VOLIBRIS TABLETS

1. PHARMACEUTICAL FORM
Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
2.5 mg film-coated tablets
Each tablet contains 2.5 mg ambrisentan.

5 mg film-coated tablets
Each tablet contains 5 mg ambrisentan. The tablets are pale-pink, square and convex, debossed with “GS” on one side and “K2C” on the other.

10 mg film-coated tablets
Each tablet contains 10 mg ambrisentan. The tablets are deep-pink, oval and convex, debossed with “GS” on one side and “KE3” on the other.

Not all presentations are marketed locally.

3. THERAPEUTIC INDICATIONS

VOLIBRIS is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment (*see section 12.1*). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

4. POSOLOGY AND METHOD OF ADMINISTRATION

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

4.2. Recommended adult dosage
Ambrisentan treatment should be initiated at a dose of 5 mg once daily and may be increased to 10 mg once daily depending upon clinical response and tolerability.

When used in combination with tadalafil, the ambrisentan starting dose of 5 mg should be titrated to 10 mg once daily, as tolerated (*see section 12.1.2.2*).

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

4.3. Use with cyclosporine A
When co-administered with cyclosporine A, the dose of ambrisentan should be limited to 5 mg once daily and the patient should be carefully monitored (see *Interactions with Other Medicinal Products and Other Forms of Interaction; Pharmacokinetic Properties, Metabolism*).

4.4. Recommended pediatric and adolescent dosage
Safety and efficacy of ambrisentan have not been established in patients under 18 years of age; therefore, the use of ambrisentan in these patients is not recommended (see *Non-clinical Information*).

4.5. Dosage instructions in special populations

4.5.1. Elderly
No dose adjustment is required in patients aged 65 years and over (see *Pharmacokinetics in Special Populations*).

4.5.2. Renal Impairment
No dose adjustment is required in patients with renal impairment (see *Pharmacokinetics*). There is limited experience of 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.

4.5.3. Hepatic Impairment
VOLIBRIS has not been studied in individuals with severe hepatic impairment or with clinically significant elevated hepatic transaminases. Since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment would be expected to increase exposure (C_{max} and AUC) of ambrisentan. Therefore, VOLIBRIS is not recommended in patients with moderate impairment, is contraindicated in patients with severe hepatic impairment (with or without cirrhosis) or with clinically significant elevated hepatic transaminases (see *Contraindications, Special Warnings and Special Precautions for Use* and *Pharmacokinetics*). Use caution when administering VOLIBRIS in patients with mild pre-existing impaired liver function who may require reduced doses of VOLIBRIS (see *Special Warnings and Special Precautions for Use* and *Pharmacokinetics in Special Populations*).

4.6. Method of Administration
It is recommended that the tablet is swallowed whole and it can be taken with or without food. It is recommended that the tablet should not be split, crushed or chewed.

5. CONTRAINDICATIONS

Ambrisentan is contraindicated in pregnancy (see *Pregnancy and Lactation*).

Ambrisentan is contraindicated in women of child-bearing potential who are not using reliable contraception (see *Pregnancy*). Women must not become pregnant for at least 3 months after stopping treatment with ambrisentan.

Ambrisentan is contraindicated in patients with severe hepatic impairment (with or without cirrhosis) (see *Special Warnings and Special Precautions for Use*).

Ambrisentan is contraindicated in 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 *Special Warnings and Special Precautions for Use*).

Ambrisentan is contraindicated in idiopathic pulmonary fibrosis (IPF) with or without secondary

pulmonary hypertension.
Ambrisentan is contraindicated in patients who exhibit or may exhibit hypersensitivity to ambrisentan or to any of the other excipients.

Ambrisentan is contraindicated in breast-feeding.

6. SPECIAL WARNINGS AND SPECIAL 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.

6.1. Hepatic Impairment

Hepatic enzyme elevations potentially related to therapy have been observed with endothelin receptor antagonists (ERAs).

The cumulative incidence of serum aminotransferase abnormalities >3x ULN 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 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 *Contraindications* and *Efficacy/Clinical Studies*).

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. Regular monitoring of aminotransferases should occur.

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.

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 optimized prior to initiation of ambrisentan and during ambrisentan therapy. If patients develop signs or symptoms of hepatitis, or suffer exacerbation of existing autoimmune hepatitis, ambrisentan should be discontinued.

