

# PRODUCT INFORMATION

## BOSENTAN MYLAN

Bosentan (as monohydrate)



BOSENTAN MYLAN may cause birth defects and is contraindicated in pregnancy. See **CONTRAINDICATIONS** and **PRECAUTIONS**.

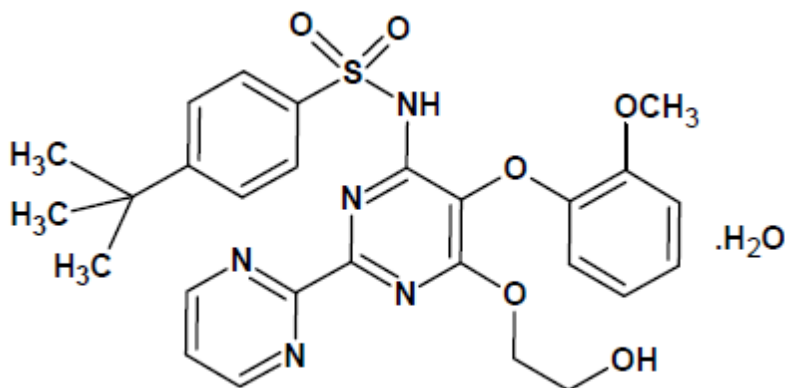
Rare cases of hepatic cirrhosis and hepatic failure have been reported in patients using BOSENTAN MYLAN. See **PRECAUTIONS**.

### NAME OF THE MEDICINE

Active Ingredient: Bosentan (as monohydrate)

Chemical Name: benzenesulphonamide, 4- (1,1-dimethylethyl)-N-[6-(2hydroxyethoxy)-5-(2-methoxyphenoxy)]2,2'-bipyrimidin]-4-yl]-, monohydrate.

Structural Formula:



Molecular Formula:  $C_{27}H_{29}N_5O_6S \cdot H_2O$

Molecular Weight: 569.64

CAS Registry No: 157212-55-0

Bosentan is the first of a new drug class, an endothelin receptor antagonist. BOSENTAN MYLAN (bosentan) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centres.

### DESCRIPTION

Bosentan monohydrate, a white to off-white powder, is practically insoluble at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0).

Solubility increases at higher pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan monohydrate is very stable, is not hygroscopic and shows no light sensitivity.

Inactive: maize starch, pregelatinised maize starch, sodium starch glycollate, povidone, glyceryl behenate, magnesium stearate, sodium lauryl sulfate, Opadry white 03K580000 (ARTG no. 108721) and Surelease aqueous ethylcellulose dispersion E-7-19040 Clear (ARTG no. 11522).

## PHARMACOLOGY

### Pharmacodynamics Properties

The neurohormone endothelin-1 (ET-1) is a potent vasoconstrictor. 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 ETA and ETB. Bosentan has a slightly higher affinity for ETA receptors than for ETB receptors.

### Pharmacokinetics

#### General

After oral administration, maximum plasma concentrations of bosentan found in a study of the 125 mg tablets taken as a single dose, were attained within  $3.7 \pm 1.7$  hours and the apparent elimination half-life ( $t_{1/2}$ ) was  $5.6 \pm 1.6$  hours in 16 fasted subjects. The pharmacokinetics of oral bosentan have not been studied in patients with pulmonary arterial hypertension. The clearance of intravenous bosentan was significantly lower in patients with primary pulmonary hypertension (3.8L/h) than in healthy volunteers (9L/h). Exposure is also expected to be greater in patients with pulmonary arterial hypertension since increased (30-40%) bosentan exposure has been observed in patients with severe chronic heart failure.

#### Absorption and Distribution

In healthy volunteers at a dose of 600 mg, the absolute bioavailability of bosentan from an oral suspension was 41%. At a dose of 125 mg, administration of bosentan with food did not have a significant effect on the extent of absorption but did increase the rate, leading to a 20% increase in peak plasma concentrations of bosentan. This is not expected to be clinically significant. The volume of distribution and clearance of bosentan are non-linear and decrease as the dose increases. The mean volume of distribution of  $17.8 \pm 3.6$  L/h and the mean clearance of  $8.8 \pm 1.9$  L were determined after a mean IV dose of 250 mg was administered to 18 healthy male volunteers. Bosentan is highly bound (>98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

#### Metabolism and Elimination

Bosentan is metabolised in the liver by the cytochrome P450 enzymes, CYP2C9 and CYP 3A4, and eliminated by biliary excretion. 94% of a radioactive oral dose was recovered in faeces (30% was unchanged). Bosentan has three metabolites, one of which is pharmacologically active and may contribute 20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP 2C19. Total clearance after a single intravenous dose is about 8L/hr. Upon multiple dosing, plasma concentrations decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolising liver enzymes.

Steady state is reached within 3-5 days. Less than 3% of an administered oral dose is recovered in urine.

#### Special Populations

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

#### Hepatic Function Impairment

The steady-state pharmacokinetics of bosentan and metabolites were studied in 8 patients with mild hepatic impairment (Child-Pugh Class A) without pulmonary hypertension. Compared to healthy controls, bosentan  $C_{max}$ , AUC and half-life were not significantly altered; AUC of the active metabolite Ro 48-5033 was increased by 33%; trough concentrations of Ro 48-5033 and Ro 64-1056 were increased by 75% and 20%, respectively. Based on these findings, no dosage adjustment is required in patients with mild hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

The pharmacokinetics of bosentan have not been studied in patients with moderate to severe hepatic impairment. Bosentan is contraindicated in patients with moderate to severe hepatic abnormalities and/or baseline elevated aminotransferases  $>3$  x Upper Limit of Normal (ULN) (see **CONTRAINDICATIONS**).

### **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 (see **DOSAGE AND ADMINISTRATION**).

### **Children**

The pharmacokinetics of bosentan at steady-state were studied in 19 children aged 3 to 15 years with PPH or PAH secondary to congenital systemic to pulmonary communications. In children weighing over 20 kg, administration of the recommended dose regimen (see **DOSAGE AND ADMINISTRATION**) led to bosentan plasma concentrations which were higher than those in healthy adults taking the recommended adult dose, but similar to those expected in adults with pulmonary hypertension. In children weighing 10-20 kg, bosentan plasma concentrations during administration of the recommended dose were lower than in healthy adults, and thus lower than those expected in adults with pulmonary hypertension. However, the recommended dose was associated with haemodynamic improvement and should not be exceeded on safety grounds. The steady-state half life of bosentan in children averaged 5 to 6 hours.

## **CLINICAL TRIALS**

### **Adult patients with pulmonary arterial hypertension**

#### **WHO Grade Functional Class III & IV**

Two randomised, double-blind, multicentre, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1, Study 352) compared the two bosentan doses pooled (125 mg twice daily and 250 mg twice daily) of bosentan with placebo. The smaller study (Study 351) compared bosentan 125 mg twice daily with placebo.

