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

The medicine is dispensed with a doctor's prescription only

Bosentan Teva 62.5 mg Coated tablets

Each coated tablet contains:
Bosentan (as monohydrate) 62.5 mg

Bosentan Teva 125 mg Coated tablets

Each coated tablet contains:
Bosentan (as monohydrate) 125 mg
Inactive ingredients and allergens in the preparation: see section 6 "Additional information".
Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine.
If you have additional questions, refer to the doctor or the pharmacist.
This medicine has been prescribed for treatment of your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness/medical condition is similar.

Patient safety information card
In addition to the leaflet, Bosentan Teva also has a patient safety information card regarding possible harm to the fetus.
This card contains important safety information that you should know and act according to before beginning and during treatment with Bosentan Teva. Please review the patient safety information card and the patient leaflet before using the medicine.
Keep the card and the leaflet for further reference, if required.

Do not use Bosentan Teva 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 this medicine if" and "Fertility, pregnancy and breastfeeding").
If you are a woman of childbearing age who can become pregnant, you should take a pregnancy test before you start taking Bosentan Teva and regularly every month while you are taking the medicine, and one month after termination of treatment. A negative result in each pregnancy test must be confirmed. You must use a reliable contraceptive method while taking Bosentan Teva and for one additional month after termination of treatment (see section 2 "Fertility, pregnancy and breastfeeding").

1. What is the medicine intended for?

- Treatment of 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. Bosentan Teva 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.
- Treatment of ulcers of the fingers (digital ulcers) in people with a condition called scleroderma. Bosentan Teva reduces the number of new finger ulcers that occur.

Therapeutic class: Endothelin receptor antagonist.

2. Before using the medicine

Do not use this medicine if:
- You are hypersensitive (allergic) to the active ingredient (bosentan) or to any of the other ingredients this medicine contains as listed in section 6 – "Additional information".
- You have liver problems (consult your doctor).
- You are pregnant, planning to become pregnant or are a woman of childbearing age who could become pregnant and you are not using appropriate contraceptive methods (hormonal contraceptives alone are not effective when taking Bosentan Teva). For additional information, please see section "Fertility, pregnancy and breastfeeding".
- You are taking cyclosporine A (a medicine used for prevention of transplant rejection after a transplant or to treat psoriasis).

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

Special warnings regarding the use of the medicine
- Before, during and after termination of the treatment certain tests should be performed - see sections "Fertility, pregnancy and breastfeeding" and "Tests and follow-up".

Tests and follow-up:

Tests your doctor will do before treatment:
- Blood tests to check liver functions and for anemia (low hemoglobin).
- A pregnancy test (if you are a woman of childbearing age who may become pregnant).

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

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

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

Drug-drug interactions:
If you are taking or have recently taken other medicines including non-prescription medicines and food supplements, tell the doctor or the pharmacist. Especially if you are taking:
- Cyclosporine (used for prevention of transplant rejection after a transplant or to treat psoriasis). Using together with Bosentan Teva is prohibited.
- Sirolimus or tacrolimus (used for prevention of transplant rejection). Using together with Bosentan Teva is not recommended.
- Glibenclamide (for diabetes); fluconazole, ketoconazole, voriconazole, itraconazole (for treatment of fungal infections); rifampicin (for treatment of tuberculosis), nevirapine, ritonavir (for treatment of AIDS/HIV infection). Using together with Bosentan Teva is not recommended.
- Other medicines for the treatment of AIDS (HIV infection). Special monitoring is required if used together with Bosentan Teva.
- Hormonal contraceptives (such as: oral contraceptive tablets, injections, implants, skin patches). These contraceptives will not be effective as the sole method of contraception when taking Bosentan Teva. Your attending doctor 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.
- Simvastatin (used for lowering cholesterol). If taken together, it is recommended to monitor cholesterol levels.
- Warfarin (for prevention of blood coagulation). It is recommended to monitor the International Normalized Ratio (INR) frequently, especially in the beginning of treatment and during dosage adjustment.
- Other medications for treatment of pulmonary hypertension: sildenafil and tadalafil.

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

Fertility, pregnancy and breastfeeding:

Fertility:
If you are a man taking Bosentan Teva, 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:
- Bosentan Teva may harm fetuses conceived before starting treatment or during treatment. If you are a woman of childbearing age who can become pregnant, your doctor will ask you to take a pregnancy test before you start taking Bosentan Teva and regularly every month while you are taking the medicine, and one month after termination of treatment. A negative result in each pregnancy test must be confirmed.
- Do not take Bosentan Teva if you are pregnant or planning to become pregnant. Inform your doctor immediately if you are pregnant, think you might be pregnant or are planning to become pregnant.
- You must use a reliable contraceptive method while taking Bosentan Teva and for one month after termination of treatment.
- Your doctor or gynecologist will instruct you about reliable contraceptive methods while taking Bosentan Teva. As the medicine may make hormonal contraceptives (e.g. oral contraceptives, injections, implants or skin patches) ineffective, this method on its own is not reliable.