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

6.2. Hematological Changes
Reductions in hemoglobin concentrations and hematocrit have been observed with ERAs including ambrisentan, and there have been cases where this has resulted in anaemia, sometimes requiring transfusion. In clinical trials, decreases in hemoglobin and hematocrit were observed within the first few weeks of therapy and generally stabilized thereafter. The mean decrease in hemoglobin 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 hemoglobin 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 hemoglobin is measured prior to initiation of ambrisentan, again at one month, and periodically thereafter. Initiation of ambrisentan therapy is not recommended for patients with clinically significant anaemia. If a clinically significant decrease in hemoglobin is observed during therapy and other causes have been excluded, discontinuation of ambrisentan 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).

6.3. Fluid Retention
Peripheral edema has been observed with ERAs including ambrisentan. Peripheral edema may also be a clinical consequence of PAH. Most cases of peripheral edema in clinical studies with ambrisentan were mild to moderate in severity, although it occurred with greater frequency and severity in elderly patients.

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.

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

6.4. 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 edema have been reported with vasodilators (mainly prostacyclin and with endothelin receptor antagonists) when used in patients with PVOD. If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as an endothelin receptor antagonist, the possibility of pulmonary veno-occlusive disease should be considered.

6.5. Excipients

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

7. PREGNANCY AND LACTATION

7.1. Pregnancy

Ambrisentan is contraindicated in pregnancy (see *Contraindications*).

Animal studies in rats and rabbits have shown that ambrisentan is teratogenic (see *Non-Clinical Information*). Teratogenicity is a class effect of ERAs.

Women of child-bearing potential should be advised of the risk of fetal harm if ambrisentan is taken during pregnancy. Pregnancy must be excluded before the start of treatment with ambrisentan and prevented thereafter by reliable contraception. Pregnancy tests during treatment with ambrisentan are recommended as clinically indicated. Women of child-bearing potential should be advised to contact their physician immediately if they become pregnant or suspect they may be pregnant (see *Contraindications, Non-Clinical Information*). If pregnancy is to be continued, VOLIBRIS should be discontinued and alternative treatment should be initiated.

7.2. Lactation

It is not known whether ambrisentan is excreted in human breast milk. The excretion of ambrisentan in milk has not been studied in animals. Therefore, breast-feeding is contraindicated in patients taking ambrisentan.

7.3. 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 characterize the effects of ambrisentan on either male or female 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.

8. EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Ambrisentan has minor or moderate influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of ambrisentan (such as hypotension, dizziness, asthenia, fatigue) should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor or cognitive skills. Patients should be aware of how they might be affected by ambrisentan before driving or using machines.

9. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The efficacy and safety of ambrisentan when co-administered with prostanoids and soluble guanylate cyclase stimulators has not been specifically studied in controlled clinical trials in PAH patients (see *section 12.1.2*). No specific drug-drug interactions with soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see *section 12.2*). However, no specific drug-drug interactions studies have been conducted with these drugs.

Ambrisentan is primarily metabolized by glucuronidation and to a lesser extent by oxidative metabolism, principally by CYP3A and to a lesser extent by CYP2C19.

Ambrisentan does not inhibit or induce phase I or II drug metabolizing enzymes at clinically relevant concentrations in non-clinical studies, suggesting a low potential for ambrisentan to alter the profile of drugs metabolized by these pathways.

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.

Steady-state co-administration of ambrisentan and cyclosporine 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 cyclosporine A (see *Posology and Method of Administration*). No clinically relevant effect of ambrisentan on cyclosporine A exposure was observed (see *Pharmacokinetic Properties, Metabolism*).

Steady-state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to ambrisentan (see *Pharmacokinetic Properties, Metabolism*).

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 *Pharmacokinetic Properties, Metabolism*).

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. 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 *Pharmacokinetic Properties, Metabolism*).

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 *Pharmacokinetic Properties, Metabolism*). Based on this pharmacokinetic study, ambrisentan would not be expected to significantly affect exposure to estrogen- or progestogen- based contraceptives.

Ambrisentan had no effects on the steady-state pharmacokinetics and anticoagulant activity of warfarin in a healthy volunteer study (see *Pharmacokinetic Properties, Metabolism*). Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in clinical studies of PAH patients, ambrisentan had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT) and international normalized ratio (INR).

In vitro, ambrisentan has no inhibitory effect on the P-gp-mediated efflux of digoxin and is a substrate for P-gp-mediated efflux. Additional *in vitro* studies in rat and human hepatocytes showed no evidence for ambrisentan inhibition of the sodium-taurocholate co-transporter (NTCP), organic anion export pump (OATP), bile salt export pump (BSEP) and multi-drug resistance related protein 2 (MRP2). Consistent with results in isolated hepatocytes, studies using cell-lines transfected with the human transporter genes showed that ambrisentan does not inhibit P-gp, breast cancer receptor protein (BCRP), MRP2, or BSEP at concentrations up to 100 µM. Ambrisentan showed weak *in vitro* inhibition in these experiments of OATP1B1, OATP1B3 and sodium-taurocholate co-transporter (NTCP) with IC_{50} values of 47 µM, 45 µM, and approximately 100 µM, respectively. *In vitro* studies in rat hepatocytes also showed that ambrisentan did not induce P-gp, BSEP or MRP2 protein expression.