Patients had severe (WHO Functional Class III-IV) pulmonary arterial hypertension: primary pulmonary hypertension (72%) or pulmonary hypertension secondary to scleroderma or other connective tissue diseases (21%), or to autoimmune disease (7%). There were no patients with pulmonary hypertension secondary to HIV, or pulmonary embolus.

In both studies, bosentan or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g. calcium channel blockers, ACE inhibitors), but not epoprostenol. Bosentan was given at a dose of 62.5 mg twice daily for 4 weeks and then at 125 mg twice daily or 250 mg twice daily for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walking distance. In addition, symptoms and functional status were assessed. Haemodynamic measurements were made at 12 weeks in Study 351. The exploratory analysis of these prospectively defined secondary parameters showed results that are consistent with the results for the primary parameter.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

### **Submaximal Exercise Capacity**

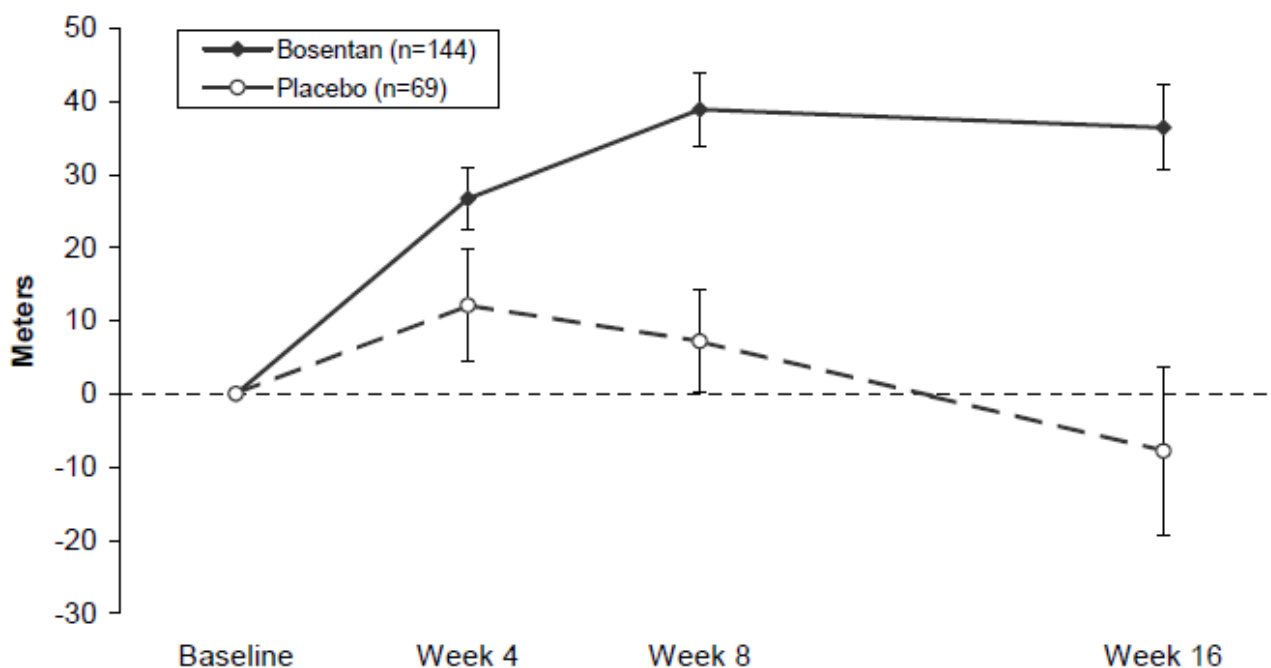
Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in **Table 1**.

**Table 1: Effects of bosentan on 6-minute walk**

	<b>BREATHE-1</b>		<b>Study 351</b>	
	125/250 mg twice daily	Placebo	125 mg twice daily	Placebo
N	144	69	21	11
Baseline	330 ± 74	344 ± 76	360 ± 86	355 ± 82
Endpoint	366 ± 109	336 ± 130	430 ± 66	350 ± 147
Change from Baseline	36 ± 70	-8 ± 96	70 ± 56	-6 ± 120
Placebo-subtracted	44**	-	76*	-

Distance in metres: mean ±SD  
Changes are to Week 16 for BREATHE-1 and Week 12 for Study 351.  
\*\*p=0.0002 for 125 mg and 250 mg doses combined by Wilcoxon test  
\*p=0.02 by Student's t-test

In both trials, treatment with bosentan resulted in a significant increase in exercise capacity. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg twice daily) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of double-blind treatment. The placebo-subtracted mean increase in walking distance was somewhat greater with 250 mg twice daily (54 m) than with 125 mg twice daily (35 m). However, the higher dose is not recommended because of the potential for increased liver injury (see **DOSAGE AND ADMINISTRATION**).

**Figure 1: Mean Change in 6-min Walk Distance (BREATHE-1)**

Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined bosentan (125 mg and 250 mg twice daily) groups. Values are expressed as mean ± standard error of the mean.

There were no apparent differences in treatment effects on walk distance among subgroups analysed by demographic factors, baseline disease severity, or disease aetiology, but the studies had little power to detect such differences.

## Haemodynamic Changes

Invasive haemodynamic parameters were assessed in Study 351. Treatment with bosentan led to a significant increase in cardiac index (CI) associated with a clinically relevant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP) (**Table 2**).

	<b>Bosentan</b>	<b>Placebo</b>
Mean CI (L/min/m <sup>2</sup> )	n=20	n=10
Baseline	2.35 ± 0.16	2.48 ± 0.33
Absolute Change	0.50 ± 0.10	-0.52 ± 0.15
Treatment Effect		1.02 ± 0.18***
Mean PAP (mmHg)	n=20	N=10
Baseline	53.7 ± 3.0	55.7 ± 3.3
Absolute Change	-1.6 ± 1.2	5.1 ± 2.8
Treatment Effect		-6.7 ± 2.5**
Mean PVR (dyn.sec.cm <sup>-5</sup> )	n=19	n=10
Baseline	896 ± 97	942 ± 136
Absolute Change	-223 ± 56	191 ± 74
Treatment Effect		-415 ± 94***
Mean RAP (mmHg)	n=19	n=10
Baseline	9.7 ± 1.3	9.9 ± 1.3
Absolute Change	-1.3 ± 0.9	4.9 ± 1.5
Treatment Effect		-6.2 ± 1.7***
Values shown are means ±SE		
** p<0.02		
*** p≤ 0.001		

## Symptoms and Functional Status

Symptoms of pulmonary arterial hypertension were assessed by Borg Dyspnoea score, WHO functional class, and rate of “clinical worsening”. In Study 351, clinical worsening was defined as death from all causes, lung transplantation or discontinuation of therapy due to clinical deterioration. In the BREATHE-1 study, clinical worsening was assessed as death from all causes, transplantation, hospitalisations or discontinuation of therapy due to worsening of PAH, need for prostacyclin or septostomy. There was a clinically relevant reduction in dyspnoea during walk tests (Borg Dyspnoea score), and clinically relevant improvement in WHO functional class in bosentan-treated patients. There was a clinically relevant reduction in the rate of clinical worsening (**Table 3**).

