PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The 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 a list of inactive ingredients and allergens in the preparation, please see section 6 "Additional information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the 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.

Patient Safety Information
Do not take Tracleer if you are pregnant, since use of this medicine may harm the unborn baby (see section 2 "Before using the medicine", sub-sections "Do not use the medicine if" and "Pregnancy, breastfeeding and fertility").
If you are a woman of childbearing age who could become pregnant, you should take a pregnancy test before you start treatment with Tracleer and regularly every month while taking the medicine, as well as a month after termination of treatment.
A negative result in each pregnancy test must be confirmed. You must use a reliable contraceptive method while using Tracleer and for one additional month after termination of treatment (see section 2 "Pregnancy, breastfeeding and fertility").
In addition to the leaflet, Tracleer has a Patient Alert Card. This card contains important safety information that you should be aware of before starting and during treatment with Tracleer and act according to it. Read the Patient Alert Card and the patient leaflet before you start using the medicine. Keep the card and the leaflet for further reading if necessary.

1. WHAT IS THE MEDICINE INTENDED FOR?

- Treatment of pulmonary arterial hypertension (PAH) in patients of World Health Organization (WHO) functional class II-IV.
- Reduction in the number of new digital ulcers in patients who are suffering from scleroderma with active digital ulcer disease.

Therapeutic group: Endothelin receptor antagonist.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- **You are sensitive (allergic) to the active ingredient (bosentan)** or to any of the additional ingredients contained in the medicine. For a list of the additional ingredients, see section 6 “Additional information”.
- **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 “Pregnancy, breastfeeding and fertility”.
- **You are taking cyclosporine A** (a medicine used after a transplant or to treat psoriasis).

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

Special warnings regarding use of the medicine

Tests and follow-up

Tests that your doctor will perform before starting treatment:

- A blood test to assess your liver function
- A blood test to detect anemia (low hemoglobin)
- A pregnancy test, if you are a woman of childbearing age

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

Tests your doctor will perform during treatment:

During treatment with Tracleer, your doctor will perform regular blood tests to check for changes in your liver function and hemoglobin level.

For all these tests please refer also to the Patient Alert Card (inside your pack of Tracleer tablets). It is important that you have these regular blood tests as long as you are taking Tracleer. We suggest you write the date of your recent test and also of your next test (ask your doctor for the date) on the Patient Alert Card, to help you remember when your next test is due.

Blood tests to assess liver function:

These tests will be performed 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 to detect anemia:

These tests will be done every month for the first 4 months of treatment with the medicine, then every 3 months after that, as patients taking Tracleer may get anemia. If the results of these tests are abnormal, your doctor may decide to reduce your dose or stop treatment with Tracleer and to perform further tests to investigate the cause of these results.

Drug interactions

If you are taking, or have recently taken, any other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. Especially if you are taking:

- Cyclosporine A (a medicine used after transplants and to treat psoriasis) – must not

be used together with Tracleer.
- Sirolimus or tacrolimus (medicines used after transplants) – are not recommended to be used together with Tracleer.
- Glibenclamide (a medicine to treat diabetes), rifampicin (a medicine to treat tuberculosis), fluconazole (a medicine to treat fungal infections), ketoconazole (a medicine to treat Cushing's syndrome) or nevirapine (a medicine to treat HIV infection [AIDS]) – these medicines are not recommended to be used together with Tracleer.
- 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 determine the contraception appropriate for you. For additional information, please see section "Pregnancy, breastfeeding and fertility" as well as the "Patient Alert Card".
- Other medications for the treatment of pulmonary hypertension: sildenafil and tadalafil.
- Warfarin (an anticoagulant agent).
- Simvastatin (a medicine to treat hypercholesterolemia).

Use of the medicine and food
The medicine can be taken with or without food.

Pregnancy, breastfeeding and fertility
Pregnancy tests:
Tracleer may harm unborn babies conceived before starting treatment or during treatment. If you are a woman of childbearing age who could become pregnant, your doctor will ask you to perform a pregnancy test before you start treatment with Tracleer and regularly every month while you are taking the medicine, as well as a month after termination of treatment. A negative result should be confirmed in every pregnancy test.
Do not take the medicine if you are pregnant or planning to become pregnant.

Contraceptives:
You must use a reliable contraceptive method while using Tracleer as well as for an additional month after termination of treatment.
Your doctor or gynecologist will advise you about reliable contraceptive methods while using Tracleer.
Tracleer may make hormonal contraceptives (e.g., oral contraceptives, injections, implants, or skin patches) ineffective; therefore, this method on its own is not reliable.
Your doctor will recommend a single highly effective method of contraception for you, such as an intra-uterine device or tubal sterilization or using a combination of methods (such as hormonal contraceptives and barrier contraceptives, 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.
A Patient Alert Card is provided with the preparation package. You should complete this card and show it to your doctor at the next visit so that your doctor or gynecologist can assess whether you need an additional or alternative reliable contraceptive methods.
Tell your doctor immediately if you become pregnant while you are using Tracleer, if you think you might be pregnant or plan to become pregnant in the near future.

