Patient package insert according to Pharmacists' Regulations (Preparations), 1986

This medicine is dispensed with a doctor's prescription only

Tracleer® 62.5 mg
Film-Coated Tablets

Active ingredient and its quantity:
Each film-coated tablet contains:
Bosentan 62.5 mg

Tracleer® 125 mg
Film-Coated Tablets

Active ingredient and its quantity:
Each film-coated tablet contains:
Bosentan 125 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.

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

Do not use Tracleer if you are pregnant, since the medicine may cause harm to the fetus (see section 2 "Before using the medicine" sub-sections "Do not use the medicine if" and "Fertility, 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 Tracleer 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 confirmed.
You must use a reliable contraceptive method while taking Tracleer and one additional month after termination of treatment (see section 2 sub-section "Fertility, Pregnancy and Breastfeeding").

1. What is the Medicine Intended for

- to treat pulmonary arterial hypertension (PAH). PAH is high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. Tracleer widens the pulmonary arteries, making it easier for the heart to pump blood through them. Widening the arteries lowers the blood pressure and relieves the symptoms.
- to treat ulcers of the fingers (digital ulcers) in people with a condition called scleroderma. Tracleer reduces the number of new finger ulcers that appear.

Therapeutic group: Endothelin receptor antagonist.

2. Before Using the Medicine

Do not use the medicine if:

- You are hypersensitive (allergic) to the active ingredient (bosentan) or to any of the other ingredients this medicine contains.
- You have liver problems (consult your doctor).
- You are pregnant or could become pregnant because you are not using reliable contraceptive methods (hormonal contraceptives alone are not effective when taking Tracleer). For additional information, please see section "Fertility, Pregnancy and Breastfeeding".
- You are taking cyclosporine A (a medicine used after a transplant or to treat psoriasis).

If any of these cases apply to you, consult your doctor.

Special warnings regarding the use of this medicine

- **Tests to be performed before, during and after termination of the treatment** – see sections "Fertility, Pregnancy and Breastfeeding" and "Tests and Follow Up".

Tell the 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:

- Cyclosporine A (a medicine used after transplants and to treat psoriasis) - using together with Tracleer is prohibited.
- Sirolimus or tacrolimus (medicines used after transplants) - using together with Tracleer is not recommended.
- Glibenclamide (for diabetes), rifampicin (to treat tuberculosis), fluconazole and ketoconazole (medicines to treat fungal infections) or nevirapine [to treat HIV infection (AIDS)] - using together with Tracleer is not recommended.
- Other medicines for the treatment of HIV infection (AIDS) - special monitoring is required if used together with Tracleer.
- Hormonal contraceptives (as these are not effective as the sole method of contraception when taking Tracleer). Your doctor and/or gynecologist will establish the contraception which is appropriate for you. For additional information, please see section "Fertility, Pregnancy and Breastfeeding" as well as the patient safety information card.
- other medications for the treatment of pulmonary hypertension: sildenafil and tadalafil;
- warfarin (an anticoagulant agent);
- simvastatin (used to treat hypercholesterolaemia).

Use of this Medicine and Food

The medicine can be taken with or without food.

Fertility, Pregnancy and Breastfeeding

Fertility:

If you are a man taking Tracleer, it is possible that this medicine may lower your sperm count. It cannot be excluded that this may affect your fertility. Talk to your doctor if you have any questions or concerns about this.

Pregnancy:

Tracleer may harm to fetuses 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 Tracleer 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 confirmed.

Do not take the medicine if you are pregnant or planning to become pregnant.

You must use a reliable contraceptive method while taking Tracleer and a month after termination of treatment.

Your doctor or gynecologist will instruct you about reliable contraceptive methods while taking Tracleer.
As Tracleer may make hormonal contraception (e.g., oral, injection, implants, or skin patches) ineffective, this method on its own is not reliable.
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 two methods (such as the hormonal method in combination with an additional barrier method e.g.: diaphragm, contraceptive sponge, or your partner must also use a condom) or two barrier methods. 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 Tracleer, if you think you might be pregnant or plan to become pregnant in the near future.

Breastfeeding:
If you are breastfeeding or planning to breastfeed, consult your doctor or pharmacist before initiating treatment with Tracleer, for fear of hurting the baby.
You are advised to stop breastfeeding if Tracleer is prescribed for you as it is not known whether this medicine passes into breast milk.

Driving and Use of Machinery
Tracleer has no or negligible influence on the ability to drive and use machines. However, Tracleer can lower blood pressure which can make you feel dizzy, affect your vision and affect your ability to drive and use machines. Therefore, if you feel dizzy or that your vision is blurred while taking Tracleer, do not drive or operate any devices or machines.

Tracleer contains sodium
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
- Treatment with Tracleer should only be initiated and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis.
- Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure.