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.

10. UNDESIRABLE EFFECTS

10.1. Experience from Pivotal Clinical Studies

The safety of ambrisentan was evaluated during clinical trials in more than 480 patients with PAH. Adverse drug reactions (ADRs) identified from 12 week placebo-controlled clinical trial data are listed below by system organ class and frequency. Frequencies are placebo corrected and defined as common (≥1/100, <1/10) and uncommon (≥1/1000, <1/100). Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice.

BLOOD AND LYMPHATIC SYSTEM DISORDERS
Common: Anemia (decreases in hemoglobin and/or hematocrit)

IMMUNE SYSTEM DISORDERS
Uncommon: Hypersensitivity (e.g. angioedema, rash)

NERVOUS SYSTEM DISORDERS
Common: Headache

CARDIAC DISORDERS
Common: Palpitations

VASCULAR DISORDERS
Common: Flushing

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Common: Nasal congestion, sinusitis, nasopharyngitis
The incidence of nasal congestion was dose-related during ambrisentan therapy.

GASTROINTESTINAL DISORDERS
Common: Abdominal pain, constipation

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Common: Fluid retention, Peripheral edema

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS
Very Common: Anemia (decreases in hemoglobin and/or hematocrit)

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, dyspnea (including dyspnea 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 generalized, rash macular, rash popular, rash pruritic)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Very Common: Fatigue, fluid retention (including fluid overload), peripheral edema
Common: Asthenia

EYE DISORDERS
Common: Visual impairment (including vision blurred)

10.3 Experience from a Clinical Study with Ambrisentan Used in Combination with Tadalafil

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS
Very Common: Anemia (decreases in hemoglobin and/or hematocrit)

IMMUNE SYSTEM DISORDERS
Common: Hypersensitivity (including drug hypersensitivity)

NERVOUS SYSTEM DISORDERS
Very Common: Dizziness, headache

CARDIAC DISORDERS
Very Common: Palpitations
Common: Cardiac failure

VASCULAR DISORDERS
Very Common: Flushing (including hot flush)
Common: Hypotension, syncope

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS
Very Common: Nasal congestion, nasopharyngitis, dyspnea (including dyspnea exertional)
Common: Epistaxis, sinusitis, rhinitis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Common: Rash (rash erythematous, rash generalized, rash popular, rash pruritic)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Very Common: Fatigue, fluid retention (including fluid overload), peripheral edema, chest pain/discomfort

Common: Asthenia

EYE DISORDERS
Common: Visual impairment (including vision blurred)

GASTROINTESTINAL DISORDERS
Very Common: Vomiting, nausea, diarrhoea
Common: Abdominal pain, constipation

In addition, the following adverse reaction was observed:

EAR AND LABYRINTH DISORDERS
Common: Tinnitus
Uncommon: Sudden hearing loss

10.4. 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.

BLOOD AND LYMPHATIC SYSTEM DISORDERS
Unknown: Anemia requiring transfusion

VASCULAR DISORDERS
Unknown: Hypotension

CARDIAC DISORDERS
Unknown: Heart failure (associated with fluid retention)

HEPATOBILIARY DISORDERS
Common: Hepatic transaminases increased
Unknown: Hepatic injury, autoimmune hepatitis (see *Special Warnings and Special Precautions for Use*)
Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury with unclear etiology have been reported during ambrisentan therapy.

11. OVERDOSE

11.1. Symptoms and Signs
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.

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

12. PHARMACOLOGICAL PROPERTIES

12.1. Pharmacodynamic properties

Pharmacotherapeutic group: Anti-hypertensives, other anti-hypertensives, ATC code: C02KX02

Invasive hemodynamic parameters were assessed in patients with PAH at baseline and after 12 weeks (n=29) in a Phase 2 study. Treatment with ambrisentan resulted in a significant increase in mean cardiac index (+0.3 L/min/m^2; 95% CI: 0.15 to 0.51; p <0.001), and a decrease in mean pulmonary artery pressure (-5.2 mmHg; 95% CI: -7.6 to -2.9; p <0.001), and mean pulmonary vascular resistance (-2.8 mmHg/L/min; 95% CI: -3.8 to -1.8; p <0.001) for the combined ambrisentan group.

