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

Sifrol® 0.25 mg
Sifrol® 1 mg
Tablets

Each tablet of Sifrol 0.25 mg contains pramipexole dihydrochloride monohydrate 0.25 mg.
Each tablet of Sifrol 1 mg contains pramipexole dihydrochloride monohydrate 1 mg.
*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?

Sifrol 0.25 mg and Sifrol 1 mg are indicated for the treatment of the signs and symptoms of Parkinson's disease (alone or in combination with levodopa).
Sifrol 0.25 mg is also indicated for treating moderate to severe symptoms of idiopathic restless legs syndrome.

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.
- You are breastfeeding.

Special warnings regarding the use of the medicine
Before taking Sifrol, tell your physician if you have (or 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 (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.
- 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.
- Severe heart or blood vessels disease. You should monitor your blood pressure regularly, especially at the beginning of treatment, and this is to avoid postural hypotension (a fall in blood pressure on standing up).
- Symptoms augmentation. You may feel that your disease symptoms start earlier in the day than usual, are more intense, and involve other limbs.

Tell your physician if you or your family or relatives notice 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 your dose or stop the treatment.
Also, tell your physician if you or your family or relatives notice 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 your dose or stop the treatment.

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

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 is not intended for 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. 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
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 heartburn 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 together with antipsychotic medicines.
If you are taking levodopa - the dose of levodopa is recommended to be reduced before you start treatment with Sifrol.
Take care if you are using any medicines that calm you down or if you are drinking alcohol. In these cases, the medicine may affect your ability to drive and operate dangerous machines.

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

Using the medicine and alcohol consumption
You should be cautious while drinking alcohol during treatment with the medicine. See above in the section "If you are taking other medicines".

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.
The effect of Sifrol 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 breastfeeding. Sifrol can reduce the production of breast milk. Also, the medicine can pass into the breast milk and can reach the breastfed child. If use of Sifrol is unavoidable, breastfeeding 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 operate dangerous machines. Sifrol 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. **Do not exceed the recommended dose.**

Sifrol can be taken with or without food. Swallow the tablet with water. There is no information about crushing, grinding or chewing the tablet. You can cut the tablets in half, on the score line and take both halves at the same time to make swallowing easier or according to the dosage prescribed for you by the physician.

The usually recommended dose is:

Parkinson's disease:
The daily dose must be divided into 3 equal doses.

During the first week, the usual daily dose is 0.125 mg SIFROL three times a day (equivalent to 0.375 mg daily):

	1st week
Number of tablets	Half a tablet of SIFROL 0.25 mg three times a day
Daily dose (mg)	0.375

This dose will be increased every 5-7 days as directed by your physician until your symptoms are controlled (maintenance dose).

	2nd week	3rd week
Number of tablets	1 tablet SIFROL 0.25 mg three times a day	2 tablets SIFROL 0.25 mg three times a day
Total daily dose (mg)	0.75 mg	1.5 mg

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) day. A lower maintenance dose of 0.375 mg a day is also possible.

Patients with kidney disease:
If you have moderate or severe kidney disease, your physician will prescribe a lower dose. In this case, you will have to take the tablets once or twice a day. If you have moderate kidney disease, the usual starting dose is half a tablet of Sifrol 0.25 mg twice a day. In severe kidney disease, the usual starting dose is half a tablet Sifrol 0.25 mg once a day.

Restless Legs Syndrome
The usual dose is taken once a day, in the evening, 2-3 hours before bedtime.

During the first week, the usual dose is half a tablet of Sifrol 0.25 mg once a day (equivalent to 0.125 mg daily):

	1st week
Number of tablets	Half a tablet of Sifrol 0.25 mg once a day
Daily dose (mg)	0.125 mg

This dose will be increased every 4-7 days as directed by your physician until your symptoms are controlled (maintenance dose).

	2nd week	3rd week	4th week
Number of tablets	1 tablet Sifrol 0.25 mg	2 tablets Sifrol 0.25 mg	3 tablets Sifrol 0.25 mg
Total daily dose (mg)	0.25	0.50	0.75

The maximum daily dose should not exceed 0.75 mg of the active ingredient pramipexole.

If you stop taking your medicine for more than a few days, you must start again at the lowest dose. You can then build up the dose again, as you did the first time. Ask your physician for advice.

Your physician will review your treatment after 3 months to decide whether or not to continue the treatment.

Patients with kidney disease:
If you have severe kidney disease, Sifrol may not be a suitable treatment for you.

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 skip the forgotten dose and take the next dose at the usual time. Do not compensate for a forgotten 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 or the pharmacist.

