

AUSTRALIAN PRODUCT INFORMATION

VOLIBRIS (ambrisentan) 5 mg and 10 mg tablets

TERATOGENICITY

VOLIBRIS may cause birth defects and is contraindicated in pregnancy (see Section 4.3 CONTRAINDICATIONS).

1 NAME OF THE MEDICINE

Ambrisentan

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Excipients with known effect:

Lactose monohydrate.

VOLIBRIS 5 mg and 10 mg film-coated tablets contain the excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, purified talc, titanium dioxide, macrogol 3350 (PEG 3350), lecithin USNF and Allura Red AC Aluminum Lake (FD&C Red #40) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Excipients).

3 PHARMACEUTICAL FORM

Film-coated tablets

VOLIBRIS 5 mg tablets are pale pink, square convex tablet engraved 'GS' on one face and 'K2C' on the other.

VOLIBRIS 10 mg tablets are deep pink, oval convex tablet engraved 'GS' on one face and 'KE3' on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VOLIBRIS is indicated for the treatment of:

- idiopathic pulmonary arterial hypertension (PAH),
- pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD),

in patients with WHO functional class II, III or IV symptoms.

VOLIBRIS in combination with Tadalafil is indicated for the treatment of WHO Group 1 pulmonary arterial hypertension in patients with WHO functional class II, III or IV symptoms.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment should only be initiated by a physician experienced in the treatment of PAH. VOLIBRIS is for oral use and can be administered with or without food.

Dose

VOLIBRIS as a single agent

VOLIBRIS should be taken orally at a dose of 5 mg once daily. Additional benefit may be obtained by increasing the dose to 10 mg [see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials].

VOLIBRIS used with tadalafil

When used in combination with tadalafil, the VOLIBRIS starting dose of 5 mg should be titrated to 10 mg once daily, as tolerated (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Limited data suggest that the abrupt discontinuation of VOLIBRIS is not associated with rebound worsening of PAH.

Use with cyclosporin A

When co-administered with cyclosporin A, the dose of ambrisentan should be limited to 5 mg once daily (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

Special populations

Paediatric use

The safety and efficacy of VOLIBRIS have not been established in patients less than 18 years of age, and therefore its use in this age group is not recommended (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.3 PRECLINICAL SAFETY DATA).

Use in the elderly

No dose adjustment is required (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment

No dose adjustment is required in patients with renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES). There is limited experience with VOLIBRIS in individuals with severe renal impairment (creatinine clearance <30 mL/min); initiate treatment cautiously in this subgroup and take particular care if the dose is increased to 10 mg.

Hepatic impairment

VOLIBRIS has not been studied in individuals with severe hepatic impairment or with clinically significant elevated hepatic transaminases. Since the main routes of metabolism of

ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment would be expected to increase exposure (C_{max} and AUC) of ambrisentan. Therefore, VOLIBRIS is not recommended in patients with moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (with or without cirrhosis) or with clinically significant elevated hepatic transaminases (see Sections 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES). Use caution when administering VOLIBRIS in patients with mild pre-existing impaired liver function who may require reduced doses of VOLIBRIS.

Method of administration

It is recommended that the tablet is swallowed whole and should not be split, crushed or chewed.

4.3 CONTRAINDICATIONS

VOLIBRIS is contraindicated in:

- Pregnancy (see Boxed Warning and Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in pregnancy).
- Women of child-bearing potential who are not using reliable contraception (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION, Use in Women of Child Bearing Potential). Women must not become pregnant for at least 3 months after stopping treatment with ambrisentan.
- Patients with severe hepatic impairment (with or without cirrhosis) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Patients with baseline values of hepatic aminotransferases (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT]) greater than 3 times the Upper Limit of Normal (ULN) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).
- Patients with idiopathic pulmonary fibrosis (IPF) with or without secondary pulmonary hypertension.
- Patients who exhibit or may exhibit hypersensitivity to ambrisentan or to any of the excipients.

The list of contraindications does not include those of Tadalafil. Reference should be made to both the VOLIBRIS and Tadalafil Product Information for PAH before prescribing the combination to patients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ambrisentan has not been studied in a sufficient number of patients to establish the benefit/risk balance in patients with WHO functional class I symptoms.

Ambrisentan has only been studied in a limited number of patients with WHO functional Class IV symptoms.

Other therapy that is recommended at the severe stage of the disease (e.g. epoprostenol) should be considered if the clinical condition deteriorates.

Liver function

Hepatic enzyme elevations have been observed with endothelin receptor antagonists (ERAs).

The cumulative incidence of serum aminotransferase abnormalities $>3\times\text{ULN}$ in all phase II and III studies for ambrisentan as a single agent (including respective open label extensions) was 17 of 483 (3.5%) subjects over a mean exposure duration of 79.5 weeks.

Liver function tests were closely monitored in all clinical studies with ambrisentan. For all ambrisentan treated patients (N=483), the 12-week incidence of aminotransferases >3 times ULN was 0.8% and >8 times ULN was 0.2%. For placebo-treated patients, the 12-week incidence of aminotransferases >3 times ULN was 2.3% and >8 times ULN was 0%. The 1-year rate of aminotransferase elevations >3 times ULN with ambrisentan was 2.8% and >6 times ULN was 0.5%. One case of aminotransferase elevations >3 times ULN has been accompanied by bilirubin elevations >2 times ULN.

Hepatic function should be evaluated prior to initiation of ambrisentan. If aminotransferases (ALT or AST) are greater than 3 times ULN, initiation of ambrisentan is contraindicated (see Sections 4.3 CONTRAINDICATIONS and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Monthly monitoring of aminotransferases is warranted for the first 6 months after ambrisentan treatment is initiated. If patients develop clinically significant aminotransferase elevations or if aminotransferase elevations are accompanied by signs or symptoms of hepatic injury (e.g. jaundice), or increases in bilirubin >2 times ULN, ambrisentan therapy should be discontinued.

Patients with clinically significant right heart failure, pre-existing liver disease, previous elevations of aminotransferases due to medications or taking concurrent medications known to elevate aminotransferases may be at increased risk for developing elevated aminotransferases on ambrisentan. Monitoring of aminotransferases should occur as clinically indicated.

If patients develop clinically significant aminotransferase elevations or if aminotransferase elevations are accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan therapy should be discontinued.

Following resolution of hepatic enzyme abnormalities, re-initiation of ambrisentan may be considered in some patients following consultation with a liver specialist. Ambrisentan should not be re-introduced if the patient had clinical symptoms of hepatic injury, jaundice (bilirubin $>2\times\text{ULN}$), or an elevation of ALT $>8\times\text{ULN}$.

Hepatic injury and autoimmune hepatitis are known to occur in PAH patients and autoantibodies are frequently found in IPAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, and hepatic injury have been reported with ambrisentan therapy, although the contribution of ambrisentan to these events is unclear.

Therefore, patients should be observed clinically for signs of hepatic injury and caution

exercised when ambrisentan is used alone or concomitantly with other medicinal products known to be associated with hepatic injury as the additive effects of ambrisentan with these agents are not known. Management of autoimmune hepatitis in PAH patients should be optimised prior to initiation of ambrisentan and during ambrisentan therapy. If patient develop signs or symptoms of hepatitis, or suffer exacerbation of existing hepatitis ambrisentan should be discontinued.

Other ERAs have been associated with elevations of aminotransferase (AST, ALT), hepatotoxicity, and cases of liver failure [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. In patients who develop hepatic impairment after ambrisentan initiation, the cause of liver injury should be fully investigated. Discontinue ambrisentan if elevations of liver aminotransferases are >5x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

Haematological changes

Reductions in haemoglobin concentrations and haematocrit have been associated with ERAs including ambrisentan, and there have been cases where this has resulted in anaemia, sometimes requiring transfusion. In clinical trials, decrease in haemoglobin and haematocrit were observed within the first few weeks of therapy and generally stabilised thereafter. The mean decrease in haemoglobin from baseline to the end of treatment for patients receiving ambrisentan in 12-week placebo-controlled studies was 0.8 g/dL. Mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in haemoglobin concentrations persisted for up to 4 years of treatment with ambrisentan in the long-term open-label extension of the pivotal Phase 3 clinical studies.

