Patient Leaflet According to the Pharmacists' Regulations (Preparations) - 1986

This medicine is sold with a doctor's prescription only

Trasentan 62.5
Trasentan 125
Tablets

Active ingredient:
Trasentan 62.5: Each tablet contains Bosentan monohydrate equivalent to 62.5 mg of Bosentan.
Trasentan 125: Each tablet contains Bosentan monohydrate equivalent to 125 mg of Bosentan.
For a list of the other ingredients, please see section 6.
Read this entire leaflet carefully before using this medicine.
This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for treating your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

Patient safety information card
In addition to the leaflet, Trasentan has a patient safety information card concerning potential harm to an unborn baby (fetus). This card contains important safety information that you should know before starting and during the treatment. Read the patient safety information card and the patient leaflet before using this medicine. Keep the card and leaflet so you can read it again if you need to.

Do not take Trasentan if you are pregnant because using this medicine may harm the fetus (see Section 2 'Before using this medicine' under the subsections 'Do not use this medicine if' and 'Fertility, pregnancy and breastfeeding'). If you are a woman of childbearing age and it is possible for you to get pregnant, perform a pregnancy test before starting treatment with Trasentan and routinely every month while taking this medicine, as well as a month after completing the treatment. Confirm each time that the pregnancy test result is negative. You must use a reliable contraceptive to prevent pregnancy while you are taking Trasentan, and for one more month after completing your treatment (see section 2 'Fertility, pregnancy and breastfeeding').

1. What is the medicine intended for?

- To treat pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. Trasentan 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.
- For treating sores on the fingers/toes (digital ulcers) in patients with a condition called scleroderma (systemic sclerosis). Trasentan reduces the number of new finger/toes ulcers that appear.

Therapeutic group: Endothelin receptor blocker.

2. Before using the medicine

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients this medicine contains (for a list of the other ingredients, please see section 6).
- You suffer or have suffered in the past from liver problems (in such a case consult your doctor).
- You are pregnant or planning to become pregnant (see section 'Fertility, pregnancy and breast-feeding').
- You are a woman of childbearing age and it is possible for you to get pregnant, and you are not using suitable contraceptives (hormonal contraceptives alone are not effective when taking Trasentan. (See the section 'Fertility, pregnancy and breastfeeding').
- You are also taking cyclosporine A (also used to prevent implant rejection after a transplant or to treat psoriasis).

Special warnings regarding the use of this medicine:
Tests to be performed before, during and upon completion of treatment – see sections 'Fertility, pregnancy and breastfeeding' and 'Tests and follow-up'.

The following tests are required before starting treatment:

- Blood tests to check your liver function and to check for anemia (low hemoglobin). See also the section 'Side effects'.

- Pregnancy test (if you are a woman of childbearing age and it is possible for you to get pregnant).

Before starting the treatment with the medicine tell your doctor if you suffer or have suffered in the past from low blood pressure.

Drug interactions:

If you are taking or have recently taken any other medicines, including non-prescription medicines and nutrition supplements, please tell your doctor or pharmacist. Especially inform your doctor or pharmacist if you are taking the following medicines (it should be noted that the following list mentions the active ingredients of the medicines. If you are unsure whether you are using one of these medicines, please consult with your doctor or pharmacist):

- Cyclosporine A: must not be used together with Trasentan. See 'Do not use the medicine if'.
- Tacrolimus, sirolimus (to prevent implant rejection): use together with Trasentan is not recommended.
- Glibenclamide (for treating diabetes); fluconazole, ketoconazole, voriconazole, itraconazole (for treating fungal infections); rifampicin (for treating tuberculosis); nevirapine, ritonavir (for treating AIDS/HIV infection): use together with Trasentan is not recommended.
- Other medicines for treating AIDS (HIV infection): special monitoring may be required if they are taken together with Trasentan.
- Hormonal contraceptives (such as: oral contraceptive pills, injections, implants, skin patches): these contraceptives are not effective as the sole method of contraception while you take Trasentan. Your doctor or gynecologist will determine the contraceptive methods that are appropriate for you. See the section 'Fertility, pregnancy and breastfeeding', as well as the Patient Safety Information Card.
- Simvastatin (for lowering cholesterol): if taken concomitantly, monitoring cholesterol levels is recommended.
- Warfarin: routine monitoring of INR is recommended, particularly when starting treatment and when adjusting the dosage.
- Other Medications for the treatment of pulmonary hypertension: Sildenafil and Tadalafil.

