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Ambrisentan

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Contents

Abstract

▲ Elevated endothelin (ET)-1 levels are strongly correlated with the pathogenesis and prognosis of pulmonary arterial hypertension (PAH). Ambrisentan is an orally active, highly selective ET_A receptor antagonist with >4000-fold higher selectivity over the ET_B receptor.

▲ In two large, well designed, 12-week, placebo-controlled, phase III trials (ARIES-1, n = 202 and ARIES-2, n = 192) in patients with PAH (WHO group I), ambrisentan 2.5–10 mg once daily significantly increased 6-minute walk distance by 31–59 m from baseline (primary outcome measure) versus placebo.

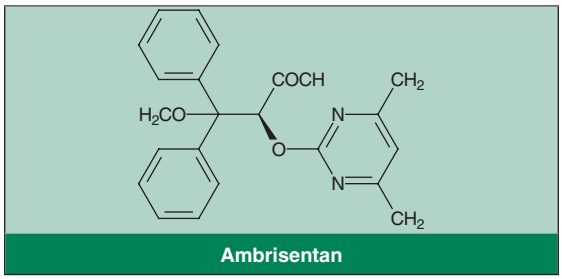
▲ The incidence of clinical worsening (secondary outcome measure) was significantly delayed for the combined ambrisentan 5 mg once daily groups versus the combined placebo groups from ARIES-1 and -2.

▲ At week 12, WHO functional class distribution was significantly improved with once-daily ambrisentan 5 mg, and Borg dyspnoea scores were significantly improved with ambrisentan 2.5–10 mg versus placebo in combined data from the ARIES-1 and -2 trials.

▲ The beneficial effects of ambrisentan on exercise capacity, WHO functional class and Borg dyspnoea scores seen at 12 weeks were maintained at 48 weeks in the ARIES-E phase III extension trial (n = 361). One-year survival rates with ambrisentan were 95–97%.

▲ Treatment with ambrisentan for up to 2.8 years was generally well tolerated in clinical trials.

Features and properties of ambrisentan (Letairis™ or Volibris®)		
Indication in the US		
Treatment of adults with pulmonary arterial hypertension (PAH) [WHO group I] with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening		
Mechanism of action		
Selective endothelin ET_A receptor antagonist		
Dosage and administration		
Route of administration	Oral	
Dose	5 mg increasing to 10 mg if 5 mg/day dosage tolerated	
Frequency of administration	Once daily	
Pharmacokinetic profile of ambrisentan 5 mg (n = 10) or 10 mg (n = 3) at steady state. Mean values unless stated otherwise		
	5 mg	10 mg
Maximum plasma concentration (C_{max}) [ng/mL]	539	1147
Trough plasma concentration (ng/mL)	63	163
Median time to C_{max} (h)	2	2
Area under the plasma concentration-time curve from time zero to 24 h (ng • h/mL)	4804	12 591
Terminal elimination half-life (h)	15	13
Most frequent adverse events		
Peripheral oedema, headache, nasal congestion		



Ambrisentan

Pulmonary arterial hypertension (PAH) is a heterogeneous group of diseases that is characterized by vascular remodelling (due to vasoconstriction, cellular proliferation and thrombosis) and luminal obstruction. This results in a progressive increase in pulmonary vascular resistance, which eventually leads to right heart failure and premature mortality.[1-3] PAH is defined by a sustained elevation in mean pulmonary arterial pressure of >25 mmHg and a pulmonary capillary wedge pressure ≤15 mmHg.[2]

The underlying pathology of PAH is incompletely understood. The disease may be idiopathic, familial or associated with a variety of conditions, including connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection and exposure to certain toxins or drugs, including anorexigens.[4] The WHO group I PAH definition includes both idiopathic PAH and PAH that is associated with these risk factors.[1,4] Although it is widely believed to be a rare disease, WHO guidelines suggest that the true burden of PAH is unknown and underestimated.[5]

Treatment options focus on symptomatic management of the disease, including improving breathlessness on exertion, chest pain and syncope. Lung transplantation is the only option available if pharmacological means fail.[6-8] Prior to the availability of specific disease-targeted therapies, the median life expectancy of patients was 2.8 years.[4,9] However, recent advances in understanding the role of the vascular endothelium in the pathogenesis of PAH has led to the development of new pharmacological approaches to managing these diseases.[2,3,10-12] The control of three key mediators is thought to underpin the pathogenesis of PAH: prostacyclin, nitric oxide and endothelin (ET)-1. Targeting one or more of these pathways is now part of current pharmacological strategies,[6] which include phosphodiesterase inhibitors such as sildenafil,[13] prostacyclin analogues such as treprostinil, iloprost and epoprostenol,[6] and ET receptor antagonists such as bosentan,[14] sitaxsentan[15] and ambrisentan[16] (Letairis™ in the US, Volibris® in the EU)[1].

