ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ambrisentan Mylan 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 26 mg of lactose and 10 micrograms of Allura red AC Aluminium lake

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pink, round, biconvex film-coated tablet with 'M' debossed on one side and 'AN' on the other, approximately 5.7 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ambrisentan Mylan is indicated for the 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 Mylan 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 Mylan 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.

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

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

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.

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 and adolescents aged below 18 years has not been established. No data are available (see section 5.3 regarding data available in juvenile animals).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance 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

Ambrisentan Mylan 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

Ambrisentan Mylan 5 mg film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Ambrisentan Mylan 5 mg film-coated tablets contain the azo-colouring agent Allura red AC Aluminium Lake (E129), which may cause allergic reactions.

Ambrisentan Mylan 5 mg film-coated tablets contains less than 1 mmol sodium (23 mg) per 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 the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A

(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 drug-drug interactions with soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see section 5.2). However, no specific drug-drug interactions studies have been conducted with these active substances. 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).

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).

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

The safety of ambrisentan has been evaluated as monotherapy and/or in combination in clinical trials of more than 1,200 patients with PAH (see section 5.1). Adverse reactions identified from 12-week placebo-controlled clinical trial data are included below by system organ class and frequency. Information from longer term non-placebo-controlled studies (ARIES-E and AMBITION

(combination with tadalafil)) is also included below. No previously unknown adverse reactions were identified with long-term treatment or for ambrisentan in combination with tadalafil. With longer observation in uncontrolled studies (mean observation of 79 weeks), the safety profile was similar to that observed in the short- term studies. Routine pharmacovigilance data are also presented.

Peripheral oedema, fluid retention and headache (including sinus headache, migraine) 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).

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. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Ambrisentan (ARIES-C and post marketing)	**Ambrisentan (AMBITION and ARIES-E)**	**Combination with tadalafil (AMBITION)**
Blood and lymphatic system disorders			
Anaemia (decreased haemoglobin, decreased haematocrit)	Common[1]	Very common	Very common
Immune system disorders			
Hypersensitivity reactions (e.g. angioedema, rash, pruritus)	Uncommon	Common	Common
Nervous system disorders			
Headache (including sinus headache, migraine)	Very common[2]	Very common	Very common
Dizziness	Common[3]	Very common	Very common
Eye disorders			
Blurred vision, visual impairment	Not known[4]	Common	Common
Ear and labyrinth disorders			
Tinnitus	NR	NR	Common
Sudden hearing loss	NR	NR	Uncommon
Cardiac disorders			
Cardiac failure	Common[5]	Common	Common
Palpitation	Common	Very common	Very common

	Ambrisentan (ARIES-C and post marketing)	**Ambrisentan (AMBITION and ARIES-E)**	**Combination with tadalafil (AMBITION)**
Vascular disorders			
Hypotension	Common[3]	Common	Common
Flushing	Common	Common	Very common
Syncope	Uncommon[3]	Common	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Common[3]	Common	Common
Dyspnoea	Common[3,6]	Very common	Very common
Upper respiratory (e.g. nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis	Common[7]		
Nasopharyngitis		Very common	Very common
Sinusitis, rhinitis		Common	Common
Nasal congestion		Very common	Very common
Gastrointestinal disorders			
Nausea, vomiting, diarrhoea	Common[3]		
Nausea		Very common	Very common
Vomiting		Common	Very common
Diarrhoea		Very common	Very common
Abdominal pain	Common	Common	Common
Constipation	Common	Common	Common
Hepatobiliary disorders			
Hepatic injury (see section 4.4)	Uncommon[3], [8]	NR	NR
Autoimmune hepatitis (see section 4.4)	Uncommon[3], [8]	NR	NR
Hepatic transaminases increased	Common[3]	NR	NR
Skin and subcutaneous tissue disorders			
Rash	NR	Common[9]	Common[9]
General disorders and administration site conditions			
Peripheral oedema, fluid retention	Very common	Very common	Very common
Chest pain/discomfort	Common	Common	Very common
Asthenia	Common[3]	Common	Common
Fatigue	Common[3]	Very common	Very common

NR – not reported

[1] See section *'Description of selected adverse reactions'*.

[2] The frequency of headache appeared higher with 10 mg ambrisentan.

[3] Data derived from routine pharmacovigilance surveillance and frequencies based on placebo controlled clinical trial experience.

