PRODUCT MONOGRAPH

[Pr]Accel-Bosentan

Bosentan Monohydrate (film coated tablet)
125 mg

Professed standard

Endothelin Receptor Antagonist

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[Pr]Accel-Bosentan

Bosentan monohydrate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet, 125 mg bosentan (from bosentan monohydrate)	Tablet contents: maize starch, magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate Film coating: hypromellose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

INDICATIONS AND CLINICAL USE

Accel-Bosentan (bosentan) is indicated for the treatment of pulmonary arterial hypertension in patients with WHO functional class III or IV primary pulmonary hypertension, or pulmonary hypertension secondary to scleroderma or congenital heart disease or human immunodeficiency virus in patients who did not respond adequately to conventional therapy. As well, a prolongation of time to clinical worsening was shown in patients with WHO functional class II.

CONTRAINDICATIONS

Accel-Bosentan is contraindicated in patients:

- who are hypersensitive to bosentan or to any excipient in the formulation. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.
- who are pregnant, or of childbearing potential unless adequate contraceptive measures are taken. Fetal malformations were reported in animals (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**);
- with moderate or severe liver impairment and/or with baseline values of liver transaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**);
- concomitant use of cyclosporine A;
- concomitant use of glyburide.

WARNINGS AND PRECAUTIONS

Hepatic/Biliary/Pancreatic

Bosentan has been associated with a reversible, dose-related increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), accompanied in some cases by elevated bilirubin. Increases in liver enzymes usually occurred within the first 26 weeks following initiation of treatment and returned to pretreatment levels without sequelae within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation. These increases may also occur late in treatment.

In the post-marketing period, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of bosentan in these cases could not be excluded.

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

Liver transaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.

Pre-existing Liver Impairment:
Use in patients with baseline values of liver transaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN, is contraindicated (see CONTRAINDICATIONS).

Management of Patients with Increased Liver Transaminases:

ALT/AST levels	**Treatment and monitoring recommendations are as follows:**
> 3 and ≤ 5 x ULN	**Confirm by another liver function test; if confirmed, reduce the daily dose or stop treatment, monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values consider continuing or reintroducing bosentan as appropriate (see Reintroduction of treatment below).**
> 5 and ≤ 8 x ULN	**Confirm by another liver function test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values consider reintroducing bosentan (see Reintroduction of treatment below).**

> 8 x ULN	**Treatment must be stopped and reintroduction of bosentan is not to be considered.**

In the case of elevations of aminotransferases accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice or unusual lethargy or fatigue) or of increases in bilirubin ≥ 2 x ULN, treatment must be stopped and reintroduction of bosentan is not to be considered.

Reintroduction of treatment

Reintroduction of treatment with bosentan should only be considered if the potential benefits of treatment with bosentan outweigh the potential risks and when aminotransferase levels are within pretreatment values. Bosentan is to be reintroduced at the starting dose and aminotransferase levels must then be checked within 3 days after reintroduction, then again after further 2 weeks, and thereafter according to the recommendations above.

General

Treatment with bosentan in patients with severe chronic heart failure was associated with an increased incidence of hospitalization due to worsening of chronic heart failure during the first 4 to 8 weeks of treatment with bosentan, which could have been the result of fluid retention. It is recommended that patients be monitored for signs of fluid retention (e.g., leg edema, weight gain). Should this occur, starting treatment with diuretics or increasing the existing dose of diuretics is recommended. Treatment with diuretics is recommended in patients with evidence of fluid retention before the start of treatment with bosentan.

Hematologic

Treatment with bosentan has been associated with dose-related decreases in hemoglobin concentration (0.9 g/dL overall average), which is likely due to hemodilution. In placebo-controlled studies bosentan -related decreases in hemoglobin concentration were not progressive, and stabilized after the first 4–12 weeks of treatment. It is recommended that hemoglobin concentrations be checked prior to the initiation of treatment, after 1 month and after 3 months, and quarterly thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and the need for specific treatment. In the post-marketing period, cases of anemia requiring red blood cell transfusion have been reported (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Cardiovascular

Bosentan should be initiated with caution if the patient has a systemic systolic blood pressure lower than 85 mm Hg.

Carcinogenesis and Mutagenesis (See Toxicology)

Special Populations

Pregnant Women: Bosentan should be considered a potential human teratogen. Bosentan has been shown to be teratogenic in rats when given at doses ≥ 60 mg/kg/day (twice the human oral

therapeutic dose of 125 mg b.i.d., on an mg/m^2 basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects including malformations of the head and face and of the major vessels. No birth defects were observed in rabbits at doses of up to 1500 mg/kg/day; however, the plasma concentrations were lower than those reached in rats. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated by other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no studies in pregnant women.

Bosentan treatment must not be initiated in women of childbearing potential unless they practice reliable contraception and the result of the pretreatment pregnancy test is negative.

Before the initiation of bosentan treatment in women of childbearing potential, the absence of pregnancy should be checked, appropriate advice on reliable method of contraception provided, and reliable contraception initiated. Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, bosentan may render hormonal contraceptives ineffective (see **DRUG INTERACTIONS, Drug-Drug Interactions, Hormonal contraceptives**). Therefore, women of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynecologist is recommended.

Because of possible hormonal contraception failure during bosentan treatment and also bearing in mind the risk that pulmonary hypertension severely deteriorates with pregnancy, monthly pregnancy tests during treatment with bosentan are recommended to allow early detection of pregnancy.

Nursing Women: It is not known whether bosentan is excreted in human milk. Because many drugs are excreted in human milk, nursing women taking Accel-Bosentan should be advised to discontinue breastfeeding.

Pediatrics (3-18 years of age): The safety and efficacy of bosentan in children was studied in a group of 19 patients ages 3-15 years with PAH either primary or secondary to various congenital heart defects, in WHO functional class II or III. Of the 19 patients, 10 were receiving concomitant Flolan® (epoprostenol). After 12 weeks of treatment with bosentan, efficacy could not be demonstrated based on increased exercise capacity. However, statistically significant improvements in certain hemodynamic indices were noted (mean pulmonary artery pressure, mean systemic artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index, systemic vascular resistance and systemic vascular resistance index, cardiac output and stroke index). No statistically significant improvement in respiratory parameters (oxygen and CO_2) or cardiac index was present. By treatment end, five patients had improved by one functional class and one deteriorated. No new safety concerns arose during the study, though one patient was withdrawn from treatment due to increased liver transaminases.

The dosing regimen used in the study was based on body-weight:

Body Weight (kg)	Initiation Dose	Maintenance Dose
$10 \leq x \leq 20$	31.25 mg q.d.	31.25 mg b.i.d.
$20 \leq x \leq 40$	31.25 mg b.i.d.	62.5 mg b.i.d.
> 40 kg	62.5 mg b.i.d.	125 mg b.i.d.

Geriatrics (> 65 years of age): Limited clinical experience with bosentan in patients aged 65 years or older has not identified any difference in response between elderly and younger patients, but the possibility of decreased hepatic function in the elderly should be considered (see **DOSAGE AND ADMINISTRATION**).

Monitoring and Laboratory Tests

Liver abnormalities management:

Liver transaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals. For liver abnormalities management (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Hemoglobin concentrations management:

Hemoglobin concentrations should be checked prior to the initiation of treatment, after 1 month and after 3 months, and quarterly thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and the need for specific treatment. **(See WARNINGS AND PRECAUTIONS, Hematologic)**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

In placebo-controlled studies 258 were patients with pulmonary arterial hypertension. They received bosentan at doses of 250 mg (n=188) or 500 mg (n=70) per day. Safety data on bosentan were obtained from placebo-controlled and open-label studies in 677 patients with pulmonary arterial hypertension or other conditions. Doses up to 8 times the currently recommended maintenance dose for pulmonary arterial hypertension were administered. The duration of treatment ranged from 1 day to 4.1 years. At the recommended maintenance dose of 125 mg b.i.d., adverse events that occurred at an incidence greater than 1% in bosentan -treated patients with pulmonary arterial hypertension are given in the following table:

Table 1 - Incidence of adverse events, regardless of drug causality, occurring in > 1% of patients treated with bosentan (125 mg b.i.d.) in placebo-controlled studies in pulmonary arterial hypertension

