ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Volibris 2.5 mg film-coated tablets
Volibris 5 mg film-coated tablets
Volibris 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Volibris 2.5 mg film-coated tablets

Each tablet contains 2.5 mg of ambrisentan.

Excipient(s) with known effect
Each tablet contains approximately 92.6 mg of lactose (as monohydrate) and approximately 0.25 mg of lecithin (soya) (E322).

Volibris 5 mg film-coated tablets

Each tablet contains 5 mg of ambrisentan.

Excipient(s) with known effect
Each tablet contains approximately 90.3 mg of lactose (as monohydrate), approximately 0.25 mg of lecithin (soya) (E322) and approximately 0.11 mg of allura red AC aluminium lake (E129).

Volibris 10 mg film-coated tablets

Each tablet contains 10 mg of ambrisentan.

Excipient(s) with known effect
Each tablet contains approximately 85.5 mg of lactose (as monohydrate), approximately 0.25 mg of lecithin (soya) (E322) and approximately 0.45 mg of allura red AC aluminium lake (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Volibris 2.5 mg film-coated tablets

White, 7 mm round, convex, film-coated tablet with “GS” debossed on one side and “K11” on the other side.

Volibris 5 mg film-coated tablets

Pale-pink, 6.6 mm square, convex, film-coated tablet with “GS” debossed on one side and “K2C” on the other side.

Volibris 10 mg film-coated tablets

Deep-pink, 9.8 mm × 4.9 mm oval, convex, film-coated tablet with “GS” debossed on one side and “KE3” on the other side.

4. CLINICAL PARTICULARS

4.1 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 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease (see section 5.1).

4.2 Posology and method of administration

Treatment must be initiated by a physician experienced in the treatment of PAH.

Posology

Adults
Ambrisentan monotherapy
Volibris is to be taken orally to begin at a dose of 5 mg once daily and may be increased to 10 mg daily depending upon clinical response and tolerability.

Ambrisentan in combination with tadalafil
When used in combination with tadalafil, Volibris should be titrated to 10 mg once daily.

In the AMBITION study, patients received 5 mg ambrisentan daily for the first 8 weeks before up titrating to 10 mg, dependent on tolerability (see section 5.1). When used in combination with tadalafil, patients were initiated with 5 mg ambrisentan and 20 mg tadalafil. Dependent on tolerability the dose of tadalafil was increased to 40 mg after 4 weeks and the dose of ambrisentan was increased to 10 mg after 8 weeks. More than 90% of patients achieved this. Doses could also be decreased depending on tolerability.

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

Ambrisentan in combination with cyclosporine A
In adults, 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 sections 4.5 and 5.2).

Paediatric patients aged 8 to less than 18 years
Ambrisentan monotherapy or in combination with other PAH therapies
Volibris is to be taken orally based on the dose regimen described below:

Body weight (kg)	Initial once daily dose (mg)	Subsequent once daily dose titration (mg)[a]
≥50	5	10
≥35 to <50	5	7.5
≥20 to <35	2.5	5
a =dependent on clinical response and tolerability (see section 5.1)		

Ambrisentan in combination with cyclosporine A
In paediatric patients, when co-administered with cyclosporine A, the dose of ambrisentan for patients ≥50 kg should be limited to 5 mg once daily, or for patients ≥20 to <50 kg should be limited to 2.5 mg once daily. The patient should be carefully monitored (see sections 4.5 and 5.2).

Special populations
Elderly patients
No dose adjustment is required in patients over the age of 65 (see section 5.2).

Patients with renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2). There is limited experience with ambrisentan in individuals with severe renal impairment (creatinine clearance <30 ml/min); therapy should be initiated cautiously in this subgroup and particular care taken if the dose is increased to 10 mg ambrisentan.

Patients with hepatic impairment
Ambrisentan has not been studied in individuals with hepatic impairment (with or without cirrhosis). Since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment might be expected to increase exposure (C_{max} and AUC) to ambrisentan. Therefore, ambrisentan must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (>3xULN); see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of ambrisentan in children below 8 years of age have not been established. No clinical data are available (see section 5.3 regarding data available in juvenile animals).

Method of administration

Volibris is for oral use. 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.

4.3 Contraindications

Hypersensitivity to the active substance, to soya, or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

Women of child-bearing potential who are not using reliable contraception (see sections 4.4 and 4.6).

Breast-feeding (see section 4.6).

Severe hepatic impairment (with or without cirrhosis) (see section 4.2).

Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT))>3xULN (see sections 4.2 and 4.4).

Idiopathic pulmonary fibrosis (IPF), with or without secondary pulmonary hypertension (see section 5.1).

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 WHO functional class I PAH.

The efficacy of ambrisentan as monotherapy has not been established in patients with WHO functional class IV PAH. Therapy that is recommended at the severe stage of the disease (e.g. epoprostenol) should be considered if the clinical condition deteriorates.

Liver function

Liver function abnormalities have been associated with PAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, hepatic injury and hepatic enzyme elevations potentially related to therapy have been observed with ambrisentan (see sections 4.8 and 5.1). Therefore, hepatic aminotransferases (ALT and AST) should be evaluated prior to initiation of ambrisentan and treatment should not be initiated in patients with baseline values of ALT and/or AST >3xULN (see section 4.3).

Patients should be monitored for signs of hepatic injury and monthly monitoring of ALT and AST is recommended. If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of ambrisentan may be considered following resolution of hepatic enzyme abnormalities. The advice of a hepatologist is recommended.

Haemoglobin concentration

Reductions in haemoglobin concentrations and haematocrit have been associated with endothelin receptor antagonists (ERAs) including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilised thereafter. 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. In the post-marketing period, cases of anaemia requiring blood cell transfusion have been reported (see section 4.8).

Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. It is recommended that haemoglobin and/or haematocrit levels are measured during treatment with ambrisentan, for example at 1 month, 3 months and periodically thereafter in line with clinical practice. If a clinically significant decrease in haemoglobin or haematocrit is observed, and other causes have been excluded, dose reduction or 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).