The 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 contraceptive methods such as a hormonal method and a barrier method (e.g. diaphragm, contraceptive sponge or use of condom by your partner) or two barrier methods. Consult your doctor regarding the use of one of these two options for 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 Bosentan Teva, if you plan to become pregnant in the near future or think you might be pregnant.

Breastfeeding
- If you are breastfeeding or planning to breastfeed, consult your doctor or pharmacist before initiating treatment with Bosentan Teva, since the medicine may cause harm to the baby.
- You are advised to stop breastfeeding if Bosentan Teva is prescribed for you as it is not known whether this medicine passes into breastmilk.

Driving and operating machinery
The medicine may have a negligible influence on the ability to drive and use machines. In accordance with the side effects listed in this leaflet, the medicine 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 blurry while taking the medicine, do not drive or operate any devices or machines. Children should be warned to be careful when riding a bicycle or playing near a road etc.

Important information about some ingredients of the medicine
This preparation contains less than 23 mg of sodium in each coated tablet, and is therefore considered sodium-free.

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.
Treatment with the medicine should only be initiated and monitored by a doctor who has experience in the treatment of PAH or systemic sclerosis.
The dosage and treatment regimen will be determined only by the doctor. The generally accepted dosage is:

Adults
The treatment in adults is usually started with 62.5 mg twice daily (morning and evening) for the first four weeks. Thereafter, your doctor will usually advise you to take a dose of 125 mg twice daily, depending on how you react to Bosentan Teva.

Children and adolescents
The optimal dosage for children under the age of 12 who suffer from pulmonary arterial hypertension is unknown. Consult your doctor.
No information is available regarding efficacy and safety of bosentan in children and adolescents under the age of 18 with scleroderma and digital ulcers.

Do not exceed the recommended dose.
If you have the impression that the effect of Bosentan Teva is too strong or too weak, talk to your doctor in order to find out whether your dosage needs to be changed.
The medicine should be taken with a glass of water. The tablets should not be halved, crushed or chewed.
If you have accidentally taken a higher dosage, contact your doctor immediately. If you took an overdose or if a child swallowed this medicine by mistake, go to the doctor or the emergency room of the hospital immediately and take 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, but do not take a double dose to compensate for the forgotten one.
Follow the treatment as recommended by the doctor.
Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the doctor.
If you stop taking this medicine
Suddenly stopping your treatment with Bosentan Teva may lead to your symptoms getting worse.
Do not stop taking the medicine unless your doctor tells you to. The doctor may tell you to reduce the dosage over a few days before stopping the medicine completely.
Do not take medicines in the dark! Check the label and the dose every time you take the medicine. Wear glasses if you need them.
If you have any other questions regarding use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using Bosentan Teva may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
The most severe side effects that may occur during treatment with Bosentan Teva are:
- Abnormal liver function which may affect more than one in 10 users.
- Anemia which may affect 1-10 users out of 100. Anemia may occasionally require blood transfusion.

During treatment with the medicine, blood tests and liver function follow-up will be taken to monitor these conditions. It is important that you have these tests as ordered by your doctor.
Refer to a doctor immediately if:
- You are suffering from the following symptoms that may indicate that your liver may not be working properly, e.g.: nausea, vomiting, fever, abdominal pain, jaundice (yellowing of your skin or the whites of your eyes), dark-colored 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
Edema (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, rash)
Gastroesophageal reflux disease (acid reflux)
Diarrhea
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):
Anaphylactic shock (a general allergic reaction)
Angioedema (swelling, most commonly around the eyes, lips, tongue, throat)
Cirrhosis, liver failure
Blurred vision has also been reported at an unknown frequency (frequency cannot be estimated from the available data).

Side effects in children and adolescents
The side effects that have been reported in children treated with Bosentan Teva are the same as those reported in adults.
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 Bosentan Teva, or if any of the side effects mentioned above worries you, **consult with you doctor.**

Reporting side effects
Side effects may be reported to the Ministry of Health by clicking on the link "report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.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 without an explicit instruction from the doctor.
Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
Store below 25°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, sodium starch glycolate type A, pregelatinized starch, glycerol dibehenate, povidone, magnesium stearate, hypromellose, titanium dioxide, talc, triacetin, yellow iron oxide, red iron oxide, ethylcellulose, cetyl alcohol, sodium lauryl sulfate
What does the medicine look like and what are the contents of the package:
Bosentan Teva is marketed in package sizes of 7, 14, 56, 60 and 112 coated tablets. Not all package sizes may be marketed.
Bosentan Teva 62.5 mg: A round, biconvex pink-orange tablet. On one side it is embossed with the number "62.5".
Bosentan Teva 125 mg: An oval, biconvex pink-orange tablet. On one side it is embossed with the number "125".
License holder and the address: Abic Marketing Ltd. P.O.B 8077 Netanya, Israel.
Name and address of the manufacturer:
Teva Pharmaceutical Industries Ltd., P.O. box 3190, Petah Tikva.
The format of this leaflet has been determined by the Ministry of Health and its content was checked and approved by the MOH in May 2019.
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