Marked decreases in haemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving ambrisentan (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo.

It is recommended that haemoglobin is measured prior to initiation of ambrisentan, again at 1 month and periodically thereafter. Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. If a clinically significant decrease in haemoglobin is observed, and other causes have been excluded discontinuation of treatment should be considered.

The incidence of anaemia was increased when ambrisentan was dosed in combination with tadalafil (15% adverse event frequency), compared to the incidence of anaemia when ambrisentan and tadalafil were given as monotherapy (7% and 11%, respectively). Anaemia led to discontinuation of drug in <1% of ambrisentan patients dosed in combination with tadalafil compared to 1% and 0% for ambrisentan and tadalafil, respectively when given as monotherapy.

Use in renal impairment

Refer to Section 5.2 PHARMACOKINETIC PROPERTIES.

Fluid retention

Peripheral oedema has been observed with ERAs including ambrisentan. Peripheral oedema

may also be a clinical consequence of PAH. Most cases of peripheral oedema in clinical studies with ambrisentan were mild to moderate although it occurred with greater frequency and severity in elderly patients. Peripheral oedema was reported more frequently with 10 mg ambrisentan in short-term clinical studies [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

The incidence of peripheral oedema was increased when ambrisentan was dosed in combination with tadalafil (45% adverse event frequency), compared to the incidence of peripheral oedema when ambrisentan and tadalafil were given as monotherapy (38% and 28%, respectively). The occurrence of peripheral oedema was highest within the first month of treatment initiation.

Post-marketing reports of fluid retention occurring within weeks after starting ambrisentan have been received and, in some cases, have required intervention with a diuretic or hospitalisation for fluid management or decompensated heart failure. If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting ambrisentan.

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

Pulmonary veno-occlusive disease

VOLIBRIS has not been studied in patients with pulmonary hypertension associated with pulmonary veno-occlusive disease (PVOD). Cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin and with endothelin receptor antagonists) when used in patients with PVOD. Consequently, should signs of acute pulmonary oedema occur when VOLIBRIS is initiated, the possibility of PVOD should be considered.

Use in patients with pre-existing hypotension

Particular caution should be exercised when initiating ambrisentan in patients with pre-existing hypotension and blood pressure in such patients should be monitored closely.

Use in the elderly

In the two placebo controlled clinical trials of ambrisentan, 21% of patients were ≥65 years old and 5% were ≥75 years old. The elderly (age ≥65 years) showed less improvement in 6MWD with ambrisentan than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral oedema was more common in the elderly than in younger patients.

Paediatric use

The safety and efficacy of ambrisentan have not been established in patients less than 18 years of age. Its use in patients under 18 years is not recommended. Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

In addition, animal studies indicated a risk of a decrease in brain weight (compared to

controls); the clinical relevance of this finding is unknown but may be considered a higher potential risk for children under 4 years of age. Refer to Section 5.3 PRECLINICAL SAFETY DATA.

Non-clinical information

Inflammation and changes in the nasal cavity epithelium and/or turbinates have been seen with chronic administration of ambrisentan and other ERAs to rodents and, to a lesser extent, dogs.

Effects on laboratory tests

See subsection, Haematological changes above.

Excipients

VOLIBRIS 5 mg and 10 mg film-coated tablets contain the azo colouring agent Allura Red AC Aluminium Lake (FD&C Red #40), which may cause allergic-type reactions.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A4, CYP2C19 and UGTs 1A9S, 2B7S and 1A3S and is a substrate of P-gp and OATP. Given the extensive enterohepatic recycling of ambrisentan there is a potential for interactions with inhibitors of OATP.

Ambrisentan does not inhibit or induce phase I or II drug metabolizing enzymes at clinically relevant concentrations in *in vitro* and *in vivo* non-clinical studies. Moreover, *in vitro* studies showed that ambrisentan does not inhibit NTCP, OATP or BSEP nor induce MRP2, P-gp or BSEP (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

The potential for ambrisentan to induce CYP3A4 activity was explored in healthy volunteers with results suggesting a lack of inductive effect of ambrisentan on the CYP3A4 isoenzyme. This is consistent with the lack of effect of ambrisentan on the pharmacokinetics of sildenafil (a CYP3A4 substrate).

Specific interaction studies have been conducted with cyclosporin A, warfarin, sildenafil and tadalafil, ketoconazole, rifampin, oral contraceptives and digoxin.

Cyclosporin A

Cyclosporin A is an inhibitor of multiple metabolic enzymes and transporters. Use caution when VOLIBRIS is co-administered with cyclosporin A.

Steady-state co-administration of ambrisentan and cyclosporin A (an inhibitor of P-glycoprotein [P-gp] and organic anion transporting polypeptide [OATP]) resulted in a 2-fold increase in ambrisentan exposure in healthy volunteers, therefore the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporin A (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). No clinically relevant effect of ambrisentan on cyclosporin A exposure was observed (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

Warfarin

Ambrisentan had no effects on the steady state pharmacokinetics and anti-coagulant activity of warfarin in a healthy volunteer study (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism). Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in patients, ambrisentan had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT). There was a small non clinically significant reduction in international normalized ratio (INR).

Sildenafil & tadalafil

Co-administration of ambrisentan with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP 3A4) in healthy volunteers did not significantly affect the pharmacokinetics of ambrisentan or the phosphodiesterase inhibitor (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

Ketoconazole

The effects of repeat dosing of a strong inhibitor of CYP3A4, ketoconazole (400 mg once daily) on the pharmacokinetics of a single dose of 10 mg ambrisentan were investigated in 16 healthy volunteers. Exposures of ambrisentan as measured by AUC(0-inf) and C_{max} were increased by 35% and 20%, respectively. The clinical significance of these changes is unknown. Patients taking both 10 mg of ambrisentan and ketoconazole should be closely monitored for any signs of adverse effects.

Rifampin

Co-administration of rifampin (an inhibitor of OATP, a strong inducer of CYP3A and 2C19, and inducer of P-gp and uridine-diphospho-glucuronosyltransferases [UGTs]) was associated with a transient (approximately 2-fold) increase in ambrisentan exposure following initial doses in healthy volunteers. However, by day 7, steady state administration of rifampin had no clinically relevant effect on ambrisentan exposure. No dose adjustment of ambrisentan is required when co-administered with rifampin (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism).

Omeprazole

In clinical studies of patients with PAH, co-administration of ambrisentan and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan.

Oral contraceptives

In a clinical study in healthy subjects, steady state dosing with ambrisentan 10 mg did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol and norethindrone components of a combined oral contraceptive (see Section 5.2 PHARMACOKINETIC PROPERTIES, Metabolism). Based on this pharmacokinetic study, ambrisentan would not be expected to significantly affect exposure to estrogen- or progestogen- based contraceptives.

Digoxin

Steady state administration of ambrisentan in healthy volunteers had no clinically relevant effects on the single-dose pharmacokinetics of digoxin, a substrate for P-gp.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Limited data from clinical studies have not demonstrated any clinically significant change in testosterone or semen quality. However, the available human data is inadequate to characterise the effects of ambrisentan on either male or female fertility. It is not known whether ambrisentan is present in semen. It is therefore not known whether there is the potential for fetal harm (teratogenicity) resulting from transfer of ambrisentan via semen.

Testicular tubular atrophy, which was occasionally associated with aspermia, was observed in oral repeat dose toxicity studies across all species tested and in fertility studies with male rats at exposures similar to that anticipated clinically. The testicular changes were not fully recoverable during off-dose periods evaluated. No consistent effects on sperm count, mating performance or fertility were observed. Based on animal data testicular effects are potential adverse effects of chronic ambrisentan administration in humans.