Use of this medicine and food: You can take this medicine irrespective of meal times (with or without food).

Fertility, pregnancy and breastfeeding:

Fertility:
If you are a man taking Trasentan, it is possible that this medicine may lower your sperm count. It is not possible to rule out an effect on your fertility. Talk to your doctor if you have any questions or concerns about this.

Pregnancy:

- Do not use Trasentan if you are pregnant or planning to become pregnant. Tell your doctor immediatly if you are pregnant, think you might be pregnant or are planning a pregnancy.
- This medicine may harm unborn babies conceived before starting treatment or during treatment. If you are a woman of childbearing age and if it is possible for you to become pregnant, your doctor will ask you to take a pregnancy test before you start treatment with Trasentan, and routinely each month while you are taking the medicine, as well as a month after completing the treatment. For each pregnancy test confirm that the result is negative.
- Do not get pregnant while using this medicine. You must use a reliable contraceptive to prevent pregnancy while you are taking Trasentan, and for one more month after completing your treatment.
- If it is possible for you to become pregnant, your doctor or gynecologist will advise you about reliable contraceptive methods that are appropriate for you while you are taking Trasentan. This medicine may make hormonal contraceptives ineffective, so using this contraceptive method on its own is not reliable (see above, the section about interactions with other medicines).
  Your doctor or gynecologist will advise you about reliable contraceptive methods such as:
  - alternative highly effective contraceptive, for example an intrauterine device, tubal ligation;
  - or a combination of two contraceptive methods such as a hormonal contraceptive and a barrier method (for example a diaphragm, contraceptive sponge, and/or your partner must use a condom), or two barrier methods.

  Please consult your doctor about using one of these two options for preventing pregnancy.
- If a vasectomy of the partner has been selected as the contraceptive method, you must use concomitantly a hormonal or a barrier contraceptive method.
- Inform your doctor immediately if you become pregnant during use of Trasentan, if you think you may be pregnant or if you plan on becoming pregnant in the near future.

Breastfeeding:

- If you are breastfeeding or are planning to breastfeed, consult your doctor before starting treatment with Trasentan for fear of harming the infant.

- You are advised to stop breastfeeding if Trasentan is prescribed for you, because it is not known whether this medicine passes into breast milk.

Driving and using machinery:
The medicine has no or negligible influence on the ability to drive and operate machinery. However, it can cause a decrease in blood pressure which can make you feel dizzy, affect your vision and affect your ability to drive and operate machinery. Therefore, if you feel dizzy or that your vision is blurred while taking the medicine, avoid driving or operating any tools or machinery. As for children, they should be warned against riding a bicycle or playing near roads etc.

3. How to use this medicine?

- Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure.
- Only a doctor with experience treating pulmonary arterial hypertension or systemic sclerosis may initiate treatment with this medicine and monitor the patient.

The dosage and the manner of treatment will be determined by the doctor only.

The standard dosage in adults is usually:
- Usually, a dose of 62.5 mg twice a day (morning and evening) is given, for the first 4 weeks of treatment in adults, and after that, depending on your condition and response to treatment, your doctor may raise the dose to 125 mg twice a day.

Use in children and adolescents:
- The medicine is not recommended for use in children who have digital ulcer.

Do not exceed the recommended dose.
If you have the impression that the effect of the medicine is too strong or too weak, inform your doctor in order to clarify whether a dosage change is required.
- Swallow the medicine with a cup of water.
- You can take this medicine irrespective of meal times (with or without food).
- There is no information about crushing and halving the tablets.

Tests and follow-up: (see also 'Special warnings regarding the use of this medicine').

- This medicine may cause changes in your liver function tests (increase in liver enzymes) and/or cause anemia (low hemoglobin). Your doctor will therefore order routine blood tests to evaluate changes in your liver function and hemoglobin levels (low hemoglobin). Take care to do these tests at the required times.