Combined analysis of results from two Phase 3 placebo-controlled studies demonstrated that plasma concentrations of BNP decreased in patients who received ambrisentan for 12 weeks. The geometric mean plasma concentration of BNP increased by 11% in the placebo group, and decreased by 29% in the 2.5 mg, 30% in the 5 mg, and 45% in the 10 mg groups (p <0.001 for each dose group).

12.1.1. Mechanism of action

Ambrisentan is an orally active, propanoic acid-class, ET_A selective, ERA. Endothelin plays a significant role in the pathophysiology of PAH.

- Ambrisentan blocks the ET_A receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.

- The selectivity of ambrisentan for the ET_A over the ET_B receptor is expected to retain ET_B receptor mediated production of the vasodilators nitric oxide and prostacyclin.

12.1.2. Efficacy/Clinical studies

12.1.2.1. Treatment of Pulmonary Arterial Hypertension

Two 12-week Phase 3, randomized, double-blind, placebo-controlled, multicenter efficacy and safety studies in 393 patients with PAH have been completed. The two studies were identical in design except for the doses of ambrisentan and the geographic region of the investigational sites. The doses selected for the first study were 5 and 10 mg daily (192 subjects), while the second study evaluated 2.5 and 5 mg daily (202 subjects). The primary study endpoint was 6-minute walk distance (6MWD). In addition, time to clinical worsening, WHO Functional Class, dyspnea, and SF-36 Health Survey were assessed for efficacy. 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.

An increase in 6MWD was observed as early as 4 weeks following initiation of treatment with ambrisentan, with a dose-response observed after 12 weeks of treatment. Results from AMB-321 demonstrated that 5 mg and 2.5 mg po qd of ambrisentan improved the placebo-corrected 6MWD by 59.4 meters ($p < 0.001$) and 32.3 meters ($p = 0.022$), respectively. Similarly, results from AMB-320 demonstrated that 10 mg and 5 mg po qd of ambrisentan improved the placebo-corrected 6MWD by 51.4 meters ($p < 0.001$) and 30.6 meters ($p = 0.008$), respectively.

A significant improvement in 6MWD was observed for each ambrisentan dose group compared to placebo; therefore, the prespecified analysis of the secondary endpoints in both the individual placebo-controlled studies, as well as the combined analysis of these studies focused on the combined ambrisentan group. The individual studies were not statistically powered to examine secondary endpoints. Because the larger sample size of the Phase 3 combined analysis had the greatest power to examine secondary endpoints, it provided more precise estimates of these ambrisentan treatment effects.

Time to clinical worsening, an indicator of disease progression, was a key secondary endpoint in the two Phase 3, placebo-controlled studies. The log-rank test for the comparison of the combined ambrisentan group versus placebo demonstrated that a significant delay in the time to clinical worsening of PAH was observed for subjects receiving ambrisentan ($p < 0.001$). Furthermore, the hazard ratio was 0.29 (95% CI: 0.14 to 0.59), indicating a 71% reduction in the probability of clinical worsening over the 12-week treatment period for subjects receiving ambrisentan compared to placebo. The conclusions of the combined analysis were supported by similar trends in the individual studies. In AMB-320, a 2-fold increase in the number of subjects with an event of clinical worsening was observed in the placebo group compared to each of the ambrisentan dose groups; however, the log-rank comparison of the combined ambrisentan group versus placebo did not demonstrate a statistically significant difference in the time to clinical worsening of PAH ($p = 0.214$). In AMB-321, a 4-fold increase in the number of subjects with an event of clinical worsening was observed in the placebo group compared to each of the ambrisentan dose groups. The log-rank test demonstrated a significant delay in time to clinical worsening of PAH for the comparison of the combined ambrisentan group versus placebo ($p < 0.001$).

The primary analysis of WHO functional class used a 7-point change from baseline scale (+3, +2, +1, 0, -1, -2, -3). Positive changes (+1, +2, or +3) indicated a deterioration in WHO functional class, and negative changes (-1, -2, or -3) indicated an improvement in WHO functional class. For the combined analysis, the combined ambrisentan group demonstrated a statistically significant overall improvement in the change from baseline WHO functional class at Week 12 compared to placebo ($p = 0.009$). The positive treatment effect observed for the combined ambrisentan group was primarily due to a 5-fold reduction in the percentage of subjects who deteriorated at least 1 WHO class compared to placebo. Similar trends were observed in the individual analyses of AMB-320 ($p = 0.036$) and AMB-321 ($p = 0.117$), but were not statistically significant according to the prespecified statistical procedures.

For the SF-36 Health Survey, a repeated measures analysis demonstrated that the improvement observed in the physical functioning scale in the combined ambrisentan group was significantly greater than placebo ($p = 0.003$). An improvement was observed for each of the ambrisentan dose groups compared to placebo; however, no dose-response was apparent. Improvements compared to placebo for the overall physical component summary and for the individual scales of role-

physical, vitality, and general health were also observed for the combined ambrisentan group.