Plasma levels of ET-1 are elevated (up to 10-fold[17]) in patients with PAH and are strongly correlated with increased mean right atrial pressure and severity of the disease.[17,18] Over expression of ET-1 is found in the muscular pulmonary arteries of patients with idiopathic PAH.[19]

Two receptor subtypes mediate the effects of ET-1.[10] Located primarily in pulmonary vascular smooth muscle cells, endothelin receptor A (ET_A) mediates vasoconstriction and cell proliferation, whereas ET_B, which is located in both pulmonary vascular endothelial cells and smooth muscle cells, primarily mediates vasodilation, antiproliferation and ET-1 clearance.[10,18] ET receptor antagonist therapy is considered to be an important cornerstone in the pharmacological management of PAH.[10] However, a clinical advantage of ET_A-selective antagonists (e.g. sitaxsentan)[15] over dual-selective antagonists (e.g. bosentan)[14] remains to be determined at the present time.[18]

Ambrisentan is a selective ET_A receptor antagonist. This article provides an overview of the pharmacological profile of ambrisentan, and reviews its clinical efficacy and tolerability in patients with PAH classified as WHO functional class I–IV, from a US perspective.

1. Pharmacodynamic Profile

Limited pharmacodynamic data are available for ambrisentan. Therefore, this section focuses mainly on the information provided in the manufacturer's US prescribing information[17] and US FDA approval history.[20] However, the ARIES (Ambrisentan in

1 The use of trade names is for identification purposes only and does not imply endorsement.

Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter Efficacy) phase III clinical trials, presented in section 3, also describe changes in the mean plasma levels of B-type natriuretic peptide (BNP), which is a secondary outcome.[21] BNP is a 32 amino-acid polypeptide secreted by ventricular myocytes in response to excessive stress. BNP has been proposed as a prognostic indicator of outcome in patients with PAH[22,23] and these data are therefore briefly discussed.

- Ambrisentan is a potent and highly selective, propanoic acid-based antagonist of the ET_A receptor that has a >4000-fold greater affinity for the ET_A receptor over the ET_B receptor in human myocardial membranes. The inhibitory constant of ambrisentan is 0.011 nmol/L.[17]

- The main metabolite of ambrisentan, 4-hydroxymethyl ambrisentan, has a 64-fold lower binding affinity for the ET_A receptor and is not pharmacologically active.[20]

- Mean pulmonary artery pressure was significantly reduced from baseline by 5.2 mmHg after 12 weeks of ambrisentan 1–10 mg once daily (all doses combined $p < 0.05$) in a phase II clinical substudy ($n = 29$).[24] Diastolic blood pressure was also decreased in healthy volunteers receiving ambrisentan 5, 7.5 and 10 mg once daily.[20]

- Healthy volunteers receiving oral ambrisentan 10 mg once daily showed no significant effect on the corrected QT (QT_c) interval; however, a single 40 mg ambrisentan dose increased the mean QT_c interval at the time of maximum plasma concentration (C_{max}) by 5 ms (95% CI upper limit 9 ms).[17] No significant prolongation of the QT interval is expected with ambrisentan 5–10 mg/day in patients who are not taking metabolic inhibitors.[17]

- Plasma ET-1 levels at baseline were 0.24 fmol/mL and 0.52 fmol/mL after 12 weeks' of ambrisentan and were not correlated with ambrisentan plasma concentrations.[20]

- BNP plasma levels were significantly reduced from baseline following 12 weeks' treatment with ambrisentan in the two phase III ARIES trials ($n = 202$ and 192) in patients with PAH. Reductions in BNP of 30% and 45% were seen with ambrisentan 5 mg or 10 mg once daily in ARIES-1, and 29% and 30% with ambrisentan 2.5 mg or 5 mg once daily in ARIES-2 (all $p < 0.003$).[21] In contrast, BNP plasma levels increased by 9% (ARIES-1) and 13% (ARIES-2) at week 12 in placebo recipients with PAH. Changes from baseline at week 12 were significantly greater with ambrisentan than placebo in both studies (all $p \leq 0.002$).[21]