Use in pregnancy

(Category X)

Teratogenicity is a class effect of endothelin receptor antagonists. Use of ambrisentan is contraindicated in women who are, or could become pregnant.

Women who become pregnant while receiving ambrisentan should be advised of the risk of foetal harm and alternative therapy should be initiated if the pregnancy is continued (see Section 4.3 CONTRAINDICATIONS).

Ambrisentan was teratogenic in rats and rabbits. Abnormalities of the lower jaw, tongue, and/or palate were observed at all doses tested. Additionally, the rat study showed an increased incidence of interventricular septal defects, trunk vessel defects, thyroid and thymus abnormalities, ossification of the basisphenoid bone, and the occurrence of the umbilical artery located on the left side of the urinary bladder instead of the right side.

Use in Women of Child Bearing Potential

In females of child-bearing potential, pregnancy should be excluded before the start of treatment with ambrisentan and prevented thereafter by the use of two reliable methods of contraception. Monthly pregnancy tests during treatment with ambrisentan are recommended.

Women must not become pregnant for at least 3 months after stopping treatment with ambrisentan. On the basis of the known half-life of ambrisentan, it would be expected that the drug would be effectively washed out one week after stopping therapy. As a precaution however, given the teratogenic nature of the drug a three month wash out is recommended.

Use in lactation

It is not known whether ambrisentan is excreted in human milk. Breastfeeding while receiving ambrisentan is not recommended. Administration of ambrisentan to female rats from late-pregnancy through to lactation caused reduced survival of newborn pups, reduced testicle

size of male progeny, and impaired reproductive capacity of offspring, at exposure 6-fold the AUC at the maximum recommended human dose.

Juvenile rodent studies may suggest potential effects on the developing human oropharynx with postnatal exposure to ambrisentan. Refer to Section 5.3 PRECLINICAL SAFETY DATA.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Pivotal clinical studies

In the pivotal clinical trials (ARIES-1 and ARIES-2) a total of 197 patients received VOLIBRIS at doses of 5 and 10 mg once daily and 132 patients received placebo. The adverse events that occurred in >3% of the patients receiving ambrisentan are shown in Table 1.

Table 1: Incidence of Most Frequently Reported Adverse Events (>3% in either placebo or combined ambrisentan groups)

Treatment group	Placebo	5 mg ambrisentan	10 mg ambrisentan	Combined ambrisentan
Preferred term	(N = 132)	(N = 130)	(N = 67)	(N = 197)
Subjects with at least 1 AE	108 (81.8)	102 (78.5)	53 (79.1)	155 (78.7)
Peripheral oedema	14 (10.6)	24 (18.5)	19 (28.4)	43 (21.8)
Headache	18 (13.6)	20 (15.4)	13 (19.4)	33 (16.8)
Dizziness	13 (9.8)	9 (6.9)	6 (9.0)	15 (7.6)
Nasal congestion	2 (1.5)	7 (5.4)	7 (10.4)	14 (7.1)
Cough	8 (6.1)	7 (5.4)	5 (7.5)	12 (6.1)
Dyspnoea exacerbated	8 (6.1)	10 (7.7)	1 (1.5)	11 (5.6)
Upper respiratory tract infection	8 (6.1)	6 (4.6)	5 (7.5)	11 (5.6)
Palpitations	3 (2.3)	5 (3.8)	3 (4.5)	8 (4.1)
Dyspnoea	4 (3.0)	7 (5.4)	3 (4.5)	10 (5.1)
Constipation	2 (1.5)	4 (3.1)	4 (6.0)	8 (4.1)
Fatigue	6 (4.5)	7 (5.4)	3 (4.5)	10 (5.1)
Nausea	12 (9.1)	5 (3.8)	3 (4.5)	8 (4.1)
Bronchitis	5 (3.8)	6 (4.6)	1 (1.5)	7 (3.6)
Flushing	1 (0.8)	5 (3.8)	1 (1.5)	6 (3.0)
Nasopharyngitis	1 (0.8)	7 (5.4)	2 (3.0)	9 (4.6)
Right ventricular failure	16 (12.1)	6 (4.6)	1 (1.5)	7 (3.6)
Abdominal pain	1 (0.8)	4 (3.1)	2 (3.0)	6 (3.0)
Chest pain	3 (2.3)	6 (4.6)	1 (1.5)	7 (3.6)
Insomnia	4 (3.0)	3 (2.3)	1 (1.5)	4 (2.0)
Epistaxis	5 (3.8)	2 (1.5)	4 (6.0)	6 (3.0)
Sinusitis	0 (0.0)	4 (3.1)	3 (4.5)	7 (3.6)
Arthralgia	5 (3.8)	1 (0.8)	2 (3.0)	3 (1.5)
Urinary tract infection	8 (6.1)	2 (1.5)	1 (1.5)	3 (1.5)
ALT and/or AST increased	5 (3.8)	2 (1.5)	2 (3.0)	4 (2.0)
Pulmonary hypertension	7 (5.3)	1 (0.8)	1 (1.5)	2 (1.0)

Ambrisentan as monotherapy

The safety of ambrisentan has been evaluated as monotherapy in more than 480 patients with PAH. The exposure to ambrisentan in these studies ranged from 1 day to 4 years (N=418) for at least 6 months and N=343 for at least 1 year. The incidence of peripheral oedema was greater in the elderly (29%, 16/56) compared to placebo (4%, 1/28). However the results of such subgroup analyses must be interpreted cautiously. The incidence of treatment discontinuations due to adverse events other than those related to pulmonary hypertension during clinical trials in patients with PAH was similar for ambrisentan (2%; 5/261 patients) compared with placebo (2%; 3/132).

Long-term clinical studies with ambrisentan

The long-term safety (>3 months) of ambrisentan was evaluated in more than 500 patients with PAH. Adverse drug reactions from non-placebo controlled clinical trial data are listed below in the Tabulated list of adverse reactions.

Clinical study with ambrisentan used in combination with tadalafil

The safety of ambrisentan used in combination with tadalafil was evaluated in 302 patients with PAH in a double-blind, active-controlled clinical trial (>3 months; median exposure 534 days). The adverse reactions observed were generally consistent with the safety profile of ambrisentan used alone.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) from clinical trial and routine pharmacovigilance data are listed below by system organ class and frequency. Frequencies are defined as: Very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1000) and very rare (less than 1/10,000) and not known (cannot be estimated from available data). For dose-related adverse reactions the frequency category reflects the higher dose of ambrisentan. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2:

	Ambrisentan ARIES-C ^a and Post- Marketing	Ambrisentan AMBITION and ARIES-E	Combination with Tadalafil AMBITION
<i>Blood and lymphatic system disorders</i>			
Anaemia (decreased haemoglobin, decreased haematocrit)	Common ¹	Very common	Very common

	Ambrisentan ARIES-C ^a and Post- Marketing	Ambrisentan AMBITION and ARIES-E	Combination with Tadalafil AMBITION
Immune system disorders			
Hypersensitivity reactions (e.g. angioedema, rash, pruritus)	Uncommon	Common	Common
Nervous system disorders			
Headache (including sinus headache, migraine)	Very common ²	Very common	Very common
Dizziness	Common ³	Very common	Very common
Eye disorders			
Blurred vision, visual impairment	Not known ⁴	Common	Common
Ear and labyrinth disorders			
Tinnitus	NR	NR	Common
Sudden hearing loss	NR	NR	Uncommon
Cardiac disorders			
Cardiac failure	Common ⁵	Common	Common
Palpitation	Common	Very common	Very common
Vascular disorders			
Hypotension	Common ³	Common	Common
Flushing	Common	Common	Very common
Syncope	Uncommon ³	Common	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Common ³	Common	Common
Dyspnoea	Common ^{3,6}	Very common	Very common
Upper respiratory (e.g. nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis	Common ⁷		
Nasopharyngitis		Very common	Very common
Sinusitis, rhinitis		Common	Common
Nasal congestion		Very common	Very common

	Ambrisentan ARIES-C ^a and Post- Marketing	Ambrisentan AMBITION and ARIES-E	Combination with Tadalafil AMBITION
Gastrointestinal disorders			
Nausea, vomiting, diarrhoea	Common ³		
Nausea		Very common	Very common
Vomiting		Common	Very common
Diarrhoea		Very common	Very common
Abdominal pain	Common	Common	Common
Constipation	Common	Common	Common
Hepatobiliary disorders			
Hepatic injury (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon ^{3, 8}	NR	NR
Autoimmune hepatitis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon ^{3, 8}	NR	NR
Hepatic transaminases increased	Common ³	NR	NR
Skin and subcutaneous tissue disorders			
Rash	NR	Common ⁹	Common ⁹
General disorders and administration site conditions			
Peripheral oedema, fluid retention	Very common	Very common	Very common
Chest pain/discomfort	Common	Common	Very common
Asthenia	Common ³	Common	Common
Fatigue	Common ³	Very common	Very common

NR – not reported

¹ See section "Laboratory Findings"

² The frequency of headache appeared higher with 10 mg ambrisentan.