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. Clinically relevant improvements in BDI were also observed at Week 12 for each ambrisentan dose group compared to placebo, and these improvements appeared to be greater for the 10 mg group compared to the 2.5 and 5 mg groups. Clinically relevant decreases from baseline in BDI were observed for the combined ambrisentan group compared to placebo in AMB-320 and AMB-321. This improvement was statistically significant in AMB-321 (p = -1.1; 0.019), but due to the prespecified multiple comparisons procedure, this improvement was not considered statistically significant in AMB-320 despite a small p-value (p = -0.6; 0.017).

Patients enrolled in the Phase 3 studies were eligible to be enrolled into an extension study. The long-term follow-up of the subjects who were treated with ambrisentan in the Phase 3, placebo-controlled studies and their open-label extension (N = 383) shows that 93% (95% CI: 90.9 to 95.9) were still alive at 1 year (Kaplan-Meier estimate) and 91% (287/314) of those still taking ambrisentan were receiving ambrisentan monotherapy. 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.

The efficacy of ambrisentan appeared similar when administered alone or in combination with sildenafil and/or a prostanoid, though study size precluded definitive subgroup comparisons.

12.1.2.2. Clinical efficacy in combination with tadalafil

A multicenter, double-blind, active comparator, event-driven, Phase 3 outcome study (AMB112565/AMBITION) was conducted to assess the efficacy of initial combination of ambrisentan and tadalafil vs. monotherapy of either ambrisentan or tadalafil alone, in 500 treatment naive PAH patients, randomised 2:1:1, respectively. No patients received placebo alone. The primary analysis was combination group vs. pooled monotherapy groups. Supportive comparisons of combination therapy group vs. the individual monotherapy groups were also made. Patients with significant anaemia, fluid retention or rare retinal diseases were excluded according to the investigators' criteria. Patients with ALT and AST values >2x ULN at baseline were also excluded.

At baseline, 96% of patients were naive to any previous PAH-specific treatment, and the median time from diagnosis to entry into the study was 22 days. Patients started on ambrisentan 5 mg and tadalafil 20 mg, and were titrated to 40 mg tadalafil at week 4 and 10 mg ambrisentan at week 8, unless there were tolerability issues. The median double-blind treatment duration for combination therapy was greater than 1.5 years.

The primary endpoint was the time to first occurrence of a clinical failure event, defined as:

- death, or
- hospitalisation for worsening PAH,
- disease progression;
- unsatisfactory long-term clinical response.

The mean age of all patients was 54 years (SD 15; range 18–75 years of age). Patients WHO FC at baseline was II (31%) and FC III (69%). Idiopathic or heritable PAH was the most common aetiology in the study population (56%), followed by PAH due to connective tissue disorders (37%), PAH associated with drugs and toxins (3%), corrected simple congenital heart disease (2%), and HIV (2%). Patients with WHO FC II and III had a mean baseline 6MWD of 353 metres.

Outcome endpoints

Treatment with combination therapy resulted in a 50% risk reduction (hazard ratio [HR] 0.502; 95% CI: 0.384 to 0.724; p=0.0002) of the composite clinical failure endpoint up to final assessment visit when compared to the pooled monotherapy group [Figure 1 and Table 1]. The treatment effect was driven by a 63% reduction in hospitalisations on combination therapy, was established early and was sustained. Efficacy of combination therapy on the primary endpoint was consistent on the comparison to individual monotherapy and across the subgroups of age, ethnic origin, geographical region, aetiology (iPAH /hPAH and PAH-CTD). The effect was significant for both FC II and FC III patients.