[4] Data derived from routine pharmacovigilance surveillance
[5] Most of the reported cases of cardiac failure were associated with fluid retention. Data derived from routine pharmacovigilance surveillance, frequencies based on statistical modelling of placebo controlled clinical trial data.
[6] Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting ambrisentan therapy.
[7] The incidence of nasal congestion was dose related during ambrisentan therapy.
[8] Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury have been reported during ambrisentan therapy.
[9] Rash includes rash erythematous, rash generalised, rash papular and rash pruritic

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.

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

There is no experience in PAH patients of ambrisentan at daily doses greater than 10 mg. 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 a potent (Ki 0.016 nM) and highly selective ET_A antagonist (approximately 4000-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 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 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 >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 a drug-drug 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 multicentre, 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 medicines and toxins (3%), corrected simple congenital heart disease (2%), and HIV (2%). Patients with WHO FC II and III had a mean baseline 6MWD of 353 metres.

Outcome endpoints

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

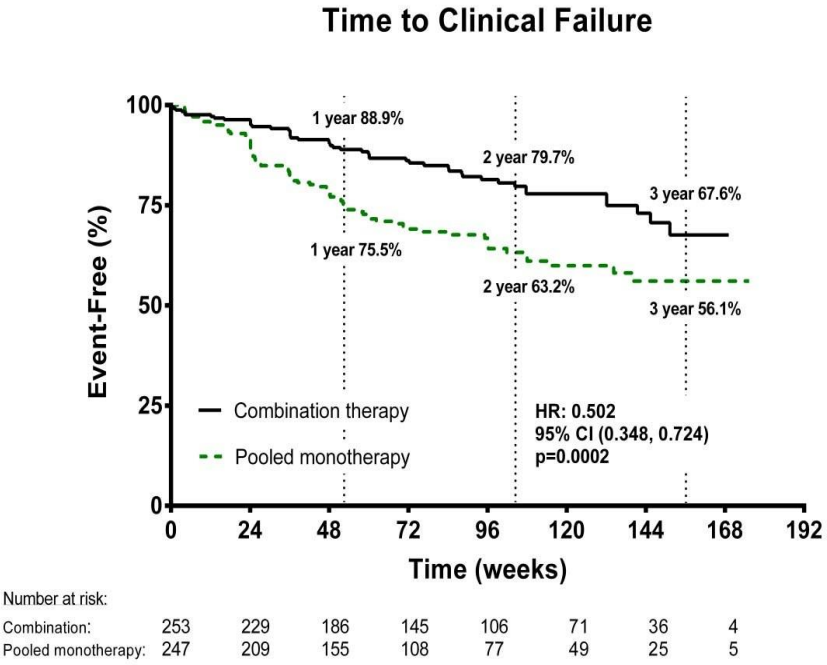

Table 1

	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 (metres, 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).

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, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (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 $AUC_{(0–\tau)}$ (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 $AUC_{(0–\infty)}$ 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 extrahepatic 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

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).

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, 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 exposures approximately 1.8 to 7 times human paediatric exposures at 10 mg (age 9 to 15 years), based on AUC. The clinical relevance of this finding to the paediatric population is not fully understood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose
Microcrystalline cellulose (E460i)
Croscarmellose sodium
Magnesium stearate (E570)

Film coat
Poly(vinyl alcohol)(partly hydrolysed)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Allura red AC Aluminium Lake (E129)
Indigo Carmine Aluminium Lake (E132).

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

PVC/PVdC blisters
Pack sizes of 30 film-coated tablets and unit dose blisters of 30x1 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117 Allée des Parcs
69800 Saint-Priest
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1368/001
EU/1/19/1368/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

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.

1. NAME OF THE MEDICINAL PRODUCT

Ambrisentan Mylan 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of ambrisentan.

Excipients with known effect

Each tablet contains approximately 52 mg of lactose and 20 micrograms of Allura red AC Aluminium lake

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Pink, capsule shaped, biconvex film-coated tablet with 'M' debossed on one side and 'AN1' on the other, approximately 9.9 mm long and 4.8 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ambrisentan Mylan is indicated for the 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 Mylan 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 Mylan 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.

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

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

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.

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 and adolescents aged below 18 years has not been established. No data are available (see section 5.3 regarding data available in juvenile animals).