2. Pharmacokinetic Profile

Fully published pharmacokinetic data for ambrisentan are limited; therefore, this section mainly focuses on the information available in the US manufacturer's prescribing information[17] supplemented by data from the US FDA approval history.[20]

Absorption and Distribution

- Oral ambrisentan is rapidly absorbed and C_{max} is achieved ≈2 hours after administration.[17] The pharmacokinetics of ambrisentan are dose-proportional at therapeutic dosages,[20,25] and steady state is achieved after 4 days of repeated administration.[25]

- After repeated administration of ambrisentan 5 or 10 mg/day, mean C_{max} values were 539 and 1147 ng/mL. Mean area under the plasma concentration-time curve from time 0 to 24 hours values were 4804 and 12 591 ng • h/mL at steady state.[20] Trough plasma ambrisentan concentrations were 63 and 163 ng/mL[20] and are ≈15% of C_{max} concentrations.[17]

- Pharmacokinetic data show that systemic exposure is greater in patients with PAH than in healthy volunteers, which suggests that oral clearance of ambrisentan is impaired in patients.[20]

- The absolute bioavailability of ambrisentan is unknown. Ambrisentan is 99% bound to plasma proteins and accumulates slightly at steady state (accumulation factor 1.2).[17]

- The pharmacokinetics of ambrisentan are not affected to a clinically significant extent by food.[17]

Metabolism and Elimination

- Non renal pathways appear to predominate in the elimination of ambrisentan with 66% excreted in faeces and 22.6% in urine.[20] *In vivo* evidence supports a biliary contribution, and *in vitro* data from human liver tissue culture suggest that metabolism via P-glycoprotein (P-gp), organic anion transport protein (OATP), cytochrome P450 (CYP) isoenzymes 3A4 and 2C19, and uridine 5′ diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S and 1A3S may be possible.[17]
- The main metabolites formed are ambrisentan glucuronide and 4-hydroxymethyl ambrisentan.[20]
- In patients with PAH, the mean clearance of oral ambrisentan is 19 mL/min,[17] and for the 5 and 10 mg dosages, the mean terminal elimination half-life at steady state is 15 and 13 hours with a mean terminal rate constant of 0.05–0.06 L/h.[17,20]

Drug Interactions

- The interaction of ambrisentan with inhibitors and/or inducers of P-gp, UGT, OATP and CYP isoenzymes remains to be fully determined, although *in vitro* studies indicate that ambrisentan is a substrate (but not an inhibitor) of P-gp and a substrate of OATP.[17] Nevertheless, caution is advised when coadministering ambrisentan with cyclosporin A (an OATP inhibitor), ketoconazole (a CYP3A4 inhibitor) or omeprazole (a CYP2C19 inhibitor), or inducers of P-gp, CYP isoenzymes or UGTs.[17]
- Coadministration of ambrisentan with warfarin in healthy volunteers and patients with PAH did not result in any clinically relevant changes in prothrombin time, international normalized ratio, or the pharmacokinetics of either warfarin or ambrisentan.[17,26]
- No clinically significant effects on the pharmacokinetics of a single dose of sildenafil 20 mg (or its active metabolite) were observed in healthy volunteers receiving ambrisentan 10 mg once daily for 7 days. Similarly, the pharmacokinetics of single-dose ambrisentan 10 mg showed no clinically meaningful change when sildenafil 20 mg was administered three times daily for 7 days.[27]

Special Populations

- Changes in the pharmacokinetic profile of ambrisentan due to sex, age and hepatic impairment remain to be determined. However, because *in vitro* and *in vivo* studies indicate hepatic and biliary involvement in ambrisentan metabolism and excretion, hepatic impairment could affect the pharmacokinetics of the drug.[17] Consequently, ambrisentan is not recommended in patients with moderate or severe hepatic impairment.[17]
- Patients with PAH with mild or moderate renal impairment show no clinically significant changes in the pharmacokinetics of ambrisentan and a dosage adjustment is not required. There is no information available for patients with severe renal impairment.[17]

3. Therapeutic Efficacy

This section focuses primarily on the short-term (12 weeks' treatment) efficacy of oral ambrisentan for the treatment of adult (aged ≥18 years) patients with WHO group I PAH in two ARIES trials.[21] ARIES-1 and -2 (AMB-320 and AMB-321) are large (n = 202 and 192), identically designed, randomized, double-blind, placebo-controlled, multicentre, phase III trials in patients with PAH that are published together.[21] ARIES-1 was conducted in the US, Mexico, South America, Australia and the EU; ARIES-2 was conducted in the EU, Israel, South America, Russia and the Ukraine.[21]

These pivotal trials were initiated following results from a small (n = 64), randomized, double-blind, dose-finding, phase II, fully published study (AMB-220),[24] which is not discussed in detail here.