Figure 1

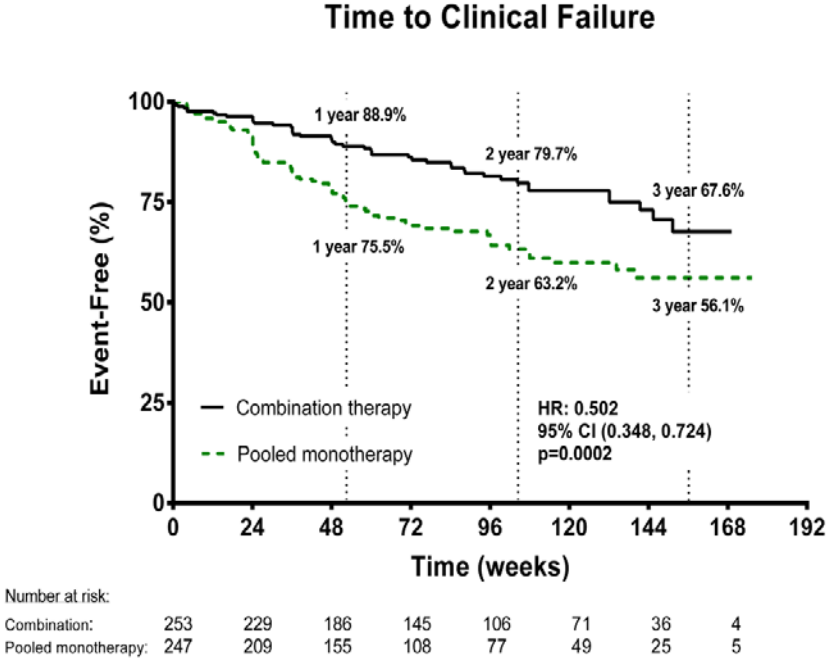
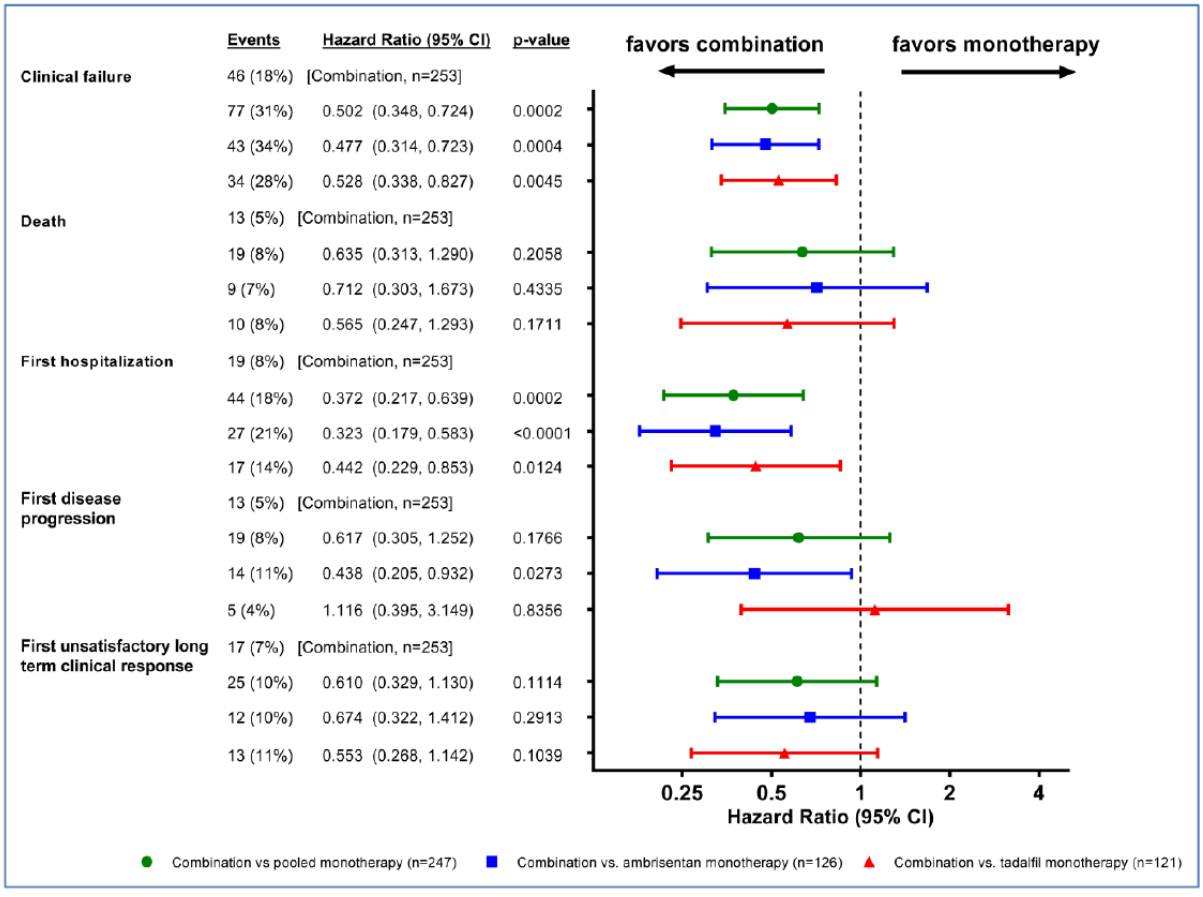