System Organ Class / Adverse Events (AEs)	Bosentan n=188		Placebo n=172	
	n	(%)	N	(%)
All system Organ Classes				
Total patients with at least one AE	155	(82)	135	(79)
Total number of AEs	504		548	
Infections and infestations				
Nasopharyngitis	16	(9)	14	(8)
Upper respiratory tract infection	15	(8)	11	(6)
Sinusitis	7	(4)	4	(2)
Bronchitis	6	(3)	12	(7)
Urinary tract infection	5	(3)	6	(4)
Respiratory tract infection	5	(3)	5	(3)
Influenza	4	(2)	8	(5)
Lower respiratory tract infection	3	(2)	4	(2)
Pharyngitis	3	(2)	1	(1)
Ear infection	3	(2)		
Gastrointestinal disorders				
Nausea	15	(8)	19	(11)
Diarrhea	8	(4)	13	(8)
Abdominal pain	5	(3)	7	(4)
Vomiting	4	(2)	10	(6)
Dyspepsia	4	(2)	4	(2)
Abdominal distension	4	(2)	3	(2)
Rectal hemorrhage	4	(2)		
Constipation	3	(2)	4	(2)
Dry mouth	3	(2)	2	(1)
Mouth ulceration	3	(2)		
Nervous system disorders				
Headache	24	(13)	25	(15)
Dizziness	18	(10)	23	(13)
Syncope	8	(4)	7	(4)
General disorders and administration site conditions				
Edema peripheral	15	(8)	13	(8)
Chest pain	10	(5)	8	(5)
Edema	5	(3)	4	(2)
Influenza like illness	4	(2)	2	(1)
Respiratory, thoracic and mediastinal disorders				
Cough	9	(5)	14	(8)
Pulmonary hypertension	8	(4)	23	(13)
Dyspnea	6	(3)	7	(4)
Epistaxis	6	(3)	7	(4)
Hemoptysis	4	(2)	4	(2)
Dyspnea exacerbated	3	(2)	6	(4)
Dyspnea exertional	3	(2)	1	(1)
Musculoskeletal and connective tissue disorders				
Back pain	7	(4)	6	(4)

Arthralgia	6	(3)	3	(2)
Muscle spasms	5	(3)	6	(4)
Shoulder pain	4	(2)	4	(2)
Investigations				
Liver function test abnormal	8	(4)	3	(2)
Hepatic enzyme increased	3	(2)		
Vascular disorders				
Flushing	8	(4)	5	(3)
Hypotension	6	(3)	3	(2)
Cardiac disorders				
Palpitations	6	(3)	3	(2)
Eye disorders				
Vision blurred	3	(2)	2	(1)
Blood and lymphatic system disorders				
Anemia	6	(3)		
Injury, poisoning and procedural complications				
Contusion	4	(2)	1	(1)

In placebo-controlled studies of bosentan in the treatment of pulmonary arterial hypertension and other diseases, a total of 677 patients were treated with bosentan and 288 patients were treated with placebo, with doses ranging from 100 mg to 2,000 mg per day. The duration of treatment ranged from four weeks to six months. Adverse events that occurred at an incidence greater than 1% in bosentan-treated patients are given in the following table:

Table 2: Incidence of adverse events, regardless of drug causality, occurring in > 1% of patients treated with bosentan in placebo-controlled studies

System Organ Class / Adverse Events (AEs)	**Bosentan**		**Placebo**	
	n=677		**n=288**	
	n	**(%)**	**n**	**(%)**
All System Organ Classes				
Total patients with at least one AE	529	(78)	220	(76)
Total number of AEs	1591		840	
Blood and Lymphatic System Disorders				
Anemia (NOS)	23	(3)	3	(1)
Cardiac Disorders				
Angina Pectoris	15	(2)	3	(1)
Cardiac failure	120	(18)	64	(22)
Edema (NOS)	16	(2)	3	(1)
Edema – Legs (Edema lower limb)	32	(5)	4	(1)
Palpitations	18	(3)	5	(2)
Gastrointestinal Disorders				
Abdominal pain (NOS)	13	(2)	11	(4)
Constipation	15	(2)	7	(2)
Diarrhea (NOS)	30	(4)	18	(6)
Dyspepsia	11	(2)	3	(1)
Nausea	31	(5)	30	(10)
Vomiting	16	(2)	12	(4)
General Disorders				
Chest pain (NEC)	27	(4)	20	(7)

Fatigue	14	(2)	12	(4)
Pyrexia	13	(2)	5	(2)
Hepato-biliary Disorders				
Hepatic function abnormal	40	(6)	6	(2)
Infections and Infestations				
Influenza	20	(3)	14	(5)
Metabolic and Nutritional Disorders				
Gout	12	(2)	7	(2)
Musculo-Skeletal, Connective Tissue and Bone Disorders				
Arthralgia	14	(2)	10	(3)
Back pain	17	(3)	8	(3)
Pain in limb	12	(2)	7	(2)
Nervous System Disorders				
Dizziness (exc. Vertigo)	80	(12)	39	(14)
Headache NOS	107	(16)	37	(13)
Vision blurred	20	(3)	7	(2)
Syncope	20	(3)	12	(4)
Respiratory, Thoracic and Mediastinal Disorders				
Bronchitis	19	(3)	10	(3)
Coughing	26	(4)	13	(5)
Dyspnea (NOS)	26	(4)	14	(5)
Nasopharyngitis	23	(3)	10	(3)
Pneumonia	11	(2)	2	(1)
Sinusitis	12	(2)	5	(2)
Lower respiratory tract infection	12	(2)	5	(2)
Upper respiratory tract infection	32	(5)	18	(6)
Renal and Urinary Disorders				
Urinary tract infection	18	(3)	12	(4)
Skin and Subcutaneous Tissue Disorders				
Pruritus (NOS)	12	(2)		
Vascular Disorders				
Epistaxis	12	(2)	5	(2)
Flushing	45	(7)	5	(2)
Hypotension (NOS)	46	(7)	22	(8)
Postural hypotension	13	(2)	14	(5)

NOS= Not otherwise specified
NEC= Not elsewhere classified
Note: The population studied included patients with pulmonary arterial hypertension as well as patients with other conditions. The doses used in some placebo-controlled studies were higher than those recommended for pulmonary arterial hypertension.

Adverse events that occurred more frequently in patients treated with bosentan than those treated with placebo were headache, flushing, abnormal hepatic function, anemia, and leg edema.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and Lymphatic System Disorders: ecchymosis, thrombocytopenia

Cardiac Disorders: complete atrioventricular block, cardiac arrest, myocardial infarction, tachycardia, ventricular arrhythmia, ventricular tachycardia

Eye Disorders: conjunctivitis, eye inflammation, photophobia, xerophthalmia

Gastrointestinal Disorders: anorexia, ascites, duodenal ulcer, flatulence, gastroenteritis, mouth ulceration, intestinal obstruction, loose stools
General Disorders: chest pain (non cardiac), feeling hot, lethargy, pain, shivering, thirst, weakness
Immune System Disorders: anaphylactic shock, urticaria
Infections and Infestations: infection
Investigations: blood alkaline phosphatase increased, blood lactate dehydrogenase increased, decreased weight, hyperglycemia, hypoglycemia, increased blood urea, increased eosinophil count, prolonged coagulation time, shortened coagulation time
Metabolism and Nutrition Disorders: dehydration, hypokalemia, hyponatremia, impaired glucose tolerance
Musculoskeletal Disorders: gout, muscle cramps, muscle twitching, musculoskeletal pain, sensation of heaviness
Nervous System Disorders: central nervous system depression, cerebrovascular accident, hemiparesis, hydrocephalus, hypoesthesia, insomnia, paresthesia, somnolence, tinnitus, tremor, vasovagal attack, vertigo
Psychiatric Disorders: anxiety, disturbance in attention, irritability, increased libido, mood swings, nightmares, panic attack
Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchospasm, hemoptysis, nasal congestion, pneumonia, respiratory depression, respiratory failure, increased sputum
Skin and Subcutaneous Tissue Disorders: dermatitis, dry skin, eczema, erythema multiforme, erythema, skin discoloration, Stevens-Johnson syndrome, increased sweating
Renal Disorders: cystitis, dysuria, hematuria, renal failure, renal impairment, urinary frequency, urine discoloration
Vascular Disorders: epistaxis, hypertension, peripheral ischemia, subarachnoid hemorrhage, restless leg syndrome

Abnormal Hematologic and Clinical Chemistry Findings
In placebo-controlled studies, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to more than three times the upper limit of normal (ULN) were observed in 11% of bosentan-treated patients (n=658) as compared to 2% of placebo-treated patients (n=280). Increase in aminotransferases equal or greater than 3 times of ULN was seen in 12.4% of 188 patients with pulmonary arterial hypertension treated with 125 mg b.i.d. and 14% of 70 patients with pulmonary arterial hypertension treated with 250 mg b.i.d. Increase in aminotransferases equal or greater than 8 times of ULN was seen in 3.8% of patients with pulmonary arterial hypertension on 125 mg b.i.d. and 7% of patients with pulmonary arterial hypertension on 250 mg b.i.d. Increases in bilirubin to more than three times the upper limit of normal were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with bosentan.

