NEW ZEALAND DATA SHEET

VOLIBRIS (ambrisentan) tablets

TERATOGENICITY

Volibris may cause birth defects and is contraindicated in pregnancy (see section 4.3 CONTRAINDICATIONS).

1 NAME OF THE MEDICINE

VOLIBRIS (ambrisentan) 5 mg and 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

VOLIBRIS 5 mg tablets

Each film-coated tablet contains 5 mg ambrisentan. The tablet contains lactose.

VOLIBRIS 10 mg tablets

Each film-coated tablet contains 10 mg ambrisentan.

Excipient(s) with known effect:

The tablets contain lactose and Allura Red AC Aluminium Lake (E129).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

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 in adults aged ≥18 years for the treatment of:

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

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.

Dose

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 UNDESIRABLE EFFECTS and 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Efficacy and Safety).

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 sections 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION and 5.2 PHARMACOKINETIC PROPERTIES).

Special populations

Paediatric population

Safety and efficacy of VOLIBRIS have not been established in patients under 18 years of age, and therefore its use in this age group is not recommended (see section 5.3 PRECLINICAL SAFETY DATA).

Elderly population

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 might 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

VOLIBRIS is for oral use and can be administered with or without food.

4.3 CONTRAINDICATIONS

VOLIBRIS is contraindicated in:

- Hypersensitivity to ambrisentan or to any of the excipients listed in section 6.1
- Pregnancy (see Boxed Warning and section 4.6 FERTILITY, PREGNANCY AND LACTATION, Pregnancy).
- Women of child-bearing potential who are not using reliable contraception (see section 4.6 FERTILITY, PREGNANCY AND LACTATION, 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.

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.

The efficacy and safety of ambrisentan when co-administered with other treatments for PAH (e.g. prostanoids and phosphodiesterase type V inhibitors) has not been specifically studied in controlled clinical trials.

Liver function

Hepatic enzyme elevations have been observed with endothelin receptor antagonists (ERAs). Monitor liver function tests as clinically indicated. If aminotransferases

(alanine aminotransferase, ALT or aspartate aminotransferase, AST) are greater than 3 times upper limit of normal, initiation of ambrisentan is not recommended.

The cumulative incidence of serum aminotransferase abnormalities >3xULN in all phase II and III studies for ambrisentan (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 aminotranferases >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.

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 >2x ULN), or an elevation of ALT >8x 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 in 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 patients develop signs or symptoms of hepatitis, or suffer exacerbation of existing hepatitis ambrisentan should be discontinued.

Other ERAs have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure (see section 4.8 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.

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. 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.

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.

Patients with 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 in severity. Peripheral oedema was reported more frequently with 10 mg ambrisentan (see section 4.8 UNDESIRABLE EFFECTS).

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 hospitalization 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.

Excipients

Ambrisentan 5 mg and 10 mg tablets contain the azo colouring agent Allura Red AC Aluminium Lake (E129), which may cause allergic-type reactions.

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.

Elderly population

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 population

Refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION.

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 CYP3A4) in healthy volunteers did not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or ambrisentan (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 $AUC_{(0\text{-}inf)}$ 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-glucuronosyltransfereases [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.

Co-administration with other PAH treatments

The efficacy and safety of ambrisentan when co-administered with other treatments for PAH (e.g. prostanoids and phosphodiesterase type V inhibitors) has not been specifically studied in controlled clinical trials. Therefore, caution is recommended in the case of co-administration.

4.6 FERTILITY, PREGNANCY AND LACTATION

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.

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 proposed.

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.

Breast-feeding

It is not known whether ambrisentan is excreted in human milk. Breast-feeding 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.

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. In preclinical testing in rats, testicular tubular atrophy was observed at exposures similar to that anticipated clinically (see section 5.3 PRECLINICAL SAFETY DATA, Fertility).