³ Data derived from routine pharmacovigilance surveillance and frequencies based on placebo-controlled clinical trial experience.

⁴ Data derived from routine pharmacovigilance surveillance

⁵ Most of the reported cases of cardiac failure were associated with fluid retention. Data derived from routine pharmacovigilance surveillance, frequencies based on statistical modelling of placebo-controlled clinical trial data.

⁶ Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting ambrisentan therapy.

⁷ The incidence of nasal congestion was dose related during ambrisentan therapy.

⁸ Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury have been reported during ambrisentan therapy.

⁹ Rash includes rash erythematous, rash generalised, rash papular and rash pruritic

^a ARIES-C = ARIES-1 and ARIES-2 studies combined

Laboratory findings

Decreased haemoglobin (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In the post-marketing period, cases of anaemia requiring blood transfusion have been reported. The frequency of decreased haemoglobin (anaemia) was higher with 10 mg VOLIBRIS. Across the 12 week placebo controlled Phase III clinical studies, mean haemoglobin concentrations decreased for patients in the VOLIBRIS groups and were detected as early as week 4 (decrease by 0.83 g/dl); mean changes from baseline appeared to stabilise over the subsequent 8 weeks. A total of 17 patients (6.5%) in the VOLIBRIS treatment groups had decreases in haemoglobin of $\geq 15\%$ from baseline and which fell below the lower limit of normal.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems>.

4.9 OVERDOSE

In healthy volunteers, single doses of 50 and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Due to its mechanism of action, an overdose of VOLIBRIS also could potentially result in hypotension.

In case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Ambrisentan is an orally active, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. Selective inhibition of the ET_A receptor inhibits phospholipase C-mediated vasoconstriction and protein kinase C-mediated cell proliferation, while preserving nitric oxide and prostacyclin production, cyclic GMP- and cyclic AMP-mediated vasodilation, and endothelin-1 (ET-1) clearance that is associated with the endothelin type B (ET_B) receptor.

Clinical trials

Treatment of Pulmonary Arterial Hypertension

Two randomised, double-blind, multi-centre, placebo controlled, Phase 3 pivotal studies were conducted (ARIES-1 and 2). ARIES-1 included 201 patients and compared VOLIBRIS 5 mg and 10 mg with placebo. ARIES-2 included 192 patients and compared VOLIBRIS 2.5 mg and 5 mg with placebo. In both studies, VOLIBRIS was added to patients' supportive/background medication, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen and vasodilators (calcium channel blockers, ACE inhibitors). Patients enrolled included those with IPAH (64%) and PAH associated with connective tissue disease (32%). The majority of patients had WHO functional Class II (38.4%), Class III (55.0%) symptoms. Patients with Class IV symptoms were also included (5%). Patients with pre-existent hepatic disease (cirrhosis or clinically significantly elevated aminotransferases) and patients using other targeted therapy for PAH (e.g. prostanooids) were excluded. Haemodynamic parameters were not assessed in these studies. The mean age of patients across both studies was 51 years, 79% were female and 77% were Caucasian.

Extension studies

Patients enrolled into ARIES-1 and 2 were eligible to enter a long term open label extension study ARIES-E (n=383). Patients who had been randomized to placebo in either ARIES-1 or ARIES-2 were randomized in a blinded 1:1 fashion to the VOLIBRIS dosages of the originating phase III study. The mean exposure to VOLIBRIS in ARIES-E was approximately 145 ± 80 weeks and the maximum exposure was approximately 295 weeks.

Exercise capacity

The primary endpoint for ARIES-1 and ARIES-2 was improvement in exercise capacity as assessed by change from baseline in 6 minute walk distance (6MWD) at 12 weeks.

In both ARIES-1 and ARIES-2 treatment with VOLIBRIS resulted in significant increases in the placebo-adjusted mean change in 6MWD at Week 12 (see Table 3).

Table 3 Mean change and placebo adjusted change in baseline 6MWD in ARIES-1 and ARIES-2 at Week 12.

	ARIES-1			ARIES-2		
	Placebo (N=67)	5 mg (N=67)	10 mg (N=67)	Placebo (N=65)	2.5 mg (N=64)	5 mg (N=63)
Baseline, mean (SD)	341.9 ± 73.5	339.6 ± 76.7	341.5 ± 78.3	342.7 ± 85.9	347.3 ± 83.8	355 ± 84
Mean change from Baseline (SD), m	-7.8 ± 78.9	22.8 ± 82.9	43.6 ± 65.9	-10.1 ± 93.8	22.2 ± 82.6	49.4 ± 75.4
Placebo-adjusted mean change from baseline, m (95% CI)		30.6 (2.9, 58.3)	51.4 (26.6, 76.2)		32.3 (1.5, 63.1)	59.4 (29.6, 89.3)
p-value†		0.008	<0.001		0.022	<0.001

Mean ± standard deviation † p-values are Wilcoxon rank sum test comparisons of VOLIBRIS to placebo at Week 12 stratified by idiopathic PAH and non-idiopathic PAH patients

Results from the extension studies also indicates that the benefits were maintained at 48 weeks. The mean change in 6MWD from baseline at week 48 was +35.2m (95% CI: 13.0 to 57.5; n=68) for the 5 mg dose, and +30.2m (95% CI: 10.8 to 49.6; n=32) for the 10 mg dose.

Subgroup analysis

Combined analysis of subgroups in pivotal studies (ARIES-1 & ARIES-2) are provided in Tables 4 and 5. However such results should be interpreted with caution.

Table 4 Change in primary and secondary endpoints in ambrisentan phase III studies (ARIES-1 & ARIES-2) by WHO functional class at baseline and at 12 weeks

		Placebo	Combined Ambrisentan		
			WHO class II	WHO class III	WHO class IV
N		132	104	138	15
Baseline 6MWD, mean (SD)		342 m (80)	375 m (66)	332 m (81)	244 m (70)
Change in 6MWD at 12 weeks, mean (95% CI)		-9.0 m (-23.8, 5.9)	42.92 m (21.93, 74.63)	26.90 m (18.84, 65.41)	44.53 m (-27.79, 116.85)
BDI at baseline, mean (SD)		3.83 (2.15)	2.98 (2.047)	4.38 (2.120)	5.23 (2.757)
Change in BDI at 12 weeks, mean (95% CI)		0.40 (-0.02, 0.82)	-0.52 (-0.82, -0.21)	-0.39 (-0.75, -0.02)	-0.67 (-2.41, 1.07)
Change in WHO class at 12 weeks, n (%)	Improved	27 (20.5)	11 (10.6)	37 (26.8)	9 (60.0)
	No change	82 (62.1)	91 (87.5)	96 (69.6)	6 (40.0)
	Deteriorated	23 (17.4)	2 (1.9)	5 (3.6)	0

Table 5: Placebo-adjusted change from baseline in 6MWD at 12 weeks in IPAH and PAH-CTD subgroups

		5 mg ambrisentan	10 mg ambrisentan
IPAH	N	83	41
	Placebo-adjusted mean change from baseline, m (95% CI)	59.1 m (32.0, 86.2)	64.0 m (32.9, 95.0)
PAH-CTD	N	40	22
	Placebo-adjusted mean change from baseline, m (95% CI)	23.49 m (-7.96, 54.94)	28.53 m (-9.71, 66.77)

Time to clinical worsening

Analysis of ARIES-1 and ARIES-2, demonstrated that the addition of VOLIBRIS significantly delayed clinical worsening (defined as the time from randomization to the first occurrence of death, lung transplantation, hospitalisation for PAH, atrial septostomy, study discontinuation due to the addition of other PAH therapeutic agents, or study discontinuation due to 2 or more early escape criteria).