Fluid retention

Peripheral oedema has been observed with ERAs including ambrisentan. Most cases of peripheral oedema in clinical studies with ambrisentan were mild to moderate in severity, although it may occur with greater frequency and severity in patients ≥65 years. Peripheral oedema was reported more frequently with 10 mg ambrisentan in short-term clinical studies (see section 4.8).

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 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.

Women of child-bearing potential

Volibris treatment must not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist should be considered. Monthly pregnancy tests during treatment with ambrisentan are recommended (see sections 4.3 and 4.6).

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilating medicinal products, such as ERAs, when used in patients with pulmonary veno-occlusive disease. Consequently, if PAH patients develop acute pulmonary oedema when treated with ambrisentan, the possibility of pulmonary veno-occlusive disease should be considered.

Concomitant use with other medicinal products

Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.5 and 5.2).

Excipients

Volibris 2.5 mg, 5 mg and 10 mg film-coated tablets
Lactose
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Lecithin (soya)
This medicinal product contains lecithin derived from soya. If a patient is hypersensitive to soya, ambrisentan must not be used (see section 4.3).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Volibris 5 mg and 10 mg film-coated tablets
Allura red AC aluminium lake
Volibris 5 mg and 10 mg tablets contain the azo colouring agent allura red AC aluminium lake (E129), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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, suggesting a low potential for ambrisentan to alter the profile of medicinal products metabolised 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.

Cyclosporine A

Steady-state co-administration of ambrisentan and cyclosporine A resulted in a 2-fold increase in ambrisentan exposure in healthy volunteers. This may be due to the inhibition by cyclosporine A of transporters and metabolic enzymes involved in the pharmacokinetics of ambrisentan. Therefore,

when co-administered with cyclosporine A, the dose of ambrisentan in adult patients or paediatric patients weighing ≥50 kg should be limited to 5 mg once daily; for paediatric patients ≥20 to <50 kg the dose should be limited to 2.5 mg once daily (see section 4.2). Multiple doses of ambrisentan had no effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted.

Rifampicin

Co-administration of rifampicin (an inhibitor of Organic Anion Transporting Polypeptide [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 8, steady state administration of rifampicin had no clinically relevant effect on ambrisentan exposure. Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.4 and 5.2).

Phosphodiesterase inhibitors

Co-administration of ambrisentan with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP3A4) in healthy volunteers did not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or ambrisentan (see section 5.2).

Other targeted PAH treatments

The efficacy and safety of ambrisentan when co-administered with other treatments for PAH (e.g. prostanoids and soluble guanylate cyclase stimulators) has not been specifically studied in controlled clinical trials in PAH patients (see section 5.1). No specific interactions between ambrisentan and soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see section 5.2). However, no specific interactions studies have been conducted with these medicinal products. Therefore, caution is recommended in the case of co-administration.

Oral contraceptives

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

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). 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) and international normalised ratio (INR).

Ketoconazole

Steady-state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to ambrisentan (see section 5.2).

Effect of ambrisentan on xenobiotic transporters

In vitro, ambrisentan has no inhibitory effect on human transporters at clinically relevant concentrations, including the P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), multi-drug resistance related protein 2 (MRP2), bile salt export pump (BSEP), organic anion transporting

polypeptides (OATP1B1 and OATP1B3) and the sodium-dependent taurocholate co-transporting polypeptide (NTCP).

Ambrisentan is a substrate for Pgp-mediated efflux.

In vitro studies in rat hepatocytes also showed that ambrisentan did not induce Pgp, 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 Pgp (see section 5.2).

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Ambrisentan treatment must not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. Monthly pregnancy tests during treatment with ambrisentan are recommended.

Pregnancy

Ambrisentan is contraindicated in pregnancy (see section 4.3). Animal studies have shown that ambrisentan is teratogenic. There is no experience in humans.

Women receiving ambrisentan must be advised of the risk of foetal harm and alternative therapy initiated if pregnancy occurs (see sections 4.3, 4.4 and 5.3).

Breast-feeding

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 (see section 4.3).

Male fertility

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of ERAs, including ambrisentan (see section 5.3). Although no clear evidence of a detrimental effect of ambrisentan long-term exposure on sperm count was found in ARIES-E study, chronic administration of ambrisentan was associated with changes in markers of spermatogenesis. A decrease in plasma inhibin-B concentration and an increase in plasma FSH concentration were observed. The effect on male human fertility is not known but a deterioration of spermatogenesis cannot be excluded. Chronic administration of ambrisentan was not associated with a change in plasma testosterone in clinical studies.

4.7 Effects on ability to drive and 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 judgement, motor or cognitive skills (see section 4.8). Patients should be aware of how they might be affected by ambrisentan before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

Peripheral oedema (37%) and headache (28%) were the most common adverse reactions observed with ambrisentan. The higher dose (10 mg) was associated with a higher incidence of these adverse reactions, and peripheral oedema tended to be more severe in patients ≥65 years in short-term clinical studies (see section 4.4).

Serious adverse reactions associated with ambrisentan use include anaemia (decreased haemoglobin, decreased haematocrit) and hepatotoxicity.

Reductions in haemoglobin concentrations and haematocrit (10%) have been associated with ERAs including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilised thereafter (see section 4.4).

Hepatic enzyme elevations (2%), hepatic injury and autoimmune hepatitis (including exacerbation of underlying disease) have been observed with ambrisentan (see sections 4.4 and 5.1).

