New Zealand Datasheet

1 PRODUCT NAME
BOSENTAN DR REDDY’S

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Bosentan (as monohydrate) 62.5 mg & 125 mg tablets

3 PHARMACEUTICAL FORM
BOSENTAN DR REDDY’S 62.5 mg tablets are orange white, film coated, round biconvex tablet debossed with ’62.5’ on one side and plain on other side.

BOSENTAN DR REDDY’S 125 mg tablets are orange white, film coated, round biconvex tablet debossed with ’125’ on one side and plain on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

Bosentan may cause birth defects and is contraindicated in pregnancy, see Contraindications and Warnings and Precautions.
Rare cases of hepatic cirrhosis and hepatic failure have been reported in patients using bosentan, see Warnings and Precautions

Bosentan 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 Class III or IV symptoms.

4.2 Dose and method of administration
General
Bosentan should be administered under the supervision of a physician experienced in the management of pulmonary arterial hypertension. Bosentan 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 and monthly thereafter for the duration of treatment (see **Warnings and 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 must not be initiated in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C) (see **Contraindications**).

Bosentan 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 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, the following actions should be taken:

Aminotransferase Abnormalities

ALT/AST levels: Treatment and Monitoring Recommendations

> 3 and ≤ 5 x ULN

Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).

> 5 and ≤ 8 x ULN

Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).

> 8 x ULN

Treatment should be stopped and re-introduction of bosentan should not be considered. There is no experience with the 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.

Bilirubin Abnormalities

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

Use in Women of Childbearing Potential

Bosentan 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 or implantable contraceptives. Double barrier contraception is recommended. Repeated monthly pregnancy tests during treatment with bosentan are recommended (see **Contraindications and Interactions**: Hormonal contraceptives including oral, injectable and implantable contraceptives). Women must not become pregnant for at least three months after stopping treatment with bosentan.

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 **Pharmacokinetics and Warnings 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 based on a pharmacokinetic study conducted in 19 children with PAH (see **Pharmacokinetics and Clinical Trials**). The pharmacokinetic findings showed that systemic exposure in children with PAH was lower than in adults with PAH. Although the number of patients studied in each dose group was generally insufficient to establish the optimal dosing regimen, the following doses are recommended in children aged 3 years and over.

Table 1 Doses recommended in children aged 3 years and over

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

4.3 Contraindications

Pregnancy

Women who are pregnant or who are likely to become pregnant: bosentan may cause foetal harm if administered to pregnant women (see **Warnings and Precautions** - Use in Pregnancy). Pregnancy must be excluded before the start of treatment with bosentan and prevented thereafter by use of reliable contraception such as double-barrier contraception. 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. Double barrier contraception is recommended (see **Interactions**: 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 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. 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 on the second day of the last normal menstrual period or 11 days after the last unprotected act of sexual intercourse, whichever is later. For women of childbearing potential, repeated monthly pregnancy tests during treatment with bosentan are recommended.

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 is contraindicated in patients with moderate or severe hepatic function impairment (Child-Pugh Class B or C and/or baseline elevated aminotransferases >3 x ULN). The risk of hepatotoxicity is increased in these patients and monitoring liver injury may be more difficult. Elimination of bosentan and its metabolites would also be markedly impaired in such patients (see **Pharmacodynamic Properties, Warnings and 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 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 is contraindicated.

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

4.4 Special warnings and precautions for use

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 95 PAH patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to ≥ 3 x 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) 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 aminotransferases (AST and ALT). These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of bosentan 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 dose 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 ≥ 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 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 is contraindicated in patients with moderate or severe hepatic impairment (see **Pharmacodynamic Properties, Contraindications and Dosage and Administration**). In addition, Bosentan should generally be avoided in patients with elevated aminotransferases (>3 x ULN) because these patients are at greater risk, monitoring liver injury may be more difficult. Patients with mild hepatic impairment (hepatic aminotransferases 1 to 3 x ULN) may be commenced on bosentan, 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 <11 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 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.

Use in patients with pre-existing anaemia
Particular caution should be exercised when initiating bosentan 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 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 co-administration 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 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.