Table 1

	Ambrisentan + Tadalafil (N=253)	**Monotherapy Pooled (N=247)**	**Ambrisentan monotherapy (N=126)**	**Tadalafil monotherapy (N=121)**
Time to First Clinical Failure Event (Adjudicated)				
Clinical failure, no. (%)	46 (18)	77 (31)	43 (34)	34 (28)
Hazard ratio (95% CI)		0.502 (0.348, 0.724)	0.477 (0.314, 0.723)	0.528 (0.338, 0.827)
P-value, Log-rank test		0.0002	0.0004	0.0045
Component as First Clinical Failure Event (Adjudicated)				
Death (all-cause), no. (%)	9 (4)	8 (3)	2 (2)	6 (5)
Hospitalisation for worsening PAH	10 (4)	30 (12)	18 (14)	12 (10)
Disease progression	10 (4)	16 (6)	12 (10)	4 (3)
Unsatisfactory long-term clinical response	17 (7)	23 (9)	11 (9)	12 (10)
Time to First Hospitalisation for Worsening PAH (Adjudicated)				
First hospitalisation, no. (%)	19 (8)	44 (18)	27 (21)	17 (14)
Hazard ratio (95% CI)		0.372	0.323	0.442
P-value, Log-rank test		0.0002	<0.0001	0.0124

Figure 2 Analysis of Adjudicated Events in the AMBITION Study



Note: The Forest Plot shows analyses of the time to first clinical failure event (adjudicated) [as in Table 1], time to death, time to first hospitalisation [as in Table 1], time to first disease progression and time to first unsatisfactory long-term response. Subjects may have had more than one type of event.

Secondary endpoints

Secondary endpoints were tested:

Table 2

Secondary Endpoints (change from baseline to week 24)	**Ambrisentan + Tadalafil**	**Monotherapy pooled**	Difference and Confidence Interval	p-value
NT-proBNP (% reduction)	-67.2	-50.4	% difference -33.8; 95% CI: -44.8, -20.7	p<0.0001
% subjects achieving a satisfactory clinical response at week 24	39	29	Odds ratio 1.56; 95% CI: 1.05, 2.32	p=0.026

6MWD (metres, median change)	49.0	23.8	22.75m; 95% CI: 12.00, 33.50	p<0.0001

12.1.2.3. Lack of Benefit and Increased Hospitalisations in Idiopathic Pulmonary Fibrosis
A study of 492 patients (ambrisentan N=329, placebo N=163) with idiopathic pulmonary fibrosis (IPF), 11% of which had secondary pulmonary hypertension (WHO group 3), was conducted but was terminated early when it was determined that the primary efficacy endpoint could not be met.

In this study, patients were randomized to ambrisentan or placebo in a 2:1 ratio. Ninety events (27%) of IPF progression (including respiratory hospitalisations) or death were observed in the ambrisentan group compared to 28 events (17%) in the placebo group.

Evaluation of the primary endpoint components indicated that there were higher rates of respiratory hospitalisations, mortality events, and decreases in respiratory function in the ambrisentan group versus placebo.

Ambrisentan is therefore contraindicated for patients with IPF with or without secondary pulmonary hypertension.

12.2. Pharmacokinetic properties

12.2.1. Absorption
Ambrisentan is absorbed rapidly in humans. Maximum plasma concentrations (C_{max}) of ambrisentan typically occur around 1.5 hours after oral administration 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% while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

12.2.2. 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 α1-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.

12.2.3. Metabolism
Ambrisentan is glucuronidated by several UGT enzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide. Ambrisentan also undergoes oxidative metabolism, mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19, to form 4-hydroxymethyl ambrisentan, which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide. In

plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4% relative to parent ambrisentan AUC. Furthermore, the binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore, 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro studies using rat and human hepatocyte cultures have demonstrated that ambrisentan is a possible substrate for the hepatic influx transporter OATP and for the efflux transporter P-gp, but not for the hepatic influx or efflux sodium-taurocholate co-transporter protein (NTCP) or bile salt export pump (BSEP), respectively.

In vitro data indicate that ambrisentan shows no marked inhibition of UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 at concentrations up to 300 µM. Further, *in vitro* studies using cell-lines transfected with the human transporter genes showed that ambrisentan does not inhibit P-gp, BCRP, MRP2, or BSEP at concentrations up to 100 µM. Ambrisentan showed weak *in vitro* inhibition of OATP1B1, OATP1B3 and sodium-taurocholate co-transporter (NTCP) with IC_{50} values of 47 µM, 45 µM, and approximately 100 µM, respectively. *In vitro* studies in rat and human hepatocytes showed no evidence for ambrisentan inhibition of NTCP, OATP, BSEP and MRP2. Furthermore, ambrisentan did not induce MRP2, P-gp or BSEP protein expression in rat hepatocytes. Taken together, the *in vitro* data suggest, ambrisentan at clinically relevant concentrations would not be expected to have an effect on UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 or transport via BSEP, BCRP, P-gp, MRP2, OATP1B1/3, or NTCP.