Tabulated list of adverse reactions

Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<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. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	**Frequency**	**Adverse reaction(s)**
Blood and lymphatic system disorders	Very common	Anaemia (decreased haemoglobin, decreased haematocrit)[1]
Immune system disorders	Common	Hypersensitivity reactions (e.g. angioedema, rash, pruritus)
Nervous system disorders	Very common	Headache (including sinus headache, migraine)[2], dizziness
Eye disorders	Common	Blurred vision, visual impairment
Ear and labyrinth disorders	Common	Tinnitus[3]
	Uncommon	Sudden hearing loss[3]
Cardiac disorders	Very common	Palpitation
	Common	Cardiac failure[4]
Vascular disorders	Very common	Flushing[5]
	Common	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea[6], upper respiratory (e.g. nasal, sinus) congestion[7], nasopharyngitis[7]
	Common	Epistaxis, rhinitis[7], sinusitis[7]

Gastrointestinal disorders	Very common	Nausea, diarrhoea, vomiting[5]
	Common	Abdominal pain, constipation
Hepatobiliary disorders	Common	Hepatic transaminases increased
	Uncommon	Hepatic injury (see section 4.4), autoimmune hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders	Common	Rash[8]
General disorders and administration site conditions	Very common	Peripheral oedema, fluid retention, chest pain/discomfort[5], fatigue
	Common	Asthenia

1 See section '*Description of selected adverse reactions*'.
2 The frequency of headache appeared higher with 10 mg ambrisentan.
3 Cases were only observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil.
4 Most of the reported cases of cardiac failure were associated with fluid retention.
5 Frequencies were observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil. Lower incidence was observed with ambrisentan monotherapy.
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 Rash includes rash erythematous, rash generalised, rash papular and rash pruritic.

Description of selected adverse reactions

Decreased haemoglobin
In the post-marketing period, cases of anaemia requiring blood cell transfusion have been reported (see section 4.4). The frequency of decreased haemoglobin (anaemia) was higher with 10 mg ambrisentan. Across the 12 week placebo controlled Phase 3 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.

Paediatric population

The safety of ambrisentan in paediatric patients with PAH aged 8 to less than 18 years was evaluated in 41 patients who were treated with once daily ambrisentan 2.5 mg or 5 mg (low dose group) or once daily ambrisentan 2.5 mg or 5 mg titrated to 5 mg, 7.5 mg, or 10 mg based on body weight (high dose group) alone or in combination with other PAH medicinal products for 24 weeks in a Phase 2b open label trial. Safety was further evaluated in a long-term extension study in 38 of the 41 subjects. The adverse reactions observed, which were assessed as related to ambrisentan, were consistent with those observed in controlled studies in adult patients, with headache (15%, 6/41 subjects during the 24 weeks of the Phase 2b open label trial and 8%, 3/38 subjects during the long-term extension study) and nasal congestion (7%, 3/41 subjects during the 24 weeks of the Phase 2b open label trial) occurring most commonly.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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 the mechanism of action, an overdose of ambrisentan could potentially result in hypotension (see section 5.3). In the case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Ambrisentan is an ET_A antagonist (approximately 4 000-fold more selective for ET_A as compared to ET_B). Ambrisentan blocks the ET_A receptor subtype, localised 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.

Clinical efficacy and safety

Two randomised, double-blind, multi-centre, placebo controlled, Phase 3 pivotal studies were conducted (ARIES-1 and 2). ARIES-1 included 201 patients and compared ambrisentan 5 mg and 10 mg with placebo. ARIES-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 medicines, which could have included a combination of digoxin, anticoagulants, diuretics, oxygen and vasodilators (calcium channel blockers, ACE inhibitors). Patients enrolled had IPAH or PAH associated with connective tissue disease (PAH-CTD). The majority of patients had WHO functional Class II (38.4%) or Class III (55.0%) symptoms. 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 primary endpoint defined for the Phase 3 studies was improvement in exercise capacity assessed by change from baseline in 6 minute walk distance (6MWD) at 12 weeks. In both studies, treatment with ambrisentan resulted in a significant improvement in 6MWD for each dose of ambrisentan.

The placebo-adjusted improvement in mean 6MWD at week 12 compared to baseline was 30.6 m (95% CI: 2.9 to 58.3; p= 0.008) and 59.4 m (95% CI: 29.6 to 89.3; p< 0.001) for the 5 mg group, in ARIES-1 and 2 respectively. The placebo-adjusted improvement in mean 6MWD at week 12 in patients in the 10 mg group in ARIES-1 was 51.4 m (95% CI: 26.6 to 76.2; p < 0.001).

A pre-specified combined analysis of the Phase 3 studies (ARIES-C) was conducted. The placebo-adjusted mean improvement in 6MWD was 44.6 m (95% CI: 24.3 to 64.9; p< 0.001) for the 5 mg dose, and 52.5 m (95% CI: 28.8 to 76.2; p< 0.001) for the 10 mg dose.

In ARIES-2, ambrisentan (combined dose group) significantly delayed the time to clinical worsening of PAH compared to placebo ($p< 0.001$), the hazard ratio demonstrated an 80% reduction (95% CI: 47% to 92%). The measure included: death, lung transplantation, hospitalisation for PAH, atrial septostomy, addition of other PAH therapeutic agents and early escape criteria. A statistically significant increase (3.41 ± 6.96) was observed for the combined dose group in the physical functioning scale of the SF-36 Health Survey compared with placebo (-0.20 ± 8.14, $p= 0.005$). Treatment with ambrisentan led to a statistically significant improvement in Borg Dyspnea Index (BDI) at week 12 (placebo-adjusted BDI of -1.1 (95% CI: -1.8 to -0.4; $p= 0.019$; combined dose group)).

Long-term data

Patients enrolled into ARIES-1 and 2 were eligible to enter a long-term open label extension study ARIES-E (n= 383). The combined mean exposure was approximately 145 ± 80 weeks, and the maximum exposure was approximately 295 weeks. The main primary endpoints of this study were the incidence and severity of adverse events associated with long-term exposure to ambrisentan, including serum LFTs. The safety findings observed with long-term ambrisentan exposure in this study were generally consistent with those observed in the 12 week placebo-controlled studies.

The observed probability of survival for subjects receiving ambrisentan (combined ambrisentan dose group) at 1, 2 and 3 years was 93%, 85% and 79% respectively.