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^2 basis). In the same study, doses greater than 2000 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 3000 mg/kg/day (no-effect dose of 2000 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 2000 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 miconucleus assay.

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 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 **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**).

4.5 Interaction with other medicines and other forms of interaction

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 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 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 (hypotentsion) 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.

Rifampicin: Co-administration in 9 healthy subjects of Bosentan Dr Reddy's 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. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. Data on other CYP3A4 inducers, eg 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.

(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.

(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.

Co-administration of tacrolimus or sirolimus and bosentan has not been studied in man 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_{max} and C_{min} 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.

Sildenafil: Co-administration of Bosentan Dr Reddy's 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: 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.

(*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 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.

4.6 Fertility, pregnancy and lactation

Impairment of 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 1500 mg/kg/day (50 times the MRHD on a mg/m^2 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 1500 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 4500 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 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 ≥ 60 mg/kg/day (twice the maximum recommended human oral therapeutic dose of 125 mg twice daily, on a mg/m^2 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 MRHD on a mg/m^2 basis). Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are 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 is contraindicated in pregnancy (see **Contraindications**).

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

4.7 Effects on ability to drive and use machines
Driving/Operating Machinery or Effects on Ability to Drive and Use Machines: Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and

operate machinery. There have been reports of hypotension with bosentan. Patients should be warned that if they feel dizzy, they should take care when driving and operating machinery.

4.8 Undesirable 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 2.

Table 2: Adverse Events in 20 placebo-controlled studies

	Placebo		**Bosentan**		**Difference from placebo**
	N=1838		**N=2486**		
Preferred Term	**n**	**%**	**n**	**%**	
Headache	172	9.4%	275	11.1%	1.7%
Upper respiratory tract infection	166	9.0%	264	10.6%	1.6%
Oedema peripheral	153	8.3%	242	9.7%	1.4%
Nasopharyngitis	107	5.8%	154	6.2%	0.4%
Anaemia	56	3.0%	153	6.2%	3.1%
Idiopathic pulmonary fibrosis*	97	5.3%	145	5.8%	0.6%
Sinusitis	59	3.2%	91	3.7%	0.5%
Haemoglobin decreased	29	1.6%	91	3.7%	2.1%
Alanine aminotransferase increased	17	0.9%	82	3.3%	2.4%
Lower respiratory tract infection	56	3.0%	81	3.3%	0.2%
Flushing	23	1.3%	79	3.2%	1.9%
Liver function test abnormal	18	1.0%	77	3.1%	2.1%
Aspartate aminotransferase increased	19	1.0%	68	2.7%	1.7%
Pyrexia	37	2.0%	57	2.3%	0.3%
Pruritus	34	1.8%	57	2.3%	0.4%
Hepatic enzyme increased	13	0.7%	56	2.3%	1.5%
Gastrooesophageal reflux disease	23	1.3%	51	2.1%	0.8%
Epistaxis	30	1.6%	46	1.9%	0.2%
Nasal congestion	22	1.2%	43	1.7%	0.5%
Oedema	19	1.0%	43	1.7%	0.7%
Angina unstable	26	1.4%	40	1.6%	0.2%
Oropharyngeal pain	24	1.3%	37	1.5%	0.2%
Vision blurred	24	1.3%	36	1.4%	0.1%
Rhinitis	16	0.9%	33	1.3%	0.5%
Haematocrit decreased	9	0.5%	32	1.3%	0.8%
Vertigo	18	1.0%	30	1.2%	0.2%
Orthostatic hypotension	16	0.9%	29	1.2%	0.3%

Influenza like illness	16	0.9%	25	1.0%	0.1%
Joint swelling	11	0.6%	25	1.0%	0.4%
Sinus congestion	9	0.5%	25	1.0%	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 3.

Table 3: Additional adverse events in 5 placebo-controlled studies in PAH

Preferred Term	Placebo N=200		Bosentan N=317		Difference from placebo
	n	%	n	%	
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 **Warning and Precautions).**

Laboratory Abnormalities
Increased liver aminotransferases, and decreased haemoglobin and haematocrit (see **Warning and 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 4 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 4 Post Marketing Adverse Events

System organ class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Not known[1]	Anemia or hemoglobin 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

1 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 mg and 1000 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 information on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension (ATC code C02KZ01).