	<b>BREATHE-1</b>		<b>Study 351</b>	
	Bosentan 125/250 mg twice daily (n=144)	Placebo (n=69)	Bosentan 125 mg twice daily (n=21)	Placebo (n=11)
Patients with clinical worsening [n (%)]	9 (6)*	14 (20)	0 (0)**	3 (27)
– Death	1 (1)	2 (3)	0 (0)	0 (0)
– Hospitalisation for PAH	6 (4)	9 (13)	0 (0)	3 (27)
– Discontinuation due to worsening of PAH	5 (3)	6 (9)	0 (0)	3 (27)
– Receipt of epoprostenol***	4 (3)	3 (4)	0 (0)	3 (27)

Note: Patients may have had more than one reason for clinical worsening.  
 \* p=0.0015 vs. placebo by log-rank test. There was no observed difference between the 125 mg and 250 mg twice daily groups.  
 \*\* p=0.033 vs. placebo by Fisher’s exact test.  
 \*\*\* Receipt of epoprostenol was always a consequence of clinical worsening. PAH = pulmonary arterial hypertension.

There are limited data available on the minimum effective dose, dose response, and the clinically useful dose-range for bosentan.

There are no studies to demonstrate beneficial effects on survival of treatment with bosentan. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled trials (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years  $\pm$  0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0  $\pm$  0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with bosentan, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

### **WHO Grade Functional Class II**

In a randomised, double-blind, multi-centre, placebo-controlled trial (AC-052-364:EARLY) 185 PAH patients in WHO functional class II (mean baseline 6-minute walk distance of 435 metres) received bosentan 62.5 mg b.i.d. for 4 weeks followed by 125 mg b.i.d. (n=93), or placebo (n=92) for 6 months. Patients were diagnosed with idiopathic/familial PAH (n= 112), PAH associated with connective tissue disease (n=34), congenital heart disease (n=32) or other (n=7). Enrolled patients were PAH-treatment naïve (n=156) or on a stable dose of sildenafil (n=29). EARLY was designed as a superiority study with co-primary endpoints of percentage change from baseline in PVR, and change from baseline in 6-minute walk distance to 6 months versus placebo. Secondary endpoints included time to clinical worsening, Borg dyspnoea score, WHO functional class, and quality of life. With 85 patients per treatment group, a  $\geq$  20% reduction in the geometric mean PVR and a  $\geq$  35-meter increase in the mean 6-minute walk distance in the active vs placebo group could be detected with  $>$  99% and 91% power, respectively. The two primary endpoints were evaluated hierarchically, with the endpoint on walk distance tested only if the endpoint regarding PVR was significant, with both tested at a two-sided type-I error of 0.05. The main analysis was on the all-randomized analysis set.

The table below illustrates the outcomes in the main analysis of the two primary endpoints

**Table 4: Percentage change from baseline to 6 months bosentan versus placebo for co-primary endpoints (PVR and 6-minute Walk Distance)**

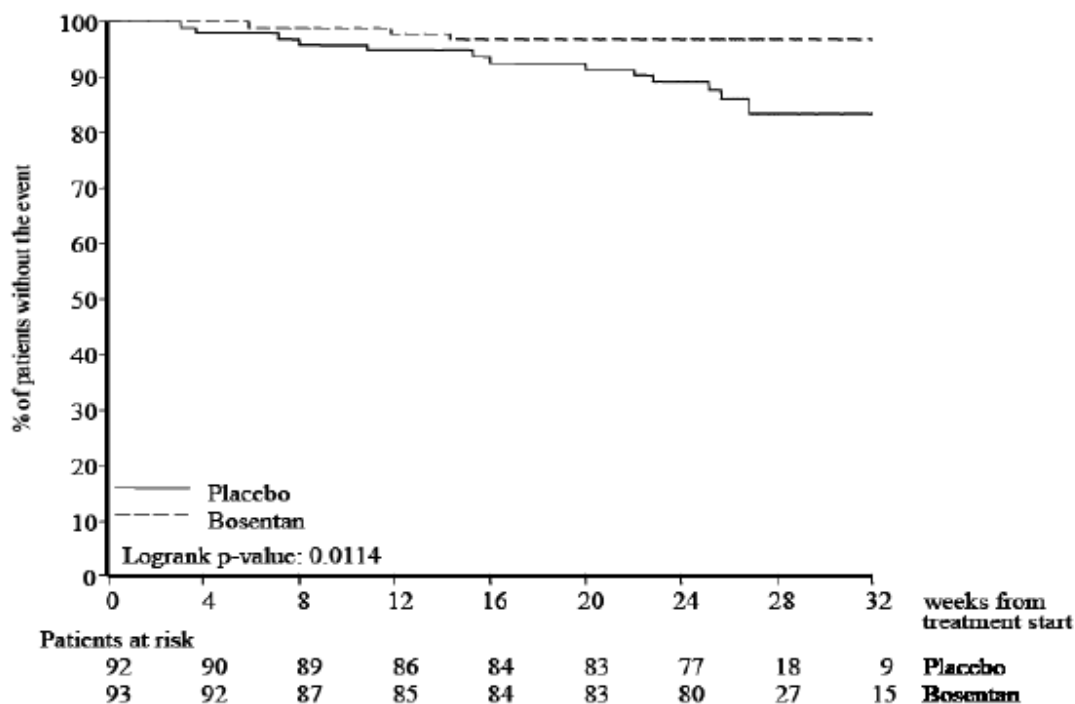
	PVR (dyn.sec/cm <sup>5</sup> )		6-Minute Walk distance (m)	
	Placebo (n=88)	Bosentan (n=80)	Placebo (n=91)	Bosentan (n=86)
Baseline (BL); mean (SD)	802 (365)	851 (535)	431 (92)	443 (83)
Change from BL; mean (SD)	128 (465)	-69 (475)	-8 (79)	11 (74)
Treatment effect	-22.6%		19	
95% CL	-34, -10		-4, 42	
p-value	<0.0001		0.0758	

Patients with WHO functional class II PAH, on average, have only moderately impaired 6MWT and may therefore have a limited response range for improvement in this parameter. This could partly explain the lack of statistical significance for the 6MWT endpoint. However, there was a clear association between an absence of deterioration from baseline in 6MWT and stable WHO functional class in the EARLY population. No patient in the bosentan group who at least maintained baseline 6MWT had deterioration in functional class.