Table 6: Delay in clinical worsening observed following VOLIBRIS treatment in a combined analysis of ARIES-1 and ARIES-2

	Placebo	2.5 mg ambrisentan	5 mg ambrisentan	10 mg ambrisentan
Events, n (%)	(N = 132)	(N = 64)	(N = 130)	(N = 67)
Death	5 (3.8)	2 (3.1)	1 (0.8)	1 (1.5)
Lung transplantation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalisation for PAH	11 (8.3)	3 (4.7)	4 (3.1)	2 (3.0)
Atrial septostomy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study withdrawal due to addition of PAH treatment	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.5)
Escape criteria ¹	10 (7.6)	2 (3.1)	1 (0.8)	2 (3.0)
Total subjects with 1 or more events	20 (15.2)	3 (4.7)	6 (4.6)	3 (4.5)
p-value ambrisentan vs. placebo ²	-	0.034	0.006	0.033

1. Subjects who met 2 or more of the following: decrease from baseline of at least 20% in the 6MWD; an increase of 1 or more WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; refractory systolic hypotension (systolic blood pressure less than 85 mmHg).
2. The Fisher exact test comparison to placebo

Borg Dyspnoea Index and SF-36®

The placebo-adjusted change from baseline in BDI was -0.85 (95% CI: -1.30 to -0.39, $p < 0.001$) for the combined ambrisentan group. A pre-specified analysis combining results observed during ARIES-1 and ARIES-2 demonstrated statistically significant improvements ($p = 0.003$) in the SF-36® Health Survey physical functional scale.

Long term survival

The long-term follow-up of the patients who were treated with VOLIBRIS in the phase 3 placebo controlled studies and their open label extension (N=383), shows that Kaplan-Meier estimates of survival at 1, 2, and 3 years were 93%, 85%, and 79%, respectively. Of the patients who remained on VOLIBRIS for up to 3 years, the majority received no other treatment for PAH.

These uncontrolled observations do not allow comparison with a group not given VOLIBRIS and cannot be used to determine the long-term effect of VOLIBRIS on mortality.

Assessment of liver function

In an open label study (AMB-222), VOLIBRIS was studied in 36 patients to evaluate the incidence of increased serum aminotransferase concentrations in patients who had previously discontinued other ERA therapy due to aminotransferase abnormalities. During a mean of 53 weeks of treatment with VOLIBRIS, none of the patients enrolled had a confirmed serum ALT $> 3 \times \text{ULN}$ that required permanent discontinuation of treatment. Fifty percent of patients had increased from 5 mg to 10 mg VOLIBRIS during this time. In ARIES-

1 and ARIES-2, a total of 4 (0.8%) of 262 patients receiving VOLIBRIS compared with three cases (out of 132) in patients receiving placebo (2.3%) had aminotransferase abnormalities >3x ULN over a period of 12 weeks. The cumulative incidence of serum aminotransferase abnormalities >3xULN in all uncontrolled Phase II and placebo controlled Phase III studies (including respective open label extensions) was 3.5% for subjects receiving VOLIBRIS over a mean exposure duration of 79.5 weeks. This is an event rate of 2.3 events per 100 patient years of exposure for VOLIBRIS.

Haemodynamic parameters

In a Phase II study (AMB-220) improvements in haemodynamic parameters were observed in patients with PAH after 12 weeks (n=29) of treatment with VOLIBRIS. Mean cardiac index significantly increased at 12 weeks compared to baseline (+0.3 L/min/m²; 95% CI: 0.15, 0.51 L/min/m²; p<0.001) and significant decreases in mean pulmonary artery pressure (-5.2 mmHg; 95% CI: -7.6, -2.9 mmHg; p<0.001), and mean pulmonary vascular resistance (-224.0 dynes/sec/cm⁵; 95% CI -304.8, -148.0; p<0.001) were observed.

In patients with PAH, reductions in B-type natriuretic peptide (BNP) have been demonstrated to parallel improvements observed in 6MWD and haemodynamics. In ARIES 1 and ARIES-2 plasma concentrations of BNP decreased in patients who received ambrisentan for 12 weeks by up to 45% (95% CI: -57%, -29%; p<0.001; 10 mg group).

Ambrisentan in combination with tadalafil for the treatment of PAH

The effect of first-line combination therapy with ambrisentan and tadalafil was demonstrated in a multicentre, double-blind, active-controlled study (AMBITION) that compared the combination of ambrisentan and tadalafil to ambrisentan or tadalafil monotherapy in patients with WHO functional class II–III PAH. The AMBITION study enrolled 610 patients; 605 patients received at least one dose of study drug and 500 met the criteria for the primary efficacy analysis. Patients were randomized 2:1:1 to once daily ambrisentan 10 mg + tadalafil 40 mg, ambrisentan 10 mg, or tadalafil 40 mg. Ambrisentan was initiated at 5 mg for 8 weeks and tadalafil at 20 mg for 4 weeks, then each was up-titrated if tolerated.

The primary study endpoint was time to first clinical failure event as adjudicated by an independent committee. In addition, change in N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), percentage of patients with satisfactory clinical response, and change from baseline 6MWD were assessed at Week 24. Patients had idiopathic PAH (53%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, HIV infection, or drugs or toxins (APAH, 44%). Median time from diagnosis to first study drug administration was 22 days. Approximately 31% and 69% of patients were in WHO functional class II and III, respectively. The mean patient age was 54.4 years (32% were ≥65 years old). Most patients were white (89%) and female (78%); 46% were North American.

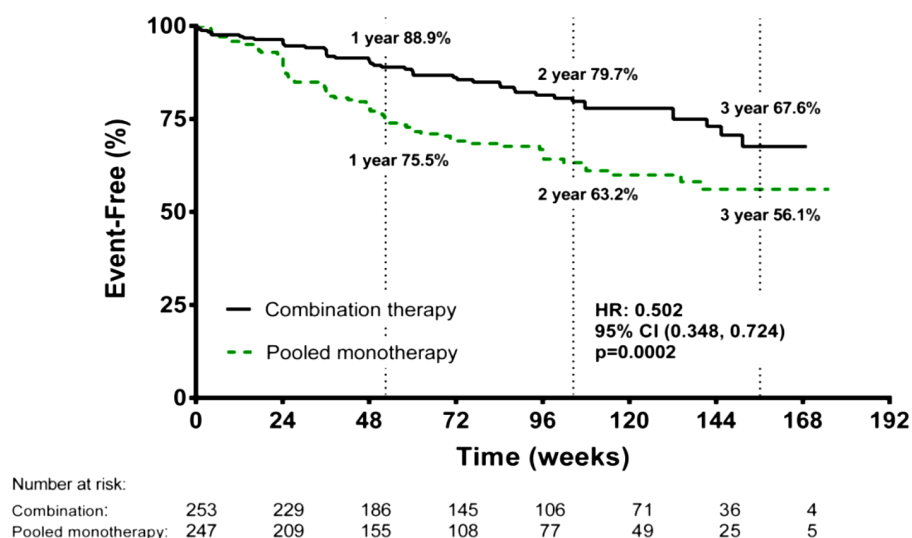
Time to clinical failure

Time to clinical failure of PAH was a composite endpoint defined as time to the first occurrence of death (all-cause), hospitalisation for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Hospitalisation for worsening PAH was defined as any hospitalisation for worsening PAH, lung or heart/lung transplant, atrial septostomy, or initiation of parenteral prostanoid therapy. Disease progression was defined as >15% decrease from baseline in 6MWD combined with WHO functional class III or IV symptoms (at 2 consecutive postbaseline visits separated by ≥14 days). Unsatisfactory long term clinical response was defined as any reduction in 6MWD below baseline combined with an assessment of functional class III status measured at visits 6 months apart.