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 ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors.

Clinical Trials

Adult patients with pulmonary arterial hypertension

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 5.

<u>Table 5: Effects of bosentan on 6-minute walk</u>

	BREATHE-1		**Study 351**	
	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**).

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.

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

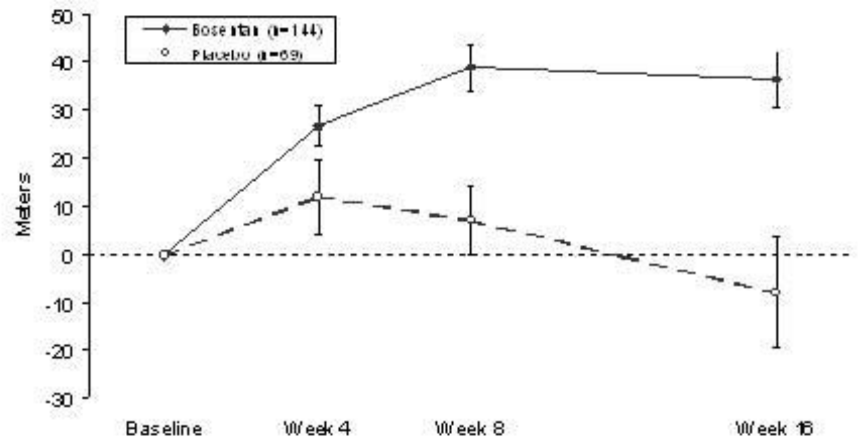

Figure 1. Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined bosentan (125 mg and 250 mg twice daily) groups. Values are expressed as mean ± standard error of the mean.

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 6).

Table 6: Change from Baseline to Week 12: Haemodynamic Parameters

	Bosentan		Placebo
Mean CI (L/min/m^2)	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^{-5})	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 ** $p<0.02$, *** $p\leq 0.001$

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 7).

Table 7: Incidence of Clinical Worsening, Intent to Treat Population

	BREATHE-1		Study 351	
	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 Dr Reddy’s. 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 ± 0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0 ± 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 Dr Reddy’s, 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.

Study performed in Children with PAH

One study has been conducted in children with pulmonary hypertension. BOSENTAN DR REDDY’S 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^2, the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn.sec.cm^{-5}. 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. Congenital heart disease was echocardiographically established as ASD ≥ 2cm effective diameter and/or VSD ≥ 1cm effective diameter and confirmed by cardiac catheterization. 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 patients), 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 **Warnings and 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.

5.2 Pharmacokinetic properties

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 ± 1.7 hours and the apparent elimination half-life ($t_{½}$) was 5.6 ± 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 ± 3.6 L/h and the mean clearance of 8.8 ± 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 CYP3A4, 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 CYP2C19. 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 is 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. The number of patients studied in each dose group was insufficient to establish the optimal dosing regimen 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.

5.3 Preclinical safety data
Not available

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Inactive: maize starch, pregelatinised maize starch, sodium starch glycollate, povidone, glyceryl dibehenate, magnesium stearate, hypromellose, talc, triacetin, titanium dioxide, iron oxide yellow, iron oxide red, ethylcellulose.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Shelf life is 24 months (2 years) from manufacture.

6.4 Special precautions for storage
Store below 25°C, protect from moisture.

6.5 Nature and contents of container
BOSENTAN DR REDDY’S (bosentan monohydrate) 62.5 mg tablets: blisters containing 60 tablets.

BOSENTAN DR REDDY’S (bosentan monohydrate) 125 mg tablets: blisters containing 60 tablets.

6.6 Special precautions for disposal
No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
Dr Reddy’s New Zealand Ltd
82 Totara Crescent

Lower Hutt 5011
WELLINGTON

Tel: 0800 362 733

9 DATE OF FIRST APPROVAL

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