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance 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

Ambrisentan Mylan 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

Ambrisentan Mylan 10 mg film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Ambrisentan Mylan 10 mg film-coated tablets contain the azo-colouring agent Allura red AC Aluminium Lake (E129), which may cause allergic reactions.

Ambrisentan Mylan 10 mg film-coated tablets contains less than 1 mmol sodium (23 mg) per 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 the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A

(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 drug-drug interactions with soluble guanylate cyclase stimulators or prostanoids are anticipated based on the known biotransformation data (see section 5.2). However, no specific drug-drug interactions studies have been conducted with these active substances. 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).

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).

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

The safety of ambrisentan has been evaluated as monotherapy and/or in combination in clinical trials of more than 1,200 patients with PAH (see section 5.1). Adverse reactions identified from 12 week placebo controlled clinical trial data are included below by system organ class and frequency. Information from longer term non-placebo-controlled studies (ARIES-E and AMBITION

(combination with tadalafil)) is also included below. No previously unknown adverse reactions were identified with long-term treatment or for ambrisentan in combination with tadalafil. With longer observation in uncontrolled studies (mean observation of 79 weeks), the safety profile was similar to that observed in the short- term studies. Routine pharmacovigilance data are also presented.

Peripheral oedema, fluid retention and headache (including sinus headache, migraine) 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).

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. Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

	Ambrisentan (ARIES-C and post marketing)	**Ambrisentan (AMBITION and ARIES-E)**	**Combination with tadalafil (AMBITION)**
Blood and lymphatic system disorders			
Anaemia (decreased haemoglobin, decreased haematocrit)	Common[1]	Very common	Very common
Immune system disorders			
Hypersensitivity reactions (e.g. angioedema, rash, pruritus)	Uncommon	Common	Common
Nervous system disorders			
Headache (including sinus headache, migraine)	Very common[2]	Very common	Very common
Dizziness	Common[3]	Very common	Very common
Eye disorders			
Blurred vision, visual impairment	Not known[4]	Common	Common
Ear and labyrinth disorders			
Tinnitus	NR	NR	Common
Sudden hearing loss	NR	NR	Uncommon
Cardiac disorders			
Cardiac failure	Common[5]	Common	Common
Palpitation	Common	Very common	Very common

	Ambrisentan (ARIES-C and post marketing)	Ambrisentan (AMBITION and ARIES-E)	Combination with tadalafil (AMBITION)
Vascular disorders			
Hypotension	Common[3]	Common	Common
Flushing	Common	Common	Very common
Syncope	Uncommon[3]	Common	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	Common[3]	Common	Common
Dyspnoea	Common[3,6]	Very common	Very common
Upper respiratory (e.g. nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis	Common[7]		
Nasopharyngitis		Very common	Very common
Sinusitis, rhinitis		Common	Common
Nasal congestion		Very common	Very common
Gastrointestinal disorders			
Nausea, vomiting, diarrhoea	Common[3]		
Nausea		Very common	Very common
Vomiting		Common	Very common
Diarrhoea		Very common	Very common
Abdominal pain	Common	Common	Common
Constipation	Common	Common	Common
Hepatobiliary disorders			
Hepatic injury (see section 4.4)	Uncommon[3], [8]	NR	NR
Autoimmune hepatitis (see section 4.4)	Uncommon[3], [8]	NR	NR
Hepatic transaminases increased	Common[3]	NR	NR
Skin and subcutaneous tissue disorders			
Rash	NR	Common[9]	Common[9]
General disorders and administration site conditions			
Peripheral oedema, fluid retention	Very common	Very common	Very common
Chest pain/discomfort	Common	Common	Very common
Asthenia	Common[3]	Common	Common
Fatigue	Common[3]	Very common	Very common

NR – not reported

[1] See section *'Description of selected adverse reactions'*.

[2] The frequency of headache appeared higher with 10 mg ambrisentan.

[3] Data derived from routine pharmacovigilance surveillance and frequencies based on placebo controlled clinical trial experience.

[4] Data derived from routine pharmacovigilance surveillance
[5] Most of the reported cases of cardiac failure were associated with fluid retention. Data derived from routine pharmacovigilance surveillance, frequencies based on statistical modelling of placebo controlled clinical trial data.
[6] Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting ambrisentan therapy.
[7] The incidence of nasal congestion was dose related during ambrisentan therapy.
[8] Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury have been reported during ambrisentan therapy.
[9] Rash includes rash erythematous, rash generalised, rash papular and rash pruritic

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.