Patients treated with ambrisentan + tadalafil experienced a significant reduction in risk of clinical failure versus patients treated with ambrisentan or tadalafil pooled monotherapy (p=0.0002), ambrisentan monotherapy (p=0.0004), or tadalafil monotherapy (p=0.0045). The

reduction in risk of a clinical failure event was 50% (HR=0.50, 95% CI: 0.348, 0.724) on combination therapy versus pooled monotherapy. The Kaplan-Meier plots of time to clinical failure for combination therapy versus pooled monotherapy are shown in Figure 1; the summary of primary endpoint events is shown in Table 7.

Figure 1: Time to Clinical Failure, Ambrisentan + Tadalafil Combination Therapy versus Pooled Monotherapy in AMBITION



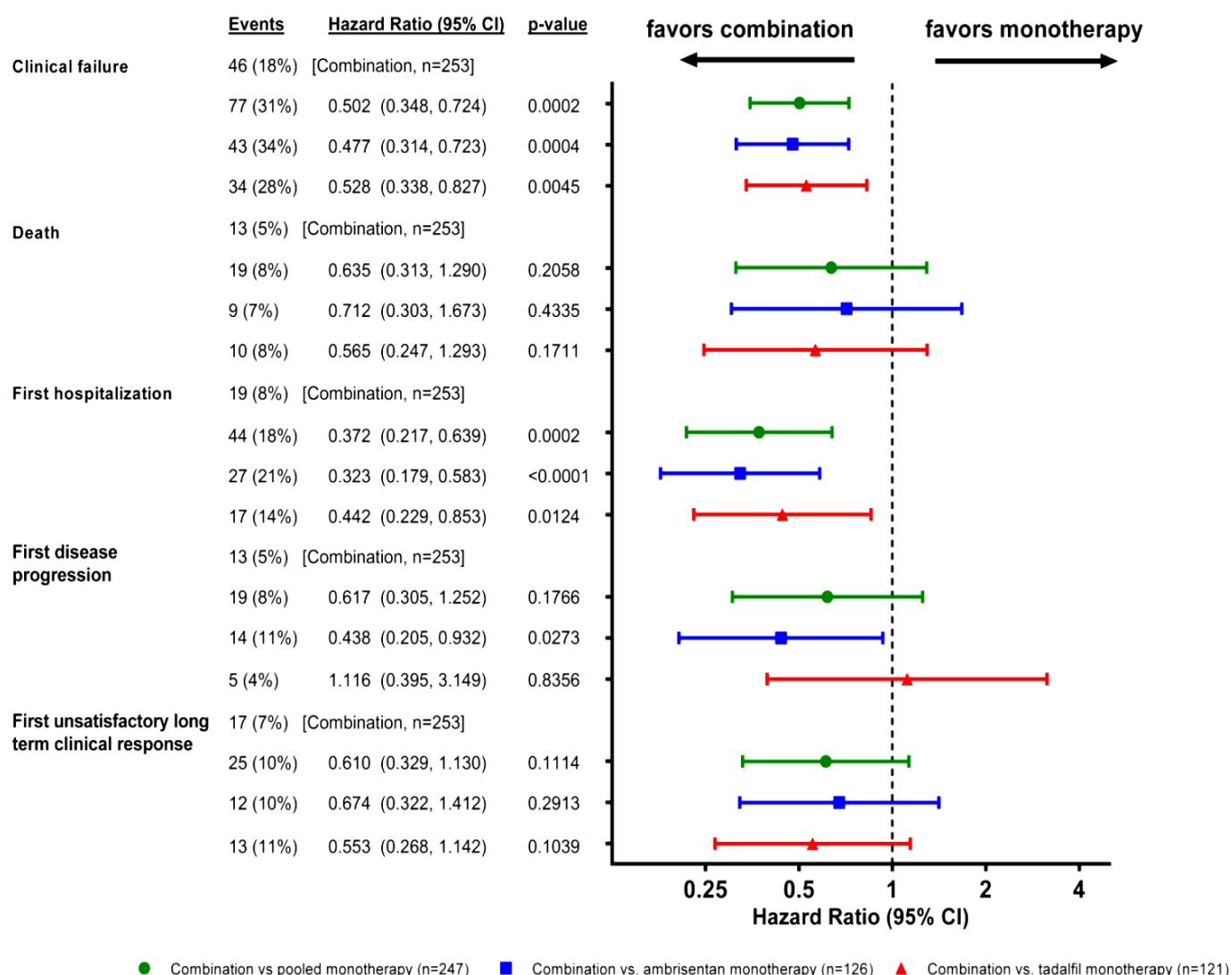
Time from randomization to first clinical failure with Kaplan-Meier estimates of the proportions event-free; p-values shown are the log-rank comparisons of ambrisentan + tadalafil combination therapy to pooled monotherapy stratified by the etiology of PAH and WHO functional class.

Table 7: Summary of Primary Endpoint Events (Adjudicated), in AMBITION

	Ambrisentan + Tadalafil (N=253) n (%)	Pooled Monotherapy (N=247) n (%)	Ambrisentan Monotherapy (N=126) n (%)	Tadalafil Monotherapy (N=121) n (%)
Component as First Clinical Failure Event				
Death (All-Cause)	9 (4%)	8 (3%)	2 (2%)	6 (5%)
Hospitalisation for Worsening PAH	10 (4%)	30 (12%)	18 (14%)	12 (10%)
Disease Progression	10 (4%)	16 (6%)	12 (10%)	4 (3%)
Unsatisfactory Long-term Clinical Response	17 (7%)	23 (9%)	11 (9%)	12 (10%)