Treatment with bosentan was associated with a reduction in the rate of clinical worsening (see **Figure 2**), defined as a composite of symptomatic progression, hospitalisation for PAH and death compared with placebo (proportional risk reduction 77%, 95% CI 20%-94%, p=0.0114). The treatment effect was driven by improvement in the component symptomatic progression (defined as appearance or worsening of right heart failure,  $\geq$  10% decrease from baseline in two 6-minute walk tests performed  $\geq$  2 weeks apart, or  $\geq$  5% decrease from baseline in two 6-minute walk tests performed  $\geq$  2 weeks apart associated with a  $\geq$  2-point increase in Borg dyspnoea index). There was one hospitalisation related to PAH worsening in the bosentan group and 3

hospitalisations in the placebo group. There was one death in each treatment group during the 6 month double-blind study period.

**Figure 2: EARLY: Kaplan-Meier estimates of time to clinical worsening, all randomised set**



Patients are censored at the end of the treatment period.

The EARLY study was designed and powered to evaluate the efficacy of bosentan in the patient population as a whole and was not powered to show statistical significance for each aetiological sub-group. No criteria to determine aetiological subgroup numbers or specific claims of a beneficial effect by subgroup were pre-specified. Subgroup analyses of treatment effects according to PAH aetiology were performed in the EARLY trial with the objective being to support absence of heterogeneity in treatment response between subgroups. For both co-primary endpoints the confidence intervals for treatment effects were overlapping between the major aetiological subgroups. The inclusion criteria for EARLY permitted recruitment of any patient with PAH determined to be idiopathic/familial or secondary to congenital heart defect, or connective tissue disease and other predefined aetiologies. For patients with congenital heart disease the defect had to be isolated and restrictive with no reverse shunt (atrial septum defect (ASD) < 2 cm, ventricular septum defect (VSD) < 1 cm or patent ductus arteriosus (PDA)). The population eventually enrolled reasonably reflected the relative incidences of PAH aetiologies seen in the real world setting. Consequently there was more data available for analysis in the most prevalent aetiological subgroups of idiopathic/familial PAH compared with the other subgroups.

Long-term data were generated from all 173 patients who were treated with bosentan in the controlled phase and/or were switched from placebo to bosentan in the open-label extension phase of the EARLY study. The mean duration of exposure to bosentan treatment was  $3.6 \pm 1.8$  years (up to 6.1 years), with 73% of patients treated for at least 3 years and 62% for at least 4 years. Patients could receive additional PAH treatment as required in the open-label extension. The majority of patients were diagnosed with idiopathic or heritable pulmonary arterial hypertension (61%). Exercise capacity (6 minute walk distance) was maintained over the duration of bosentan treatment (mean change from baseline to end of treatment -3.7m).

Overall, 78% of patients remained in WHO functional class I or II. Kaplan-Meier estimates of survival were 90% and 85% at 3 and 4 years after the start of treatment, respectively. At the same timepoints, 88% and 79% of patients remained free from PAH worsening (defined as all-cause death, lung transplantation, atrial septostomy or start of intravenous or subcutaneous prostanoid treatment). The relative contributions of previous placebo treatment in the double-blind phase and of other medications started during the open-label extension period are unknown.

### Study performed in children with PAH

One study has been conducted in children with pulmonary hypertension. Bosentan has been evaluated in an open-label non-controlled study in 19 paediatric patients with pulmonary arterial hypertension (AC-052-356, BREATHE-3: primary pulmonary hypertension 10 patients and pulmonary arterial hypertension related to congenital heart diseases 9 patients). This study was primarily designed as a pharmacokinetic study. Patients were divided into and dosed according to three body-weight groups for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the trial. The age range was 3-15 years. Patients were in WHO functional class II (n=12 patients, 79%) or class III (n=4 patients, 21%) at baseline.

Haemodynamics were measured in 17 patients. The mean increase from baseline in cardiac index was 0.51/min/m<sup>2</sup>, the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn.sec.cm<sup>-5</sup>. These haemodynamic improvements from baseline were similar with or without co-administration of epoprostenol. Changes in exercise test parameters at week 12 from baseline were highly variable and none were significant. The mean distance travelled in a 6 minute walk test decreased in the sub-group of children with CHD.

### PAH associated with Eisenmenger's physiology

In a prospective, multi-centre, randomised, double-blind, placebo-controlled study (BREATHE-5), patients with pulmonary arterial hypertension WHO Class III and Eisenmenger physiology associated with congenital heart disease received bosentan 62.5 mg bid for 4 weeks, then 125 mg bid for a further 12 weeks (n=37, of whom 31 had a predominantly right to left, bidirectional shunt). Patients with ductus arteriosus were excluded. The primary objective was to show that bosentan did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI-0.7; - 2.8%) as compared to the placebo group (n=17), showing that bosentan did not worsen hypoxaemia. The mean pulmonary vascular resistance was significantly reduced in the bosentan group (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6-minute walk distance was 53 metres (p=0.0079) reflecting improvement of exercise capacity (see **PRECAUTIONS**).

In the OL extension study (AC-052-409) of AC-052-405 (BREATHE-5) in patients with PAH WHO functional class III and Eisenmenger physiology associated with congenital heart disease, 26 patients continued to receive bosentan during a 24-week treatment period (mean 24.4 ± 2.0 weeks). The effects of bosentan demonstrated in the double-blind treatment period were generally maintained during longer term treatment (a total treatment period of 40 weeks).

### Combination with epoprostenol

The combination of bosentan and epoprostenol has been investigated in two studies: AC-052-355 (BREATHE-2) and AC-052-356 (BREATHE-3). AC-052-355 was a multi-centre, randomised, double-blind, parallel-group trial of bosentan versus placebo in 33 patients with severe pulmonary arterial hypertension who were receiving concomitant epoprostenol therapy. AC-052-356 was an open-label, non-controlled trial; 10 of the 19 paediatric patients were on concomitant bosentan and epoprostenol therapy during the 12-week trial. The safety profile of the combination was not different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.

## INDICATIONS

BOSENTAN MYLAN is indicated for the treatment of

- idiopathic pulmonary arterial hypertension
- familial pulmonary arterial hypertension
- pulmonary arterial hypertension associated with scleroderma or
- pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology



in patients with WHO functional Class II, III or IV symptoms

## CONTRAINDICATIONS

### Pregnancy (Pregnancy Category X)

Women who are pregnant or who are likely to become pregnant: BOSENTAN MYLAN is expected to cause foetal harm if administered to pregnant women (see **PRECAUTIONS – Use in Pregnancy**). Pregnancy must be excluded before the start of treatment with BOSENTAN MYLAN and prevented thereafter by use of reliable contraception such as double-barrier contraception. It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives may not be reliable in the presence of BOSENTAN MYLAN and should not be used as the sole contraceptive method in patients receiving BOSENTAN MYLAN. Double barrier contraception is recommended (see **INTERACTIONS WITH OTHER MEDICINES**).- Hormonal contraceptives, including oral, injectable, transdermal and implantable contraceptives). Input from a gynaecologist or similar expert on adequate contraception should be sought as needed.