Long-term (≤2.8 years of treatment) efficacy of ambrisentan has been evaluated in a large (n = 383) integrated analysis of the phase III ARIES-1 and -2 trials,[28] including 361 patients who entered into the extension phase (ARIES-E).[21] Similarly, a long-term (≤1 year) follow-up of the AMB-220 study[24] has been evaluated in 64 patients (AMB-222-E)[29]

and in a smaller (n = 19) subset of patients with PAH associated with connective tissue diseases,[30] which have been published as abstracts.

In the ARIES-1 and -2 trials,[21] patients were enrolled with idiopathic PAH or PAH associated with connective tissue disease, HIV infection or anorexigen use as defined by current treatment guidelines.[2,4] Patients were included regardless of WHO class symptoms,[31] if their 6-minute walk distance (6MWD) was ≥150 but ≤450 m[21,31] and they met the following haemodynamic criteria: mean pulmonary arterial pressure ≥25 mmHg; pulmonary vascular resistance >3 mmHg • min/L; pulmonary capillary wedge pressure or left end-diastolic pressure <15 mmHg; and a total lung capacity ≥70% and a forced expiratory volume in 1 second ≥65% of predicted normal.[31]

Background therapy of digoxin, anticoagulants, diuretics, oxygen and vasodilators, such as calcium-channel antagonists or ACE inhibitors, was permitted.[17] However, treatment with bosentan, sitaxsentan, sildenafil or prostanoids was not permitted, and patients who were previously treated with these agents within 4 weeks of the screening period were excluded.[21] Additionally, patients with congenital heart disease, portopulmonary hypertension, PAH associated with coronary artery disease, left heart disease, chronic obstructive pulmonary disease, veno-occlusive disease, chronic thromboembolic disease, sleep apnoea, or serum aminotransferase levels ≥1.5 times the upper limit of normal (ULN) were also excluded from these trials.[31]

To be eligible for the extension trial (ARIES-E), subjects must have completed the ARIES-1 or -2 trials and met two or more early escape criteria, which included (i) >20% decrease in 6MWD; (ii) an increase in WHO functional class; (iii) worsening right ventricular failure; (iv) hepatic or renal failure; and (v) systolic blood pressure <85 mmHg.[21]

Selection criteria for the AMB-220 follow-up studies[29,30] were similar to those in the other studies; however, if these patients were previously treated with conventional therapy for PAH, which included diuretics, digoxin or supplemental oxygen, they had to be stable for ≥4 weeks prior to screening.[32]

Patients were randomized equally to receive placebo or oral ambrisentan 5 or 10 mg once daily (ARIES-1) or oral ambrisentan 2.5 or 5 mg once daily (ARIES-2) for 12 weeks.[21] At the end of these trials, patients who had received placebo were randomized to ambrisentan 2.5, 5 or 10 mg once daily for the ARIES-E extension trial.[21,28] Patients received ambrisentan for a mean exposure period of 1.4 years (maximum exposure 2.8 years) with data presented as an integrated analysis of all patients who had received at least one dose of ambrisentan in ARIES-1, -2 and -E trials.[28] In AMB-220-E,[29,30] patients who had received randomized, blinded dosages of oral ambrisentan 1, 2.5, 5 or 10 mg once daily for 12 weeks followed by open-label treatment for 12 weeks,[24] received open-label treatment for the remainder of the extension trial.

The primary outcome measure in the ARIES-1 and -2 trials was the change from baseline to week 12 in exercise capacity as determined by the 6MWD.[21]

Secondary outcome measures in the ARIES-1 and -2 trials included the change at either week 12[31] or long-term[33,34] (period not defined) from baseline in the Borg dyspnoea index, WHO functional classification, Short Form (SF)-36 Health Survey scores and time to clinical worsening,[31,33] and in both extension trials (ARIES-E and AMB-220-E) the change from baseline in exercise capacity as determined by the 6MWD.[33,34] The time to clinical worsening was defined as the time between randomization and the date at which the first of the following events occurred: death, lung transplantation, hospitalization due to PAH, atrial septostomy, withdrawal due to addition of other PAH-related pharmacotherapies, or early escape criteria.[21]

