Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Bosentan Taro 62.5 mg

Film-coated tablets

Active ingredient
Each film-coated tablet contains:
bosentan (as monohydrate) 62.5 mg

Bosentan Taro 125 mg

Film-coated tablets

Active ingredient
Each film-coated tablet contains:
bosentan (as monohydrate) 125 mg

Inactive ingredients and allergens in this medicine: see section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.

Read the 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 to treat 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.

Safety information for patients
Do not take Bosentan Taro if you are pregnant, since the medicine may cause harm to your unborn baby (see section 2 'Before using the medicine' under 'Do not use the medicine if' and 'Pregnancy, breastfeeding, and fertility').
If you are a woman of child-bearing age who could become pregnant, you should take a pregnancy test before you start taking Bosentan Taro and regularly every month while you are taking the medicine as well as a month after end of treatment. A negative result in each pregnancy test must be confirmed. You must use a reliable contraceptive method while taking Bosentan Taro and for one more month after end of treatment (see section 2 under, 'Pregnancy, breastfeeding, and fertility').
In addition to the leaflet, Bosentan Taro also has a Patient Alert Card about possible harm to your unborn baby. This card contains important safety information that you should know before and during treatment with Bosentan Taro. Read the Patient Alert Card and the patient information leaflet before using the medicine. Keep the card and the patient information leaflet for future reference if required.

1. What is this medicine intended for?

- to treat pulmonary arterial hypertension (PAH) in patients of WHO (World Health Organization) functional class II-IV.
- to reduce the number of new digital ulcers in patients with systemic sclerosis (scleroderma) with active digital ulcers.

Therapeutic group: endothelin receptor antagonist.

2. Before using this medicine

Do not use this medicine if:

- **you are sensitive (allergic) to the active ingredient (bosentan)** or to any of the other ingredients in this medicine (see section 6)
- **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 Bosentan Taro). For more information, please see the 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 about using this medicine

Children and adolescents

Bosentan Taro is not recommended for use in children who have systemic sclerosis with digital ulcers.

Tests and follow-up

Tests that your doctor will perform before starting treatment:

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

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

Tests your doctor will perform during treatment:

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

For information regarding these tests, refer also to the Patient Alert Card (included in the package of the medicine). It is important that you have these regular blood tests as long as you are being treated with Bosentan Taro. We suggest you write the date of your most recent test and also of your next test (ask your doctor for the date) on the Patient Alert Card in order to help you remember when you need to take your next test.

Blood tests to assess liver function:

These tests will be performed every month for the duration of treatment with Bosentan Taro. An additional test will be done 2 weeks after an increase in dose.

Blood tests to detect anemia:

These tests will be done every month for the first four months of treatment with the medicine and every three months after that, as patients taking Bosentan Taro may develop anemia.

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

Interactions with other medicines:

If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:

- cyclosporine A (a medicine used after transplants and to treat psoriasis) - using together with

Bosentan Taro is prohibited.

- sirolimus or tacrolimus (medicines used after transplants) - use together with Bosentan Taro is not recommended.
- glibenclamide (a medicine for treatment of diabetes), rifampicin (a medicine for treatment of tuberculosis), fluconazole (a medicine for treatment of fungal infections), ketoconazole (a medicine for treatment of Cushing's syndrome) or nevirapine (a medicine for treatment of HIV infection [AIDS]) - use of these medicines together with Bosentan Taro is not recommended.
- other medicines for treatment of HIV infection (AIDS) – special monitoring is required when using Bosentan Taro.
- hormonal contraceptives (as these are not effective as the sole method of contraception when taking Bosentan Taro). Your doctor and/or gynecologist will determine which method of contraception is appropriate for you. For additional information, please see the section 'Pregnancy, breastfeeding, and fertility' as well as the Patient Alert Card.
- other medicines for the treatment of pulmonary hypertension: sildenafil and tadalafil.
- warfarin (to prevent blood clotting).
- simvastatin (used to treat hypercholesterolemia).

Using this medicine and food
You can take this medicine with or without food.

Pregnancy, breastfeeding, and fertility
Pregnancy:
Bosentan Taro may harm unborn babies that were conceived before 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 Bosentan Taro and regularly every month while you are taking the medicine as well as a month after end 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.
Contraceptives:
You must use a reliable contraceptive method while taking Bosentan Taro and for one month after end of treatment.
Your doctor or gynecologist will instruct you about reliable contraceptive methods while using Bosentan Taro.
As Bosentan Taro may make hormonal contraceptives (e.g., oral, injections, implants, and skin patches) ineffective; therefore, this method on its own is not reliable.
Your doctor will recommend one highly effective method of contraception such as an intra-uterine device or tubal ligation, or a combination of two methods (such as a hormonal method and a barrier method such as a diaphragm, contraceptive sponge, or your partner must also use a condom), or two barrier methods. Consult your doctor about using two methods of contraception.
If the chosen method of contraception is your partner's vasectomy, you must also use hormonal or barrier contraception at the same time.
The medicine package contains a Patient Alert Card. You should complete this card and show it to your doctor at your next visit so that your doctor or gynecologist can assess whether you need additional or alternative reliable contraceptives.
Tell your doctor immediately if you become pregnant while you are using Bosentan Taro, think you might be pregnant, or plan to become pregnant in the near future.