Blood tests for liver function will be done every month or more frequently if necessary (for example, after an increase in dose an additional test will be done after 2 weeks).
  - Blood tests for anemia will be done every month for the first 4 months of treatment, and after that every 3 months.

If results of these tests are abnormal, your doctor may decide to reduce your dosage or stop treatment with the medicine and to perform further tests to investigate the reason for these results.
- Pregnancy tests: see section 'fertility, pregnancy and breastfeeding'.

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 forgot to take the medicine at the set time, take the dose as soon as you remember, and then go back to your usual schedule ,but under no circumstances do not take two doses together, to compensate for the forgotten dose.

Continue with the treatment as recommended by the doctor.

Even if your state of health improves, do not stop the treatment with this medicine without consulting your doctor.

If you stop taking the medicine:
Abruptly stopping treatment may lead to your symptoms getting worse. Do not stop taking the medicine unless your doctor instructs you to. If your doctor decides to stop the treatment, you may be advised to reduce the dose gradually over a few days before stopping the medicine completely.

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

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

4. Side effects

Like any medicine, the use of Trasentan 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 following serious side effects may occur during treatment with Trasentan:

- Abnormal liver function (Very common side effect. Appears in more than one user out of ten).
- Anemia and reduced hemoglobin (Common side effect. Appears in 1-10 users out of 100) and may occasionally require a blood transfusion.

Your liver and blood values will be monitored for such conditions during treatment with the medicine. It is important that you have these tests as ordered by your doctor. See section 'Tests and follow-up'.

Refer to the doctor immediately if the following side effects occur:

- Symptoms which may indicate that your liver function may be impaired, such as: nausea, vomiting, fever, abdominal pain, jaundice (yellowing of your skin or the whites of your eyes), dark-colored urine, itching of your skin, tiredness (including lethargy or fatigue - unusual tiredness or exhaustion), flu-like syndrome (joint and muscle pain with fever).
- Symptoms of an allergic reaction such as swelling of the face, throat, or tongue, inflammation of the skin, rash, itch.

Additional side effects:

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

- 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):

- Flushing or redness of the skin;
- Hypersensitivity reactions (including skin inflammation, itching and rash);
- Gastroesophageal reflux disease (acid reflux);
- Diarrhea;
- Fainting;
- Palpitations (abnormal, fast or irregular heartbeat);
- 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);
- High values in liver function evaluation tests with hepatitis (inflammation of the liver), 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):

- Severe allergic reactions such as anaphylactic shock (general allergic reaction), angioedema (which include: swelling, most commonly around the eyes, lips, tongue, throat);
- liver cirrhosis, liver failure.

Side effects of unknown frequency (effects whose frequency has not yet been determined):

- Blurred vision.

Side effects in children and adolescents

The side effects that have been reported in children treated with Trasentan are the same as those in adults.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, or if symptoms of an allergic reaction appear (e.g. swelling in the face or tongue, rash, itch) while taking the medicine, or if you are concerned about any of the side effects listed above, consult your doctor.

Side effects can be reported to the Ministry of Health (MoH) by clicking on the link "Report on side effects following medicinal treatment" 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, must be stored in a closed place out of the reach and eyesight 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.
- Storage conditions: store below 25ºC.
- Medicines are not to be thrown into the sewer or trash. Ask the pharmacist how to destroy medicines not in use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, the tablets also contain the following ingredients:
Pregelatinized maize starch 1500, povidone, sodium starch glycolate type A, magnesium stearate, purified water, hydroxypropyl methylcellulose, titanium dioxide, triacetin, iron oxide yellow, iron oxide red.

What does the medicine look like and what does the package contain?
Trasentan 62.5 mg: round, orange-white tablets, a 'B' embossed on one side and '62.5' on the other side.
Trasentan 125 mg: oval, orange-white tablets, a 'B' embossed on one side and '125' on the other side.
The tablets are packaged in blisters; 60 tablets in a package.

Registration holder: Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301.

Manufacturer: Genvion Corp., Canada

Medicine registration number in the National Medicines Registry of the Ministry of Health:
Trasentan 62.5: 157 19 34657
Trasentan 125: 157 20 34656

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