or in combination with levodopa.

4.2 Posology and method of administration

Posology

SIFROL extended-release tablets are a once-a-day oral formulation of pramipexole.

Initial treatment
Doses should be increased gradually from a starting dose of 0.375 mg of salt (0.26 mg of base) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of SIFROL extended-release tablets		
Week	Daily dose (mg of salt)	Daily dose (mg of base)
1	0.375	0.26
2	0.75	0.52
3	1.5	1.05

If a further dose increase is necessary the daily dose should be increased by 0.75 mg of salt (0.52 mg of base) at weekly intervals up to a maximum dose of 4.5 mg of salt (3.15 mg of base) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg of salt (1.05 mg of base) per day (see section 4.8).

Patients already taking SIFROL tablets may be switched to SIFROL extended-release tablets overnight, at the same daily dose. After switching to SIFROL extended-release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).

Maintenance treatment
The individual dose of pramipexole should be in the range of 0.375 mg of salt (0.26 mg of base) to a maximum of 4.5 mg of salt (3.15 mg of base) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.5 mg of salt (1.05 mg of base). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.5 mg of salt (1.05 mg of base). In advanced Parkinson's disease, pramipexole doses higher than 1.5 mg of salt (1.05 mg of base) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with SIFROL, depending on reactions in individual patients (see section 4.5).

Missed dose
When the intake of a dose is missed, SIFROL extended-release tablets should be taken within 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.

Treatment discontinuation
Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome or a dopamine agonist withdrawal syndrome. Pramipexole should be tapered off at a rate of 0.75 mg of salt (0.52 mg of base) per day until the daily dose has been reduced to 0.75 mg of salt (0.52 mg of base). Thereafter the dose should be reduced by 0.375 mg of salt (0.26 mg of base) per day (see section 4.4). Dopamine agonist withdrawal syndrome could still appear while tapering and a temporary increase of the dose could be necessary before resuming tapering (see section 4.4)

Renal impairment
The elimination of pramipexole is dependent on renal function. The following dose 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, doses should be increased by 0.375 mg pramipexole salt at weekly intervals up to a maximum dose of 2.25 mg of salt (1.57 mg pramipexole base) per day.

The treatment of patients with a creatinine clearance below 30 mL/min with SIFROL extended-release tablets is not recommended as no data are available for this patient population.
If renal function declines during maintenance therapy, the recommendations given above should be followed.

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

Paediatric population
The safety and efficacy of SIFROL in children below 18 years has not been established. There is no relevant use of SIFROL extended-release tablets in the paediatric population for the indication of Parkinson's Disease.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

When prescribing SIFROL in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2.

Hallucinations
Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur.

Dyskinesia
In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia can occur during the initial titration of SIFROL. If they occur, the dose of levodopa should be decreased.

Dystonia
Axial dystonia including antecollis, camptocormia and pleurothotonus (Pisa Syndrome) has occasionally been reported in patients with Parkinson's disease following initiation or incremental dose increase of pramipexole. Although dystonia may be a symptom of Parkinson's disease, the symptoms in these patients have improved after reduction or withdrawal of pramipexole. If dystonia occurs, the dopaminergic medication regimen should be reviewed and an adjustment in the dose of pramipexole considered.

Sudden onset of sleep and somnolence
Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with SIFROL.

Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of the dose or termination of therapy may be considered. Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.5, 4.7 and section 4.8).

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including SIFROL. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Mania and delirium
Patients should be regularly monitored for the development of mania and delirium. Patients and carers should be made aware that mania and delirium can occur in patients treated with pramipexole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Patients with psychotic disorders
Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5).

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

Severe cardiovascular disease
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.

Neuroleptic malignant syndrome
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2).

Dopamine agonist withdrawal syndrome (DAWS)
DAWS has been reported with dopamine agonists, including pramipexole (see section 4.8). To discontinue treatment in patients with Parkinson's disease, pramipexole should be tapered off (see section 4.2). 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 re-administration 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.

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 medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with

anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

Inhibitors/competitors of active renal elimination pathway
Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with SIFROL.

Combination with levodopa
When SIFROL is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of SIFROL.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.4, 4.7 and 4.8).

Antipsychotic medicinal products
Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

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 (see section 5.3). SIFROL should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus.

Breast-feeding
As pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma. In the absence of human data, SIFROL should not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued.

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.

4.7 Effects on ability to drive and use machines

SIFROL can have a major influence on the ability to drive and use machines.

Hallucinations or somnolence can occur.

Patients being treated with SIFROL and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also sections 4.4, 4.5 and 4.8).

4.8 Undesirable effects

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 tend to disappear even as therapy is 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 (≥ 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).

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 (see section 4.2). 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.

Body System	**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		
Eye disorders		visual impairment including diplopia, vision blurred, visual acuity reduced			
Cardiac disorders			cardiac failure[1]		
Vascular disorders		hypotension			
Respiratory, thoracic, and			dyspnoea, hiccups		

mediastinal disorders					
Gastrointestinal disorders	nausea	constipation, vomiting			
Skin and subcutaneous tissue disorders			hypersensitivity, pruritus, rash		
Reproductive system and breast disorder				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		

[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

Somnolence

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

Libido disorders

Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including SIFROL (see section 4.4).

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 behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age (≤ 65 years), not being married and self-reported family history of gambling behaviours.

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 4.4).

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 (observed risk ratio 1.86; 95% CI, 1.21-2.85).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

4.9 Overdose

There is no clinical experience with massive overdose. The expected adverse reactions would be those related to the pharmacodynamic profile of a dopamine agonist, including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. 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, administration of activated charcoal and electrocardiogram monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-Parkinson drugs, dopamine agonists, ATC code: N04BC05.

