Patient leaflet in accordance with the Pharmacists' Regulations (preparations) - 1986
This medicine is to be supplied upon physician's prescription only

Sifrol® ER 0.375
Sifrol® ER 0.75
Sifrol® ER 1.5

Extended-release tablets
Each tablet of Sifrol ER 0.375 contains pramipexole dihydrochloride monohydrate 0.375 mg
Each tablet of Sifrol ER 0.75 contains pramipexole dihydrochloride monohydrate 0.75 mg
Each tablet of Sifrol ER 1.5 contains pramipexole dihydrochloride monohydrate 1.5 mg

*For the list of inactive ingredients and allergens in the medicine - see section 6, "Additional information".

Read the entire leaflet carefully before using this medicine. This leaflet contains essential information about this medicine. If you have any further questions, refer to the physician or the pharmacist.
This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. What is this medicine intended for?

This medicine is indicated for the treatment of the signs and symptoms of Parkinson's disease (alone or in combination with levodopa).
Therapeutic group: medicines that activate the dopamine receptor (dopaminergic medicines).

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients that this medicine contains (for the list of inactive ingredients, see section 6).
- You are breastfeeding.

Special warnings regarding the use of the medicine
Before taking Sifrol ER, tell your physician if you have (had) or if you develop any symptoms or medical conditions, especially any of the following:

- Kidney disease.
- Hallucinations (seeing, hearing or feeling things that are not there). Most hallucinations are visual.
- You suffer from dyskinesia (e.g. abnormal, uncontrolled movements of the limbs). If you have advanced Parkinson's disease and are taking levodopa, you might develop dyskinesia during the up-titration of Sifrol ER.
- You experience difficulty keeping your body and neck straight and upright (dystonia). In particular, you may experience forward bending of the head and neck, the lower back, or sideward bending of the back.
- Sleepiness and episodes of suddenly falling asleep.
- Psychosis (comparable with symptoms of schizophrenia).
- Vision impairment. You should have regular eye examinations during treatment with Sifrol ER.
- Severe heart or blood vessels disease. You will need to monitor your blood pressure regularly, especially at the beginning of treatment. This is to avoid postural hypotension (a fall in blood pressure on standing up).

Tell your physician if you or your family notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviors such as addictive gambling, excessive eating, spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts. Your physician may need to adjust or stop your dose.

Also, tell your physician if you or your family notices that you are developing mania (agitation, feeling extremely elated and over-excited) or delirium (decreased awareness, confusion, loss of contact with reality). Your physician may need to adjust or stop your dose.

Tell your physician if you experience symptoms such as depression, apathy, anxiety, fatigue, sweating or pain after stopping or reducing your Sifrol ER dose. If the symptoms persist more than a few weeks, your physician may need to adjust your dose.

Sifrol ER tablets is a specially designed tablet from which the active ingredient is gradually released, once the tablet has been ingested. Parts of the tablets may show up in your stool and may even look like whole tablets. Tell your physician if you notice tablet pieces in your stool (faeces).

Tell your physician if you develop difficulty keeping your body and neck straight and upright. Your physician may need to adjust your dose or change your treatment.

Children and adolescents
Sifrol ER is not intended for use in children and adolescents under the age of 18.

Tests and follow-up
Use of the medicine may cause blurred vision. You should have regular eye examinations during treatment with Sifrol ER. You will also need to have your blood pressure checked regularly, especially at the beginning of treatment (see section 2 "Special warnings regarding the use of the medicine").

Other medicines and Sifrol ER
If you are taking or have recently taken other medicines, including non-prescription medicines and food supplements, tell the physician or the pharmacist. Particularly if you are taking:

- Cimetidine (to treat excess stomach acid and stomach ulcers).
- Amantadine (to treat Parkinson's disease).
- Mexiletine (to treat irregular heartbeats - a condition known as ventricular arrhythmia).
- Zidovudine (to treat the acquired immune deficiency syndrome, AIDS/HIV).
- Cisplatin (to treat various types of cancers).
- Quinidine (used for the prevention of painful night-time leg cramps and for the treatment of a type of malaria known as falciparum malaria).
- Procainamide (to treat irregular heart beat).

Do not take Sifrol ER together with antipsychotic medicines.

If you are taking levodopa - the dose of levodopa is recommended to be reduced before you start treatment with Sifrol ER.

Take care if you are using any medicines that calm you down (have a sedative effect) or if you are drinking alcohol. In these cases this medicine may affect your ability to drive and operate machinery.

Using the medicine and food
Sifrol ER can be taken with or without food.

Using the medicine and alcohol consumption
You should be cautious while drinking alcohol during treatment with this medicine.