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

There is no experience in PAH patients of ambrisentan at daily doses greater than 10 mg. 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 a potent (Ki 0.016 nM) and highly selective ET_A antagonist (approximately 4000-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 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 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 6minute 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 a drug-drug 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 multicentre, 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 medicines and toxins (3%), corrected simple congenital heart disease (2%), and HIV (2%). Patients with WHO FC II and III had a mean baseline 6MWD of 353 metres.

Outcome endpoints

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

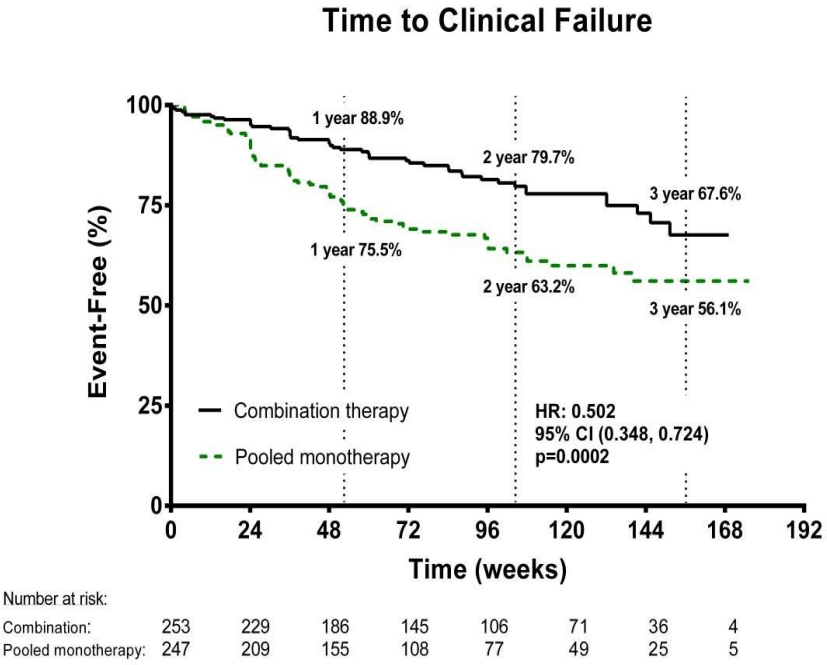

Table 1

	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 (metres, 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).

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, the dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (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 $AUC_{(0–\tau)}$ (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 $AUC_{(0–\infty)}$ 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 extrahepatic 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

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).

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, 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 exposures approximately 1.8 to 7 times human paediatric exposures at 10 mg (age 9 to 15 years), based on AUC. The clinical relevance of this finding to the paediatric population is not fully understood.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose
Microcrystalline cellulose (E460i)
Croscarmellose sodium
Magnesium stearate (E570)

Film coat
Poly(vinyl alcohol) (partly hydrolysed)
Titanium dioxide (E171)
Macrogol
Talc (E553b)
Allura red AC Aluminium Lake (E129)
Indigo Carmine Aluminium Lake (E132).

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

PVC/PVdC blisters
Pack sizes of 30 film-coated tablets and unit dose blisters of 30x1 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Mylan S.A.S.
117 Allée des Parcs
69800 Saint-Priest
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1368/003
EU/1/19/1368/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Generics (UK) Limited,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom

or

McDermott Laboratories t/a Gerard Laboratories,
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
Ireland

or

Mylan Hungary Kft, Mylan utca 1,
2900 Komárom,
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The requirements for submission of periodic safety update reports 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 THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The 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**

The MAH will agree the distribution plan with the National Competent Authorities before the product launch in each territory and will ensure that all patients taking Ambrisentan Mylan have been provided with the relevant educational materials.