In an open label study (AMB222), 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.

The cumulative incidence of serum aminotransferase abnormalities >3xULN in all Phase 2 and 3 studies (including respective open label extensions) was 17 of 483 subjects 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. In the ARIES-E open label long-term extension study, the 2 year risk of developing serum aminotransferase elevations >3xULN in patients treated with ambrisentan was 3.9%.

Other clinical information

An improvement in haemodynamic parameters was observed in patients with PAH after 12 weeks (n= 29) in a Phase 2 study (AMB220). Treatment with ambrisentan resulted in an increase in mean cardiac index, a decrease in mean pulmonary artery pressure, and a decrease in mean pulmonary vascular resistance.

Decrease in systolic and diastolic blood pressures has been reported with ambrisentan therapy. In placebo controlled clinical trials of 12 weeks duration mean reduction in systolic and diastolic blood pressures from base line to end of treatment were 3 mm Hg and 4.2 mm Hg respectively. The mean decreases in systolic and diastolic blood pressures persisted for up to 4 years of treatment with ambrisentan in the long-term open label ARIES-E study.

No clinically meaningful effects on the pharmacokinetics of ambrisentan or sildenafil were seen during an interaction study in healthy volunteers, and the combination was well tolerated. The number of patients who received concomitant ambrisentan and sildenafil in ARIES-E and AMB222 was 22 patients (5.7%) and 17 patients (47%), respectively. No additional safety concerns were identified in these patients.

Clinical efficacy in combination with tadalafil

A multi-centre, 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 >2xULN 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 m.

Outcome endpoints
Treatment with combination therapy resulted in a 50% risk reduction (hazard ratio [HR] 0.502; 95% CI: 0.348 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

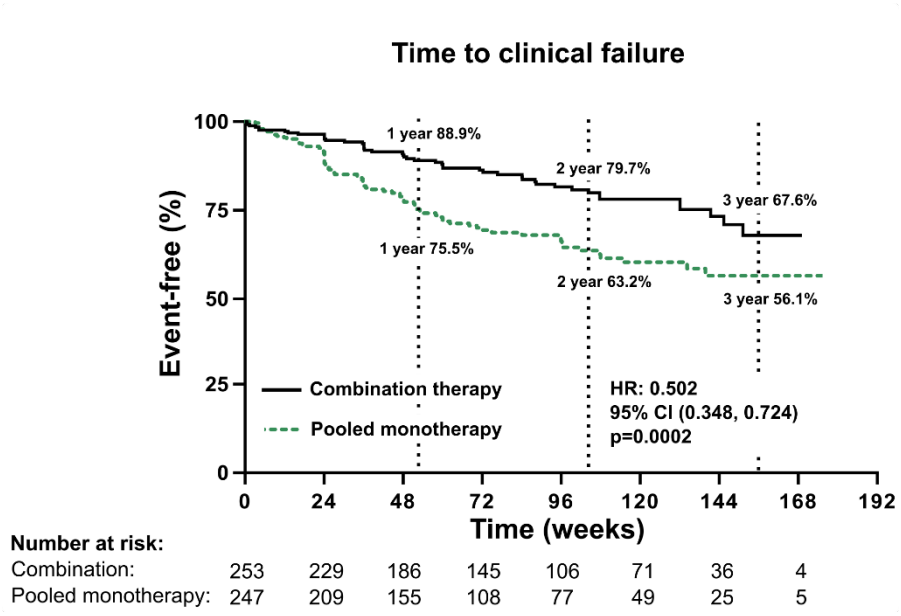


Table 1

	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)	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

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

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), has been conducted, but was terminated early when it was determined that the primary efficacy endpoint could not be met (ARTEMIS-IPF study). 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. Ambrisentan is therefore contraindicated for patients with IPF with or without secondary pulmonary hypertension (see section 4.3).

Paediatric population

AMB112529 study
The safety and tolerability of ambrisentan once daily for 24 weeks was evaluated in an open-label uncontrolled study in 41 paediatric patients with PAH aged 8 to less than 18 years (median: 13 years). The aetiology of PAH was idiopathic (n= 26; 63%), persistent congenital PAH despite surgical repair (n= 11; 27%), secondary to connective tissue disease (n= 1; 2%), or familial (n= 3; 7.3%). Among the

11 subjects with congenital heart disease, 9 had ventricular septal defects, 2 had atrial septal defects and 1 had a persistent patent ductus. Patients were in WHO functional class II (n= 32; 78%) or class III (n= 9; 22%) at start of study treatment. At study entry, patients were treated with PAH medicinal products (most frequently PDE5i monotherapy [n= 18; 44%], PDE5i and prostanoid combination therapies [n= 8; 20%]) or prostanoid monotherapy [n= 1; 2%], and they continued their PAH treatment during the study. Patients were divided into two dose groups: once daily ambrisentan 2.5 mg or 5 mg (low dose, n= 21) and once daily ambrisentan 2.5 mg or 5 mg titrated to 5 mg, 7.5 mg, or 10 mg based on body weight (high dose, n= 20). A total of 20 patients from both dose groups were titrated at 2 weeks based on clinical response and tolerability; 37 patients completed the study; 4 patients withdrew from the study.

There was no dose trend observed in the effect of ambrisentan on the main efficacy outcome of exercise capacity (6MWD). The mean change from baseline at week 24 in 6MWD for patients in the low and high dose groups with a measurement at baseline and at 24 weeks was + 55.14 m (95% CI: 4.32 to 105.95) in 18 patients and + 26.25 m (95% CI: -4.59 to 57.09) in 18 patients, respectively. The mean change from baseline at week 24 in 6MWD for the 36 total patients (both doses pooled) was + 40.69 m (95% CI: 12.08 to 69.31). These results were consistent with those observed in adults. At week 24, 95% and 100% of patients in the low and high dose groups, respectively, remained stable (functional class unchanged or improved). The Kaplan-Meier event-free survivor estimate for worsening of PAH (death [all cause], lung transplantation, or hospitalisation for PAH worsening or PAH-related deterioration) at 24 weeks was 86% and 85% in the low- and high dose groups, respectively.