Pregnancy, breastfeeding, and fertility
If you are pregnant, think you may be pregnant, planning to have a baby or are breastfeeding, you should consult a physician before starting to take this medicine. Your physician will discuss with you if you should continue to take Sifrol ER.
The effect of Sifrol ER on the unborn child is not known. Therefore, do not take this medicine unless your physician tells you to do so.
Do not use this medicine during breast-feeding. Sifrol ER can reduce the production of breast milk. Also, the medicine can pass into the breast milk and can reach the breast-fed child. If use of Sifrol ER is unavoidable, breast-feeding should be stopped.

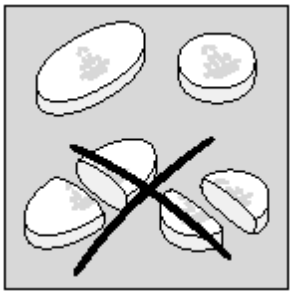
Driving and using machines
The medicine can cause hallucinations (hearing, seeing or feeling things that are not there). If affected by the medicine in this manner, do not drive or use dangerous machines.
Sifrol ER can cause sleepiness and episodes of suddenly falling asleep, particularly in patients with Parkinson's disease. If you experience these side effects, you must not drive or operate dangerous machines. You should tell your physician if this occurs.

3. How should you use the medicine?

Always use according to the physician's instructions. You should check with the physician or the pharmacist if you are not sure about your dose or about how to take this medicine.

The dosage and treatment will be determined only by the physician. The usually recommended dose is:
Take the medicine once a day, at about the same time.
You can take Sifrol ER with or without food. Swallow the tablet whole with water.

Do not chew, divide or crush the extended-release tablets. Chewing/crushing or dividing the tablet may cause an overdose, because the medicine may be released into your body too quickly.



During the first week, the usual daily dose is 0.375 mg Sifrol ER. The dose will be increased every 5-7 days as directed by your doctor until your symptoms are controlled (maintenance dose).

Ascending dose schedule of Sifrol ER		
Week	Dose (mg)	Number of tablets
1	0.375	one Sifrol ER 0.375 mg tablet
2	0.75	one Sifrol ER 0.75 mg tablet OR two Sifrol 0.375 mg tablets
3	1.5	one Sifrol ER 1.5 mg tablet OR four Sifrol ER 0.375 mg tablets

The usual maintenance dose is 1.5 mg per day. However, your dose may have to be increased even further. If necessary, your dose may be increased up to a maximum of 4.5 mg of pramipexole (the active ingredient) a day. A lower maintenance dose of 0.375 mg a day is also possible.

Patients with kidney disease:
If you have kidney disease, your doctor may advise you to take the usual starting dose of 0.375 mg Sifrol ER only every other day for the first week. After that, your doctor may increase the dosing frequency to one 0.375 mg Sifrol ER tablet every day. If a further dose increase is necessary, your doctor will adjust it in increments of 0.375 mg pramipexole (the active ingredient) at a time.

If you have serious kidney problems, your physician may need to switch you to a different pramipexole medicine. If during treatment your kidney problems get worse, you should contact your physician as soon as possible.

If you are switching from Sifrol immediate release tablets - Your physician will base your dose of Sifrol ER extended-release tablets on the dose of Sifrol immediate release tablets you were taking.
Take your Sifrol (immediate release) tablets as normal the day before you switch. Then take your Sifrol ER extended-release tablets next morning. Do not take any more Sifrol (immediate release) tablets.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose or if a child has accidentally swallowed the medicine, go immediately to a physician or a hospital emergency room and bring the medicine package with you.
Taking an overdose may cause vomiting, restlessness, or any of the side effects as described in section 4, Side effects section.

If you forget to take the medicine at the scheduled time, but remember within 12 hours of your usual time, take your tablet straightaway and then take your next tablet at the usual time. If you forget for more than 12 hours, skip the forgotten dose and take the next dose at the usual time.
Do not take a double dose to make up for a forgotten tablet dose.
Persist with the treatment as recommended by the physician.
Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the physician. If you have to stop taking this medicine, your physician will reduce the dose gradually to reduce the risk of worsening symptoms.

If you stop taking the medicine
Do not stop taking Sifrol ER without first talking to your physician. If you have to stop taking this medicine, your physician will reduce the dose gradually. This reduces the risk of worsening symptoms.

If you suffer from Parkinson's disease you should not stop treatment with this medicine abruptly. A sudden stop could cause to a severe medical condition called neuroleptic malignant syndrome. The symptoms of the syndrome include: akinesia (loss of muscle movement), rigid muscles, fever, unstable blood pressure, tachycardia (increased heart rate), confusion, depressed level of consciousness (e.g. coma).