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) associated with bosentan are dose-dependent, occur most often early but occasionally late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with bosentan. In the post-marketing period, rare cases

of liver cirrhosis and liver failure have been reported (see **WARNINGS AND PRECAUTIONS**).

In the placebo-controlled trials of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline and < 11 g/dL) were observed in 6.2% of bosentan-treated patients as compared to 2.9% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 mg and 250 mg b.i.d., marked decreases in hemoglobin occurred in 4.3% of patients compared to 1.2% in placebo-treated patients.

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

During the course of treatment, the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage, hemolysis or bone marrow toxicity.

In the post-marketing period, cases of anemia requiring red blood cell transfusion have been reported (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).
It is recommended that hemoglobin concentrations be checked after 1 month and after 3 months of treatment and every 3 months thereafter.

Pulmonary veno-occlusive disease
Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary edema 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 edema in patients treated with bosentan who had a suspected diagnosis of pulmonary veno-occlusive disease.

Fluid Retention
In a placebo-controlled study, 1,611 patients with severe chronic heart failure were treated with bosentan for a mean duration of 1.5 years. In this study there was one new safety finding that was not previously observed in the pulmonary arterial hypertension studies. This was an early increased incidence of hospitalization due to worsening of chronic heart failure with no difference in mortality between bosentan and placebo-treated patients. At the end of the study, there was no difference in overall hospitalizations for heart failure or in mortality between bosentan and placebo-treated patients. This effect was observed during the first 4–8 weeks of treatment with bosentan and could have been the result of fluid retention. In this trial, fluid retention was reflected by early weight gain, decreased hemoglobin concentration, and increased incidence of leg edema.

In the placebo-controlled trials with pulmonary arterial hypertension patients, peripheral edema and decreased hemoglobin concentrations were reported with no evidence for increased incidence of early hospitalization due to clinical worsening.

It is recommended that patients be monitored for signs of fluid retention (e.g., leg edema, weight gain). Should this occur, starting treatment with diuretics or increasing the existing dose of diuretics is recommended. Treatment with diuretics is recommended in patients with evidence of fluid retention before the start of treatment with bosentan.

Testicular Function

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of bosentan 62.5 mg b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled; 23 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.

Pediatric Patients

In a study in children and adolescents 17 of the 19 patients (89.5%) reported at least one adverse event. The most frequent adverse events were flushing (four patients), headache, and abnormal hepatic function (three patients each). Dizziness, fluid retention, aggravated PAH, pyrexia, and a variety of infections occurred in two patients each.

Flushing was noted only in patients also on epoprostenol. Mild fluid retention was reported for two patients and moderate edema for one, but unlike most cases in previous studies did not occur early in treatment, but rather after at least 79 days of treatment. The incidences of these and other adverse events did not appear to have any relationship to weight group.

Combination with Epoprostenol

In study AC-052-355 (BREATHE-2) in adult patients, the most frequent adverse event experienced with the combination was jaw pain (59.1% on bosentan + epoprostenol and 90.9% on placebo + epoprostenol), a known side effect of epoprostenol therapy. Among the events associated with bosentan therapy, only leg edema was more frequent on bosentan plus epoprostenol than placebo plus epoprostenol (27.3% vs 9.1%). Few patients in either group experienced a serious adverse event or had treatment discontinued because of an adverse event. Two patients on combination therapy died during the study from progression of disease, and another died 36 days after having been withdrawn from the study because of a worsening

condition. None of the deaths were considered by the investigator to be related to treatment but rather a reflection of the natural progression of the disease.

Incidences of elevated liver aminotransferases to clinically relevant values were higher on placebo plus epoprostenol (18.2%) than on bosentan plus epoprostenol therapy (9.5%). Similarly, the incidences of clinically relevant decreases in hemoglobin were higher on placebo plus epoprostenol (10.0%) than on bosentan plus epoprostenol therapy (0%). The clinical pattern of laboratory abnormalities in the bosentan plus epoprostenol group was consistent with previous findings. No meaningful changes in ECG parameters were seen in either group, and no change in pulse rate was observed with bosentan plus epoprostenol. Decreases in blood pressures were observed in both groups, but the decrease in systolic blood pressure was smaller in the group on combination therapy than on placebo plus epoprostenol. No cases of hypotension or postural hypotension were reported on the combination therapy.

Post-Market Adverse Drug Reactions

Based on an exposure of about 49,000 patients to bosentan in the post-marketing period, the majority of adverse events have been similar to those reported in clinical trials.

Undesirable effects are ranked under headings of frequency using the following convention: very common (≥ 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, ≤ 1/100); rare (> 1/10,000, ≤ 1/1,000); very rare (≤ 1/10,000).

Gastrointestinal disorders:

Common: nausea.

Uncommon: vomiting, abdominal pain, diarrhea.

Hepato-biliary disorders:

Uncommon: aminotransferase elevations associated with hepatitis and/or jaundice.

Rare: hepatic cirrhosis and liver failure (see **WARNINGS AND PRECAUTIONS**).

Skin and subcutaneous tissue disorders:

Uncommon: hypersensitivity reaction including dermatitis pruritus and rash.

Immune system:

Rare: anaphylaxis and/or angioedema.

Blood and lymphatic system disorders:

Common: anemia or hemoglobin decreases, sometimes requiring red blood cell transfusion (see **WARNINGS AND PRECAUTIONS**).

Uncommon: thrombocytopenia.

Rare: neutropenia, leucopenia.

DRUG INTERACTIONS

Overview

Cytochrome P_{450} System: Bosentan had no relevant inhibitory effect on cytochrome P_{450} isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Consequently, bosentan is not expected to increase plasma concentrations of drugs metabolized by these enzymes.

Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes may be decreased when bosentan is co-administered.
Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or voriconazole) and a CYP3A4 inhibitor (such as ketoconazole, itraconazole or ritonavir) with bosentan may theoretically lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor with bosentan is not recommended.

Drug-Drug Interactions

Warfarin: Co-administration of bosentan 500 mg twice daily decreased plasma concentrations of both S-warfarin and R-warfarin by approximately 30%. In patients with pulmonary arterial hypertension, bosentan 125 mg b.i.d. had no clinically significant effect on prothrombin time/INR when administered to patients receiving chronic warfarin therapy. No additional dose adjustment should be needed for warfarin, but routine INR monitoring is recommended.

Simvastatin and other statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin, and of its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4.
The possibility of reduced efficacy should be considered for these statins.

Glyburide: An increased risk of elevated transaminases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of bosentan and glyburide is contraindicated, and alternative hypoglycemic agents should be considered (see **CONTRAINDICATIONS**).

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

Ketoconazole: Co-administration of bosentan and ketoconazole increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment is necessary. However, increased effects of bosentan should be considered.

Nimodipine, Digoxin, and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine. Losartan has no effect on plasma levels of bosentan.

Cyclosporine A: Co-administration of bosentan decreased the blood concentrations of cyclosporine A by approximately 50%. This is most likely due to induction of CYP3A4 by bosentan. Initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. However, at steady state, bosentan plasma concentrations were only 3- to 4-fold higher. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The concomitant administration of bosentan and cyclosporine A is contraindicated (see **CONTRAINDICATIONS**).

Tacrolimus and sirolimus: No drug-interaction study was performed with tacrolimus or sirolimus but a similar interaction with cyclosporine A can be expected. It is recommended to exclude concomitant administration of bosentan and tacrolimus or sirolimus.

Hormonal Contraceptives: Co-administration of bosentan decreased the plasma concentrations of ethinyl estradiol and norethindrone by 31 and 14% respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Bosentan is also expected to reduce plasma concentrations of other contraceptive steroids that have significant metabolism by CYP3A4. Therefore, hormone-based contraceptives alone, regardless of the route of administration (i.e. oral, injectable, transdermal, and implantable forms), are not considered as reliable methods of contraception (see **WARNINGS AND PRECAUTIONS, Pregnant Women**).

Sildenafil: In healthy volunteers co-administration of bosentan 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (steady state) resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. The combination was well tolerated. A dose adjustment of neither drug is considered necessary.

Rifampicin: Co-administration 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. Therefore a significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. 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.

Epoprostenol: Data obtained in a study in pediatric PAH patients (refer to clinical section) show that after both single- and multiple-dose administration, the C_{max} and AUC values of bosentan were similar in patients with or without continuous infusion of epoprostenol.

Antiretroviral agents: Lopinavir+Ritonavir (and other boosted protease inhibitors): 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, on Day 3-4 of bosentan that were approximately 48-fold higher than those measured after bosentan

administered alone. On day 9, plasma concentrations of bosentan declined to 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. When started in patients on concomitant lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, bosentan should be initiated at a dose of 62.5 mg once daily and the patient's tolerability of bosentan should be closely monitored with special attention, at the beginning of the initiation phase and during titration to the maintenance dose of 125 mg twice daily, to the risk of hypotension and to liver function tests.