Haemodynamics were measured in 5 patients (low dose group). The mean increase from baseline in cardiac index was + 0.94 L/min/m^2, the mean decrease in mean pulmonary arterial pressure was - 2.2 mmHg, and the mean decrease in PVR was - 277 dyn s/cm^5 (- 3.46 mmHg/L/min).

In paediatric patients with PAH who received ambrisentan for 24 weeks, geometric mean decrease from baseline in NT-pro-BNP was 31% in the low dose group (2.5 and 5 mg) and 28% in the high dose group (5, 7.5, and 10 mg).

AMB114588 study

Long-term data were generated from 38 of the 41 paediatric patients with PAH aged 8 to less than 18 years who were treated with ambrisentan in the 24-week randomised study. Most of the subjects who transitioned into this long-term extension had idiopathic or heritable PAH (68%) as per AMB112529 Baseline. The mean duration of exposure (± standard deviation) to ambrisentan treatment was approximately 4.0 ± 2.5 years (range: 3 months to 10.0 years). Patients could receive additional PAH treatment as required in the open-label extension and ambrisentan dose could be adjusted by 2.5 mg increments. Overall, 66% of patients who continued in the extension study remained on the same dose of ambrisentan used in AMB112529.

Clinical worsening was defined as death (all cause), listing for lung transplant or atrial septostomy, or PAH deterioration leading to hospitalisation, change in ambrisentan dose, addition of or change in dose of existing targeted PAH therapeutic agent, increase in WHO Functional class; 20% decrease in 6MWD or signs/symptoms of right sided heart failure. At the same timepoints, a total of 71% of patients remained free from PAH worsening, while 11 participants (29%) across all 4 dose groups experienced an occurrence of clinical worsening of PAH based on at least 1 criterion, with more than 1 clinical worsening criterion met by 5 of 11 participants (45%). Kaplan-Meier estimates of survival were 94.74% and 92.11% at 3 and 4 years after the start of treatment.

Changes from AMB112529 baseline to the end of the extension study showed a mean increase in 6MWD of 58.4 ± 88 metres (17% improvement vs. baseline) across all dose groups.

At AMB114588 Study Entry, all 4 WHO Functional Classes (I, II, III and IV) were represented by participants with over half meeting Class II (n=22; 58%) and the remaining participants meeting Class I (n=9; 24%), Class III (n=6; 16%) or Class IV (n=1; 3%). Changes from AMB112529 baseline to the

end of the extension study (N=29) showed an improvement (45%) or no change (55%), and no deterioration, in WHO functional class as well as a mean increase in 6MWD of 17.0%. respectively.

5.2 Pharmacokinetic properties

Absorption

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% while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

Distribution

Ambrisentan is highly plasma protein bound. The *in vitro* plasma protein binding of ambrisentan was, on average, 98.8% and independent of concentration over the range of 0.2–20 microgram/ml. Ambrisentan is primarily bound to albumin (96.5%) and to a lesser extent to alpha$_1$-acid glycoprotein.

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

Biotransformation

Ambrisentan is a non-sulphonamide (propanoic acid) ERA.

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 4% relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro data indicate that ambrisentan at 300 μM resulted in less than 50% inhibition of UGT1A1, UGT1A6, UGT1A9, UGT2B7 (up to 30%) or of cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 (up to 25%). *In vitro*, ambrisentan has no inhibitory effect on human transporters at clinically relevant concentrations, including Pgp, BCRP, MRP2, BSEP, OATP1B1, OATP1B3 and NTCP. Furthermore, ambrisentan did not induce MRP2, Pgp or BSEP protein expression in rat hepatocytes. Taken together, the *in vitro* data suggest ambrisentan at clinically relevant concentrations (plasma C_{max} up to 3.2 μM) 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, Pgp, MRP2, OATP1B1/3, or NTCP.

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 PT and 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 did not affect the pharmacokinetics of ambrisentan (see section 4.5).

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 (see section 4.5).

The effects of steady-state ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of tadalafil, and the effects of steady-state tadalafil (40 mg once daily) on the pharmacokinetics of a single dose of ambrisentan were studied in 23 healthy volunteers. Ambrisentan did not have any clinically relevant effects on the pharmacokinetics of tadalafil. Similarly, co-administration with tadalafil did not affect the pharmacokinetics of ambrisentan (see section 4.5).

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.

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 $AUC(0\text{-}_{\tau})$ of ambrisentan increased (48% and 121%, respectively) in the presence of multiple doses of cyclosporine A. Based on these changes, when co-administered with cyclosporine A, the dose of ambrisentan in adult patients or paediatric patients weighing ≥ 50 kg should be limited to 5 mg once daily; for paediatric patients ≥ 20 to < 50 kg the dose should be limited to 2.5 mg once daily (see section 4.2). 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 acute and repeat dosing of rifampicin (600 mg once daily) on the steady-state pharmacokinetics of ambrisentan (10 mg once daily) were studied in healthy volunteers. Following initial doses of rifampicin, a transient increase in ambrisentan $AUC(0\text{–}_{\tau})$ (121% and 116% after first and second doses of rifampicin, respectively) was observed, presumably due to a rifampicin-mediated OATP inhibition. However, there was no clinically relevant effect on ambrisentan exposure by day 8, following administration of multiple doses of rifampicin. Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin (see sections 4.4 and 4.5).

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 digoxin is warranted (see section 4.5).

The effects of 12 days dosing with ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of oral contraceptive containing ethinyl estradiol (35 μg) and norethindrone (1 mg) were studied in healthy female volunteers. The C_{max} and $AUC_{(0\text{–}\infty)}$ 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 (see section 4.5).

Elimination

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. 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

Adult population (gender, age)
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 section 4.2).

