PATIENT PACKAGE INSERT ACCORDING TO PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

This medicine can be sold with a doctor's prescription only

Opsumit® film-coated tablets 10 mg

Active ingredient and its quantity:
Each film-coated tablet contains:
Macitentan 10 mg

For list of inactive ingredients, please see section 6.

Read this entire leaflet carefully before you start using this medicine. This leaflet contains concise information about the medicine. If you have any further questions, ask your doctor or pharmacist.
This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if you think that their illness is similar to yours.

Do not use this medicine in children under 18 years of age.

Patient Safety Information Card
In addition to the leaflet, Opsumit also has a patient safety information card regarding potential harm to the fetus.
This card contains important safety information that you should know, before beginning and during treatment with Opsumit. Refer to the patient safety information card and patient information leaflet before using the medicine. Keep the card and the leaflet for further reference if required.

Do not use Opsumit if you are pregnant, since this medicine may cause harm to the fetus (see section 2 "Before you take the medicine" sub-sections "Do not use the medicine if" and "Pregnancy and breastfeeding").
If you are a woman of child-bearing age who could become pregnant, you should take a pregnancy test before you start taking Opsumit and regularly every month while you are taking the medicine and a month after termination of treatment. A negative result in each pregnancy test must be assured.
You must use a reliable contraceptive method while taking Opsumit and one additional month after termination of treatment (see section 2 sub section "Pregnancy and breastfeeding").

1. What is the medicine used for?

- The medicine is intended for treatment of pulmonary arterial hypertension (PAH) in adults, and is used to slow down disease progression.
- Pulmonary arterial hypertension is high blood pressure in the blood vessels that carry blood from the heart to the lungs (the pulmonary arteries).
- Opsumit widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure, relieves the symptoms and improves the course of the disease.

- The medicine can improve your ability to perform physical activity, relieve the symptoms and postpone the need for additional treatment. Additionally, the medicine can reduce your chances of hospitalization as a result of the disease.

Therapeutic group: endothelin receptor antagonists

2. Before you take the medicine:

Do not use the medicine if:

- You are allergic to the active ingredient (macitentan), soya or to any of the other ingredients of this medicine.
- You are pregnant, planning pregnancy, or if you may get pregnant because you are not using reliable contraceptives. See also "Pregnancy and breastfeeding" section.
- You are breastfeeding. See also "Pregnancy and breastfeeding" section.
- You suffer from liver disease or if you have very high levels of liver enzymes in your blood. Consult the doctor, who will decide whether this medicine is suitable for you.

Special warnings regarding the use of this medicine

Before treatment with Opsumit tell your doctor if:

- You suffer from anemia.
- You suffer from kidney problems. The medicine may cause further reduction of blood pressure and decrease in hemoglobin levels in patients with kidney problems.
- You are sensitive to any type of food or medicine, inform your doctor before you start taking the medicine.

In patients with pulmonary veno-occlusive disease (obstruction of the lung veins), the use of medicines for treatment of PAH, including Opsumit, may lead to pulmonary oedema. If you have signs of pulmonary oedema when using Opsumit, such as a sudden, important increase in breathlessness and low oxygen, tell your doctor immediately. Your doctor may perform additional tests, and will determine what treatment regimen is most suitable for you.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including non-prescription drugs and nutrition supplements.

Especially if you are taking:

- Rifampicin, clarithromycin, telithromycin (antibiotics used to treat infections)
- Phenytoin (a medicine used to treat seizures)
- Carbamazepine (used to treat depression and epilepsy)
- St. John's Wort (hypericum, an herbal preparation used to treat depression)
- Ritonavir, saquinavir (used to treat HIV)
- Nefazodone (used to treat depression)
- Ketoconazole (except shampoo), itraconazole, voriconazole (used to treat fungal infections)

Use of this medicine and food:

Can be taken with or without food.

Pregnancy and breastfeeding:
Opsumit may harm unborn babies conceived before starting treatment or during treatment. If you are a woman of child-bearing age who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Opsumit and regularly every month while you are taking the medicine and a month after termination of treatment. A negative result in each pregnancy test must be assured.
Do not take the medicine if you are pregnant or planning to become pregnant.
You must use a reliable contraceptive method while taking Opsumit and for an additional month after termination of treatment.

Your doctor or gynecologist will instruct you about reliable contraceptive methods while taking Opsumit.
Your doctor will recommend a highly effective method of contraception to you such as intra-uterine device or tubal sterilization or using a combination of methods [such as hormonal method and barrier method (such as diaphragm, contraceptive sponge, or your partner must also use a condom) or two barrier methods of contraception]. Consult your doctor regarding the use of two methods of contraception. If the chosen method of contraception is the partner's vasectomy, hormonal or barrier contraception must be used concomitantly.

Tell your doctor immediately if you become pregnant while you are taking Opsumit, think you might be pregnant or plan to become pregnant in the near future.

It is unknown whether the medicine passes to breast milk. Do not breastfeed while using the medicine, discuss this with your doctor.

Use in the elderly:
There is limited experience with this medicine in patients over 75 years of age. Use with caution in this age group.