After co-administration of bosentan for 9.5 days, the plasma exposures to 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 further decrease of protease inhibitors cannot be excluded. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors.

Other antiretroviral agents:
No specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasized that due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan potential impact on the liver, this combination is not recommended.

Drug-Food Interactions
Co-administration of bosentan with food results in small clinically irrelevant increases in C_{max} (22%) and AUC (10%). Bosentan can be given with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established (see **ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **Dosage in Patients with Hepatic Impairment:** No dose adjustment of Accel-Bosentan is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A). Use of Accel-Bosentan in patients with moderate or severe liver impairment is contraindicated (see **ACTION AND CLINICAL PHARMACOLOGY, CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

- **Use with protease inhibitors:**
  Co-administration of bosentan in patients already on protease inhibitors for at least 10 days:
  Start at 62.5 mg once daily or every other day based upon individual tolerability.
  Co-administration of protease inhibitors/antiretroviral agents in patients on bosentan:

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

Recommended Dose and Dosage Adjustment

Accel-Bosentan should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the recommended maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily do not confer additional benefit sufficient to offset the increased risk of liver injury.

Accel-Bosentan should be taken morning and evening, consistently, with or without food.

- **Dosage in Pediatric Patients:** There is only limited experience with bosentan in patients under the age of 18 years (see **WARNINGS AND PRECAUTIONS, Pediatrics**)

- **Dosage in the Elderly:** Clinical studies of bosentan did not include a sufficient number of patients aged 65 and over to determine if they respond differently than younger patients with pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made cautiously, reflecting a possible decrease in renal and/or cardiac function, concomitant disease, other drug therapy, and, particularly, decrease in hepatic function.

- **Dosage in Patients with Renal Impairment:** The effect of renal impairment on the pharmacokinetics of bosentan is small. No dosing adjustment is required including patients undergoing dialysis.

Missed Dose

If a scheduled dose of Accel-Bosentan is missed, a double dose should not be taken to make up for the forgotten individual dose. The patient should take the next tablet at the usual scheduled time.

Discontinuation of Treatment

There is no experience with abrupt discontinuation of Accel-Bosentan at the recommended doses in pulmonary arterial hypertension patients. However, to avoid the possible occurrence of sudden clinical deterioration as has been seen with the discontinuation of other medications for this disease, patients should be monitored closely and reducing the dose by half for 3 to 7 days prior to discontinuation should be considered.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 two months in patients, without any major clinical consequences. The most common side effect was headaches of mild-to-moderate intensity. In the cyclosporine A interaction study, where doses of 500 and 1,000 mg of bosentan were given concomitantly with cyclosporine A,

initial trough plasma concentrations of bosentan increased 30-fold resulting in severe headaches, nausea, and vomiting, but no serious adverse events occurred. 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, blurred vision. He recovered completely within 24 hours with blood pressure support. Note: bosentan is not removed through dialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

Bosentan is a dual endothelin receptor antagonist with affinity for both ET_A and ET_B receptors. Bosentan decreases both pulmonary and systemic vascular resistance, resulting in increased cardiac output without increasing heart rate.

The neurohormone endothelin is a potent vasoconstrictor with the ability to promote fibrosis, cell proliferation, and tissue remodeling. Endothelin concentrations in plasma and tissues are increased in a number of cardiovascular disorders, including pulmonary hypertension, suggesting a pathological role for endothelin in these diseases. In pulmonary arterial hypertension, endothelin plasma concentrations strongly correlate with poor prognosis.

Bosentan is specific for endothelin receptors. Bosentan competes with the binding of endothelin for both ET_A and ET_B receptors with a slightly higher affinity for ET_A receptors. In animal models of pulmonary hypertension, chronic oral administration of bosentan reduced pulmonary vascular resistance and reversed pulmonary vascular and right ventricular hypertrophy. In an animal model of pulmonary fibrosis, bosentan reduced collagen deposition.

Pharmacokinetics

Table 3 - Summary of bosentan's pharmacokinetic parameters in patients with pulmonary arterial hypertension

	C_{max}	$t_{1/2}$	$AUC_{0-\infty}$
14 days (125 mg twice a day)	2286 ng/ml	2.3 hr	8912 ng·hr/ml
	(1234, 3337)	(1.0 – 6.0)	(6296, 11531)

Data are expressed as arithmetic mean (and 95% confidence limits) or, for t_{max}, as median (and range). Data were obtained from PAH patients treated for at least two weeks with the maintenance dose of 125 mg b.i.d.

Absorption: The absolute bioavailability of bosentan is approximately 50% and is unaffected by food. Maximum plasma concentrations are attained within 3–5 hours after oral administration. Pharmacokinetic data following both oral and intravenous administration in adult patients with pulmonary arterial hypertension have been obtained. The data show that the exposure to bosentan in adult pulmonary arterial hypertension patients is about 2-fold greater than in healthy adult subjects.

Distribution: The volume of distribution is about 18 L and the clearance is about 8 L/h. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism: Bosentan is metabolized in the liver by the cytochrome P_{450} isoenzymes, CYP3A4 and CYP2C9. Three metabolites of bosentan were identified in human plasma. Only one metabolite, Ro 48-5033, is pharmacologically active. In adult patients, the exposure to this active metabolite is greater than in healthy subjects and it may contribute up to 25% to the effect of bosentan. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

Excretion: Bosentan is eliminated by biliary excretion. The apparent elimination half-life ($t_{1/2}$) is 5.4 hours.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of single and multiple oral doses of bosentan have been studied (see **WARNINGS AND PRECAUTIONS, Pediatric Patients**) in pediatric patients with pulmonary arterial hypertension**.** The exposure to bosentan decreased with time in a manner consistent with the known auto-induction properties of bosentan. The mean AUC (CV%) values of bosentan in pediatric patients treated with 31.25, 62.5 or 125 mg b.i.d. were 3496 (49), 5428 (79), and 6124 (27) ng·h/ml, respectively, and were lower than the value of 8149 (47) ng·h/ml observed in adult patients receiving 125 mg b.i.d.

Geriatrics: The pharmacokinetics of bosentan have not been evaluated in patients over the age of 65 years.

Gender: No significant relationship or trend was noted between bosentan pharmacokinetic parameters and gender.

Race: The pharmacokinetics of bosentan were compared between Caucasian and Japanese subjects both after single- and multiple-dose administration. The bosentan pharmacokinetics were similar and dose-proportional in Caucasian and Japanese subjects. Other ethnic differences in bosentan pharmacokinetics have not been evaluated.

Hepatic Insufficiency: In patients with mildly impaired liver function (Child-Pugh class A) no relevant changes in the pharmacokinetics have been observed and no dose adjustment is required in these patients. The steady-state AUC of bosentan was 9% greater and the AUC of the major metabolite, Ro 48-5033, was 33% greater in patients with mild hepatic impairment than in healthy volunteers. The pharmacokinetics of bosentan have not been studied in patients with Child-Pugh class B or C hepatic impairment and bosentan is contra-indicated in this patient population. (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: In patients with severe renal impairment (creatinine clearance 15–30 ml/min), plasma concentrations of bosentan decreased by approximately 10%, and plasma concentrations of the three metabolites increased about 2-fold as compared to volunteers with normal renal function. No dose adjustment is required in patients with renal impairment, as less

than 3% of an administered dose is excreted in urine. The degree to which bosentan is removed by hemodialysis has not been established.

STORAGE AND STABILITY

Accel-Bosentan should be stored at room temperature between 15°C and 30°C.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for Accel-Bosentan.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Accel-Bosentan is available as 125 mg bosentan (from bosentan monohydrate) tablets for oral administration containing the following excipients: maize starch, magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate. The film-coating is composed of hypromellose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

Accel-Bosentan is supplied as follows:
- 125 mg: Orange-white, oval, biconvex, film-coated tablets, debossed with “IB2” on one side and plain on other side carton box containing 4 blisters of 14 tablets each (56 tablets in total) and HDPE bottle containing 100 Tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

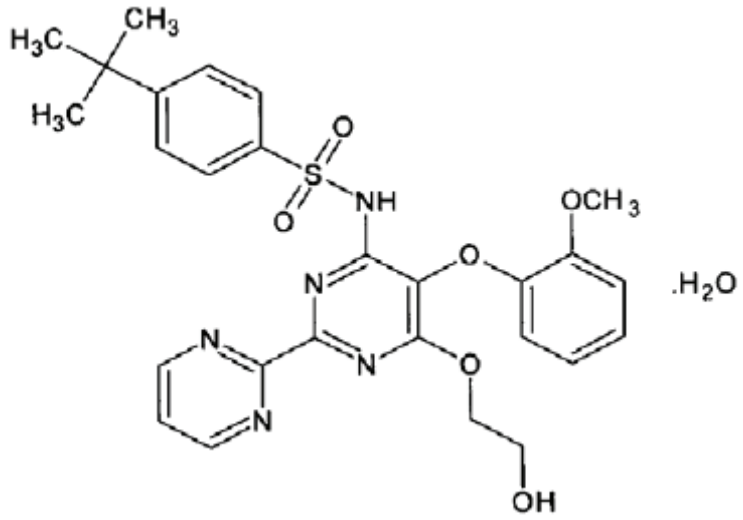
Proper name: Bosentan monohydrate

Chemical name: Bosentan (bosentan monohydrate) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. Its chemical designation is 4-tert-butyl-N - [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2'] bipyrimidin-4-yl] - benzenesulfonamide monohydrate.