Paediatric population
There are limited pharmacokinetic data available in the paediatric population. Pharmacokinetics were studied in paediatric subjects 8 to less than 18 years of age in one clinical study (AMB112529).

Ambrisentan pharmacokinetics following oral administration in subjects 8 to less than 18 years of age with PAH were broadly consistent with the adult pharmacokinetics after accounting for body weight. Model derived paediatric exposures at steady state (AUCss) for the low doses and high doses for all body weight groups were within the 5^{th} and 95^{th} percentiles of the historical adult exposure at low dose (5 mg) or high dose (10 mg), respectively.

Renal impairment
Ambrisentan does not undergo significant renal metabolism or renal clearance (excretion). In a population pharmacokinetic analysis, creatinine clearance was found to be a statistically significant covariate affecting the oral clearance of 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 (see section 4.2).

Hepatic impairment
The main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile and therefore hepatic impairment might be expected to increase exposure (C_{max} and AUC) of ambrisentan. In a population pharmacokinetic analysis, the oral clearance was shown to be decreased as a function of increasing bilirubin levels. However, the magnitude of effect of bilirubin is modest (compared to the typical patient with a bilirubin of 0.6 mg/dl, a patient with an elevated bilirubin of 4.5 mg/dl would have approximately 30% lower oral clearance of ambrisentan). The pharmacokinetics of ambrisentan in patients with hepatic impairment (with or without cirrhosis) has not been studied. Therefore, ambrisentan should not be initiated in patients with severe hepatic impairment or clinically significant elevated hepatic aminotransferases (> 3xULN) (see sections 4.3 and 4.4).

5.3 Preclinical safety data

Due to the class primary pharmacologic effect, a large single dose of ambrisentan (i.e. an overdose) could lower arterial pressure and have the potential for causing hypotension and symptoms related to vasodilation.

Ambrisentan was not shown to be an inhibitor of bile acid transport or to produce overt hepatotoxicity.

Inflammation and changes in the nasal cavity epithelium have been seen in rodents after chronic administration at exposures below the therapeutic levels in humans. In dogs, slight inflammatory responses were observed following chronic high dose administration of ambrisentan at exposures greater than 20–fold that observed in patients.

Nasal bone hyperplasia of the ethmoid turbinates has been observed in the nasal cavity of rats treated with ambrisentan, at exposure levels 3-fold the clinical AUC. Nasal bone hyperplasia has not been observed with ambrisentan in mice or dogs. In the rat, hyperplasia of nasal turbinate bone is a recognised response to nasal inflammation, based on experience with other compounds.

Ambrisentan was clastogenic when tested at high concentrations in mammalian cells *in vitro*. No evidence for mutagenic or genotoxic effects of ambrisentan were seen in bacteria or in two *in vivo* rodent studies.

There was no evidence of carcinogenic potential in 2 year oral studies in rats and mice. There was a small increase in mammary fibroadenomas, a benign tumor, in male rats at the highest dose only. Systemic exposure to ambrisentan in male rats at this dose (based on steady-state AUC) was 6-fold that achieved at the 10 mg/day clinical dose.

Testicular tubular atrophy, which was occasionally associated with aspermia, was observed in oral repeat dose toxicity and fertility studies with male rats and mice without safety margin. The testicular changes were not fully recoverable during the off-dose periods evaluated. However no testicular changes were observed in dog studies of up to 39 weeks duration at an exposure 35–fold that seen in humans based on AUC. In male rats, there were no effects of ambrisentan on sperm motility at all doses tested (up to 300 mg/kg/day). A slight (< 10%) decrease in the percentage of morphologically normal sperms was noted at 300 mg/kg/day but not at 100 mg/kg/day (> 9-fold clinical exposure at 10 mg/day). The effect of ambrisentan on male human fertility is not known.

Ambrisentan has been shown to be teratogenic in rats and rabbits. Abnormalities of the lower jaw, tongue, and/or palate were seen at all doses tested. In addition, 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. Teratogenicity is a suspected class effect of ERAs.

Administration of ambrisentan to female rats from late-pregnancy through lactation caused adverse events on maternal behaviour, reduced pup survival and impairment of the reproductive capability of the offspring (with observation of small testes at necropsy), at exposure 3-fold the AUC at the maximum recommended human dose.

In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36 or 62 (corresponding from neonates to late adolescence in humans), a decrease in brain weight (-3% to -8%) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnoea and hypoxia were observed. These effects occurred at AUC levels which were 1.8 to 7 times higher than the human paediatric exposure at 10 mg. In another study, when 5-week old rats (corresponding to an age of approximately 8 years in humans) were treated, brain-weight decrease was observed only at a very high dose in males only. Available non-clinical data do not allow an understanding of the clinical relevance of this finding in children younger than 8 years old.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film-coat

Volibris 2.5 mg film-coated tablets
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Macrogol
Lecithin (soya) (E322)

Volibris 5 mg and 10 mg film-coated tablets
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Macrogol
Lecithin (soya) (E322)
Allura red AC aluminium lake (E129)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Volibris 2.5 mg film-coated tablets

2 years

Volibris 5 mg and 10 mg film-coated tablets

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Volibris 2.5 mg film-coated tablets

Opaque, white high density polyethylene (HDPE) bottles closed with polypropylene child-resistant closures with a polyethylene faced induction heat seal liner.
The bottles contain 30 film-coated tablets.