BOSENTAN MYLAN should be started only in patients known not to be pregnant. Women must not become pregnant for at least three months after stopping treatment with BOSENTAN MYLAN. For female patients of childbearing potential, a prescription for BOSENTAN MYLAN 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 on the second day of the last normal menstrual period or 11 days after the last unprotected act of sexual intercourse, whichever is later. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking BOSENTAN MYLAN.

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 the foetus.

### Moderate or Severe Hepatic Impairment

BOSENTAN MYLAN is contraindicated in patients with moderate or severe hepatic function impairment (Child Pugh Class B or C and/or baseline elevated aminotransferases  $>3 \times$  ULN). The risk of hepatotoxicity is increased in these patients and monitoring liver injury may be more difficult. Elimination of BOSENTAN MYLAN and its metabolites would also be markedly impaired in such patients (see **PHARMACOLOGY, PRECAUTIONS – Potential Liver Injury and Hepatic Impairment**, and **DOSAGE AND ADMINISTRATION**).

### Cyclosporine A

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of BOSENTAN MYLAN and cyclosporine A is contraindicated.

### Glibenclamide

An increased risk of liver enzyme elevations was observed in patients receiving glibenclamide concomitantly with bosentan. Therefore co-administration of glibenclamide and BOSENTAN MYLAN is contraindicated.

### Hypersensitivity

BOSENTAN MYLAN is also contraindicated in patients who are hypersensitive to bosentan or any component of the medication.

## PRECAUTIONS

### Potential Liver Injury

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of 658 bosentan-treated patients compared to 2% of 280 placebo-treated patients. Three-fold increases were seen in 12% of 188 PAH patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 4% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to  $\geq 3$  x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) patients treated with bosentan. The combination of hepatocellular injury (increases in aminotransferases) and increases in total bilirubin has in many cases indicated potential for serious liver injury.

Bosentan has been associated with dose-related, and treatment duration related, elevations in liver aminotransferases, i.e. aspartate and alanine aminotransferase (AST and ALT). These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of BOSENTAN MYLAN or after dose reduction, but interruption or cessation may be necessary. In the clinical programme, liver enzyme changes generally occurred within the first 26 weeks of treatment but may also occur late in treatment. These increases usually developed gradually, and were mainly asymptomatic, but some patients also reported abdominal pain, fever, fatigue or flu-like syndrome. The liver enzyme elevations returned, in 97% of cases during the clinical programme, to pre-treatment levels, without sequelae, within a few days to 9 weeks either spontaneously or after does reduction or discontinuation. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported

The increases in liver aminotransferases may partly be due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved in the occurrence of liver dysfunction. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP) e.g. rifampicin, glibenclamide and cyclosporine A, are co-administered with bosentan, but limited data are available.

Elevations in gamma GT were observed in 11% of bosentan-treated patients. Elevations in bilirubin or alkaline phosphatase were less common (bilirubin: bosentan 0.4% vs placebo 2.4%; alkaline phosphatase: bosentan 1.9% vs placebo 1.9%). Few patients developed jaundice.

Liver aminotransferase levels must be measured prior to initiation of treatment and monthly thereafter. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated (see **DOSAGE AND ADMINISTRATION**). If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, lethargy, fatigue, abdominal pain or jaundice) or increases in bilirubin  $\geq 2$  x ULN, treatment must be stopped. There is no experience with the reintroduction of bosentan in these circumstances.

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. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with bosentan (see information about patients who develop hepatic abnormalities during treatment under **DOSAGE AND ADMINISTRATION**). The contribution of bosentan in these cases could not be excluded.

### Hepatic Impairment

BOSENTAN MYLAN is contraindicated in patients with moderate or severe hepatic impairment (see **PHARMACOLOGY, CONTRAINDICATIONS** and **DOSAGE AND ADMINISTRATION**). In addition, BOSENTAN MYLAN should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because these patients are at a greater risk and monitoring liver injury may be more difficult. Patients with mild hepatic impairment (hepatic aminotransferases 1 to 3 x ULN) may be commenced on BOSENTAN MYLAN, but have an increased risk of hepatotoxicity (see **ADVERSE EFFECTS**).

## **Haematological Changes**

Treatment with bosentan caused a dose-related decrease in haemoglobin and haematocrit. 10% of 693 bosentan patients had clinically significant reductions in haematocrit or haemoglobin, with decreases in erythrocytes, and 5% had anaemia. Haemoglobin levels should be monitored periodically. 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.

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 haemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of bosentan 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 < 1 g/dL) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. 3% of bosentan patients had serious anaemia requiring withdrawal from the studies and/or blood transfusion. In patients with pulmonary arterial hypertension treated with doses of 125 mg and 250 mg twice daily, marked decreases in haemoglobin occurred in 3% compared to 1% in placebo-treated patients. Stopping bosentan generally resulted in patients' haemoglobin or haematocrit returning to baseline levels quickly.

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 haemoglobin is not known, but it does not appear to be haemorrhage or haemolysis.

In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported.

## **Pulmonary veno-occlusive disease**

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema occur when BOSENTAN MYLAN is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary oedema in patients treated with bosentan who had a suspected diagnosis of pulmonary veno-occlusive disease.

## **Pulmonary arterial hypertension patients with concomitant left ventricular failure**

No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular dysfunction. However, 1611 patients (804 bosentan - and 807 placebo-treated patients with severe chronic heart failure (CHF) were treated for a mean duration of 1.5 years in a placebo-controlled study. In this study there was an increased incidence of hospitalisation due to CHF during the first 4-8 weeks of treatment with bosentan, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisation for heart failure nor in mortality between bosentan and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g. weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased.

Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with BOSENTAN MYLAN.

**Use in patients with pre-existing anaemia**

Particular caution should be exercised when initiating BOSENTAN MYLAN in patients with haemoglobin or haematocrit more than 30% below the lower limit of normal. Such patients were excluded from clinical trials of bosentan. The cause of anaemia should be determined and managed as appropriate, and haematological parameters should be checked more frequently than usual.

**Use in patients with pre-existing hypotension**

Particular caution should be exercised when initiating BOSENTAN MYLAN in patients with pre-existing hypotension, and blood pressure in such patients should be monitored closely. Patients with systolic blood pressure < 85 mmHg were excluded from clinical trials of bosentan.

**Use in patients receiving epoprostenol**

In a randomised, double blind trial (BREATHE-2), 32 patients were commenced on epoprostenol, to which bosentan (n=22) or placebo (n=11) was added two days later. The treatments were then carried out for 16 weeks. The trial failed to show any significant clinical benefit (6 minute walk, dyspnoea score, WHO functional class) or pharmacodynamic effect. The coadministration of bosentan with epoprostenol is, therefore, not recommended.

**Use in CHD patients**

In the BREATHE-5 trial, oxygen saturation did not deteriorate in patients treated with bosentan compared with placebo. However, it is recommended as standard medical care that CHD patients have their oxygen saturation monitored as clinically indicated.