- Patient Reminder Card

<u>Patient reminder card should include the following messages</u>

- That Ambrisentan Mylan is teratogenic in animals
- That pregnant women must not take Ambrisentan Mylan
- That women of reproductive potential must use effective contraception
- The need for monthly pregnancy tests
- The need for regular monitoring of liver function because Ambrisentan Mylan may cause liver injury.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ambrisentan Mylan 5 mg film-coated tablets

ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose and Allura red AC Aluminium Lake (E129). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
30x1 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

Mylan S.A.S.
117 Allée des Parcs
69800 Saint-Priest
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1368/001
EU/1/19/1368/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ambrisentan Mylan 5 mg film-coated tablets

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 OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ambrisentan Mylan 10 mg film-coated tablets

ambrisentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg ambrisentan

3. LIST OF EXCIPIENTS

Contains lactose and Allura red AC Aluminium Lake (E129). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
30x1 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

Mylan S.A.S.
117 Allée des Parcs
69800 Saint-Priest
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1368/003
EU/1/19/1368/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ambrisentan Mylan 10 mg film-coated tablets

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

Ambrisentan Mylan 5 mg film-coated tablets

ambrisentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan S.A.S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE MEDICINAL PRODUCT

Ambrisentan Mylan 10 mg film-coated tablets

ambrisentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan S.A.S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ambrisentan Mylan 5 mg film-coated tablets
Ambrisentan Mylan 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 Ambrisentan Mylan is and what it is used for

Ambrisentan Mylan 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. 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.

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

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

2. What you need to know before you take Ambrisentan Mylan

Do not take Ambrisentan Mylan:
- if you are **allergic** to ambrisentan 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, pharmacist or nurse before taking this medicine if you have:
- liver problems
- anaemia (a reduced number of red blood cells)
- swelling in the hands, ankles or feet caused by fluid *(peripheral oedema)*
- lung disease where the veins in the lungs are blocked *(pulmonary veno-occlusive disease)*.

Your doctor will decide whether Ambrisentan Mylan is suitable for you.

You will need regular blood tests
Before you start taking Ambrisentan Mylan, and at regular intervals while you're 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 Ambrisentan Mylan.

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 and adolescents

Ambrisentan Mylan is not recommended for children and adolescents aged under 18 years as the safety and effectiveness is not known in this age group.

Other medicines and Ambrisentan Mylan

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

Your doctor may need to adjust your dose of Ambrisentan Mylan if you start taking cyclosporine A (a medicine used after transplant or to treat psoriasis).

If you're taking rifampicin (an antibiotic used to treat serious infections) your doctor will monitor you when you first start taking Ambrisentan Mylan.

If you're taking other medicines used 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

Ambrisentan Mylan 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're taking Ambrisentan Mylan. Talk to your doctor about this.

→ **Don't take Ambrisentan Mylan if you are pregnant or planning to become pregnant.**

→ **If you become pregnant or think that you may be pregnant** while you're taking Ambrisentan Mylan, 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 Ambrisentan Mylan and regularly while you are taking this medicine.

Breast-feeding

It is not known if Ambrisentan Mylan is transferred to breast milk.

→ **Don't breast-feed while you're taking** Ambrisentan Mylan. Talk to your doctor about this.

Fertility

If you are a man taking Ambrisentan Mylan, 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

Ambrisentan Mylan 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're feeling unwell.**

Ambrisentan Mylan tablets contains lactose and Allura red (E129)

Ambrisentan Mylan 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.

Ambrisentan Mylan tablets contain a colouring agent called Allura red AC Aluminium Lake (E129) which may cause allergic reactions.

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

3. How to take Ambrisentan Mylan

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

How much Ambrisentan Mylan to take
The usual dose of Ambrisentan Mylan 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 Ambrisentan Mylan once a day.

How to take Ambrisentan Mylan
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 Ambrisentan Mylan with or without food.

If you take more Ambrisentan Mylan 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 Ambrisentan Mylan
If you forget a dose of Ambrisentan Mylan, just take the tablet as soon as you remember, then carry on as before.

→ Don't take two doses at the same time to make up for a forgotten dose

Don't stop taking Ambrisentan Mylan without your doctor's advice
Ambrisentan Mylan is a treatment that you will need to keep on taking to control your PAH.

→Don't stop taking Ambrisentan Mylan 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.

Conditions you and your doctor need to look out for:

Allergic reactions

This is a common side effect that may affect **up to one 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 one in 10** people.

Heart failure

This is due to the heart not pumping out enough blood, causing shortness of breath, extreme tiredness and swelling in the ankles and legs. This is a common side effect that may affect **up to one in 10** people.

Anaemia (reduced number of red blood cells)

This is a blood disorder which can cause tiredness, weakness, shortness of breath, and generally feeling unwell. Sometimes this requires a blood transfusion. This is a very common side effect that may affect **more than one in 10** people

Hypotension (low blood pressure)

This can cause light-headedness. This is a common side effect that may affect **up to one in 10** people.