Volibris 5 mg and 10 mg film-coated tablets

PVC/PVDC/aluminium foil blisters.
Pack sizes with unit dose blisters of 10 × 1 or 30 × 1 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Volibris 2.5 mg film-coated tablets

EU/1/08/451/005

Volibris 5 mg film-coated tablets

EU/1/08/451/001
EU/1/08/451/002

Volibris 10 mg film-coated tablets

EU/1/08/451/003
EU/1/08/451/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 April 2008
Date of latest renewal: 14 January 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to use of Volibris in each Member State the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Volibris is marketed, all patients who are expected to use Volibris are provided with the following educational material:

- Patient reminder card

Patient reminder card should include the following key elements:

– That Volibris is teratogenic in animals;

- That pregnant women must not take Volibris;
- That women of reproductive potential must use effective contraception;
- The need for monthly pregnancy tests;
- The need for regular monitoring of liver function because Volibris may cause liver injury.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Volibris 2.5 mg film-coated tablets
ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose, lecithin (soya) (E322). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/451/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

volibris 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Volibris 2.5 mg film-coated tablets
ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2.5 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose, lecithin (soya) (E322). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/451/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Volibris 5 mg film-coated tablets
ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose, lecithin (soya) (E322) and allura red AC aluminium lake (E129). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

10 x 1 film-coated tablets
30 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/451/001 10 film-coated tablets
EU/1/08/451/002 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

volibris 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Volibris 5 mg tablets
ambrisentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
GSK (Ireland) Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Volibris 10 mg film-coated tablets
ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose, lecithin (soya) (E322) and allura red AC aluminium lake (E129). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

10 x 1 film-coated tablets
30 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/451/003 10 film-coated tablets
EU/1/08/451/004 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

volibris 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Volibris 10 mg tablets
ambrisentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
GSK (Ireland) Ltd

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Volibris 2.5 mg film-coated tablets
Volibris 5 mg film-coated tablets
Volibris 10 mg film-coated tablets
ambrisentan

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Volibris is and what it is used for

Volibris contains the active substance ambrisentan. It belongs to a group of medicines called other antihypertensives (used to treat high blood pressure).

It is used to treat pulmonary arterial hypertension (PAH) in adults, adolescents and children aged 8 years and over. PAH is high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy and short of breath.

Volibris widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure and relieves the symptoms.

Volibris may also be used in combination with other medicines used to treat PAH.

2. What you need to know before you take Volibris

Don't take Volibris:
- if you are **allergic** to ambrisentan, soya, or any of the other ingredients of this medicine (listed in section 6)
- **if you are pregnant,** if you are **planning to become pregnant,** or if you **could become pregnant** because you are not using reliable birth control (contraception). Please read the information under 'Pregnancy'
- if you are **breast-feeding**. Read the information under 'Breast-feeding'
- if you have **liver disease**. Talk to your doctor, who will decide whether this medicine is suitable for you
- if you have **scarring of the lungs**, of unknown cause (*idiopathic pulmonary fibrosis*).

Warnings and precautions
Talk to your doctor before taking this medicine:
- if you have liver problems

- if you have anaemia (a reduced number of red blood cells)
- if you have swelling in the hands, ankles or feet caused by fluid (*peripheral oedema*)
- if you have lung disease where the veins in the lungs are blocked (*pulmonary veno-occlusive disease*).

→ **Your doctor will decide** whether Volibris is suitable for you.

You will need regular blood tests
Before you start taking Volibris, and at regular intervals while you are taking it, your doctor will take blood tests to check:
- whether you have anaemia
- whether your liver is working properly.

→ It is important that you have these regular blood tests for as long as you are taking Volibris.

Signs that your liver may not be working properly include:
- loss of appetite
- feeling sick (*nausea*)
- being sick (*vomiting*)
- high temperature (*fever*)
- pain in your stomach (*abdomen*)
- yellowing of your skin or the whites of your eyes (*jaundice*)
- dark-coloured urine
- itching of your skin.

If you notice any of these signs:

→ **Tell your doctor immediately.**

Children
Do not give this medicine to children aged under 8 years as the safety and effectiveness is not known in this age group.

Other medicines and Volibris
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If you start taking **cyclosporine A** (a medicine used after transplant or to treat psoriasis), your doctor may need to adjust your dose of Volibris.

If you are taking **rifampicin** (an antibiotic used to treat serious infections), your doctor will monitor you when you first start taking Volibris.

If you are taking other medicines to treat PAH (e.g. iloprost, epoprostenol, sildenafil) your doctor may need to monitor you.

→ **Tell your doctor or pharmacist** if you are taking any of these medicines.

Pregnancy
Volibris may harm unborn babies conceived before, during or soon after treatment.

→ **If it is possible you could become pregnant, use a reliable form of birth control** (contraception) while you are taking Volibris. Talk to your doctor about this.

→ **Don’t take Volibris if you are pregnant or planning to become pregnant.**

→ If you become pregnant or think that you may be pregnant while you are taking Volibris, **see your doctor immediately.**

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking Volibris and regularly while you are taking this medicine.

Breast-feeding
It is not known if the active substance of Volibris can pass into breast milk.

→ Don't breast-feed while you are taking Volibris. Talk to your doctor about this.

Fertility
If you are a man taking Volibris, it is possible that this medicine may lower your sperm count. Talk to your doctor if you have any questions or concerns about this.

Driving and using machines
Volibris may cause side effects, such as low blood pressure, dizziness, tiredness (see section 4), that may affect your ability to drive or use machines. The symptoms of your condition can also make you less fit to drive or use machines.

→ Don't drive or use machines if you are feeling unwell.

Volibris contains lactose
Volibris tablets contain small amounts of a sugar called lactose. If you have been told by your doctor that you have an intolerance to some sugars:

→ Contact your doctor before taking this medicinal product.

Volibris contains lecithin derived from soya
If you are allergic to soya, do not use this medicine (see section 2 'Don't take Volibris').

Volibris 5 mg and 10 mg tablets contain a colouring called allura red AC aluminium lake (E129)
This may cause allergic reactions (see section 4).

Volibris contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Volibris

Always take this medicine exactly as your doctor or pharmacist has told you to. Check with your doctor or pharmacist if you are not sure.

How much Volibris to take

Adults
The usual dose of Volibris is one 5 mg tablet, once a day. Your doctor may decide to increase your dose to 10 mg, once a day.

If you take cyclosporine A, do not take more than one 5 mg tablet of Volibris, once a day.

