AUSTRALIAN PRODUCT INFORMATION

AMBRISENTAN VIATRIS

(ambrisentan) film coated tablets

TERATOGENICITY

AMBRISENTAN VIATRIS 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

Each tablet contains 5 mg or 10 mg of ambrisentan as the active ingredient.

Excipients with known effect: Lactose.

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

3 PHARMACEUTICAL FORM

AMBRISENTAN VIATRIS 5 mg tablets are pink, film-coated, round, biconvex tablets debossed with 'M' on one side of the tablet and 'AN' on the other side.

AMBRISENTAN VIATRIS 10 mg tablets are pink, film-coated, capsule shaped, biconvex tablets debossed with 'M' on one side of the tablet and 'AN1' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AMBRISENTAN VIATRIS is indicated for 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

It is recommended that the tablet is swallowed whole and should not be split, crushed or chewed. AMBRISENTAN VIATRIS 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS).

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

Use with Ciclosporin A

When co-administered with ciclosporin 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 5.2 PHARMACOKINETIC PROPERTIES, METABOLISM).

Special Populations

Paediatric Use

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

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 ambrisentan 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

Ambrisentan 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, ambrisentan 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 Section 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES). Use caution when administering AMBRISENTAN VIATRIS in patients with mild pre-existing impaired liver function who may require reduced doses of AMBRISENTAN VIATRIS.

4.3 CONTRAINDICATIONS

Ambrisentan 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.

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.

Use in Hepatic Impairment

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

The cumulative incidence of serum aminotransferase abnormalities >3xULN 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 Section 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 >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 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

Ambrisentan 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 ERAs) when used in patients with PVOD. Consequently, should signs of acute pulmonary oedema occur when ambrisentan 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.

Effects on Laboratory Tests

Refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, HAEMATOLOGICAL CHANGES.

Excipients

AMBRISENTAN VIATRIS 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 metabolised 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 metabolising 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 ciclosporin A, warfarin, sildenafil and tadalafil, ketoconazole, rifampin, oral contraceptives and digoxin.

Ciclosporin A

Ciclosporin A is an inhibitor of multiple metabolic enzymes and transporters. Use caution when ambrisentan is co-administered with ciclosporin A.

Steady-state co-administration of ambrisentan and ciclosporin 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 ciclosporin A (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). No clinically relevant effect of ambrisentan on ciclosporin 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 normalised ratio (INR).

Sildenafil and 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 $AUC_{(0\text{-}inf)}$ 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-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 ERAs. 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 fetal 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 Childbearing Potential

In females of childbearing 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.

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 studies 1 and 2 (ARIES-1 and ARIES-2), a total of 197 patients received ambrisentan 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 (ADRs) from non-placebo controlled clinical trial data are listed below in the Tabulated List of Adverse Reactions.

Tabulated List of Adverse 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: Tabulated list of adverse reactions

	Ambrisentan Combined Clinical Trial Studies 1 and 2 and Post-Marketing	**Ambrisentan Combination Therapy Study and Open Label Extension Study**
Blood and lymphatic system disorders		
Anaemia (decreased haemoglobin, decreased haematocrit)	Common[1]	Very common
Immune system disorders		
Hypersensitivity reactions (e.g. angioedema, rash, pruritus)	Uncommon	Common
Nervous system disorders		
Headache (including sinus headache, migraine)	Very common[2]	Very common
Dizziness	Common[3]	Very common
Eye disorders		

Blurred vision, visual impairment	Not known[4]	Common
Ear and labyrinth disorders		
Tinnitus	NR	NR
Sudden hearing loss	NR	NR
Cardiac disorders		
Cardiac failure	Common[5]	Common
Palpitation	Common	Very common
Vascular disorders		
Hypotension	Common[3]	Common
Flushing	Common	Common
Syncope	Uncommon[3]	Common
Respiratory, thoracic and mediastinal disorders		
Epistaxis	Common[3]	Common
Dyspnoea	Common[3, 6]	Very common
Upper respiratory (e.g. nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis	Common[7]	
Nasopharyngitis		Very common
Sinusitis, rhinitis		Common
Nasal congestion		Very common
Gastrointestinal disorders		
Nausea, vomiting, diarrhoea	Common[3]	
Nausea		Very common
Vomiting		Common
Diarrhoea		Very common
Abdominal pain	Common	Common
Constipation	Common	Common
Hepatobiliary disorders		
Hepatic injury (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon[3, 8]	NR
Autoimmune hepatitis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)	Uncommon[3, 8]	NR
Hepatic transaminases increased	Common[3]	NR
Skin and subcutaneous tissue disorders		
Rash	NR	Common[9]

General disorders and administration site conditions		
Peripheral oedema, fluid retention	Very common	Very common
Chest pain/discomfort	Common	Common
Asthenia	Common[3]	Common
Fatigue	Common[3]	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.

