

# BOSENTAS Tablets (Bosentan)

## Black Box Warning

Use of bosentan requires attention to two significant concerns:

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

### **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 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 ( $> 3 \times$  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 with bosentan 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<sub>A</sub> and ET<sub>B</sub> 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<sub>A</sub> and ET<sub>B</sub>. Bosentan has a slightly higher affinity for E<sub>A</sub> receptors than for ET<sub>B</sub> receptors. The clinical impact of dual endothelin blockage is unknown.

## **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***

#### ***Paediatrics***

The average plasma exposure to bosentan at steady state (AUCs) in pediatric patients with PAH aged 3 to 15 years treated with 31.25, 62.5 or 125 mg (approximately 2 mg/kg) film-coated tablet twice daily is 37% lower than that observed in adult patients with PAH receiving 125 mg filmcoated tablet twice daily. Following administration of 4 mg/kg twice daily doses of dispersible tablet in

patients with PAH aged 2 to 11 years, the average systemic exposure to bosentan at steady state is similar to that observed with 2 mg/kg. The average exposure to bosentan in these pediatric patients was approximately half the exposure in adult patients treated with 125 mg filmcoated tablets twice daily. The exposure to bosentan at 2 mg/kg three times daily dosing of dispersible tablet is similar to that of 2 mg/kg twice daily dosing in patients with PAH aged 3 months to 12 years. Based on these findings, exposure to bosentan reaches a plateau at lower doses in pediatric patients than in adults, and doses higher than 2 mg/kg twice daily do not increase the exposure to bosentan in pediatric patients.

### **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 (PAH) (WHO Group I) in patients with WHO Class III to 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.**

Table 1: Dosage adjustment and monitoring in patients developing aminotransferase abnormalities

<b>ALT/AST levels</b>	<b>Treatment and monitoring recommendations</b>
$> 3$ 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.

## Use with Ritonavir

### *Coadministration of Bosentan in Patients on Ritonavir*

In patients who have been receiving ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.

### *Coadministration of Ritonavir in Patients on Bosentan*

Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.

## Use in Patients with Pre-existing Hepatic Impairment

Bosentan should generally be avoided in patients with moderate or severe liver impairment. Initiation of bosentan should generally be avoided in patients with elevated aminotransferases  $>3 \times$  ULN. No dose adjustment is required in patients with mildly impaired liver function.

## Treatment Discontinuation

There is limited experience with abrupt discontinuation of bosentan. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

## Contraindications

### Pregnancy Category X

Bosentan is expected to cause fetal harm if administered to pregnant women. Bosentan was teratogenic in rats given oral doses  $\geq 60$  mg/kg/day (twice the maximum recommended human oral dose of 125 mg, b.i.d., on mg/m<sup>2</sup> 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 mg/m<sup>2</sup> 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. Throughout treatment and for one month after stopping bosentan, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. 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. Observed reactions include rash and angioedema.

# **Warnings & Precautions**

## **Potential Liver Injury**

Elevations in ALT or AST by more than  $3 \times$  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  $\geq 3 \times \text{ULN}$  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  $> 3 \times \text{ULN}$ ) and increases in total bilirubin ( $\geq 2 \times \text{ULN}$ ) 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  $\geq 2 \times \text{ULN}$ , 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 ( $> 3 \times \text{ULN}$ ) because monitoring liver injury in these patients may be more difficult.

In WHO Functional Class II patients, consider whether the benefits of bosentan are sufficient to offset the risk of hepatotoxicity, which may preclude future use as their disease progresses.

### **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.

### **Haematologic Changes**

Treatment with bosentan caused a dose-related decrease in hemoglobin and haematocrit. Haemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. The overall mean decrease in haemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of haemoglobin concentration was detected during the first few weeks of bosentan treatment and haemoglobin levels stabilized by 4-12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in haemoglobin ( $> 15\%$  decrease from baseline resulting in values  $< 11 \text{ g/dL}$ ) 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 haemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in haemoglobin 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 treatment, the haemoglobin 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 haemoglobin 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**

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of bosentan and other endothelin receptor antagonists. In PAH clinical trials with bosentan, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients. 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.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as bosentan or underlying heart failure, and the possible need for treatment or discontinuation of bosentan.

## **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**

### ***Cytochrome P450 Summary***

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***

Drug interaction studies show that bosentan reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in

patients using bosentan and should not be used as a patient's only contraceptive method.

Females of childbearing potential using bosentan must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNG 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing bosentan therapy. Females of childbearing potential using bosentan should seek contraception counseling from a gynecologist or other expert as needed.

An interaction study demonstrated that co-administration of bosentan and the oral hormonal contraceptive containing 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. 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  $\beta$ -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.