If you stop or reduce your Sifrol ER dose you may develop a medical condition called dopamine agonist withdrawal syndrome (DAWS). The symptoms include depression, apathy, anxiety, fatigue, sweating or pain. If you experience these symptoms you should contact your physician.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the medicine. Wear glasses if you need them.
If you have any further questions regarding the use of this medicine, consult the physician or the pharmacist.

4. <u>Side Effects</u>

As with any medicine, use of Sifrol ER may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

Very common side effects: may affect more than 1 in 10 users:
- Movement disorders - Dyskinesia (e.g. abnormal, uncontrolled movements of the limbs).
- Sleepiness.
- Dizziness.
- Nausea (sickness).

Common side effects: may affect up to 1 in 10 users:
- Urge to behave in an unusual way.
- Hallucinations (hearing, seeing or feeling things that are not there).
- Confusion.
- Tiredness (fatigue).
- Sleeplessness (insomnia).
- Excess of fluid, usually in the legs (peripheral oedema).
- Headache.
- Hypotension (low blood pressure).
- Abnormal dreams.
- Constipation.
- Visual impairment.
- Vomiting (being sick).
- Weight loss including decreased appetite.

Uncommon side effects: may affect up to 1 in 100 users:
- Paranoia.
- Delusion.
- Excessive daytime sleepiness or suddenly falling asleep.
- Memory disturbance.
- Increased movements and inability to keep still (hyperkinesia).
- Weight increase.
- Allergic reactions (e.g. rash, itching, hypersensitivity).
- Fainting.
- *Cardiac failure (heart problems which can cause shortness of breath or ankle swelling).
- *Syndrome of inappropriate antidiuretic hormone (ADH) secretion.
- Restlessness.
- Difficulties to breathe (Dyspnoea).
- Hiccups.
- Pneumonia (infection of the lungs).
- Inability to resist the impulse to perform an action that could be harmful to you or others, which may include:
  - Strong impulse to gamble excessively despite serious personal or family consequences.
  - Altered or increased sexual interest and behavior of significant concern to you or to others, for example, an increased sexual drive.
  - Uncontrollable excessive shopping or spending.
  - *Binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger).
- Delirium (decreased awareness, confusion, loss of reality).

Rare side effects: may affect up to 1 in 1,000 users:
- Mania (agitation, feeling extremely elated or over-excited).

Side effects with unknown frequency (the frequency of these effects has not been established yet):
- After stopping or reducing your Sifrol ER treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (also known as dopamine agonist withdrawal syndrome or DAWS).

* The precise frequency is not known, since these side effects were not observed in clinical studies among 2,762 patients treated with pramipexole. The frequency category for these side effects is probably not greater than “uncommon side effects".

If a side effect occurs, if any of the side effects gets worse, or if you suffer from a side effect not mentioned in the leaflet, you should consult your physician.

Side effects can be reported to the Ministry of Health (MoH) by clicking on the "Report on side effects due to medication therapy" link on the MoH home page (www.health.gov.il) which refers to the online form for side effects reporting, or by entering the link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from your physician.
- Do not use the medicine after the expiration date (exp. date) that appears on the box. The expiration date refers to the last day of that month.
- **Storage conditions:** Store in the original package to protect from moisture. Store below 25°C.
- Do not discard the medicine to the wastewater or household waste. Consult the pharmacist about how to throw away medicines you no longer use. These measures will help in environmental protection.

6. Additional information

- In addition to the active ingredient the medicine also contains –
  maize starch, hypromellose 2208, carbomer 941, silica colloidal anhydrous, magnesium stearate.
- What does the medicine look like and what is the content of the package -
  Sifrol ER 0.375 and Sifrol ER 0.75 are white to off-white tablets of round shape, convex on both sides. One side is debossed with the Boehringer Ingelheim company symbol, "BI"; and the other side is debossed with "P1" (Sifrol ER 0.375) and "P2" (Sifrol ER 0.75).
  Sifrol ER 1.5 are white to off-white tablets of oval shape, convex on both sides. One side is debossed with the Boehringer Ingelheim company symbol, "BI"; and the other side is debossed with "P3".
  The tablets are packed in blister strip. Each package containing 10 or 30 Extended-release tablets. Not all pack sizes may be marketed.
- **Registration holder:** Boehringer Ingelheim Israel Ltd., 89 Medinat Ha-Yehudim, P.O.B. 4124, Hertzliya-Pituach 4676672.
- **Manufacturer name:** Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.
- **This leaflet was revised in April 2020**.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Sifrol ER 0.375 - 144-95-33088-00
  Sifrol ER 0.75 - 144-96-33089-00
  Sifrol ER 1.5 - 144-97-33090-00