The ARIES-E and AMB-220-E extension studies[28-30] considered these endpoints after long-term treatment, as well as long-term tolerability (discussed in section 4).[33,34]

A fixed sequence of multiple comparisons was followed for each efficacy endpoint (intent-to-treat last observation carried forward) analysis in each of

the ARIES-1 and -2 trials.[21] Thus, if statistical analysis of the primary endpoint using the higher ambrisentan dose versus placebo showed a significant effect ($\alpha = 0.05$), the lower dose was compared with placebo. If significance was identified for at least one ambrisentan dose in primary endpoint analysis, the time to clinical worsening and WHO functional class were also tested. If these showed significance ($\alpha = 0.04$ and $\alpha = 0.01$, respectively, or $\alpha = 0.05$ for both combined), the SF-36 index was tested and, finally, the Borg dyspnoea score was tested if the SF-36 index showed a significant effect. The combined ambrisentan dosage groups that showed significance versus placebo in primary endpoint analyses constituted the main comparison for secondary endpoints in each of the trials. A prespecified analysis of the combined 5 mg and placebo groups, stratified by study, WHO functional class and cause of PAH, was also conducted.[21]

Baseline characteristics were similar in each treatment arm of ARIES-1 and -2 trials. Patients had a mean age of 48–53 years, a mean 6MWD of 340–355 m, mean pulmonary arterial pressure of 47–51 mmHg, mean plasma BNP levels of 84–146 ng/mL, a mean SF-36 Health Survey physical functioning index of 28.6–31.9. Most patients (68–88%) were female.[21] Idiopathic PAH was diagnosed in 41–43% of patients and 19–22% presented with PAH associated with connective tissue disease. PAH associated with either HIV infection or anorexigen use accounted for ≤3% of patients.[21] Patients were WHO functional class I–IV, although most were either class II (38%) or class III (55%).[21]

ARIES-1 and ARIES-2 Trials

- Ambrisentan improved exercise capacity in patients with PAH.[21] The improvement in 6MWD from baseline over 12 weeks' treatment (primary endpoint) was significantly greater with ambrisentan 5 or 10 mg once daily (recommended dosages) [ARIES-1] and with ambrisentan 2.5 or 5 mg once daily (ARIES-2) than with placebo and increased dose-proportionally (figure 1).[21]
- In both the ARIES-1 and -2 trials, 6MWD improved or remained stable with ambrisentan from week 4 to week 12, but deteriorated between weeks 8 and 12 with placebo (figure 1).[21]
- The mean placebo-corrected increase in 6MWD at week 12 was 31 m (95% CI 3, 59; p = 0.008) and 51 m (95% CI 27, 76; p < 0.001) with ambrisentan 5 and 10 mg once daily in ARIES-1, and was 32 m (95% CI 2, 63; p = 0.022) and 59 m (95% CI 30, 89; p < 0.001) with ambrisentan 2.5 and 5 mg once daily in ARIES-2.[21]
- The incidence of clinical worsening was significantly reduced in ambrisentan 2.5 mg (p = 0.005) and 5 mg (p = 0.008) once daily recipients (5% of patients in each dosage arm) versus placebo (22%) in ARIES-2 (p < 0.001 for combined ambrisentan