Coadministration of bosentan 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

### **Co-administration of bosentan in Patients on Ritonavir**

In patients who have been receiving ritonavir for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability.

### **Co-administration of Ritonavir in Patients on bosentan**

Discontinue use of bosentan at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.

## **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 (Child-Pugh Class A) was shown not to impact the pharmacokinetics of bosentan. The pharmacokinetics of bosentan has not been evaluated in patients with severe liver impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the systemic exposures to bosentan and its active metabolite increased significantly. Bosentan should generally be avoided in patients with moderate or severe liver impairment.

## **Pregnancy**

### ***Category X: Teratogenic Effects [See Contraindications]***

Use of bosentan is contraindicated in females who are or may become pregnant. While there are no adequate and well-controlled studies in pregnant females, animal studies show that bosentan is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If bosentan is used during pregnancy or if a patient becomes pregnant while taking bosentan, the patient should be apprised of the potential hazard to the fetus.

## **Lactation**

There are no data on the presence of bosentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions, such as fluid retention and hepatotoxicity, in breastfed infants from bosentan, advise women not to breastfeed during treatment with bosentan.

## 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.

## Paediatric Use

The efficacy of bosentan in patients is supported by data from an uncontrolled trial in which 19 pediatric patients were treated with bosentan. This study, cardiopulmonary hemodynamic improvements were similar to those seen in adults treated with bosentan. Safety in pediatric patients is supported by data from 100 pediatric patients treated with bosentan for a median of 17 months.

## 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 following important adverse reactions are described elsewhere in the labeling:

- Potential liver injury [see **Boxed Warning, Warnings and Precautions**]
- Fluid retention [see **Warnings and Precautions**]
- Embryo-fetal Toxicity

## Clinical Studies Experience

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 unexplained hepatic cirrhosis, liver failure, hypersensitivity, thrombocytopenia, rash, jaundice, anemia requiring transfusion, neutropenia and leucopenia.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data on bosentan were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (n=94 for 1 year; n=61 for 1.5 years and n=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (n=328) to bosentan ranged from 1 day to 1.7 years (n=174 more than 6 months and n=28

more than 12 months).

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 (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on bosentan was abnormal liver function.

The adverse drug events that occurred in  $\geq 3\%$  of the bosentan -treated patients and were more common on bosentan in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

Table 2. Adverse events\* occurring in  $\geq 3\%$  of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo- controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan n = 258		Placebo n = 172	
	No.	%	No.	%
Respiratory Tract Infection	56	22	30	17
Headache	39	15	25	14
Edema	28	11	16	9
Chest Pain	13	5	8	5
Syncope	12	5	7	4
Flushing	10	4	5	3
Hypotension	10	4	3	2
Sinusitis	9	4	4	2
Arthralgia	9	4	3	2
Serum Aminotransferases, abnormal	9	4	3	2
Palpitations	9	4	3	2
Anemia	8	3	-	

\*Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population. Combined data from Study 351, BREATHE-1 and EARLY

## Decreased Sperm Counts

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of bosentan 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count

remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. Based on these 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.

## **Decreases in Haemoglobin and Haematocrit**

Treatment with bosentan can cause a dose-related decrease in haemoglobin and haematocrit. It is recommended that haemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in haemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in haemoglobin concentration for bosentan-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of haemoglobin concentration was detected during the first few weeks of bosentan treatment and haemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in haemoglobin (> 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 PAH treated with doses of 125 and 250 mg twice daily, marked decreases in haemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in haemoglobin 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 haemoglobin 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 haemolysis.

## **Post marketing Experience**

There have been several post marketing reports of angioedema associated with the use of bosentan. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing bosentan.

The following additional adverse reactions have been reported during the post-approval use of bosentan. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to bosentan exposure:

- Unexplained hepatic cirrhosis [see **Boxed Warning**]
- Liver failure [see **Boxed Warning**]
- Hypersensitivity [see **Contraindications**]
- Thrombocytopenia
- Rash
- Jaundice
- Anemia requiring transfusion
- Neutropenia and leukopenia
- Nasal congestion

If you experience any side effects, talk to your doctor or pharmacist or write to [drugsafety@cipla.com](mailto:drugsafety@cipla.com). You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side effects you can help provide more information on the safety of this product.

## 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.

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.

Bosentan is unlikely to be effectively removed by dialysis due to the high molecular weight and extensive plasma protein binding.

## 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 Information

**BOSENTAS 62.5:** Blister pack of 10 tablets

**BOSENTAS 125:** Blister pack of 10 tablets

*Last Updated: June 2018*

*Last Reviewed: June 2018*