Molecular formula: The molecular formula is $C_{27}H_{29}N_5O_6S \cdot H_2O$.

Molecular weight: Bosentan monohydrate has a molecular weight of 569.63 g/mol.

Structural formula:



Physicochemical properties: Bosentan monohydrate is a white to yellowish powder.

Solubility: It is poorly soluble in water (1 mg/100 ml) and in aqueous solutions 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 is very stable, is not hygroscopic, and is not light sensitive.

CLINICAL TRIALS

COMPARATIVE BIOAVALABILITY STUDIES

Summary of studies establishing bioequivalence of Accel-Bosentan 125 mg to Tracleer® (bosentan) 125 mg film-coated tablets (Reference Listed Drug)

A double blind, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Accel-Bosentan tablets 125 mg (Accel Pharma Inc.) with that of Tracleer® (Bosentan) 125 mg film-coated tablets of Actelion Pharmaceuticals Canada Inc. in 53 healthy, adult male, human subjects under fasting conditions.

Bosentan (1 x 125 mg) From measured data **Uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90 % Confidence Interval**
AUC_T (ng.h / mL)	12421.89, 3458.77 (40.7%)	11248.52, 12270.20 (42.2%)	110.4	104.3-117.0%
AUC_I (ng.h / mL)	12582.73, 13601.58 (40.2%)	11415.38, 12413.21 (41.6%)	110.2	104.1-116.7%
C_{max} (ng / mL)	2405.85, 2662.12 (42.8%)	2206.97, 2485.59 (48.6%)	109.0	99.2-119.8%
T_{max} (h)§	4.00 (2.000 - 4.667)	4.00 (2.00 - 4.67)		
$T_{½}$ (h)	6.14 (39.2%)	6.65 (43.6%)		

* Accel-Bosentan 125 mg (Accel Pharma Inc.)
† Tracleer® (Bosentan) 125 mg Film-Coated Tablets – Marketed by: Actelion Pharmaceuticals Canada Inc. were purchased in Canada.
§ Expressed as the median (range) only

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
AC-052-351	Randomized, double – blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 8 weeks.	Placebo n=11 Bosentan n=21	Placebo: 47.4 (25-67) Bosentan: 52.2 (33-73)	Placebo: 0M 11F Bosentan: 4M 17F
AC-052-352	Randomized, double-blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to either 125 mg b.i.d., oral, or 250 mg b.i.d., oral, for 12 weeks.	Placebo n=69 Bosentan n=144	Placebo: 47.2 (12-80) Bosentan: 48.7 (13-80)	Placebo: 15M 54F Bosentan: 30M 114F
AC-052-353	Open-label, single-arm extension of AC-052-351	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral. Duration: 706 ± 146 days.	n=29	50.2 (26-74)	4M 25F
AC-052-354	Open-label, single-arm extension of AC-052-352	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral. Duration: 479 ± 164 days	n=200	48.5 (13-81)	42M 158F
AC-052-364	Randomized, double-blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral for 5 months.	Placebo n=92 Bosentan n=93	Placebo: 44.2 (19-79) Bosentan: 45.2 (15-85)	Placebo: 34M 58F Bosentan: 22M 71F
AC-052-405	Randomized, double-blind, placebo-controlled Patients with PAH/CHD	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks.	Placebo n=17 Bosentan n=37	Placebo: 44.2 (30-56) Bosentan: 37.2 (15-73)	Placebo: 7M 10F Bosentan: 14M 23F
AC-052-355	Randomized, double-blind, placebo-controlled, combination therapy bosentan + epoprostenol	Bosentan: starting dose at 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks. Epoprostenol: initiated at 2 ng/kg/min, i.v., 4 days	Placebo n=11 Bosentan n=22	Placebo : 46.6 (15-68) Bosentan : 44.8 (16-69)	Placebo: 5M 6F Bosentan: 5M 17F

		up to 4 ng/kg/min, i.v. Up-titrated by 2 ng/kg/min, i.v., each 2 weeks. Target dose of 12 to 16 ng/kg/min, i.v., by weeks 14 and 16.			
AC-052-362	Open-label, non-comparative Patients with PAH/HIV	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks.	n=16	39.2 (29-61)	9M 7F

Study results

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 (Study AC-052-351) and 213 patients (Study AC-052-352 - BREATHE-1) respectively, with WHO functional class III or IV primary pulmonary hypertension (PPH) or pulmonary arterial hypertension secondary to scleroderma or other connective tissue diseases. The BREATHE-1 study compared 2 doses (125 mg b.i.d. and 250 mg b.i.d.) of bosentan with placebo. Study AC-052-351 compared 125 mg b.i.d. with placebo.

In both studies, bosentan or placebo was added to patients' existing therapy (oral vasodilators, anticoagulants, diuretics, cardiac glycosides and/or supplemental oxygen, but not epoprostenol). Patients received bosentan 62.5 mg or matching placebo twice daily for 4 weeks and then bosentan 125 mg or 250 mg b.i.d. or matching placebo twice daily for either 8 (Study AC-052-351) or 12 (BREATHE-1) additional weeks. The primary study endpoint was 6-minute walk distance. In addition, symptoms and functional status were assessed. Hemodynamic measurements were made at 12 weeks in Study AC-052-351.

At week 12 (study AC-052-351) or week 16 (BREATHE-1) the main evaluations were performed and patients were followed for up to 28 weeks. In both trials, treatment with bosentan was associated with a significant increase in walking distance. The placebo-corrected increases in the primary efficacy parameter, distance in the 6-minute walk test, compared to baseline were 75.9 ± 31.0 m (95% CL = 12.5, 139.2; t-test, p = 0.0205) and 44.2 ± 11.6 (95% CL = 21.4, 67.0; Mann-Whitney U-test, p = 0.0002). The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg b.i.d.) and fully developed by about 2 months of treatment. It was maintained for up to 7 months of double-blind treatment. (see **DOSAGE AND ADMINISTRATION**).

Invasive hemodynamic parameters were assessed in Study AC-052-351. As compared to placebo significant improvement from baseline to week 12 was observed with bosentan in pulmonary arterial pressure (PAP), cardiac index (CI), pulmonary vascular resistance (PVR), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP).

Table 5 - Change from baseline to week 12 in hemodynamic parameters in study AC-052-351

	Baseline		Absolute Change		Treatment Difference
	Bosentan	**Placebo**	**Bosentan**	**Placebo**	
Mean PAP (mm Hg)	n=20 53.7 ± 13.4	n=10 55.7 ± 10.5	n=20 -1.6 ± 5.1	n=10 5.1 ± 8.8	-6.7*
Cardiac index (L/min/m^2)	n=20 2.35 ± 0.73	n=10 2.48 ± 10.33	n=20 0.50 ± 0.46	n=10 -0.52 ± 0.48	1.02**
PVR (dyn·sec/cm^5)	n=19 896 ± 425	n=10 942 ± 430	n=19 -223 ± 245	n=10 191 ± 235	-415**
Mean RAP (mm Hg)	n=19 9.7 ± 5.6	n=10 9.9 ± 4.13	n=19 -1.3 ± 4.1	n=10 4.9 ± 4.6	-6.2**
PCWP (mm Hg)	n=19 9.3 ± 2.4	n=10 8.3 ± 3.4	n=19 0.1 ± 3.6	n=10 3.9 ± 5.6	-3.8*

Values are mean ± SD
* $p < 0.05$
** $p < 0.001$

Symptoms of pulmonary arterial hypertension were assessed by WHO functional class, Borg dyspnea score and rate of "clinical worsening". There was a reduction in dyspnea during walk test (Borg dyspnea score), an improvement in WHO functional class and a significant reduction in the rate of clinical worsening in bosentan-treated patients.