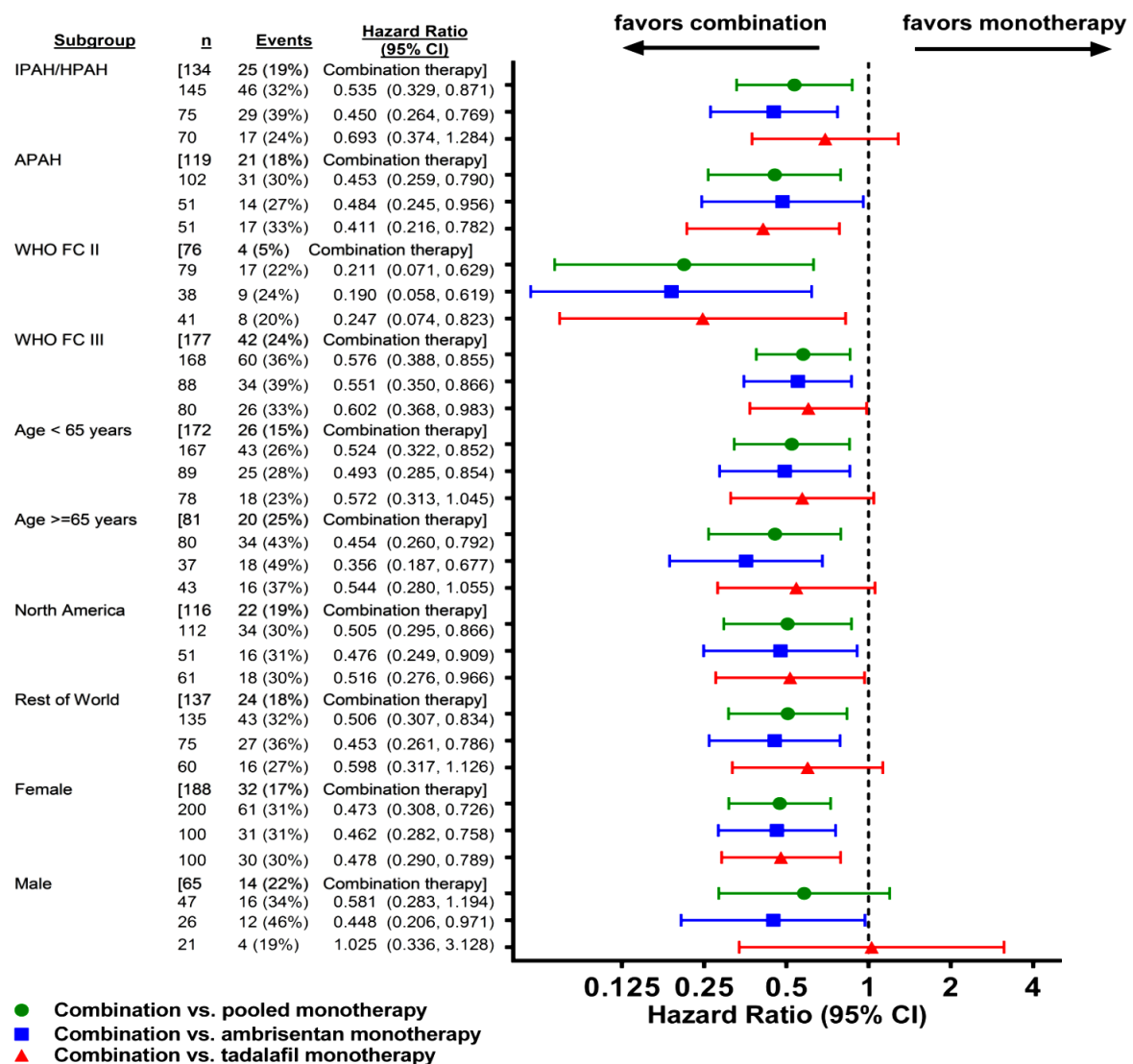
The results for analyses of time to adjudicated clinical failure and to the first of each component of clinical failure are shown in Figure 2.

Figure 2: Analysis of Adjudicated Events in the AMBITION Study



Efficacy of first-line treatment with ambrisentan + tadalafil on time to clinical failure was seen across subgroups (Figure 3).

Figure 3: Subgroup Analysis of the AMBITION Study



Clinical response

Satisfactory clinical response at Week 24 was a composite secondary endpoint defined as $\geq 10\%$ improvement in 6MWD compared to baseline, improvement to or maintenance of WHO class I or II symptoms, and no events of clinical worsening prior to or at the Week 24 visit. The percentage of patients achieving satisfactory clinical response at Week 24 in the combination therapy group (39%) was greater than in the pooled monotherapy group (29%, odds ratio 1.563, 95% CI: 1.054, 2.319), and greater than in the tadalafil monotherapy group (27%, odds ratio 1.723, 95% CI: 1.047, 2.833). No difference was observed between combination therapy and ambrisentan monotherapy in satisfactory clinical response.

Exercise ability

Results of the 6MWD at 24 weeks for the AMBITION study are shown in Table 8.

Wilcoxon Rank Sum Test (with LOCF/worst rank imputation) showed greater median change from baseline at Week 24 in 6MWD in the combination therapy group (48.98 meters, 95% CI: 39.00, 57.50) compared with the pooled monotherapy group (23.80 meters, 95% CI: 19.00, 33.50) (median difference=22.75 meters, 95% CI: 12.00, 33.50), between the combination therapy group compared with the ambrisentan monotherapy group (27.00 meters, 95% CI:

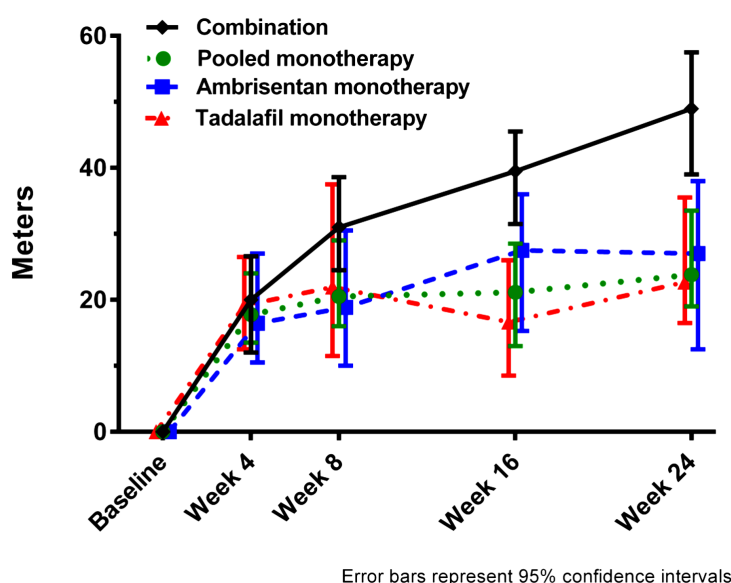
12.50, 38.00) (median difference=24.75 meters, 95% CI: 11.00, 38.50) and between the combination therapy group compared with the tadalafil monotherapy group (22.70 meters, 95% CI: 16.50, 35.50) (median difference=20.85 meters, 95% CI: 8.00, 33.70).

Table 8: Changes from Baseline in 6-Minute Walk Distance at Week 24 (meters)^a in AMBITION

	Ambrisentan + Tadalafil (N=253)	Pooled Monotherapy (N=247)	Ambrisentan Monotherapy (N=126)	Tadalafil Monotherapy (N=121)
Baseline (median)	357.0	365.5	368.5	363.3
Change from Baseline (median)	48.98	23.80	27.00	22.70
Median Difference from ambrisentan + tadalafil (95% CI)		22.75 (12.00, 33.50)	24.75 (11.00, 38.50)	20.85 (8.00, 33.70)

^a Missing values at Week 24 were imputed using Worst Rank scores for patients with an adjudicated clinical failure event of death or hospitalisation, and Last Observed Carried Forward otherwise.

Figure 4: Median Change in 6-Minute Walk Distance (meters), in AMBITION



In patients with PAH who received first-line combination therapy with ambrisentan and tadalafil, a greater decrease from baseline in NT-pro-BNP relative to pooled monotherapy was observed (geometric least-squares mean percent decreases of 67% versus 50%, respectively). Similar results were observed for the comparisons of combination therapy versus ambrisentan monotherapy group (56% decrease) and tadalafil monotherapy group (44% decrease). The decrease in NT-pro-BNP was observed early (Week 4) and was sustained through Week 24.

All treatment groups had clinical improvements to WHO functional class, Borg Dyspnoea Index and Quality of Life measures however; there were no statistically significant

differences between the treatment groups.

Dose titration

In the AMBITION study, patients received 5 mg ambrisentan daily for the first 8 weeks before up titrating to 10 mg, dependent on tolerability. When used in combination with tadalafil, patients were initiated with 5 mg ambrisentan and 20 mg tadalafil. Dependent on tolerability the dose of tadalafil was increased to 40 mg after 4 weeks and the dose of ambrisentan was increased to 10 mg after 8 weeks. More than 90% of patients achieved this. Doses could also be decreased depending on tolerability.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The absolute bioavailability of ambrisentan is not known. Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (C_{max}) of ambrisentan typically occur around 1.5 hours post dose under both fasted and fed conditions. C_{max} and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range. Steady-state is generally achieved following 4 days of repeat dosing.

A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 12% (90% CI: 0.78 - 1.00) while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

Distribution

Ambrisentan is highly plasma protein bound. The *in vitro* plasma protein binding of ambrisentan was, on average, 98.8% and independent of concentration over the range of 0.2 – 20 microgram/mL. Ambrisentan is primarily bound to albumin (96.5%) and to a lesser extent to alpha1-acid glycoprotein.

The distribution of ambrisentan into red blood cells is low, with a mean blood:plasma ratio of 0.57 and 0.61 in males and females, respectively.