**Use in patients with HIV Infection**

If treatment with bosentan is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of BOSENTAN MYLAN should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Due to the potential for interactions related to the inducing effect of bosentan on CYP450 (see **INTERACTIONS WITH OTHER MEDICINES**), which could affect the efficacy of antiretroviral therapy, these patients should also be monitored carefully regarding their HIV infection.

**Effects on Fertility / Testicular Function**

Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible.

In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 1,500 mg/kg/day (50 times the MRHD on a mg/m<sup>2</sup> basis) or intravenous doses of up to 40 mg/kg/day, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest dose tested) for two years but not at doses as high as 1,500 mg/kg/day (about 50 times the MRHD) for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4,500 mg/kg/day (about 75 times the MRHD), or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 30 times the MRHD).

Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were treated with bosentan 62.5 mg bid for 4 weeks followed by 125 mg bid for 5 months to assess any effects on testicular function. Twenty three completed the study and 2 discontinued due to adverse events not related to testicular function. 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 two months the sperm count had returned to baseline levels. The relevance of this observation is uncertain considering the large natural intrasubject variability of sperm counts. Although, based on this finding, it cannot be excluded that endothelin receptor antagonists such as BOSENTAN MYLAN may have an effect on spermatogenesis, the absence of a systematic effect of chronic bosentan treatment on testicular function in humans observed in this study is in line with the toxicology data for bosentan.

### **Use in Pregnancy (Category X)**

Bosentan was teratogenic in rats given oral doses  $\geq 60$  mg/kg/day (twice the maximum recommended human oral therapeutic dose of 125 mg twice daily, on a mg/m<sup>2</sup> basis). In an embryo-foetal 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 mg and 300 mg/kg/day (2 and 10 times, respectively, the maximum recommended human dose on a mg/mg<sup>2</sup> basis). Although birth defects were not observed in rabbits given oral doses of up to 1,500 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 minimal data on the use of bosentan in pregnant women from very few cases received in the post-marketing period. The potential risk for humans is still unknown, but bosentan must be considered a human teratogen and must not be used during pregnancy. Women must not become pregnant for at least 3 months after stopping treatment with bosentan. BOSENTAN MYLAN is contraindicated in pregnancy (see **CONTRAINDICATIONS**).

### **Use in 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 MYLAN is not recommended.

### **Paediatric Use**

Various doses of bosentan have been assessed in a clinical study in paediatric patients with PPH or PAH related to congenital systemic to pulmonary communications, either as monotherapy or combined with epoprostenol (see **CLINICAL TRIALS**). The results indicate that the doses used were effective and appropriate in terms of safety and pharmacokinetics (see **DOSAGE AND ADMINISTRATION – Dosage Adjustment in Children**).

### **Use in the Elderly**

Clinical studies of bosentan were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects; greater sensitivity to bosentan cannot be ruled out. Conditions more common in the elderly, such as hepatic impairment, renal impairment and decreased cardiac function, as well as concomitant diseases and other drug therapy, can have clinically significant effects on bosentan pharmacokinetics (see **PHARMACOLOGY - Pharmacokinetics**). Caution should be exercised in treating elderly patients, and close clinical monitoring is required. The lowest effective dose should be used to prevent the occurrence of side effects (see **DOSAGE AND ADMINISTRATION**).

### **Carcinogenicity**

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and combined adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 12 mg twice daily on a mg/m<sup>2</sup> basis). In the same study, doses greater than 2,000 mg/kg/day (about 32 times the [MRHD]) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the [MRHD]; no effect dose of 125 mg/kg/day, about 4 times the MRHD) and females at doses of 3,000 mg/kg/day (no-effect dose of 2,000 mg/kg/day, about 128 times the MRHD). An increased incidence of

thyroid follicular adenomas was also observed in male rats at doses as low as 2,000 mg/kg/day (about 32 times the MRHD). However, the relevance of these findings to humans is not known.

There was no evidence for mutagenic or clastogenic activity of bosentan in a standard battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay.

### **Effects on Driving/Operating Machinery**

No studies on the effect of bosentan on the ability to drive and use machines have been performed. BOSENTAN MYLAN may cause dizziness, which could influence the ability to drive or use machines.

## **INTERACTIONS WITH OTHER MEDICINES**

### **Other drugs that affect bosentan**

#### ***(a) Demonstrated interactions***

Co-administration of bosentan 125 mg twice daily for 6 days and ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to bosentan 83%. No dose adjustment of bosentan is considered necessary, however, due to the possibility of increased exposure to bosentan, more frequent liver function monitoring is recommended during concomitant ketoconazole use.

Co-administration of bosentan and cyclosporine A is contraindicated. When co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone.

Co-administration of bosentan and glibenclamide is contraindicated. Concomitant, steady state administration of bosentan 125 mg twice daily and glibenclamide decreased bosentan concentrations 30%. Concomitant glibenclamide administration predisposed patients to an increased risk of elevated liver aminotransferases.

Co-administration of bosentan and rifampicin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose. Co-administration in 9 healthy subjects of bosentan 125 mg twice daily for 7 days and rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case. The effect of bosentan on rifampicin levels has not been assessed. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. 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. Data on other CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St John's Wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.

Co-administration of bosentan 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after bosentan administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher than with bosentan administered alone. Inhibition by ritonavir of transport protein mediated uptake into hepatocytes and of CYP3A4, thereby reducing the clearance of bosentan, most likely causes this interaction. If administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of bosentan should be monitored. In particular, markers of liver dysfunction such as LFTs and vascular (hypotension) adverse events should be monitored. After co-administration of bosentan for 9.5 days, the plasma exposures of lopinavir and ritonavir decreased to a clinically non significant extent (by approximately 14% and 17%, respectively). However, full induction by bosentan might not have been reached and a further decrease of protease inhibitors cannot be excluded. Appropriate monitoring of HIV therapy and indices of HIV infection progression are also recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors (refer to **PRECAUTIONS** section).

Other antiretroviral agents: no specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasised that due to the marked hepatotoxicity of nevirapine, which could accumulate with bosentan liver toxicity, this combination is not recommended.

Losartan, digoxin and simvastatin did not affect bosentan plasma levels.

*(b) Theoretical interactions*

Concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) in combination with bosentan may result in increased plasma levels of bosentan.

Caution should be exercised when bosentan is co-administered with known hepatotoxic drugs.

Concomitant use of bosentan with fluconazole is not recommended. Although not studied, this combination may lead to large increases in plasma concentrations of bosentan.

*(c) Other interactions investigated*

Digoxin, phenytoin and tolbutamide may cause a slight increase in free bosentan, but this slight increase is unlikely to be of clinical importance. There was no indication of a serum protein binding interaction between warfarin and bosentan.

Concomitant administration of bosentan and epoprostenol has shown to be safe and efficacious in a clinical study with paediatric PPH/PAH patients. The pharmacokinetics were similar to those in adult patients and healthy subjects in other studies.

