140 mm

230 mm

*For the use of a registered medical practitioner or a hospital or a laboratory only*

# Bosentan Tablets IP

## SAFEBO

**Box Warning**

1. Due to potential of the drug to cause serious liver injury,serum aminotransferase levels should be measured in patients prior to initiation of treatment and then monthly. Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferases elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2x ULN, treatment should be stopped

2. Bosentan is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Therefore, pregnancy must be excluded before the start of treatment with bosentan and prevented thereafter by the use of a reliable method of contraception. Monthly pregnancy tests should be obtained.

**COMPOSITION:**

**SAFEBO 62.5**

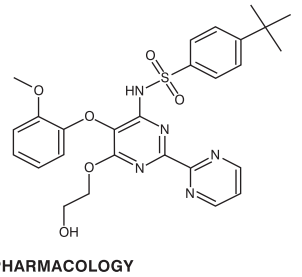
Each film coated tablet contains:
Bosentan Monohydrate IP
Equivalent to Bosentan 62.5 mg
Colour: Titanium Dioxide IP.

**SAFEBO 125**

Each film coated tablet contains:
Bosentan Monohydrate IP
Equivalent to Bosentan 125 mg
Colour: Titanium Dioxide IP.

**DESCRIPTION**

Bosentan is the first of a new drug class, an endothelin receptor antagonist. Bosentan belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2- methoxy-phenoxy)-[2,2´]-bipyrimidin-4-yl]- benzenesulfonamide monohydrate and has the following structural formula




**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to $ET_A$ and $ET_B$ receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterail hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitiveanatagonist at endothelin receptor types $ET_A$ and $ET_B$. Bosentan has a slightly higher affinity for $ET_A$ receptors than for $ET_B$ receptors.

**Pharmacokinetics**

**General**

After oral administration, maximum plasma concentrations of bosentan are attained within 3-5 hours and the terminal elimination half-life (t1/2) is about 5 hours in healthy adult subjects. The exposure to bosentan after intervenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

**Absorption and Distribution**

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. The volume of distribution is about 18 L. Bosentan is highly bound (> 98%) to plasma, proteins mainly albumin. Bosentan does not penetrate into erythrocytes.

**Metabolism and Elimination**

Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10% to 20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3-5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

**Special Populations**

It is not known whether bosentan pharmacokinetics is influenced by gender, body weight, race, or age.

**Liver Function Impairment:** In vitro and In vivo evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases > 3 x ULN (Upper limit of Normal)

**Renal Impairment :** In patients with severe renal impairment , plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2fold compared to people with normal renal function. These differences do not appear to be clinically important.

**INDICATIONS**

BOSENTAN Tablet is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

**DOSAGE AND ADMINISTRATION**

Bosentan tablets treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury.

Tablets should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

| ALT/AST levels | Treatment and monitoring recommendations |
|---|---|
| > 3 and = 5 x ULN | Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below). |
| > 5 and = 8 x ULN | Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, consider re introduction of the treatment (see below). |
| > 8 x ULN | Treatment should be stopped and re -introduction of Bosentan should not be considered. There is no experience with re-introduction of Bosentan in these circumstances. |

140 mm

230 mm

**Dosage Adjustment in Renally Impaired Patients**
The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

**CONTRAINDICATIONS**
Pregnancy Category X. Bosentan tablets is expected to cause fetal harm if administered to pregnant women.
Pregnancy must be excluded before the start of treatment with Bosentan tablets and prevented thereafter by use of reliable contraception. It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives may not be reliable in the presence of Bosentan tablets and should not be used as the sole contraceptive method in patients receiving Bosentan tablets Input from a gynecologist or similar expert on adequate contraception should be sought as needed.
Bosentan tablets should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescripition for Bosentan tablets should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine orserum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse.
Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking Bosentan tablets. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

**Hypersensitivity:** Bosentan tablets is also contraindicated in patients who are hypersensitive to bosentan or any component of the medication.

**DRUG INTERACTIONS:**
Cyclosporine A: Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Bosentan tablets and cyclosporine A is contraindicated.
Glyburide: An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and Bosentan tablets is contraindicated.
Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of lopinavir/ritonavir and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Bosentan tablets and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated.

**WARNING:**
Bosentan has rarely caused very serious liver problems. Your doctor will monitor your liver function blood tests monthly. Tell your doctor immediately if you develop symptoms of liver disease, including persistent nausea/vomiting, stomach/abdominal pain, extreme tiredness, dark urine, yellowing eyes/skin. This medication must not be used during pregnancy because it can cause harm to a fetus/unborn baby. Hematologic Changes

**PRECAUTIONS**
**Hematologic changes**
Treatment with bosentan tablets caused a dose-related decrease in hemoglobin and hematocrit. Hemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4 12 weeks of bosentan treatment.
During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.
It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

**Fluid retention**
In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with bosentan tablets. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting bosentan tablets. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

**Pulmonary Veno-Occlusive Disease (PVOD)**
Should signs of pulmonary edema occur when bosentan tablets is administered the possibility of associated PVOD should be considered and bosentan tablets should be discontinued.

**SIDE EFFECTS**
Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function.

**OVERDOSE**
Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

**STORAGE**
**Store Below 25°C.** Keep out of reach of children

**PRESENTATION**
**SAFEBO 62.5**
Blister Pack of 10 Tablets

**SAFEBO 125**
Blister Pack of 10 Tablets

Manufactured by:
**MSN Laboratories Private Limited**
(Formulations Division), Plot No. 42,
Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325,
Telangana, INDIA.

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