

BOSENTAS

Use of bosentan requires attention to two significant concerns:

1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury

Bosentan causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (alanine aminotransferase; ALT and aspartate aminotransferase AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of bosentan in these cases could not be excluded.

In at least one case the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of bosentan. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping bosentan with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction.

Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (> 3 × ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase 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 $\geq 2 \times$ ULN, treatment should be stopped. There is no experience with the re-introduction of bosentan in these circumstances.

CONTRAINDICATION: Pregnancy

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. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan. Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

COMPOSITION

BOSENTAS 62.5 mg

Each film-coated tablet contains
Bosentan ...62.5 mg

BOSENTAS 125 mg

Each film-coated tablet contains
Bosentan ...125 mg

DOSAGE FORM

Tablets

PHARMACOLOGY

Pharmacodynamics

Bosentan is the first of a new drug class, an endothelin receptor antagonist. 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 arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist 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 ($t_{1/2}$) is about 5 hours in healthy adult subjects. The exposure to Bosentan after intravenous 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 18L. 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 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's 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 $>3 \times$ ULN.

Renal Impairment

In patients with severe renal impairment (creatinine clearance 15–30 mL/min), plasma concentrations of Bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important.

INDICATIONS

Bosentan 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 & ADMINISTRATION

General

Bosentan 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 \leq 5 \times 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.
> 5 and \leq 8 \times 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 pre-treatment values, consider re-introduction of the treatment.
> 8 \times 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.

If bosentan is **re-introduced** it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

If liver aminotransferase 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 \geq 2 \times ULN, treatment should be stopped. There is no experience with the re-introduction of bosentan in these circumstances.

Dosage Adjustment in Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d.

CONTRAINDICATIONS

Pregnancy Category X. Bosentan 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/m^2 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/m^2 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 in pregnant women.

Pregnancy must be excluded before the start of treatment with bosentan 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 and should not be used as the sole contraceptive method in patients receiving bosentan. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Bosentan should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for bosentan 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 or serum 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. 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 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 is contraindicated.

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

WARNINGS & PRECAUTIONS

Potential Liver Injury

Elevations in ALT or AST by more than 3 × ULN were observed in 11% of Bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). Three-fold increases were seen in 12% of 95 PAH patients on 125 mg b.i.d. and 14% of 70 PAH patients on 250 mg b.i.d. Eight-fold increases were seen in 2% of PAH patients on 125 mg b.i.d. and 7% of PAH patients on 250 mg b.i.d. Bilirubin increases to $\geq 3 \times$ ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with Bosentan.

The combination of hepatocellular injury (increases in aminotransferases of $> 3 \times$ ULN) and increases in total bilirubin ($\geq 3 \times$ ULN) is a marker for potential serious liver injury.

Elevations of AST and/or ALT associated with Bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with bosentan.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase 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 $\geq 2 \times$ ULN, treatment should be stopped. There is no experience with the re-introduction of bosentan in these circumstances.

Pre-existing Liver Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Bosentan should generally be avoided in patients with moderate or severe liver impairment. In addition, bosentan should generally be avoided in patients with elevated aminotransferases ($> 3 \times$ ULN) because monitoring liver injury in these patients may be more difficult.

Decreased Sperm Counts

Based on recent findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as bosentan have an adverse effect on spermatogenesis. The sperm count had returned to baseline levels after 2 months of discontinuation of bosentan in the reported cases.

Hematologic Changes

Treatment with bosentan 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. 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 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 (CHF), 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. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting bosentan. 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 is administered the possibility of associated PVOD should be considered and bosentan should be discontinued.

Drug Interactions

Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these enzymes may increase the plasma concentration of Bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a CYP3A4 inhibitor (such as ketoconazole, itraconazole, or ritonavir) with Bosentan will likely lead to large increases in plasma concentrations of Bosentan. Co-administration of such combinations of a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor with BOSENTAN is not recommended.

Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when BOSENTAN is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme *in vitro* (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). Consequently, BOSENTAN is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives

An interaction study demonstrated that co-administration of Bosentan and the oral hormonal contraceptive Ortho-Novum[®] (norethindrone and ethinylestradiol) produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when bosentan is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking bosentan.

Specific interaction studies have demonstrated the following:

Cyclosporine A

During the first day of concomitant administration, trough concentrations of Bosentan were increased by about 30-fold. Steady-state Bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. The concomitant administration of Bosentan and cyclosporine A is contraindicated. Co-administration of Bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A4 substrate) by approximately 50%.

Tacrolimus

Co-administration of tacrolimus and Bosentan has not been studied in man. Co-administration of tacrolimus and Bosentan resulted in markedly increased plasma concentrations of Bosentan in animals. Caution should be exercised if tacrolimus and Bosentan are used together.

Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of bosentan and glyburide is contraindicated, and alternative hypoglycemic agents should be considered.

Co-administration of Bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of Bosentan were also decreased by approximately 30%. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered.

Ketoconazole:

Co-administration of Bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of Bosentan by approximately 2-fold. No dose adjustment of Bosentan is necessary, but increased effects of Bosentan should be considered.

Simvastatin and Other Statins

Co-administration of Bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β -hydroxy acid metabolite, by approximately 50%. The plasma concentrations of Bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after bosentan is initiated to see whether the statin dose needs adjustment.

Warfarin

Co-administration of Bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of Bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin

dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among Bosentan- and placebo-treated patients.

Digoxin, Nimodipine and Losartan:

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of Bosentan.

Sildenafil

In healthy subjects, co-administration of multiple doses of 125 mg b.i.d Bosentan and 80 mg t.i.d. sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased Bosentan plasma concentrations by 50%. A dose adjustment of neither drug is necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost

In a small, randomized, double-blind, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg bid for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

Rifampicin

Coadministration of bosentan and rifampicin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose, but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampicin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure LFTs weekly for the first 4 weeks before reverting to normal monitoring.

Lopinavir and ritonavir

Co-administration of Bosentan 125 mg twice daily and lopinavir + ritonavir 400 mg + 100 mg twice daily during 9.5 days in healthy subjects resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Bosentan administered alone. At steady state, plasma concentrations of bosentan were approximately 5-fold higher than with Bosentan administered alone. Inhibition by ritonavir of OATP-mediated uptake into hepatocytes, reducing the clearance of bosentan, most likely explains this interaction. After co-administration of Bosentan, the plasma exposures to lopinavir and ritonavir at steady state decreased by approximately 14% and 17%,

respectively. When Bosentan is administered concomitantly with lopinavir + ritonavir or other ritonavir-boosted protease inhibitors, there should be appropriate monitoring of Bosentan tolerability and ongoing HIV status

Renal Impairment

The effect of renal impairment on the pharmacokinetics of Bosentan is small and does not require dosing adjustment.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of Bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of Bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of Bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Bosentan should generally be avoided in patients with moderate or severe liver impairment.

Pregnancy

Category X (See Contraindications)

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking bosentan is not recommended.

Use in Women of Child-bearing Potential

Bosentan treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable, transdermal, or implantable contraceptive. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking bosentan.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of bosentan did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

UNDESIRABLE EFFECTS

The most common adverse events occurring in patients treated with Bosentan were headache, nasopharyngitis, flushing, abnormal hepatic function, lower limb edema, hypotension, palpitations, dyspepsia, edema, fatigue and pruritis. There have been post-marketing reports of angioneurotic edema and unexplained hepatic cirrhosis also.

OVERDOSAGE

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.

There is no specific experience of overdosage with Bosentan beyond the doses described above. Massive overdosage may result in pronounced hypotension requiring active cardiovascular support

STORAGE & HANDLING INSTRUCTIONS

Store at 20°C-25°C (68°F-77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

PACKAGING

BOSENTAS 62.5: Blister pack of 10 tablets

BOSENTAS 125: Blister pack of 10 tablets