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 UNDESIRABLE EFFECTS:

Experience from 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 VOLIBRIS 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)

Safety of VOLIBRIS has been evaluated in more than 480 patients with PAH. The exposure to VOLIBRIS 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).

Adverse drug reactions (ADRs) from clinical trial data are listed below by system organ class and frequency. Frequencies are placebo corrected and 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).

Blood and lymphatic system disorders	
Common	Anaemia* (decreases in haemoglobin and/or haematocrit)
Immune system disorders	
Uncommon	Hypersensitivity (e.g. angiodema, rash)
Nervous system disorders	
Very Common	Headache* (including sinus headache, migraine)
Cardiac disorders	
Common	Palpitations
Vascular disorders	
Common	Flushing
Respiratory, thoracic and mediastinal disorders	
Common	Nasal congestion**, sinusitis, nasopharyngitis
Gastrointestinal disorders	
Common	Abdominal pain, constipation

General disorders and administration site conditions	
Very Common	Peripheral oedema*, fluid retention*

*The frequency of these ADRs appeared higher with 10 mg ambrisentan.

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

Experience from long-term clinical studies

The long-term safety (>3 months) of ambrisentan was evaluated in more than 500 patients with PAH. ADRs from non-placebo controlled clinical trial data are listed below. Frequencies are defined as: very common (≥1/10) and common (≥1/100, <1/10).

Blood and lymphatic system disorders	
Very Common	Anaemia (decreases in haemoglobin and/or haematocrit)
Immune system disorders	
Common	Hypersensitivity (including drug hypersensitivity)
Nervous system disorders	
Very Common	Dizziness, headache
Cardiac disorders	
Very Common	Palpitations
Vascular disorders	
Very Common	Flushing (including hot flush)
Respiratory, thoracic and mediastinal disorders	
Very Common	Nasal congestion, sinusitis, nasopharyngitis, dyspnoea (including dyspnoea exertional)

Gastrointestinal disorders	
Very Common	Abdominal pain (including upper and lower), nausea
Common	Vomiting, constipation
Skin and subcutaneous tissue disorders	
Common	Rash (rash erythematous, rash generalised, rash macular, rash papular, rash pruritic)
General disorders and administration site conditions	
Very Common	Fatigue, fluid retention (including fluid overload), peripheral oedema
Common	Asthenia
Eye disorders	
Common	Visual impairment (including vision blurred)

Post-marketing experience

In addition to adverse reactions identified from clinical studies, the following adverse reactions were identified during post-approval use of ambrisentan. Events of 'unknown' frequency have been reported voluntarily from a population of unknown size, therefore estimates of frequency cannot be made.

Hepatobiliary disorders	
Common:	Hepatic transaminases increased
Unknown:	Hepatic injury, autoimmune hepatitis (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury of unclear aetiology have been reported during ambrisentan therapy.	
Cardiac disorders	
Unknown:	Heart failure (associated with fluid retention)

Vascular disorders	
Unknown:	Hypotension
Blood and Lymphatic System disorders	
Unknown:	Anemia requiring transfusion
Cardiac disorders	
Unknown:	Heart failure (associated with fluid retention)
Vascular disorders	
Unknown:	Hypotension

Laboratory findings

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

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 ≥15% from baseline and which fell below the lower limit of normal.

Reporting of suspected adverse reactions

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

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antihypertensives, other anti-hypertensives

ATC code: C02KX02

Mechanism of action / Pharmacodynamic effects

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 efficacy and safety

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. prostanoids) 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 38.6 weeks and the maximum exposure was 109 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 2).

Table 2 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	355.3 ± 84.5
Mean change from Baseline (SD), m	-7.8 ± 78.9	22.8 ± 83.0	43.6 ± 65.9	-10.1 ± 93.8	22.2 ± 82.7	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 +35.2 m (95% CI: 13.0 to 57.5; n=68) for the 5 mg dose, and +30.2 m (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 3 and 4. However such results should be interpreted with caution.