In study AC-052-351, 9 patients (42.8%) treated with bosentan, had their WHO functional class of pulmonary hypertension improved from class III to class II. In the placebo group, 1 patient (9.1%) improved from class III to class II, and 2 patients (18.1%) deteriorated from class III to class IV. In trial AC-052-352 (BREATHE 1) 92% of the 213 patients were classified at baseline as WHO functional class III and 8% as class IV. Treatment with bosentan led to a WHO functional class improvement in 42.4% of patients (placebo 30.4%).

Clinical worsening was assessed as the time to death or hospitalizations for PAH or discontinuation of therapy because of PAH or need for epoprostenol. Figure 1 below shows the Log-rank test reflecting clinical worsening over 28 weeks and the incidences of each component of the clinical worsening endpoint are described in the Table 6 below.

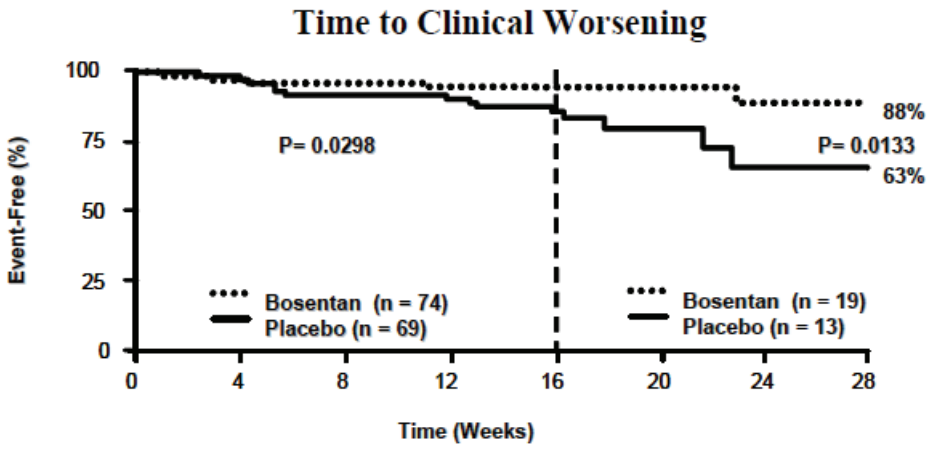
Table 6 - Incidence of clinical worsening*

	BREATHE-1		Study AC-052-351	
	Bosentan 125 mg b.i.d. (n=74)	Placebo (n=69)	Bosentan 125 mg b.i.d. (n=21)	Placebo (n=11)
Patients with clinical worsening [n (%)]	5 (7%)[(a)]	14 (20%)	0 (0%)[(b)]	3 (27%)
Death	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Hospitalization for PAH	3 (4%)	9 (13%)	0 (0%)	3 (27%)
Discontinuation due to Worsening of PAH	3 (4%)	6 (9%)	0 (0%)	3 (27%)
Receipt of epoprostenol[(c)]	2 (3%)	3 (4%)	0 (0%)	3 (27%)

Note: Patients may have had more than one reason for clinical worsening.
[(a)] p=0.015 vs. placebo by log-rank test.
[(b)] p=0.033 vs. placebo by Fisher's exact test.
[(c)] Receipt of epoprostenol was always a consequence of clinical worsening.

*shortest time to death, premature withdrawal or hospitalization due to PHT worsening, or initiation of epoprostenol therapy

Figure 1 - Time from randomization to clinical worsening up to Week 28 in BREATHE-1 Study

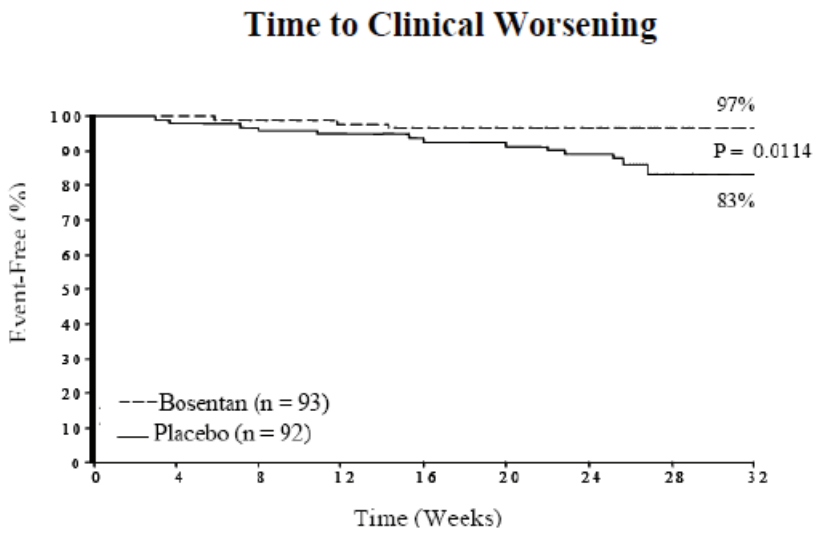


Time from randomization to clinical worsening with Kaplan-Meier estimate of the proportions of failures in BREATHE-1. All patients (n=74 in the bosentan group and n=69 in the placebo group) participated in the first 16 weeks of the study. A subset of this population (n=19 in the bosentan group and 13 in the placebo group) continued double-blind therapy for up to 28 weeks.

In a randomized, double-blind, multicenter, placebo-controlled trial, 185 mildly symptomatic PAH patients with WHO Functional Class II (mean baseline 6-minute walk distance of 443 meters) received bosentan 62.5mg bid for 4 weeks followed by 125mg bid (n = 93), or placebo (n = 92) for 5 months. Enrolled patients were treatment-naive (n= 156) or on a stable dose of sildenafil (n= 29). The co-primary endpoints were change from baseline to month 6 in PVR and 6-minute walk distance. Time to clinical worsening (assessed as death, hospitalization due to PAH complications, or symptomatic progression of PAH), Borg dyspnea index, change in WHO functional class and hemodynamics were assessed as secondary endpoints.

After 6 months treatment, there was a 22.6% reduction in PVR compared with placebo ($p < 0.0001$). The increase in 6-minute walk distance with bosentan and decrease with placebo resulted in +19.1 meter and +13.8 meter mean and median treatment effects, respectively. The effect did not reach statistical significance ($p = 0.0758$ for median treatment effect). There was a significant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) with bosentan compared with placebo (hazard ratio 0.227, $P = 0.0114$). Compared with placebo, bosentan treatment was also associated with a reduced incidence of worsening of at least one functional class (3.4% bosentan vs 13.2% placebo, $p = 0.0285$), and statistically significant improvement in hemodynamic variables (mPAP, TPR, cardiac index, and SVO2; $p < 0.05$). Findings were consistent in strata with or without treatment with sildenafil at baseline.

Figure 2 – Time from randomization to clinical worsening up to Week 32 in EARLY study



Time from randomization to clinical worsening with Kaplan-Meier estimate in EARLY.

Long-term treatment

The long-term effect of bosentan was further assessed in two open-label studies (open-label extensions of study AC-052-351 and AC-052-352) with 229 patients treated with bosentan for up to 2.5 years with a mean treatment duration of 1.9 ± 0.7 years. During this period, the effects of bosentan were maintained in the patients previously treated with bosentan. Treatment with bosentan in those patients previously on placebo, resulted in an improvement in exercise capacity. Improvement in functional class observed in the initial period of the study tended to decline later.

Long-term survival

Long-term survival was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled trials and their open-label extension studies. The results show that 93% and 84% of patients were still alive after 1 and 2 years, respectively, after the start of treatment with bosentan. These estimates may be influenced by the initiation of epoprostenol treatment in 43/235 patients. In a subset of primary pulmonary hypertension (PPH) patients (n=169) the Kaplan-Meier survival estimates were 96% at 1 year and 89% at 2 years as compared to the predicted survival (calculated by the NIH registry formula) of 69% and 57% respectively.

Patients with Pulmonary Arterial Hypertension associated with Congenital Heart Disease

A randomized, double-blind, multi-center, placebo-controlled study were conducted in 54 patients with WHO functional class III pulmonary arterial hypertension associated with Eisenmenger physiology associated with congenital heart disease (resulting in right to left shunt). Patients received bosentan 62.5 mg (n=37) or matching placebo (n=17) twice daily for 4 weeks and then bosentan 125 mg b.i.d. or matching placebo twice daily for 12 additional weeks.

In this study there were two primary endpoints. The first primary endpoint was to show that bosentan did not worsen the shunt or increase hypoxemia. The second primary endpoint was the mean change from baseline versus placebo in pulmonary vascular resistance indexed (PVRi) at Week 16. In addition 6-minute walk distance was assessed.