Driving and use of machinery:
This medicine may cause side effects such as headaches and hypotension , the symptoms of your disease may also make you less fit to drive.

Important information about some of the ingredients of this medicine:
Opsumit contains lactose, lecithin from soya and sodium
Opsumi tablets contain a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking the medicine.

Additionally, Opsumit tablets contain lecithin derived from soya. If you are allergic to soya, do not take this medicine (see section "Do not use the medicine if").
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to use this medicine:

- This medicine should only be prescribed to you by a doctor experienced in treatment of pulmonary arterial hypertension.
- Always use according to your doctor instructions. Check with your doctor or pharmacist if you are not sure.

The dosage and administration will be determined by the doctor only. The usual recommended dosage is:
One 10 mg tablet, once daily, preferably at the same time every day.

Do not exceed the recommended dose.

- Swallow the tablet whole with a glass of water.
- Do not chew, split or crush the tablet.

Tests and follow up-
Before beginning use of this medicine and during it the doctor will refer you to perform blood tests to check if you suffer from have anemia (low number of red blood cells) or liver dysfunction.

If you have anaemia (a reduced number of red blood cells), you may have the following signs:
- dizziness
- fatigue/malaise/weakness
- fast heart rate, palpitations
- pallor

If you notice any of these signs, **tell your doctor**.

Signs indicating liver dysfunction include:
- Nausea (urge to vomit)
- Vomiting
- High fever
- Abdominal pain
- Jaundice (yellowing of the skin or the whites of your eyes)
- Dark-colored urine
- Itching of your skin
- Unusual tiredness or exhaustion
- Flu like syndrome (joint and muscle pain accompanied by fever)

If you feel any of these effects, **tell your doctor immediately**.

If you have accidentally taken a higher dosage
If you have taken more tablets than you have been told to take, you may experience headache, nausea, or vomiting. If you have taken an overdose or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.

If you forget to take this medicine at the specified time, take the next dose as soon as you remember, then continue at the usual times. Do not take a double dose to make up for a forgotten one.

Continue the treatment as recommended by your doctor.
Even if there is an improvement in your health, do not stop treatment with this medicine without consulting your doctor.

If you stop taking this medicine

Continue taking this medicine in order to control your disease. Do not stop taking the medicine unless instructed to do so by your doctor.

- Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult your doctor or pharmacist.

4. Side effects:

Like all medicines, the use of Opsumit can cause side effects in some users. Do not be alarmed while reading the list of side effects. You may not suffer from any of them.

Refer to a doctor immediately if:

- You suffer from symptoms that may indicate liver dysfunction such as: nausea, vomiting, fever, abdominal pain, yellowing of the skin and eyes (jaundice), dark-colored urine, itchy skin, unusual tiredness or exhaustion (fatigue or lethargy), flu like syndrome (joint and muscle pain accompanied by fever).

Additional side effects:

Very common side effects - effects that appear in more than 1 in 10 users:

- Anemia (low number of red blood cells) or reduced hemoglobin
- Headache
- Bronchitis (inflammation of the airways)
- Inflammation of the nose and throat
- Edema (swelling especially of the ankles and feet)

Common side effects - effects that appear in up to 1 in 10 users:

- Inflammation of the throat
- Flu
- Urinary tract inflammation
- Hypotension (low blood pressure)
- Nasal congestion (blocked nose)
- Elevated liver tests
- Leukopenia (decreased white blood cell counts)
- Thrombocytopenia (decreased blood platelet counts)

Uncommon side effects - effects that appear in up to 1 in 100 users

Allergic reactions (swelling around the eyes, face, lips, tongue or throat, itching and/or rash). If you notice any of these signs, tell your doctor immediately.

If a side effect appears, if any of the side effects worsens or if you experience a side effect not mentioned in this leaflet, consult your doctor.

Side effects can be reported to the Ministry of Health using the online form for reporting side effects found on the home page of the Ministry of Health's website: www.health.gov.il
or via the following link: https://sideeffects.health.gov.il

5. How to store the medicine:

- Avoid poisoning! This medicine, and all other medicines must be stored in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.
- Do not store at temperature above 30^{O}C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer used. These measures will help to protect the environment.

6. Additional information:

In addition to the active ingredient, this medicine also contains:

Lactose monohydrate, microcrystalline cellulose (E460i), povidone *K*-30, sodium starch glycolate Type A, magnesium stearate (E572), polysorbate 80 (E433), polyvinyl alcohol (E1203), titanium dioxide (E171), talc (E553b), soya bean lecithin (E322), and xanthan gum (E415).
each tablet contains about 37 mg lactose.

What the medicine looks like and contents of the pack:

White to off-white, biconvex, round, film-coated tablets with the inscription "10" both sides

Each Opsumit pack contains 15 or 30 tablets in a blister.
Not all pack sizes are marketed.

Registration holder and address:

J-C Health Care Ltd, Kibbutz Shefayim 6099000,
Israel.

Manufacturer and address:

Actelion Pharmaceuticals Ltd, Allschwil, Switzerland.

Drug registration number at the national medicines registry of the Ministry of Health:

152-72-34061-00
152-72-34061-01

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