Coadministration of tacrolimus or sirolimus with bosentan has not been studied in humans but may result in increased plasma concentrations of bosentan in analogy to co-administration with cyclosporine A. Concomitant bosentan may reduce the plasma concentrations of tacrolimus and sirolimus. Therefore, concomitant use of bosentan and tacrolimus or sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to bosentan and for tacrolimus and sirolimus blood concentrations..

**Effects of bosentan on other drugs**

*(a) Demonstrated interactions*

Co-administration of bosentan and glibenclamide is contraindicated. Concomitant, steady state administration of bosentan 125 mg twice daily and glibenclamide decreased glibenclamide concentrations 40%. Concomitant glibenclamide administration predisposed patients to an increased risk of elevated liver aminotransferases.

Co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of S- and R-warfarin by 29% and 38%, respectively. Clinical experience of concomitant administration of bosentan with warfarin in patients with pulmonary arterial hypertension did not result in clinically relevant changes in International Normalized Ratio (INR) or warfarin dose (baseline versus end of the clinical studies). In addition, the frequency of changes in warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during the bosentan initiation and the up-titration period.

Co-administration of bosentan 500 mg twice daily for 7 days decreased the AUC, C<sub>max</sub> and C<sub>min</sub> of digoxin by 12%, 9% and 23%, respectively. Higher doses of digoxin may be required.

Co-administration of bosentan 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin, and its active b-hydroxy acid metabolite by 49% and 60%, respectively. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.

Co-administration of bosentan and cyclosporine A is contraindicated. Concomitant, steady state administration of bosentan 500 mg twice daily and cyclosporine A decreased cyclosporine A concentrations 50%.

Single dose bosentan did not affect nimodipine plasma levels.

Co-administration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration. The reduction in sildenafil plasma concentration with co-administration of bosentan has also been reported in a study of patients with primary arterial hypertension.

### **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 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 practise additional methods of contraception and not rely on hormonal contraception alone when taking BOSENTAN MYLAN.

#### ***(b) Theoretical interactions***

Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of drugs metabolized by these isoenzymes will be decreased when bosentan is co-administered. The possibility of altered efficacy of medicinal products metabolized by these isoenzymes should be considered. The dosage of these products may need to be adjusted after initiation, dose change or discontinuation of concomitant bosentan treatment. Specifically, bosentan is expected to reduce the exposure to statins and oral hypoglycaemic agents that are predominantly metabolized by CYP3A4 or CYP2C9.

Bosentan is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with BOSENTAN MYLAN is not recommended.

Nimodipine concentrations could decrease after multiple-dose administration of bosentan.

#### ***(c) Other interactions investigated***

Bosentan did not lead to any significant changes in the serum protein binding of digoxin, glibenclamide, phenytoin, or warfarin. However, bosentan slightly increased the free serum concentrations of tolbutamide, but this slight increase is unlikely to be of clinical importance.

*In vitro* data demonstrated that bosentan had no relevant inhibitory effect on the CYP isoenzymes tested (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4). Consequently, bosentan is not expected to increase the plasma concentrations of medicinal products metabolised by these isoenzymes.

## **ADVERSE EFFECTS**

In 20 placebo-controlled studies, conducted in a variety of therapeutic indications, a total of 2,486 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 1,838 patients were treated with placebo. The mean treatment duration was 45 weeks. In 5 controlled clinical studies in patients with PAH 317 patients were treated with bosentan at daily doses ranging from 125 to 500 mg and 200 patients were treated with placebo. The mean treatment duration was 21 weeks.

The most commonly reported adverse events (occurring in at least 1% of patients on bosentan and more frequently than on placebo) were headache (11.1% vs 9.4%), upper respiratory tract infection (10.6% vs 9.0%),



oedema peripheral (9.7% vs 8.3%), anaemia (6.2% vs 3.0%), haemoglobin decreased (3.7% vs 1.6%), alanine aminotransferase increased (3.3% vs 0.9%), flushing (3.2% vs 1.3%) and liver function test abnormal (3.1% vs 1.0%), see Table 5.

Preferred Term	Bosentan N = 2486		Placebo N = 1838		Difference from placebo
	No.	%	No.	%	
Upper respiratory tract infection	264	10.6%	166	9.0%	1.6%
Nasopharyngitis	154	6.2%	107	5.8%	0.4%
Lower respiratory tract infection	81	3.3%	56	3.0%	0.2%
Sinusitis	91	3.7%	59	3.2%	0.5%
Anaemia	153	6.2%	56	3.0%	3.1%
Idiopathic pulmonary fibrosis*	145	5.8%	97	5.3%	0.6%
Headache	275	11.1%	172	9.4%	1.7%
Haemoglobin decreased	91	3.7%	29	1.6%	2.1%
Alanine aminotransferase increased	82	3.3%	17	0.9%	2.4%
Flushing	79	3.2%	23	1.3%	1.9%
Oedema peripheral	242	9.7%	153	8.3%	1.4%
Oedema	43	1.7%	19	1.0%	0.7%
Liver function test abnormal	77	3.1%	18	1.0%	2.1%
Aspartate aminotransferase increased	68	2.7%	19	1.0%	1.7%
Pyrexia	57	2.3%	37	2.0%	0.3%
Pruritus	57	2.3%	34	1.8%	0.4%
Hepatic enzyme increased	56	2.3%	13	0.7%	1.5%
Gastroesophageal reflux disease	51	2.1%	23	1.3%	0.8%
Epistaxis	46	1.9%	30	1.6%	0.2%
Nasal congestion	43	1.7%	22	1.2%	0.5%
Angina unstable	40	1.6%	26	1.4%	0.2%
Oropharyngeal pain	37	1.5%	24	1.3%	0.2%
Vision blurred	36	1.4%	24	1.3%	0.1%
Rhinitis	33	1.3%	16	0.9%	0.5%
Haematocrit decreased	32	1.3%	9	0.5%	0.8%
Vertigo	30	1.2%	18	1.0%	0.2%
Orthostatic hypotension	29	1.2%	16	0.9%	0.3%
Influenza-like illness	25	1.0%	16	0.9%	0.1%
Joint swelling	25	1.0%	11	0.6%	0.4%
Sinus congestion	25	1.0%	9	0.5%	0.5%

\* Events of idiopathic pulmonary fibrosis (IPF) referred to progression of the underlying disease in studies conducted in IPF patients

Additional adverse events occurring in the subset of patients treated for PAH, in at least 3% of patients on bosentan and more frequently than on placebo are presented in Table 6.

Preferred Term	Placebo N=200		Bosentan N=317		Difference from placebo
	No.	%	No.	%	
Diarrhoea	16	8.0%	27	8.5%	0.5%
Chest pain	9	4.5%	16	5.0%	0.5%
Palpitations	3	1.5%	14	4.4%	2.9%
Syncope	8	4.0%	13	4.1%	0.1%
Arthralgia	3	1.5%	11	3.5%	2.0%
Hypotension	6	3.0%	10	3.2%	0.2%
Hot flush	2	1.0%	10	3.2%	2.2%

Treatment with bosentan has been associated with dose-dependent elevations in liver aminotransferases and decreases in haemoglobin concentration (see **PRECAUTIONS**).

