SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ambrisentan axunio 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of ambrisentan.

Excipients with known effect:
Each tablet contains approximately 37.50 mg of lactose (as monohydrate), approximately 0.14 mg of lecithin (soya) (E322) and approximately 0.08 mg of allura red AC aluminium lake (E129).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Ambrisentan axunio 5 mg film-coated tablets
Light pink, round, biconvex film-coated tablets debossed with ‘5’ on one side and with dimensions of approximately 7.0 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ambrisentan 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.

4.2 Posology and method of administration

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

Posology

Ambrisentan monotherapy
Ambrisentan 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, ambrisentan 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*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).

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 (Cmax 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 (> 3 x ULN); 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

Ambrisentan 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 (see section 4.4).

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 > 3 x ULN (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 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. 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

Ambrisentan treatment must not be initiated in women of child-bearing potential unless the result of a pretreatment 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

Lactose
This medicinal product contains lactose (as monohydrate):
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, this medicinal product must not be used (see section 4.3).

Allura red AC aluminium lake
This medicinal product contains the azo colouring agent allura red AC aluminium lake (E 129), which may cause allergic reactions.

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

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 section5.2). 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), multidrug 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).

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 an ongoing 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 (8 %, 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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5.1 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 (ETA) 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, 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.

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 10mg 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 medication, 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 > 3 x ULN 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 > 3 x ULN 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 > 3 x ULN 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 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 > 2 x 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 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

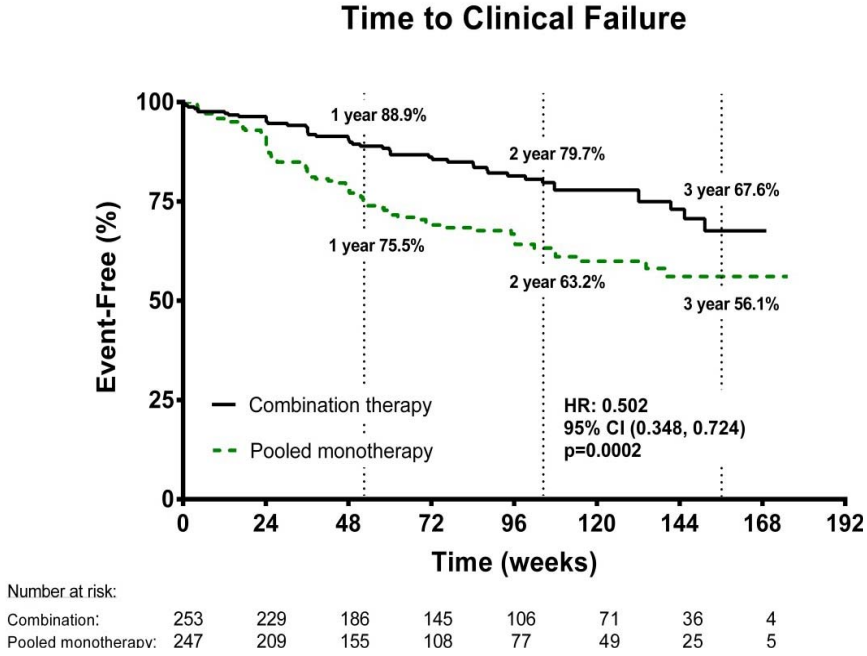

Table 1

	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	22.75m; 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 mm Hg, and the mean decrease in PVR was -277 dyn s/cm^5 (-3.46 mm Hg/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).

AMB112588 study

Long-term data were generated from 38 of the 41 patients who were treated with ambrisentan in the 24-week randomised study. The mean duration of exposure to ambrisentan treatment was 3.4 ± 1.8 years (up to 6.4 years), with 63 % of patients treated for at least 3 years and 42 % for at least 4 years. Patients could receive additional PAH treatment as required in the open-label extension. The majority of patients were diagnosed with idiopathic or heritable PAH (68 %). Overall, 46 % of patients remained in WHO functional class II. Kaplan-Meier estimates of survival were 94.42 % and 90.64 % at 3 and 4 years after the start of treatment, respectively. At the same timepoints, 77.09 % and 73.24 % of patients remained free from PAH worsening, where 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; decrease in 6MWD or signs/symptoms of right sided heart failure.

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 alpha1-acid glycoprotein.

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

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 Cmax 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 cyclosporineA (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-τ) 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–τ) (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 Cmax and AUC (0–∞) 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 (> 3 x ULN) (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

Cellulose, microcrystalline

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Film coat

Polyvinyl alcohol-partial hydrolysed

Titanium dioxide (E171)

Talc

Macrogol

Lecithin (Soya) (E322)

Allura red AC aluminium lake (E129)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/Aluminium foil blisters

Pack sizes with unit dose blisters of 10x1 and 30x1 film-coated tablets.

PVC/PVdC/Aluminium foil blisters

Pack sizes with unit dose blisters of 10x1 and 30x1 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

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