1.6.3 Patient information Leaflet (PIL)

Patient information Leaflet (PIL) of **PULMOFIRST 62.5** (Bosentan Tablets 62.5 mg) has been enclosed in the following pages.

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.

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.

In the postmarketing period, there was one reported overdose of 10,000 mg of bosentan taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

STORAGE : Do not store above 30^{0}C. Protect from light and moisture.

Keep out of reach of children.

PACKING INFORMATION:

Pulmofirst 62.5…Alu-Alu Blister Pack of 10 Tablets
Pulmofirst 125….Alu-Alu 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.

B31682-00

Prescription only medication

Pulmofirst 62.5,125

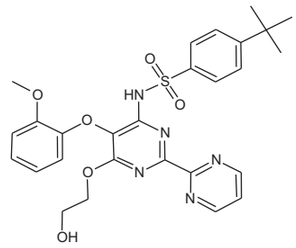
COMPOSITION:

Pulmofirst 62.5

Each film coated tablet contains
Bosentan Monohydrate
Equivalent to Bosentan 62.5 mg

Pulmofirst 125

Each film coated tablet contains
Bosentan Monohydrate
Equivalent to Bosentan 125 mg



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 35 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%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 enzyms. 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. In a study comparing 8 patients with mild liver impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan were not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases > 3 x ULN (Upper limit of Normal)

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.

Dimensions (Front - 280 x 210 mm - Back - 280 x 210 mm)
Folded size : 70 x 35 mm
MAPLITHO PAPER 60 GSM

Recommendations in case of ALT/AST elevations

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ℝ 5 × ULN	Confirm by another liver test; if confirmed, a decision should be made on an individual basis to continue Bosentan, possibly at a reduced dose, or to stop Bosentan administration. Continue to monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider continuing or re-introducing Bosentan according to the conditions described below.
> 5 and ℝ 8 × ULN	Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider re-introducing Bosentan according to the conditions described below.
> 8 × ULN	Treatment must be stopped and re-introduction of Bosentan is not to be considered.

In the case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Bosentan is not to be considered.

Re-introduction of treatment

Re-introduction of treatment with Bosentan should only be considered if the potential benefits of treatment with Bosentan outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.

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.

CONTRAINDICATIONS

Pregnancy Category X. Bosentan tablets is expected to cause fetal harm if administered to pregnant women. Bosentan was teratogenic in rats given oral doses = 60 mg/kg/day (twice the maximum recommended human oral dose of 125 mg, b.i.d., on a mg/ m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day (2 and 10 times, respectively, the maximum recommended human dose on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of Bosentan tablets in 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.

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 .

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

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

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 412 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 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