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 ambrisentan. Across the 12 week placebo controlled Phase III clinical studies, mean haemoglobin concentrations decreased for patients in the ambrisentan 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 ambrisentan treatment groups had decreases in haemoglobin of ≥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 ambrisentan 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, 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, ERA selective for the endothelin 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 (studies 1 and 2). Study 1 included 201 patients and compared ambrisentan 5 mg and 10 mg with placebo. Study 2 included 192 patients and compared ambrisentan 2.5 mg and 5 mg with placebo. In both studies, ambrisentan 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 studies 1 and 2 were eligible to enter a long-term open label extension study (n=383). Patients who had been randomised to placebo in either study 1 or study 2 were randomised in a blinded 1:1 fashion to the ambrisentan dosages of the originating phase III study. The mean exposure to ambrisentan in the extension study was approximately 145 ± 80 weeks and the maximum exposure was approximately 295 weeks.

Exercise Capacity

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

In both studies 1 and 2 treatment with ambrisentan 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 study 1 and study 2 at week 12

	Study 1			Study 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 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 ambrisentan to placebo at week 12 stratified by idiopathic PAH and non-idiopathic PAH patients

Results from the extension studies also indicate 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 (study 1 and study 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 (study 1 and study 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 studies 1 and 2, demonstrated that the addition of ambrisentan significantly delayed clinical worsening (defined as the time from randomisation 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 ambrisentan treatment in a combined analysis of study 1 and study 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 studies 1 and 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 ambrisentan 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 ambrisentan 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 ambrisentan and cannot be used to determine the long-term effect of ambrisentan on mortality.

Assessment of Liver Function

In an open label study (AMB-222), ambrisentan 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 ambrisentan, 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 ambrisentan during this time. In studies 1 and 2, a total of 4 (0.8%) of 262 patients receiving ambrisentan 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 ambrisentan 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 ambrisentan.

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 ambrisentan. Mean cardiac index significantly increased at 12 weeks compared to baseline (+0.3 L/min/m^2; 95% CI: 0.15, 0.51 L/min/m^2; $p<0.001$) 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 studies 1 and 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).

Dose Titration

In the Combination Therapy Study, patients received 5 mg ambrisentan daily for the first 8 weeks before up titrating to 10 mg, dependent 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 ciclosporin 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 ciclosporin 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 ciclosporin A. Based on these changes, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with ciclosporin A (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). However, multiple doses of ambrisentan had no clinically relevant effect on ciclosporin A exposure, and no dose adjustment of ciclosporin 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 Normalised 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 $AUC_{0\text{-last}}$ 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.

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 Section 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 neurobehavioural 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 young children under 4 years of age, since the human oropharynx repositions with age. The safety and efficacy of ambrisentan have not been established in patients less than 18 years of age, and therefore its use in this age group is not recommended.

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.

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 tumour, in male rats at the highest dose only.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

AMBRISENTAN VIATRIS 5 mg and 10 mg tablets contain lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and OPADRY II complete film coating system 85F540046 PINK (ID 107526).

6.2 INCOMPATIBILITIES

Please see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/aluminium foil blisters

Pack size: 30 film-coated tablets

Australian Register of Therapeutic Goods (ARTG)

AUST R 298940 – AMBRISENTAN VIATRIS ambrisentan 5 mg film-coated tablet blister pack

AUST R 298941 – AMBRISENTAN VIATRIS ambrisentan 10 mg film-coated tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

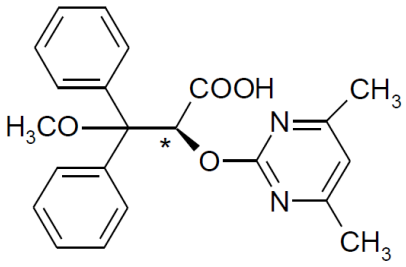
6.7 PHYSICOCHEMICAL PROPERTIES

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.

Chemical Structure

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

The structural formula is:



* Chiral centre

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

Molecular weight: 378.42

CAS Number

177036-94-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30 - 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

01/04/2020

10 DATE OF REVISION

05/09/2025

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.2, 4.4, 5.3	Addition of nonclinical information relevant to paediatric use

AMBRISENTAN VIATRIS_pi\Sep25/00