## Laboratory Abnormalities

Increased liver aminotransferases, and decreased haemoglobin and haematocrit (see **PRECAUTIONS**).

In the post-marketing period cases of anaemia requiring red blood cell transfusion have been reported.

## Post-marketing experience

Based on an exposure of about 121,000 patients to bosentan in the post-marketing period, the majority of adverse events have been similar to those reported in clinical trials.

The following additional adverse reactions in Table 7 have been reported in the post marketing use. The reactions are ranked under headings of frequency using the following convention: common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000).

**Table 7 Post Marketing Adverse Events**

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known <sup>1</sup>	Anaemia or haemoglobin decreases requiring red blood cell transfusion
	Uncommon	Thrombocytopenia
	Uncommon	Neutropenia, leukopenia
Immune system disorders	Common	Hypersensitivity reactions (including dermatitis, pruritus and rash)
	Rare	Anaphylaxis and/or angioedema
Hepatobiliary disorders	Uncommon	Aminotransferase elevations associated with hepatitis and/or jaundice
	Rare	Liver cirrhosis, liver failure

<sup>1</sup> Frequency cannot be estimated from the available data

In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with bosentan.

## DOSAGE AND ADMINISTRATION

### General

BOSENTAN MYLAN should be administered under the supervision of a physician experienced in the management of pulmonary arterial hypertension. BOSENTAN MYLAN treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks. Efficacy was demonstrated in clinical trial subjects who increased to a maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily 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.

Serum liver aminotransferase (AST & ALT) levels must be measured prior to initiation of treatment with BOSENTAN MYLAN and monthly thereafter for the duration of treatment (see **PRECAUTIONS- Potential Liver Injury**). If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated, as detailed below.

### Dosage in Patients with Hepatic Impairment

#### Patients with hepatic abnormalities before starting bosentan treatment

BOSENTAN MYLAN must not be initiated in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) (see **CONTRAINDICATIONS**).

BOSENTAN MYLAN may be initiated at the usual starting dose in patients with mild hepatic impairment (Child-Pugh Class A, hepatic aminotransferases less than 3 x ULN). However, the use of BOSENTAN MYLAN in these patients may be associated with an increased risk of hepatotoxicity (see **ADVERSE EFFECTS**).

### **Patients who develop hepatic abnormalities during treatment**

In patients who develop hepatic abnormalities during treatment with BOSENTAN MYLAN, the following actions should be taken:

#### **Aminotransferase Abnormalities**

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##### **ALT/AST levels: Treatment and Monitoring Recommendations**

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> 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).

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> 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 pre-treatment values, consider re-introduction of the treatment (see below).

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> 8 x ULN

Treatment should be stopped and re-introduction of BOSENTAN MYLAN should not be considered. There is no experience with the re-introduction of BOSENTAN MYLAN in these circumstances.

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If BOSENTAN MYLAN 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.

#### **Bilirubin Abnormalities**

If liver aminotransferase elevations are accompanied by increases in bilirubin  $\geq 2$  x ULN, treatment should be stopped. There is no experience with the re-introduction of BOSENTAN MYLAN in these circumstances.

#### **Clinical Symptoms or Signs of Liver Injury**

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), treatment must be stopped. There is no experience with the re-introduction of BOSENTAN MYLAN in these circumstances.

#### **Use in Women of Childbearing Potential**

BOSENTAN MYLAN treatment should only be initiated in women of childbearing potential following a negative pregnancy test and only in those who practice reliable contraception that does not depend solely upon hormonal contraceptives including oral, injectable, transdermal or implantable contraceptives. Double barrier contraception is recommended. Repeated monthly pregnancy tests during treatment with BOSENTAN MYLAN are recommended (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES - Hormonal contraceptives including oral, injectable, transdermal and implantable contraceptives**). Women must not become pregnant for at least three months after stopping treatment with BOSENTAN MYLAN.

#### **Dosage in Renally Impaired Patients**

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. 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 (see **PHARMACOLOGY – Pharmacokinetics, Special Populations – Renal Impairment**).

### Dosage in Geriatric Patients

Clinical studies of bosentan were not adequate to determine whether subjects aged 65 and older respond differently than younger subjects; greater sensitivity to bosentan cannot be ruled out. Conditions more common in the elderly, such as hepatic impairment, renal impairment and decreased cardiac function, as well as concomitant diseases and other drug therapy, can have a clinically significant effect on bosentan pharmacokinetics (see **PHARMACOLOGY – Pharmacokinetics** and **PRECAUTIONS**). Caution should be exercised in dose selection for elderly patients, and close clinical monitoring is required. The lowest effective dose should be used to prevent the occurrence of side effects (see **DOSAGE and ADMINISTRATION**).

### Dosage Adjustment in Children

There is limited experience with the use of bosentan in children. On the basis of the available information (see **PHARMACOLOGY – Pharmacokinetics** and **CLINICAL TRIALS**) the following doses are recommended in children aged 3 years and over:

	Starting dose (First 4 weeks)	Maintenance dose (Week 5 onwards)
Body weight 10 to 20 kg	31.25 mg ONCE daily	31.25 mg twice daily
Body weight > 20 to 40 kg	31.25 mg twice daily	62.5 mg twice daily
Body weight > 40 kg	62.5 mg twice daily	125 mg twice daily

### 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 twice daily.

### Discontinuation of Treatment

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. Intensified monitoring is recommended during the discontinuation period.

## OVERDOSAGE

Bosentan has been given as a single dose of up to 2,400 mg in normal volunteers, or up to 2,000 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 mg and 1,000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but not serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

Massive overdosage may result in pronounced hypotension requiring active cardiovascular support. In the post-marketing 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 completely within 24 hours with blood pressure support. Note: bosentan is not removed through dialysis

For advice on the management of overdose, contact the Poisons Information Centre (Australia call 13 11 26).

## **PRESENTATION AND STORAGE CONDITIONS**

BOSENTAN MYLAN 62.5 mg - white to off-white, film-coated, round, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “BN1” on the other side. Available in blister packs (PVC/PVdC/Al) or bottles (HDPE) of 60 tablets.

BOSENTAN MYLAN 125 mg - white to off-white, film-coated, oval, biconvex, beveled edge tablet debossed with “M” on one side of the tablet and “BN2” on the other side. Available in blister packs (PVC/PVdC/Al) or bottles (HDPE) of 60 tablets.

Some strengths and/or pack types may not be marketed.

Store below 25°C. Protect from moisture.

## **NAME AND ADDRESS OF THE SPONSOR**

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30-34 Hickson Road

Millers Point NSW 2000

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## **POISON SCHEDULE OF THE MEDICINE**

Prescription Only Medicine

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

19 December, 2016

## **DATE OF MOST RECENT AMENDMENT**

8 June 2017

BOSENTAN MYLAN\_pi\June17/00