→ **Tell your doctor straight away** if you get these effects or if they happen suddenly after taking Ambrisentan Mylan.

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 include

Very common side effects:

- headache
- dizziness
- palpitations (fast or irregular heart-beats)
- worsening shortness of breath shortly after starting Ambrisentan Mylan
- 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 side effects:

- 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)* only when taking the combination treatment.

Uncommon side effects:

- liver injury
- inflammation of the liver caused by the body's own defences (autoimmune hepatitis)

In combination with tadalafil

- sudden hearing loss.

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 Ambrisentan Mylan

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 carton after EXP.

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

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 Ambrisentan Mylan contains

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

The other ingredients are lactose, see section 2, 'Ambrisentan Mylan contains lactose', microcrystalline cellulose (E460i), sodium croscarmellose, magnesium stearate (E570), polyvinyl alcohol part hydrolysed, titanium dioxide (E171), macrogol/PEG, talc (E553b), Allura red (E129), see section 2 'Ambrisentan Mylan contains Allura red (E129)', Indigo carmine (E132)

What Ambrisentan Mylan looks like and contents of the pack

Ambrisentan Mylan 5 mg film-coated tablet (tablet) is a pink round biconvex tablet engraved with 'M' on one side and 'AN' on the other side.

Ambrisentan Mylan 10 mg film-coated tablet (tablet) is a pink, capsule shaped tablet engraved with 'M' on one side of the tablet and 'AN1' on the other side.

Ambrisentan Mylan is supplied as 5 mg and 10 mg film-coated tablets in packs of 30 tablets and unit dose blister packs of 30x1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Mylan S.A.S.
117 Allée des Parcs
69800 Saint-Priest
France

Manufacturer

Generics (UK) Limited, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom

McDermott Laboratories t/a Gerard Laboratories, 35/36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland

Mylan Hungary Kft, Mylan utca 1, 2900 Komárom, Hungary

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

België/Belgique/Belgien
Mylan bvba/sprl
Tél/Tel: + 32 (0)2 658 61 00

България
Майлан ЕООД
Тел: +359 2 44 55 400

Česká republika
Mylan Pharmaceuticals.s.r.o.
Tel: + 420 222 004 400

Danmark
BGP Products ApS
Tlf: + 45 28116932

Deutschland
Mylan Healthcare GmbH
Tel: + 49 800 0700 800

Eesti
BGP Products Switzerland GmbH Eesti filiaal
Tel: + 372 6363 052

Ελλάδα
Generics Pharma Hellas ΕΠΕ
Τηλ: +30 210 993 6410

España
Mylan Pharmaceuticals, S.L
Tel: + 34 900 102 712

France
Mylan S.A.S
Tél : +33 4 37 25 75 00

Hrvatska
Mylan Hrvatska d.o.o.
Tel: +385 1 23 50 599

Ireland
Mylan Ireland Limited
Tel: +353 (0) 87 1694982

Lietuva
BGP Products UAB
Tel: +370 5 205 1288

Luxembourg/Luxemburg
Mylan bvba/sprl
Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Magyarország
Mylan EPD Kft
Tel: + 36 1 465 2100

Malta
V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland
Mylan BV
Tel: +31 (0)20 426 3300

Norge
Mylan Healthcare Norge AS
Tel: + 47 66 75 33 00

Österreich
Arcana Arzneimittel GmbH
Tel: +43 1 416 2418

Polska
Mylan Healthcare Sp. z.o.o.
Tel: + 48 22 546 64 00

Portugal
Mylan, Lda.
Tel: + 351 21 412 72 56

România
BGP Products SRL
Tel: +40 372 579 000

Slovenija
Mylan Healthcare d.o.o.
Tel: + 386 1 236 31 80

Ísland
BGP Products ApS
Tel: + 45 28116932
(Danmörk)

Italia
Mylan Italia S.r.l.
Tel: + 39 02 612 46921

Κύπρος
Pharmaceutical Trading Co. Ltd.
Τηλ: + 357 99403969

Latvija
BGP Products SIA
Tel: +371 676 055 80

Slovenská republika
Mylan s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland
Mylan Finland OY
Puh/Tel: +358 20 720 9555

Sverige
Mylan AB
Tel: + 46 855 522 750

United Kingdom
Generics [UK] Ltd
Tel: +44 1707 853000

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.