Breastfeeding:
Before starting treatment with Tracleer, inform your doctor immediately if you are breastfeeding or plan to breastfeed, due to concern of harm to the baby.
You are advised to stop breastfeeding if Tracleer is prescribed for you, because it is not known whether this medicine passes into breast milk.

Fertility:
If you are a man taking Tracleer, this medicine may lower your sperm count. It cannot be excluded that this may affect your ability to father a child. Consult your doctor if you have any questions or concerns about this.

Driving and use of machinery
Tracleer has no effect or has a negligible effect on the ability to drive and operate machinery. However, Tracleer can cause a decrease of 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 tools or machines.

Important information about some of the ingredients in the medicine
Tracleer contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e., it is essentially ‘sodium-free’.

3. HOW SHOULD THE MEDICINE BE USED?

- Treatment with Tracleer should only be started and monitored by a doctor who has experience in the treatment of pulmonary hypertension or systemic sclerosis (scleroderma).
- Always use the preparation according to the doctor’s instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only. The usual recommended dosage is:
Adults
A dosage of 62.5 mg twice daily (in the evening and in the morning) is usually given for the first four weeks of treatment in adults. Thereafter, your doctor will usually advise you to take a dosage of 125 mg twice daily, depending on how you react to Tracleer.

Children and adolescents

Tracleer is not recommended for use in children and adolescents 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 weak or too strong, inform your doctor in order to find out whether your dose needs to be changed.

Method of administration
Swallow the tablet with water, with or without food.

Crushing/halving/chewing the tablets
Do not crush, halve or chew the tablets.

If you have accidentally 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 the forgotten tablets.

If you stop taking the medicine
Suddenly stopping treatment with Tracleer may lead to worsening of your symptoms. Do not stop taking the medicine unless your doctor tells you to. Your doctor may advise you to reduce the dose over a few days before stopping the medicine completely.
Adhere to the treatment regimen as recommended by the doctor.
Even if there is an improvement in your health, do not stop treatment with this medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

Like any medicine, 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 during treatment with Tracleer
- Abnormal liver function, which may affect more than one in 10 users.
- Anemia, which may affect up to 1-10 users. Anemia may occasionally require blood transfusion.

Your liver function and blood test values will be monitored during the course of treatment with Tracleer (see section 2 “Tests and follow-up”). It is important that these tests be performed according to the doctor’s instructions.

Refer to a doctor immediately if
- You suffer from the following signs that indicate liver dysfunction: nausea (urge to

vomit), vomiting, fever (high temperature), abdominal pain, jaundice (yellowing of your skin or the whites of your eyes), dark-colored urine, itching of the skin, fatigue (unusual tiredness or exhaustion), flu-like syndrome (muscle and joint pain with fever).

Additional Side Effects

Very common side effects – may affect more than one user in 10

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

Common side effects – may affect up to one user in 10

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

Uncommon side effects – may affect up to one user in 100

- Thrombocytopenia (low number of blood platelets)
- Neutropenia/leukopenia (low number of white blood cells)
- High values in test results to assess liver function together with liver inflammation, including possible exacerbation of latent hepatitis and/or jaundice (yellowing of the skin or whites of the eyes)

Rare side effects – may affect up to one user in 1,000

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

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 can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il), that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine, and any other medicine, must be kept in a closed

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) which is stated on the package. The expiry date refers to the last day of that month.
- Store below 30°C.
- Use within 30 days after the first opening.
- Medicines should not be disposed of via wastewater or household waste. Ask the pharmacist how to dispose of medicines no longer being used. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, the medicine also contains:
Corn starch, Pre-gelatinised starch, Sodium starch glycolate type A, Povidone K90, Glycerol dibehenate and Magnesium stearate.

The film-coat contains:
Hypromellose 6 mPa.s, Glycerol triacetate, Talc, Titanium dioxide (CI 77891 E171), Iron oxide yellow (CI 77492 E172), Iron oxide red (CI 77492 E172) and Ethylcellulose aqueous dispersion (solid part).

What the medicine looks like and the contents of the package:
Tracleer 62.5 mg tablets are orange-white, round, film-coated tablets imprinted with “62.5” on one side.
Tracleer 125 mg tablets are orange-white, oval, film-coated tablets imprinted with “125” on one side.
Each bottle contains 60 tablets.

Manufacturer: Actelion Pharmaceuticals Ltd., Gewerbestrasse 16 4123 Allschwil, Switzerland**.**

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

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Tracleer 62.5 mg: 125-57-30487-01
Tracleer 125 mg: 125-58-30488-01

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