After 16 weeks, bosentan increased mean oxygen saturation by 1.0% (95% CL = –0.7; 2.8) as compared to placebo, demonstrating that bosentan did not relevantly worsen hypoxemia. In comparison with placebo, treatment with bosentan statistically significantly decreased the indexed pulmonary vascular resistance by -472.0 ± 221.9 dyn·sec·cm^{-5} compared with placebo (95% CL = -917.6, -26.5; t-test, p = 0.0383).

Treatment with bosentan was associated with a statistically significant improvements in walk distance with a placebo-corrected increases of 53.1 ± 19.2 m (95% CL = 14.5, 91.7; t-test, p = 0.0079) compared to placebo.

Patients with Pulmonary Arterial Hypertension associated with human immunodeficiency virus

In an open-label study without a control group 16 epoprostenol-naive patients with pulmonary arterial hypertension associated with human immunodeficiency virus (HIV) infection (stable, with CD4 cell > 100 cells/mm^3) with WHO functional class III and IV were treated with bosentan 62.5 mg b.i.d. for 4 weeks and then up-titrated to 125 mg b.i.d. for the remaining 12 weeks of the study.

The distance in 6-minute walk test after 16 weeks of treatment with bosentan improved significantly by 91.4 ± 59.5 m from baseline (95% CL = 59.7, 123.3; t-test, p<0.001). Improvement in Borg dyspnea index was also observed and was significantly reduced at week 16 (1.5 ± 1.6) compared with baseline (3.4 ± 2.5) (95% CL = -3.3, -0.5; t-test, p<0.013).

At baseline, 15 of the 16 patients were functional class III and one patient was class IV. After 4 weeks of treatment with bosentan at the 62.5-mg b.i.d. dose, 9 (56.3%) patients showed improvement in functional class. After an additional 12 weeks of treatment at the 125 mg b.i.d. dose, 14 of 16 patients (87.5%) improved from their baseline class including the one patient in class IV. Three patients improved from class III at baseline to class I and no patients deteriorated in functional class. One patient experienced clinical worsening in pulmonary arterial hypertension and was hospitalized.

Improvement from baseline to week 16 was observed with bosentan with a mean increase in cardiac index (0.88 L/min/m^2 ± 0.72; 95% CL = 0.49, 1.26; t-test, p <0.001) and mean decreases in mean PAP (-11.0 mmHg; 95% CL = -17.4, -4.7; t-test, p = 0.0002), and PVR (-339 dyn·sec/cm^5; 95% CL = -454, -223; t-test, p < 0.001). This was an open-label study without a control group. These data should be interpreted cautiously.

Patients Treated 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 multicentre, randomized, 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-control trial in pediatric patients. Ten of the 19 pediatric patients were on concomitant bosentan and epoprostenol therapy during the 12-week trial.

Combination therapy with bosentan and epoprostenol was safe and well tolerated in children and adults. In children, bosentan treatment, with or without epoprostenol, resulted in significantly improved hemodynamics. In adults, combination therapy was associated with a larger improvement in hemodynamics compared to epoprostenol alone, although in no case did the differences between the groups reached statistical significance.

DETAILED PHARMACOLOGY

In vivo Animal Studies:

Bosentan has an effect not only on hemodynamic variables but also on structural changes and disease progression in rat models of pulmonary hypertension.

In chronic hypoxia and monocrotaline rat models, bosentan at doses of 100 mg/kg/day for up to four weeks decreases pulmonary vascular resistance and reverses pulmonary vascular and right ventricular hypertrophy.

In a rat model of bleomycin-induced pulmonary fibrosis, bosentan at doses of 100 mg/kg/day for up to four weeks decreases pulmonary interstitial fibrosis by reducing collagen deposition in the lungs.

In acute pulmonary hypertension pig models, i.v. administration of bosentan at doses of 3–10 mg/kg prevents acute pulmonary hypertension.

In Vivo Human Studies:

The clinical pharmacology program for bosentan included 23 studies of < 14 days duration, involving 350 healthy subjects and 221 patients, with a total of 434 individuals receiving bosentan.

Pharmacokinetics

The pharmacokinetics of bosentan have mainly been documented in healthy subjects. Limited data in patients show that the exposure to bosentan in adult pulmonary arterial hypertension patients is approximately 2-fold greater than in healthy adult subjects.

In healthy subjects, bosentan displays dose- and time-dependent pharmacokinetics. Clearance and volume of distribution decrease with increased intravenous doses and increase with time. After oral administration, the systemic exposure is proportional to dose up to 500 mg. At higher oral doses C_{max} and AUC increase less than proportionally to the dose.

Upon multiple dosing, plasma concentrations of bosentan decrease gradually to 50%–65% of those seen after single dose administration. This decrease is probably due to auto-induction of metabolizing liver enzymes. Steady-state conditions are reached within 3–5 days.

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Based on the available data it is not expected that the pharmacokinetics of bosentan will be influenced by gender, body weight, race, or age in the adult population to any relevant extent. No kinetic data are available in children under 3 years.

Pharmacodynamics
In healthy subjects, oral administration of bosentan has no clinically relevant effect on heart rate and blood pressure in single and multiple-dose studies at doses up to 1,000 mg.

Plasma endothelin levels increase in a dose- and concentration-dependent manner after i.v. and oral doses of bosentan are administered in healthy subjects. No consistent changes in the plasma levels of other hormonal parameters are found. In these subjects, dose-related headaches of mostly mild-to-moderate intensity are the most frequent adverse event.

In patients with primary pulmonary arterial hypertension and pulmonary arterial hypertension secondary to scleroderma or human immunodeficiency virus, oral bosentan significantly decreases pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP) and significantly increases cardiac index (CI) as compared to placebo.

MICROBIOLOGY

Not applicable. Bosentan does not have antimicrobial potential.

TOXICOLOGY

Animal toxicity studies
Bosentan had a low order of acute toxicity. The highest non-lethal doses were in the 125 to 250 mg/kg range by the i.v. and intraperitoneal routes of administration, 1,000 mg/kg or more by the subcutaneous route and 2,000 to > 4,000 mg/kg by the oral route.

Repeated-dose toxicity - oral administration
Oral repeated-dose toxicity studies were conducted with bosentan in rats, dogs, and marmosets. Three repeated-dose toxicity studies of up to 6 months duration in rats and four studies of up to 12 months duration in dogs were conducted.

There was no substantial toxicity observed in any of the rat studies. Mild decreases (within normal limits) in red blood cell (RBC) parameters were noted that may be due to the vasodilating effects of bosentan and to the associated increase in plasma volume. Increases in liver weight were observed in rat studies; however, there was no histopathological evidence of hepatotoxicity in any of the repeated-dose studies in rats.

In most of the dog studies, a mild decrease in RBC parameters was also observed. In a 4-week study conducted at very high doses (500 and 1,000 mg/kg), increased serum liver enzymes and, histologically, bile duct proliferation and single cell necrosis were observed. In the 6-month study (10, 60 and 400 mg/kg), no significant toxicity was observed at doses up to 400 mg/kg. In the 12-month study (60, 180, and 500 mg/kg), histological changes indicative of a mild cholestasis and increased serum bile salts were observed at high doses. Mild increases in alkaline phosphatase, along with increased liver weights and hepatocellular hypertrophy, are compatible with the microsomal enzyme inducing properties of the drug in dogs. There were no signs of centrolobular necrosis in any studies.

Oral administration (10, 80, and 500 mg/kg/day) to marmosets was generally well tolerated. No signs of systematic toxicity were observed.

Mutagenicity

The mutagenic and clastogenic potential of bosentan was evaluated in a comprehensive battery of tests *in vitro* and *in vivo*. In these tests, there was no evidence for any mutagenic or clastogenic activity with bosentan, including the lots with a higher level of impurities.

Carcinogenicity

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., on a mg/m^2 basis). In the same study, doses greater than 2,000 mg/kg/day (about 32 times the [MRDH]) were associated with an increased incidence of colon adenomas in both males and females.

In rats, oral administration of bosentan for 2 years produced a small, significant increase in the combined incidence of thyroid follicular cell adenomas and carcinomas in male rats treated at doses of 3,000 mg/kg/day, about 600 times the human oral therapeutic dose in a 50-kg patient. There was no significant increase in the incidence of tumors in female rats or at sites other than the thyroid gland in male rats. There was evidence for a mild thyroid hormonal imbalance induced by bosentan in rats. There was no increase in mortality at any dose in mice and rats.

Bosentan is a microsomal enzyme inducer in mice; therefore the formation of liver tumors is not unexpected. Likewise, rats, particularly males, are susceptible to the development of thyroid follicular tumors secondary to thyroid hormone imbalance. No other rat or mouse tumor was considered related to bosentan treatment. The thyroid in rats and the liver in mice are among the most common tumor sites in carcinogenicity studies with pharmaceutical agents and this combination of tumors is found with many other drugs. Since an extensive battery of tests showed bosentan has no genotoxic potential, these findings are considered not to represent a relevant cancer risk.