The effects of repeat dosing of cyclosporine 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 cyclosporine 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 cyclosporine A. Based on these changes, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (see *Posology and Method of Administration*). However, multiple doses of ambrisentan had no clinically relevant effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted.

The effects of repeat dosing of 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. This change in exposure is unlikely to be of any clinical relevance and therefore ambrisentan may be co-administered with ketoconazole. Based on the results from this study, no dose adjustment of ambrisentan is warranted upon concomitant administration with CYP3A inhibitors.

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 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 volunteers. With the exception of a 13% increase 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.

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 microgrammes 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 steady-state ambrisentan (10 mg once daily) on the pharmacokinetics and pharmacodynamics of a single dose of warfarin (25 mg), as measured by prothrombin time (PT) and international normalized ratio (INR), were investigated in 20 healthy volunteers. 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.

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.

12.2.4. Elimination

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. In the feces, 40% of the dose is recovered as parent ambrisentan and 21% as the 4-hydroxymethyl ambrisentan. Approximately 22% of the administered dose is recovered in the urine following oral administration with 3.3% being unchanged ambrisentan and the remainder as glucuronide metabolites. Steady-state plasma elimination half-life ranged from 13.6 to 16.5 hours in healthy volunteers and from 12.9 to 17.9 hours in patients with PAH.

12.2.5. Pharmacokinetics in special populations

12.2.5.1. Age and Gender

Based on the results of a population pharmacokinetic analysis in healthy volunteers and patients with PAH, the pharmacokinetics of ambrisentan were not significantly influenced by gender or age (see *Posology and Method of Administration*).

12.2.5.2. Hepatic Impairment
The pharmacokinetics of ambrisentan have not been studied in subjects with severe hepatic impairment or with clinically significant elevated hepatic transaminases. However, hepatic impairment might be expected to increase exposure (C_{max} and AUC) to ambrisentan, since its main routes of metabolism are glucuronidation and, to a lesser extent by oxidation, with subsequent elimination in the bile. The magnitude of this effect and any impact on safety and efficacy have 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 *Contraindications, Special Warnings and Special Precautions for Use* and *Posology and Method of Administration*).

Based on a final population pharmacokinetic model developed based on pharmacokinetic data from clinical trial subjects receiving ambrisentan, there was a significant relationship between ambrisentan CL/F and hepatic function as assessed by total bilirubin. However, the magnitudes of change in total bilirubin were relatively small.

12.2.5.3. Renal Impairment
The pharmacokinetics of ambrisentan have not been studied in subjects with renal impairment. However, renal metabolism and excretion of ambrisentan is minimal, so 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.

13. NON-CLINICAL INFORMATION

Teratogenicity is a class effect of ERAs. The effect of ambrisentan on embryo-fetal development has been assessed in rats and rabbits after oral dose administration on gestation days 6-17. In both species, abnormalities of the lower jaw, tongue, and/or palate were consistently observed at all doses. 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.

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.

There was no evidence of carcinogenic potential in 2-year oral daily dosing studies in rats and mice. There was a small increase in mammary fibroadenomas, a benign tumor, in male rats at the highest dose only.

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 characterize the effects of ambrisentan on either male or female 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.

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, apnea and hypoxia were observed, at exposures approximately 1.8 to 7.0 times human pediatric exposures at 10 mg (age 9 to 15 years), based on AUC. The clinical relevance of this finding to the pediatric population is not fully understood; however, the hypoxia was associated with a mechanically-induced apnea, which may be considered a potential risk only for young children (0 to 3 years) since the human oropharynx repositions with age (see *Recommended Pediatric and Adolescent Dosage*).

14. PHARMACEUTICAL PARTICULARS

14.1. List of excipients

Tablet Core
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose

Film-coat
FD&C Red 40 Aluminium Lake [5 mg and 10 mg tablets only, see section 6.5 *Excipients*]
Lecithin (Soya) USNF
Macrogol / PEG 3350
Polyvinyl alcohol (Partially Hydrolyzed)
Talc
Titanium dioxide

14.2. Incompatibilities

Not applicable.

14.3. Shelf life

The expiry date is indicated on the outer packaging.

14.4. Special precautions for storage

No special storage conditions are required. Store up to 30°C.

14.5. Nature and contents of container

Blister packs containing 3 strips of 10 tablets.

14.6. Special precautions for disposal

No special requirements.

14.7. Preparation of the medicinal product
Not applicable.

14.8. Preparation of extemporaneous formulations
Not applicable.

Not all presentations are available in every country.

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