Table 3 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 (29.01, 56.83)	26.90 m (14.21, 39.59)	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)	10 (66.7)
	No change	82 (62.1)	91 (87.5)	96 (69.6)	5 (33.3)
	Deteriorated	23 (17.4)	2 (1.9)	5 (3.6)	0 (0.0)

Table 4: 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, hospitalization 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 5: 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)
Hospitalization 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 two pivotal studies and their open label extension (N=383) shows that 93% (CI: 90.9 to 95.9) were still alive at one year (Kaplan-Meier estimate) and 91% (287/314) of those still taking ambrisentan were still receiving VOLIBRIS monotherapy. In the subgroup of patients with IPAH (n=241) the observed 1-year survival for patients receiving any dose of VOLIBRIS was 96% (95% CI: 94% to 99%) compared with the predicted values of 72% based on the NIH formula. At 2 years, 85% (95% CI: 81.7 to 88.9) were still alive (Kaplan-Meier estimate) and 83% (214/259) of those still taking ambrisentan were receiving ambrisentan monotherapy. At 3 years, 79% (95% CI: 75.2 to 83.4) were still alive (Kaplan-Meier estimate) and 79% (147/186) of those still taking ambrisentan were receiving ambrisentan monotherapy. Improvements from

baseline in 6MWD, WHO functional class, and BDI were maintained with long term treatment of up to 3 years in the extension of the Phase 3 studies.

Improvements in 6MWD, WHO functional class and BDI were generally maintained for up to 3 years in the Phase 2 studies.

These uncontrolled observations do not allow comparison with a group not given VOLIBRIS. The effect of VOLIBRIS on the outcome of the disease is unknown.

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 >3xULN 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 0 (0%) of 261 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 versus placebo; 10 mg group).

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 $alpha_1$-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.

Biotransformation

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 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

INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

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 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION).

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 $AUC_{0\text{-last}}$ 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.

Elimination

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 might be expected to increase exposure (Cmax 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 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 PRECLINICAL SAFETY DATA

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.

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%) 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 only for young children (0 to 3 years) since the human oropharynx repositions with age (see section 4.2 DOSE AND METHOD OF ADMINISTRATION, Paediatric population).

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.

Effect on fertility

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.

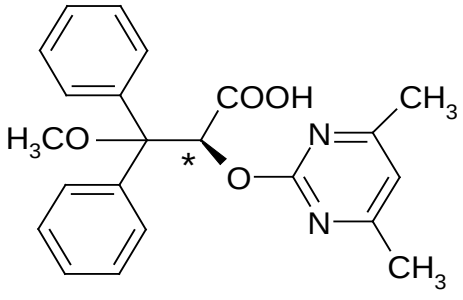
6 PHARMACEUTICAL PARTICULARS

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 (ETA) receptor. The chemical name (IUPAC) for ambrisentan is (S)-2-(4,6-dimethylpyrimidin-2-yloxy)-3-methoxy-3,3-diphenylpropionic acid.

Molecular formula: $C_{22}H_{22}N_2O_4$

Molecular weight: 378.42

Chemical structure



* Chiral centre

CAS number

177036-94-1

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.

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose,

Lactose

Croscarmellose sodium

Magnesium stearate

Polyvinyl alcohol

Purified Talc

Titanium dioxide

Macrogol 3350 (PEG 3350)

Lecithin USNF

Allura Red AC Aluminum Lake (FD&C Red #40) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

5 years

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 PVC/PVDC/aluminium foil blister packs of 30.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

GlaxoSmithKline NZ Limited

Private Bag 106600

Downtown

Auckland

NEW ZEALAND

Ph (09) 367 2900
Fax (09) 367 2910

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
13 August 2009

10 DATE OF REVISION OF THE TEXT

25 November 2020

Summary table of changes:

Section changed	Summary of new information
2, 4.4 and 6.1	Addition of azo warning for FD&C Red 40 Aluminium Lake (Allura red) excipient
4.8	Editorial updates

Version 19.0