Testicular findings in bosentan-treated rats

In the 2-year carcinogenicity study in rats, an increase in the incidence of testicular tubular atrophy was observed in the treated groups as compared to the control groups. There was no increase in the incidence of testicular tubular atrophy in rats treated for 6 months or in dogs treated up to 12 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. In various fertility studies, fertility was normal and sperm parameters (motility and counts), testis and epididymal weights, and histopathology were normal.

Reproductive toxicity

In the fertility studies in rats, no effects were observed on mating performance or fertility, on the development of the preimplantation embryo, or on implantation. There were no changes in sperm count, motility, or viability or on testis weights.

Bosentan has been shown to be teratogenic in rats when given at doses about 6 times the human oral therapeutic dose in a 50-kg patient. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head and face and of the major vessels. No birth defects were observed in rabbits at doses of up to 1,500 mg/kg/day. Similarities in the pattern of malformations observed with other endothelin receptor antagonists and in endothelin knock-out mice indicate a class effect.

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PART III: CONSUMER INFORMATION

IMPORTANT: PLEASE READ

[PR]Accel-Bosentan
(bosentan monohydrate)
125 mg film-coated tablets

This leaflet is part III of a three-part "Product Monograph" published when Accel-Bosentan was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Accel-Bosentan. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Accel-Bosentan is prescribed for the treatment of pulmonary arterial hypertension (high blood pressure in the blood vessels between the heart and the lungs).

What it does:
Bosentan reduces abnormally high blood pressure by relaxing these blood vessels. Accel-Bosentan belongs to the class of medicines known as endothelin receptor antagonists.

Before you take Accel-Bosentan:
Tests your doctor will do before treatment:

- a blood test for liver function;
- a blood test for anemia (reduction in red blood cells);
- a pregnancy test.

When it should not be used:
Do not use Accel-Bosentan if you:

- are hypersensitive (allergic) to bosentan or any other ingredients in the tablet (**See What the important nonmedicinal ingredients are);**
- have liver problems;
- are pregnant or planning to become pregnant (hormonal contraceptives alone are not effective when you take Accel-Bosentan);
- are a woman of childbearing age and not using adequate contraceptive methods;
- are being treated with cyclosporine A, or glyburide.

Tell your doctor immediately if you are pregnant or plan to become pregnant in the near future. This is because Accel-Bosentan may harm your unborn baby and you must not take Accel-Bosentan if you are pregnant. You must also not become pregnant while taking Accel-Bosentan. If you are a woman of childbearing age, your doctor or gynecologist will advise you about adequate contraceptive methods while taking Accel-Bosentan. Because bosentan may make hormonal contraception (e.g., oral, injection, implant or skin patches) ineffective, this method on its own is not reliable. Therefore, if you use hormonal contraceptives you must also use a barrier method (e.g., female condom, diaphragm, contraceptive sponge or your partner must also use a condom). Monthly pregnancy tests are recommended while you are taking Accel-Bosentan and you are of childbearing age.

Tell your doctor immediately if you are breastfeeding. You are advised to stop breastfeeding if Accel-Bosentan is prescribed for you because it is not known if this drug passes into the milk in women who are taking bosentan.

If you feel dizzy while taking Accel-Bosentan, do not drive or operate any tools or machines.

Accel-Bosentan is not recommended for children.

What the medicinal ingredient is:
Bosentan monohydrate.

What the important nonmedicinal ingredients are:
Maize starch, magnesium stearate, povidone, pregelatinized starch and sodium starch glycolate. The film-coating is composed of hypromellose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

What dosage forms it comes in:
Accel-Bosentan 125 mg tablets are also available as orange-white, oval, biconvex, film-coated tablets, debossed with “IB2” on one side and plain on other.

WARNINGS AND PRECAUTIONS

Warnings and Precautions
Before you use Accel-Bosentan talk to your doctor or pharmacist if you are:

- **known to have liver problems;**
- **pregnant or thinking of becoming pregnant;**
- **a woman of childbearing age and not using adequate contraceptive methods;**
- **breastfeeding;**
- **hypersensitive (allergic) to bosentan or any other ingredients of Accel-Bosentan.**

Before starting bosentan treatment, tell your doctor and your pharmacist if you are taking or have recently taken any other medicines, even those you have bought yourself. It is especially important to tell your doctor if you are taking:

- hormonal contraceptives (as these may not be effective as the sole method of contraception when you take Accel-Bosentan);
- glyburide (for diabetes);

- cyclosporine A (a medicine used after transplants and to treat psoriasis), or any other drugs used to prevent rejection of transplanted organs;
- fluconazole (to treat fungal infections);
- rifampicin (to treat tuberculosis).

Tests during treatment:
Some patients taking Accel-Bosentan were found to have abnormal liver function values (increase in liver enzymes) and some patients developed anemia (reduction in red blood cells). Because these findings may not cause symptoms you can feel or observe yourself, your doctor will do regular blood tests to assess any changes in your liver function and hemoglobin level.

Liver function:
This blood test will be done:

- every month or more frequently, if needed.

If you develop abnormal liver function, your doctor may decide to reduce your dose or stop treatment with Accel-Bosentan. When your blood test results for liver function return to normal, your doctor may decide to restart treatment with Accel-Bosentan.

Anemia:
This blood test will be done:
- after 1 month and after 3 months of treatment;
- every 3 months during treatment thereafter.

If you develop anemia, your doctor may decide to perform further tests to investigate the cause.

Your regular blood tests, both for liver function and anemia, are an important part of your treatment. We suggest you write in a diary the date of your most recent test and also that of your next test (ask your doctor for the date) to help you remember when your next test is due.
Pregnancy tests for women of childbearing age:
Due to the risk of failure of hormonal contraception when taking Accel-Bosentan and the risk in patients with pulmonary hypertension of rapid and severe deterioration of the disease, monthly pregnancy tests are recommended before and during treatment with bosentan.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with bosentan include: warfarin, simvastatin and other statins, glyburide, ketoconazole, cyclosporine A, tacrolimus, sirolimus and hormonal contraceptives.

PROPER USE OF THIS MEDICATION

Always take Accel-Bosentan exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Usual dose:
The usual dose is one tablet, swallowed twice daily (morning and evening), consistently with or without food. For the first 4 weeks, you will take a 62.5 mg tablet twice daily, from then on, your doctor will advise you to take a 125 mg tablet twice daily, depending on how you react to bosentan.

Overdose:
If you take more tablets than you have been told to take, see a doctor or go to a hospital immediately.

Missed Dose:
If you forget to take Accel-Bosentan, take a dose as soon as you remember, then continue to take your tablets at the usual time. Do not take a double dose to make up for forgotten tablets.

Stopping treatment:
Suddenly stopping your treatment with bosentan may lead to a worsening of your symptoms. Do not stop taking Accel-Bosentan unless your doctor tells you to. Your doctor may tell you to reduce the dose over a few days before stopping completely.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Accel-Bosentan can have side effects even when used as directed.

If you notice yellowing of the skin or eyes (jaundice) or other symptoms such as nausea, vomiting, fever, abdominal pain or unusual tiredness, see your doctor immediately because this may be related to abnormal liver function.

Headaches were the most common side effect in clinical studies.

You may also notice one or more of the following side effects
- flushed appearance, inflammation of the throat and nasal passages, swelling of the legs and ankles, or other signs of fluid retention, low blood pressure, irregular heartbeat, heartburn, tiredness, itching, nausea. If these side effects become bothersome, contact your doctor.

Other less common side effects that you might notice:
- vomiting, abdominal pain, diarrhea, skin rash.

If you notice any other side effects or signs of allergic reaction (e.g. swelling of the face or tongue, rash, pruritus) while you are taking Accel-Bosentan or if any of the side

effects mentioned above worries you, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common	**Abdominal pain**		√	
	Itching	√		
	Nausea	√		
	Other signs of fluid retention	√		
	Swelling of the legs and ankles		√	
	Tiredness	√		
	Vomiting		√	
Uncommon	**Rash**	√		
	Swelling of the face, throat or tongue		√	
Rare	**Asthma like symptoms (wheezing)**		√	
	Yellowing of the skin and eyes (jaundice)		√ Call your doctor immediately	

This is not a complete list of side effects. For any unexpected effects while taking Accel-Bosentan, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach and sight of children. Store at room temperature between 15°C and 30°C. Do not use after the expiry date stated on the blister.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

· Online at MedEffect;
· By calling 1-866-234-2345 (toll-free);
· By completing a Consumer Side Effect Reporting Form and sending it by:
- Fax to 1-866-678-6789 (toll-free), or
- Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Accel Pharma Inc. at:

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