If you stop taking the medicine
Do not stop taking Sifrol without first talking to your 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 suffer from Parkinson's disease you should not stop treatment with this medicine abruptly. A sudden stop could cause a severe medical condition called neuroleptic malignant syndrome. The symptoms of the syndrome include: loss of muscle movement (akinesia), rigid muscles, fever, unstable blood pressure, increased heart rate (tachycardia), confusion, depressed level of consciousness (e.g. coma).

If you stop or reduce your Sifrol 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 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.
If you have Parkinson's disease you may experience the following side effects:
Very common side effects: may affect more than 1 in 10 users:
Movement disorders (e.g. abnormal, uncontrolled movements of the limbs), sleepiness, dizziness, nausea.

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), edema (mainly in the legs), headache, hypotension (low blood pressure), abnormal dreams, constipation, visual impairment, vomiting, weight loss including decreased appetite.

Uncommon side effects: may affect up to 1 in 100 users:
Paranoia (excessive fear for your own well-being), delusion, excessive daytime sleepiness or suddenly falling asleep, forgetfulness, increased movements and inability to keep still (hyperkinesia), weight increase, allergic reactions (e.g. rash, itching, hypersensitivity), fainting, *heart failure (heart problems which can cause shortness of breath or leg edema), *syndrome of inappropriate antidiuretic hormone (ADH) secretion, restlessness, difficulty breathing (dyspnoea), hiccups, pneumonia, delirium (decreased awareness, confusion, losing touch with reality), inability to resist the impulse to perform an action that could harm yourself or others. Such acts 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).

Rare side effects: may affect up to 1 in 1000 users:
Mania, for example feeling agitated, elated and overexcited.

Side effects with unknown frequency (the frequency of these effects has not been established yet):

- After stopping or reducing your Sifrol 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. 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 you have restless legs syndrome you may experience the following side effects:
Very common side effects: may affect more than 1 in 10 users:
Nausea.

Common side effects: may affect up to 1 in 10 users:
Changes in your sleeping pattern, such as insomnia and drowsiness, fatigue, headache, unusual dreams, constipation, dizziness, vomiting.
Uncommon side effects: may affect up to 1 in 100 users:
*Urge to behave in an unusual way, *heart failure (problems with your heart which can cause shortness of breath or edema in your ankles), *syndrome of inappropriate antidiuretic hormone (ADH) secretion, movement disorders (such as uncontrollable and abnormal limb movements), *excessive body movement and inability to keep still (hyperkinesia), *paranoia (excessive fear for your own well-being), *delusions, *forgetfulness, hallucination (hearing, seeing or feeling things that are not there), confusion, increased drowsiness during the day or suddenly falling asleep, weight gain, low blood pressure, edema (mainly in the legs), allergic reactions (such as rash, itch, hypersensitivity), fainting, restlessness, disturbed vision, weight loss with loss of appetite, difficulty breathing, hiccups, *pneumonia, mania (for example feeling agitated, elated and overexcited), delirium (decreased awareness, confusion, losing touch with reality), inability to resist the impulse to perform an act that may could harm yourself or others. Such acts include:

- *Strong impulse to gamble excessively despite serious personal or family consequences.
- *Unusual sexual behavior and interests of significant concern to you and your environment, such as increased sexual drive.
- *Excessive, uncontrollable shopping or spending.
- *Binge eating (eating large amounts over a short period of time) or compulsive eating (eating more than usual and more than you need to satisfy your hunger).

Side effects with unknown frequency (the frequency of these effects has not been established yet):

- After stopping or reducing your Sifrol treatment: Depression, apathy, anxiety, fatigue, sweating or pain may occur (also known as dopamine agonist withdrawal syndrome or DAWS).

** Precise frequency is unknown. These side effects did not appear in clinical trials conducted in 1,395 patients taking 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 at a temperature below 25˚C.

6. Additional information

- In addition to the active ingredient the medicine also contains –
  mannitol, maize starch dried, maize starch, magnesium stearate, colloidal anhydrous silica, povidone K25.
- What does the medicine look like and what is the content of the package -
  Sifrol 0.25 mg – white, oval, flat-faced, beveled-edge tablet, with a score line on both sides. Tablets have P7 on one side, on both sides of the score line, and the symbol of Boehringer Ingelheim embossed on the other side, on both sides of the score line.
  Sifrol 1 mg – white, oval, flat-faced, beveled-edge tablet, with a score line on both sides. Tablets have P9 on one side, on both sides of the score line, and the symbol of Boehringer Ingelheim on the other side, on both sides of the score line.
  The tablets are packed in a blister strip. Each package containing 100 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, Ingelheim am Rhein, Germany.

- **This leaflet was revised in April 2020.**
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Sifrol 0.25 mg – 126-17-30500-00
  Sifrol 1 mg – 126-16-30501-00