Breastfeeding:
Bosenan Taro passes into breast milk. You are advised to stop breastfeeding if you are prescribed Bosentan Taro, as it is not known whether the passage of the drug in breast milk might harm the baby. Consult your doctor about it.
Fertility:
If you are a man and you are taking Bosentan Taro, this medicine may lower your sperm count. An effect on fertility cannot be ruled out. Consult your doctor if you have any questions or concerns about this.

Driving and using machines

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

Important information about some of this medicine's ingredients

This medicine contains less than 1 millimole sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to use this medicine?

Treatment with Bosentan Taro should only be started and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis (scleroderma).
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually:
Adults
The treatment in adults is usually 62.5 mg twice daily (in the morning and evening) for the first four weeks of treatment in adults. Then your doctor will usually advise you to take a dose of 125 mg twice daily, depending on how you respond to Bosentan Taro.
Children and adolescents
Bosentan Taro is not recommended for use in children with systemic sclerosis with digital ulcers.

Do not exceed the recommended dose.

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

Method of administration

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

If you have accidentally taken a higher dose, contact your doctor immediately.
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled 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 make up for the forgotten tablets.

If you stop taking this medicine
Suddenly stopping your treatment with Bosentan Taro may lead to your symptoms getting worse. Do not stop taking this medicine unless your doctor tells you to. Your doctor may advise you to reduce the dosage over a few days before stopping the medicine completely.
Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and the dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>
As with any medicine, using Bosentan Taro may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

The most serious side effects during treatment with Bosentan Taro:
- Abnormal liver function, which may affect more than one in 10 users.
- Anemia, which may affect up to 1-10 in 100 users. Anemia may occasionally require blood transfusion.

Your liver function and blood test values will be monitored during treatment with Bosentan Taro (see section 2 under 'Tests and follow-up'). It is important that these tests are done as ordered by your doctor.

Consult your doctor immediately if:
You have the following signs that indicate liver dysfunction: nausea, vomiting, fever, 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 appear in more than one in ten users):
- Headache
- Edema (swelling of the legs and ankles or other signs of fluid retention)

Common side effects (may appear in up to 1 in 10 users):
- Flushed appearance or redness of the skin
- Hypersensitivity reactions (including skin inflammation, itching and rash)
- Gastroesophageal reflux disease (acid reflux)
- Diarrhea
- Fainting
- Palpitations (fast or irregular heartbeats)
- Low blood pressure
- Nasal congestion

Uncommon side effects (may appear in up to 1 in 100 users):
- Thrombocytopenia (low number of platelets)
- Neutropenia/leukopenia (low number of white blood cells)

- High values in liver function test results with hepatitis, including possible exacerbation of latent hepatitis and/or jaundice (yellowing of the skin or the whites of the eyes)

Rare side effects (may appear in up to 1 in 1,000 users):

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

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

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 signs of an allergic reaction appear (such as swelling of the face or tongue, rash, itching) while you are taking Bosentan Taro, or if any of the side effects mentioned above worry you, consult your doctor.

You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il) which opens an online form for reporting side effects. You can also use this link:
https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your 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.

Storage conditions

- Store below 25°C.
- Do not throw away medicines via wastewater or household waste. Ask the pharmacist how to dispose of medicines you no longer use. These measures will help protect the environment.

6. Additional Information

In addition to the active ingredient, this medicine also contains:
maize starch, pregelatinized starch, sodium starch glycolate, povidone k-30, glycerol dibehenate, magnesium stearate.

The coating contains:
Opadry 21k520019 (yellow) consists of hypromellose, titanium dioxide E171, triacetin, talc, ethylcellulose, iron oxide yellow E172, iron oxide red E172.

What the medicine looks like and contents of the pack:
Bosentan Taro 62.5 mg tablets are light peach to peach, round, convex, film-coated tablets with one side debossed with "62.5" and the other side blank.
Bosentan Taro 125 mg tablets are light peach to peach, oval, convex, film-coated tablets with one side debossed with "125" and the other side blank.
Each pack contains 56 film-coated tablets.

Manufacturer and registration holder's name and address:
Taro International Ltd., 14 Hakitor St., Haifa Bay, 2624761.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
Bosentan Taro 62.5 mg: 169-32-35794-00
Bosentan Taro 125 mg: 169-33-35795-00

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