Mechanism of action
Pramipexole is a dopamine agonist that binds with high selectivity and specificity to the D2 subfamily of dopamine receptors of which it has a preferential affinity to D3 receptors, and has full intrinsic activity.

Pramipexole alleviates parkinsonian motor deficits by stimulation of dopamine receptors in the striatum. Animal studies have shown that pramipexole inhibits dopamine synthesis, release, and turnover.

Pharmacodynamic effects
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 (every 3 days) than recommended up to 3.15 mg pramipexole base (4.5 mg of salt) per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Clinical efficacy and safety in Parkinson's disease
In patients pramipexole alleviates signs and symptoms of idiopathic Parkinson's disease. Placebo-controlled clinical trials included approximately 1,800 patients of Hoehn and Yahr stages I – V treated with pramipexole. Out of these, approximately 1,000 were in more advanced stages, received concomitant levodopa therapy, and suffered from motor complications.

In early and advanced Parkinson's disease, efficacy of pramipexole in controlled clinical trials was maintained for approximately six months. In open continuation trials lasting for more than three years there were no signs of decreasing efficacy.

In a controlled double blind clinical trial of 2 year duration, initial treatment with pramipexole significantly delayed the onset of motor complications, and reduced their occurrence compared to initial treatment with levodopa. This delay in motor complications with pramipexole should be balanced against a greater improvement in motor function with levodopa (as measured by the mean change in UPDRS-score). The overall incidence of hallucinations and somnolence was generally

higher in the escalation phase with the pramipexole group. However, there was no significant difference during the maintenance phase. These points should be considered when initiating pramipexole treatment in patients with Parkinson's disease.

The safety and efficacy of SIFROL extended-release tablets in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of three randomised, controlled trials. Two trials were conducted in patients with early Parkinson's disease and one trial was conducted in patients with advanced Parkinson's disease.

Superiority of SIFROL extended-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (CGI-I and PGI-I responder rates) efficacy endpoints in a double-blind placebo-controlled trial including a total of 539 patients with early Parkinson's disease. Maintenance of efficacy was shown in patients treated for 33 weeks. SIFROL extended-release tablets were non-inferior to pramipexole immediate release tablets as assessed on the UPDRS Parts II+III score at week 33.

In a double-blind placebo-controlled trial including a total of 517 patients with advanced Parkinson's disease who were on concomitant levodopa therapy superiority of SIFROL extended-release tablets over placebo was demonstrated after 18 weeks of treatment on both the primary (UPDRS Parts II+III score) and the key secondary (off-time) efficacy endpoints.

The efficacy and tolerability of an overnight switch from SIFROL tablets to SIFROL extended-release tablets at the same daily dose were 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.
Only one patient switched to SIFROL extended-release tablets experienced a drug-related adverse event leading to withdrawal.

5.2 Pharmacokinetic properties

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

In a Phase I trial, where pramipexole immediate release and extended-release tablets were assessed in fasted state, the minimum and peak plasma concentration (C_{min}, C_{max}) and exposure (AUC) of the same daily dose of SIFROL extended-release tablets given once daily and SIFROL tablets given three times a day were equivalent.

The once daily administration of SIFROL extended-release tablets causes less frequent fluctuations in the pramipexole plasma concentration over 24 hours compared to the three times daily administration of pramipexole immediate release tablets.

The maximum plasma concentrations occur at about 6 hours after administration of SIFROL extended-release tablets once daily. Steady state of exposure is reached at the latest after 5 days of continuous dosing.

Concomitant administration with food does generally not affect the bioavailability of pramipexole. Intake of a high fat meal induced an increase in peak concentration (C_{max}) of about 24% after a single dose administration and about 20% after multiple dose administrations and a delay of about 2 hours in time to reach peak concentration in healthy volunteers. Total exposure (AUC) was not affected by concomitant food intake. The increase in C_{max} is not considered clinically relevant. In the Phase III studies that established safety and efficacy of SIFROL extended-release tablets, patients were instructed to take study medication without regard to food intake.

While body weight has no impact on the AUC, it was found to influence the volume of distribution and therefore the peak concentrations C_{max}. A decreased body weight by 30 kg results in an increase in C_{max} of 45%. However, in Phase III trials in Parkinson's disease patients no clinically meaningful influence of body weight on the therapeutic effect and tolerability of SIFROL extended-release tablets was detected.

Pramipexole shows linear kinetics and a 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 (400 L). 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. Approximately 90% of ^{14}C-labelled dose is excreted through the kidneys while less than 2% is found in the faeces. The total clearance of pramipexole is approximately 500 mL/min and the renal clearance is approximately 400 mL/min. The elimination half-life (t½) varies from 8 hours in the young to 12 hours in the elderly.

5.3 Preclinical safety data

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

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.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

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

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Maize starch
Hypromellose 2208
Carbomer 941
Colloidal anhydrous silica
Magnesium stearate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C in the original package in order to protect from moisture.

6.5 Nature and contents of container
Aluminium blisters - PVC/PVAC/aluminium.
Each blister strip contains 10 extended-release tablets.
Cartons containing 1or 3 blister strips (10 or 30 extended-release tablets).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7. Manufacturer
Boehringer Ingelheim Pharma GmbH & CO.KG
Binger Strasse 173, D-55216 Ingelheim am Rhein
Germany

8. Marketing authorisation holder:
Boehringer Ingelheim Israel LTD
Medinat Ha-Yehudim 89 St.
P.O. Box 4124
Herzliya Pituach 4676672

9. Marketing authorisation numbers:

Sifrol ER 0.375 mg	144 95 33088-00
Sifrol ER 0.75 mg	144 96 33089-00
Sifrol ER 1.5 mg	144 97 33090-00

Revised in October 2024.