Adolescents and children aged 8 years to less than 18 years

Usual starting dose of Volibris	
Weighing 35 kg or more	One **5 mg** tablet, once a day
Weighing at least 20 kg, and less than 35 kg	One **2.5 mg** tablet, once a day

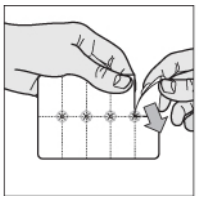
Your doctor may decide to increase your dose. It's important that children attend their regular doctor's appointments, as their dose needs to be adjusted as they get older or gain weight.

If taken in combination with cyclosporin A, the dose of Volibris for adolescents and children weighing less than 50 kg will be limited to 2.5 mg once daily, or 5 mg once daily if they weigh 50 kg or more.

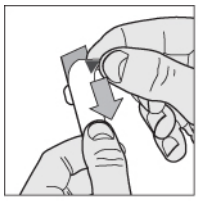
How to take Volibris
It is best to take your tablet at the same time each day. Swallow the tablet whole, with a glass of water, do not split, crush or chew the tablet. You can take Volibris with or without food.

Taking out a tablet from a blister pack (5 mg and 10 mg tablets only)
These tablets come in special packaging to prevent children removing them.

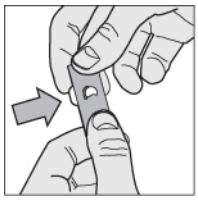
1. Separate one tablet: tear along the cutting lines to separate one "pocket" from the strip.



2. Peel back the outer layer: starting at the coloured corner, lift and peel over the pocket.



3. Push out the tablet: gently push one end of the tablet through the foil layer.



Volibris 2.5 mg tablets are provided in a bottle, not a blister pack.

If you take more Volibris than you should
If you take too many tablets you may be more likely to have side effects, such as headache, flushing, dizziness, nausea (feeling sick), or low blood pressure that could cause light-headedness:

→ **Ask your doctor or pharmacist for advice** if you take more tablets than prescribed.

If you forget to take Volibris
If you forget a dose of Volibris, just take the tablet as soon as you remember, then carry on as before.

Don't take a double dose at the same time to make up for a forgotten dose.

If you stop taking Volibris
Volibris is a treatment that you will need to keep on taking to control your PAH.

→ Don't stop taking Volibris unless you have agreed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor if you get any of these:
Allergic reactions
This is a common side effect that may affect **up to 1 in 10** people. You may notice:
- a rash or itching and swelling (usually of the face, lips, tongue or throat), which may cause difficulty in breathing or swallowing.

Swelling (*oedema*), especially of the ankles and feet
This is a very common side effect that may affect **more than 1 in 10** people.

Heart failure
This is due to the heart not pumping out enough blood. This is a common side effect that may affect **up to 1 in 10** people. Symptoms include:
- shortness of breath
- extreme tiredness
- swelling in the ankles and legs.

Reduced number of red blood cells (*anaemia*)
This is a very common side effect that may affect **more than 1 in 10** people. Sometimes this requires a blood transfusion. Symptoms include:
- tiredness and weakness
- shortness of breath
- generally feeling unwell.

Low blood pressure (*hypotension*)
This is a common side effect that may affect **up to 1 in 10** people. Symptoms include:
- light-headedness.

→ **Tell your doctor straight away** if you (or your child) get these effects or if they happen suddenly after taking Volibris.

It is important to have regular blood tests, to check for anaemia and that your liver is working properly. **Make sure that you have also read the information in section 2** under 'You will need regular blood tests' and 'Signs that your liver may not be working properly'.

Other side effects
Very common (may affect **more than 1 in 10** people)
- headache
- dizziness
- palpitations (fast or irregular heart beats)
- shortness of breath getting worse shortly after starting Volibris
- a runny or blocked nose, congestion or pain in the sinuses
- feeling sick (*nausea*)
- diarrhoea
- feeling tired.

In combination with tadalafil (another PAH medicine)

In addition to the above:
- flushing (redness of the skin)
- being sick (*vomiting*)
- chest pain/discomfort.

Common (may affect **up to 1 in 10** people)
- blurry or other changes to vision
- fainting
- abnormal blood test results for liver function
- a runny nose
- constipation
- pain in your stomach (*abdomen*)
- chest pain or discomfort
- flushing (redness of the skin)
- being sick (*vomiting*)
- feeling weak
- nose bleed
- rash.

In combination with tadalafil
In addition to the above, (except abnormal blood test results for liver function):
- ringing in the ears (*tinnitus*).

Uncommon (may affect **up to 1 in 100** people)
- liver injury
- inflammation of the liver caused by the body's own defences (*autoimmune hepatitis*).

In combination with tadalafil
- sudden hearing loss.

Side effects in children and adolescents
These are expected to be similar to those listed above for adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Volibris

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the package after EXP.

The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Volibris contains

The active substance is ambrisentan.
Each film-coated tablet contains 2.5 mg, 5 mg or 10 mg ambrisentan.

For the 2.5 mg tablets:
The other ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), macrogol and lecithin (soya) (E322).

For the 5 mg or 10 mg tablets:
The other ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), macrogol, lecithin (soya) (E322) and allura red AC aluminium lake (E129).

What Volibris looks like and contents of the pack

Volibris 2.5 mg film-coated tablet (tablet) is a white, 7 mm round, convex tablet engraved with 'GS' on one side and 'K11' on the other.

Volibris 5 mg film-coated tablet (tablet) is a pale pink, 6.6 mm square, convex tablet engraved with 'GS' on one side and 'K2C' on the other.

Volibris 10 mg film-coated tablet (tablet) is a deep pink, 9.8 mm × 4.9 mm oval, convex tablet engraved with 'GS' on one side and 'KE3' on the other.

Volibris is supplied as 2.5 mg film-coated tablets in bottles. Each bottle contains 30 tablets.

Volibris is supplied as 5 mg and 10 mg film-coated tablets in unit dose blister packs of 10 × 1 or 30 ×1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer

GlaxoSmithKline Trading Services Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.