Metabolism

Ambrisentan is excreted largely unchanged (45.6% of the dose). Ambrisentan is glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S, and UGT1A3S) to form ambrisentan glucuronide (13%). Ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan (21%) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5%). The binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore at concentrations observed in the plasma (approximately 2% relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro data have shown that at therapeutic concentrations, ambrisentan does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4. Additional *in vitro* studies showed that ambrisentan does not inhibit sodium-taurocholate co-transporter (NTCP), organic anion export pump (OATP) or bile salt export pump (BSEP). Furthermore, ambrisentan does not induce multi-drug resistance protein isoform-2 (MRP2), P-glycoprotein (P-gp), or BSEP.

The effects of repeat dosing of cyclosporin A (100 – 150 mg twice daily) on the steady-state pharmacokinetics of ambrisentan (5 mg once daily), and the effects of repeat dosing of

ambrisentan (5 mg once daily) on the steady-state pharmacokinetics of cyclosporin A (100 – 150 mg twice daily) were studied in healthy volunteers. The C_{max} and $AUC_{(0-\tau)}$ of ambrisentan increased (48% and 121%, respectively) in the presence of multiple doses of cyclosporin A. Based on these changes, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporin A (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). However, multiple doses of ambrisentan had no clinically relevant effect on cyclosporin A exposure, and no dose adjustment of cyclosporin A is warranted.

The effects of acute and repeat dosing of rifampin (600 mg once daily) on the steady-state pharmacokinetics of ambrisentan (10 mg once daily) were studied in healthy volunteers. Following initial doses of rifampin, a transient increase in ambrisentan $AUC_{(0-\tau)}$ (87% and 79% after first and second doses of rifampin, respectively) was observed. However, there was no clinically relevant effect on ambrisentan exposure by day 7, following administration of multiple doses of rifampin. No dose adjustment of ambrisentan is warranted upon concomitant administration with rifampin.

The effects of steady-state ambrisentan (10 mg once daily) on the pharmacokinetics and pharmacodynamics of a single dose warfarin (25 mg), as measured by Prothrombin Time (PT) and International Normalized Ratio (INR), were investigated in 20 healthy subjects. Ambrisentan did not have any clinically relevant effects on the pharmacokinetics or pharmacodynamics of warfarin. Similarly, co-administration with warfarin does not affect the pharmacokinetics of ambrisentan (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The effect of 7-day dosing of sildenafil (20 mg three times daily) on the pharmacokinetics of a single dose of ambrisentan, and the effects of 7-day dosing of ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of sildenafil were investigated in 19 healthy adults. With the exception of a 13% increase (90% CI: 99.6% - 129.1%) in sildenafil C_{max} following co-administration with ambrisentan, there were no other changes in the pharmacokinetic parameters of sildenafil, N-desmethyl-sildenafil and ambrisentan. This slight increase in sildenafil C_{max} is not considered clinically relevant (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In healthy volunteers receiving tadalafil (40 mg once daily), concomitant administration of a single dose of ambrisentan (10 mg) had no clinically relevant effect on the pharmacokinetics of either ambrisentan or its metabolite, 4 hydroxymethyl ambrisentan. Similarly, the single dose pharmacokinetics of tadalafil (40 mg) were unaffected by multiple doses of ambrisentan (10 mg once daily).

The effects of 12 days dosing with ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of oral contraceptive containing norethindrone 1 mg and ethinyl estradiol 35 micrograms were studied in healthy female volunteers. The C_{max} and $AUC_{(0-\infty)}$ were slightly decreased for ethinyl estradiol (8% and 4%, respectively), and slightly increased for norethindrone (13% and 14%, respectively). These changes in exposure to ethinyl estradiol or norethindrone were small and are unlikely to be clinically significant.

The effects of repeat dosing of ambrisentan (10 mg) on the pharmacokinetics of single dose digoxin were studied in 15 healthy volunteers. Multiple doses of ambrisentan resulted in slight increases in digoxin AUC_{0-last} and trough concentrations, and a 29% increase in digoxin C_{max} . The increase in digoxin exposure observed in the presence of multiple doses of ambrisentan was not considered clinically relevant, and no dose adjustment of ambrisentan would be warranted.

Excretion

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism with approximately 66% of the oral dose excreted in the faeces, the majority of which is unchanged ambrisentan (41% of the dose). Approximately 22% of the administered dose is recovered in the urine following oral administration with 3.3% being

unchanged ambrisentan. Plasma elimination half-life in humans ranges from 13.6 to 16.5 hours.

Special populations:

Renal impairment

No pharmacokinetic studies have been conducted in renally impaired patients. However, the renal excretion of ambrisentan is minimal, therefore renal impairment is unlikely to significantly increase exposure to ambrisentan. The magnitude of the decrease in oral clearance is modest (20-40%) in patients with moderate renal impairment and therefore is unlikely to be of any clinical relevance. However, caution should be used in patients with severe renal impairment.

Hepatic impairment

The pharmacokinetics of ambrisentan in patients with severe hepatic impairment has not been studied. However, since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment would be expected to increase exposure (C_{max} and AUC) to ambrisentan, however the magnitude of this and any effect on safety and efficacy has not been evaluated. Therefore, ambrisentan is not recommended in patients with moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment or with clinically significant elevated hepatic transaminases (see Sections 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 PRECLINICAL SAFETY DATA

In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36, or 62, a decrease in brain weight (-3% to -8%, compared to controls) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnoea and hypoxia were observed, at exposures approximately 1.8 to 7.0 times human paediatric exposures at 10 mg (age 9 to 15 years), based on AUC. The clinical relevance of this finding to the paediatric population is not fully understood; however, the hypoxia was associated with a mechanically induced apnoea, which may be considered a potential risk for children under 4 years of age since the human oropharynx repositions with age. The safety and efficacy of VOLIBRIS have not been established in patients less than 18 years of age, and therefore its use in this age group is not recommended.

Genotoxicity

The genotoxicity of ambrisentan was assessed in a comprehensive battery of *in vitro* and *in vivo* studies. Ambrisentan was clastogenic when tested at high concentrations in mammalian cells *in vitro*. No evidence for genotoxic effects of ambrisentan was seen in bacteria or in two *in vivo* rodent studies.

Carcinogenicity

There was no evidence of carcinogenic potential in 2 year oral studies in mice and rats treated with ambrisentan at low relative exposures (*ca.* 5 or less based on AUC). There was a small increase in mammary fibroadenomas, a benign tumor, in male rats at the highest dose only.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

VOLIBRIS (ambrisentan) is supplied as film-coated tablets in blister packs of 10 or 30.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

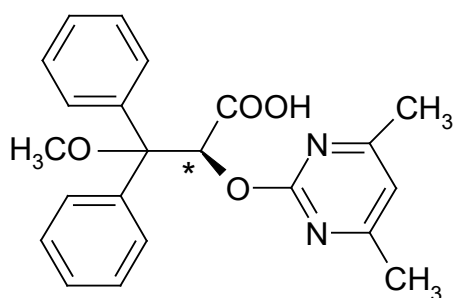
VOLIBRIS film-coated tablets contain ambrisentan which is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. The chemical name (IUPAC) for ambrisentan is (S)-2-(4,6-dimethylpyrimidin-2-ylloxy)-3-methoxy-3,3-diphenylpropionic acid.

Ambrisentan is a white to off-white crystalline substance, and its solubility in water is 0.06 mg/mL (practically insoluble) and in 0.1N NaOH is >100 mg/mL at 25 °C.

Molecular formula: C₂₂H₂₂N₂O₄

Molecular weight: 378.42

Chemical structure



* Chiral centre

CAS number

177036-94-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford VIC 3067

9 DATE OF FIRST APPROVAL

24 November 2008

10 DATE OF REVISION

25 July 2025

Summary table of changes

Section changed	Summary of new information
4.2, 4.4, 5.3	Addition of nonclinical information relevant to paediatric use
	Updated copyright statement

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