The dosage and administration will be determined by the doctor only. Usual recommended dosage:
Adults
The treatment in adults is usually started for the first four weeks with 62.5 mg twice daily (morning and evening). Thereafter, your doctor will usually advise you to take a 125 mg tablet twice daily, depending on how you react to Tracleer. Swallow the tablets with a glass of water. Do not split, crush or chew the tablets.

Children and Adolescents
Tracleer is not recommended in pediatric patients with systemic sclerosis and digital ulcer disease.

Do not exceed the recommended dose.

If you have the impression that the effect of Tracleer is too strong or too weak, talk to your doctor in order to find out whether your dose needs to be changed.

Test and Follow Up
Tests your doctor will do before treatment:

- a blood test to check your liver function
- a blood test to check for anemia (low hemoglobin)
- a pregnancy test if you are a woman of child-bearing age

Some patients taking Tracleer have been found to have anemia (low hemoglobin) and abnormal liver function tests.

Tests your doctor will do during treatment:
During treatment with Tracleer, your doctor will arrange for regular blood tests to check for changes in your liver function and hemoglobin level.
Blood tests for liver function:
These tests will be done every month for the duration of treatment with Tracleer. After an increase in dose an additional test will be done after 2 weeks.
Blood tests for anemia:
These tests will be done every month for the first four months of treatment, then every three months after that, as patients taking Tracleer may develop anemia.

If these results are abnormal, your doctor may decide to reduce your dose or stop treatment with Tracleer and to perform further tests to investigate the cause.

If you have accidently taken a higher dosage contact your doctor immediately
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 set time, take a dose as soon as you remember and continue taking the tablets at the usual time. Do not take a double dose to compensate for a forgotten one.

If you stop taking this medicine
Suddenly stopping your treatment with Tracleer may lead to your symptoms getting worse.
Do not stop taking Tracleer unless your doctor tells you to. Your doctor may tell you to reduce the dosage over a few days before stopping the medicine completely.

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

The most serious side effects with Tracleer:
Abnormal liver function which may affect more than one in 10 users.
Anemia which may affect 1-10 users out of 100. Rarely, anaemia may occasionally require blood transfusion.
Your liver function and blood values will be monitored during treatment with Tracleer. It is important that you have these tests as ordered by your doctor.

Refer to a doctor immediately if:

- You suffer from signs that your liver may not be working properly which include: nausea, vomiting, fever, abdominal pain, jaundice (yellowing of your skin or the whites of your eyes), dark-coloured urine, itching of skin, fatigue (unusual tiredness or exhaustion), flu-like syndrome (joint and muscle pain with fever).

Additional Side Effects:

Very common side effects (appear in more than one out of ten users)**:**

- Headache
- Oedema (swelling of the legs and ankles or other signs of fluid retention)

Common side effects (appear in 1-10 users out of 100):

- Flushed appearance or redness of the skin
- Hypersensitivity reactions (including skin inflammation, itching and rash)
- Gastroesophageal reflux disease (acid reflux)
- Diarrhoea
- Fainting
- Palpitations (fast or irregular heartbeats)
- Low blood pressure
- Nasal congestion

Uncommon side effects (appear in 1-10 users out of 1,000):

- Thrombocytopenia (low number of blood platelets)
- Neutropenia/leukopenia (low number of white blood cells)
- Elevated liver function tests with hepatitis (inflammation of the liver) including possible exacerbation of underlying hepatitis and/or jaundice (yellowing of the skin or the whites of the eyes)

Rare side effects (appear in 1-10 users out of 10,000):

- Anaphylaxis (general allergic reaction), angioedema (swelling, most commonly around the eyes, lips, tongue or throat)
- Cirrhosis, liver failure

Blurred vision has also been reported at an unknown frequency (frequency cannot be estimated from the available data).

If a side effect appears, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet or signs of allergic reaction appear (such as swelling of the face or tongue, rash, itch) while you are taking Tracleer, or if any of the side effects mentioned above worry you, consult your doctor.

Side effects in children and adolescents
The side effects that have been reported in children treated with Tracleer are the same as those in adults.

Side effects can be reported to the Ministry of Health via the link "Report Side Effects of Drug Treatment" found on the home page of the Ministry of Health's website (www.health.gov.il), which refers to the online form for reporting side effects, 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 the 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.
- Store at a temperature below 30°C.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer in use. These measures will help to protect the environment.

6. Additional Information

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

Maize starch, pregelatinised starch, sodium starch glycollate, povidone, glycerol dibehenate and magnesium stearate.

The **film-coat** contains:

Hypromellose, glycerol triacetate, talc, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172) and ethylcellulose.

What the medicine looks like and the content of the package:

Tracleer 62.5 mg tablets are orange-white, round film-coated tablets with “62.5” on one side.
Tracleer 125 mg tablets are orange-white, oval film-coated tablets with “125” on one side.
Each bottle contains 60 tablets.

Importer and Registration Holder: J-C Health Care Ltd., Kibbutz Shefayim, 6099000, Israel.

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

Tracleer 62.5 mg: 125-57-30487-00/01
Tracleer 125 mg: 125-58-30488-00/01

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