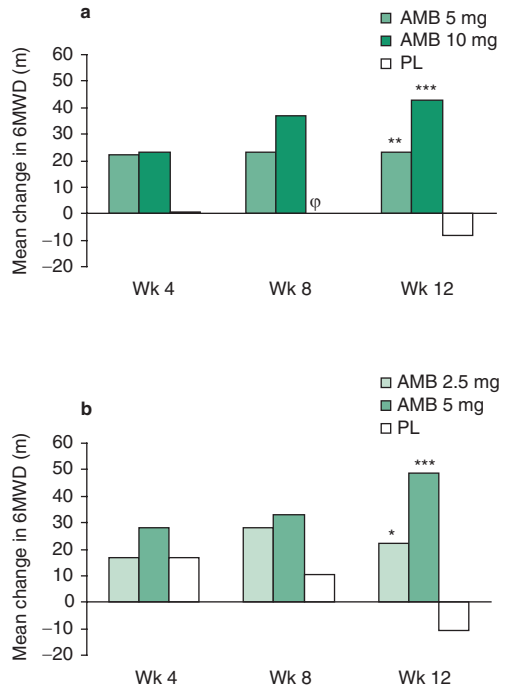


Fig. 1. Efficacy of oral ambrisentan (AMB) on exercise capacity in patients with pulmonary arterial hypertension. Mean change from baseline to 12 weeks in the distance walked in 6 minutes (6MWD) [primary endpoint] in two randomized, double-blind, placebo-controlled, multicentre, phase III trials (n = 393). All values estimated from a graph.[21] (**a**) ARIES-1 patients received AMB 5 mg (n = 67), AMB 10 mg (n = 67) or placebo (PL) [n = 67] once daily, (**b**) ARIES-2 patients received AMB 2.5 mg (n = 64), AMB 5 mg (n = 63) or PL (n = 65) once daily. * p = 0.022, ** p = 0.008, *** p < 0.001 versus PL, φ = zero value.

dosages vs placebo).[21] Although a statistical significant difference in the incidence of clinical worsening was not observed between placebo and the 5 or 10 mg treatment groups in ARIES-1, worsening was significantly improved when the integrated data from the ambrisentan 5 mg groups in both trials were compared with the combined placebo groups ($p = 0.005$).[21]

- A significant improvement from baseline in the distribution of WHO functional class was seen in ambrisentan recipients at week 12 in ARIES-1 ($p = 0.036$ vs placebo) but not in ARIES-2. However, integrated analysis of the 5 mg once daily dosage from both trials at week 12 indicated that WHO functional class distribution was significantly ($p = 0.025$) improved from baseline versus placebo.[21]
- Recipients in the combined ambrisentan dosage groups showed significant ($p = 0.005$) improvements in health-related quality of life in ARIES-2 compared with placebo (SF-36 Health Survey physical functioning values of 3.41 vs −0.20). Improvements versus placebo were significant for both the ambrisentan 2.5 mg ($p = 0.005$) and 5 mg ($p = 0.04$) groups. Statistical significance was not achieved in ARIES-1.[21]
- Borg dyspnoea scores were significantly improved for the combined ambrisentan dosage groups versus placebo at week 12 in ARIES-1 (−0.6 [95% CI −1.2, 0.0; $p = 0.017$]) and in ARIES-2 (−1.1 [95% CI −1.8, −0.4; $p = 0.019$]). Improvements versus placebo were significant for the ambrisentan 10 mg dosage group in ARIES-1 ($p = 0.002$), for the 2.5 and 5 mg groups in ARIES-2 (both $p < 0.05$) and for the combined 5 mg groups from both studies ($p = 0.031$)[21]

One-Year Extension Studies

- Exploratory analyses indicated that improvements in 6MWD reported in the phase III ARIES-1 and -2 trials at week 12 in the 298 patients who received at least 48 weeks of ambrisentan in ARIES-E were maintained at week 48.[21] The mean change from baseline in 6MWD in this group of patients was 40 m at week 12 (95% CI 33, 48) and 39 m at week 48 (95% CI 29, 49).[21]
- Sustained improvements in WHO functional class and Borg dyspnoea index were also maintained in ARIES-E at 48 weeks. Furthermore, 1-year survival rates were 95–97% with ambrisentan 2.5–10 mg once daily.[28]
- Similarly, at week 48 in the AMB-222-E trial, the mean change from baseline in 6MWD for ambrisentan 1–10 mg once daily was 54 m ($p < 0.0001$) and the mean improvement in the Borg dyspnoea index was −0.9 ($p < 0.001$) in 64 patients.[29]
- Ambrisentan 1–10 mg once daily showed sustained efficacy in a small ($n = 19$) subset of patients with PAH associated with connective tissue diseases in a phase II extension study.[30] 6MWD had significantly improved from baseline following ambrisentan treatment at week 12 (+19 m; $p = 0.05$), and continued to improve at week 24 (+33 m; $p = 0.011$) and week 48 (+29 m; $p = 0.029$). Improvements in WHO functional class and Borg dyspnoea achieved at week 12 were also maintained.[30]

4. Tolerability

The tolerability of ambrisentan has been evaluated in the short-term ARIES-1 and -2 trials described in section 3.[21] Long-term follow-up safety data are provided in the ARIES-E (≤2.8 years treatment; mean exposure 1.4 years)[28] and AMB-220-E (<1 year)[35] studies. These data are supplemented by data from the US manufacturers prescribing information.[17] Further 1-year follow-up safety data are provided in an open-label phase II study (AMB-222) in patients ($n = 36$) with idiopathic or familial PAH who received ambrisentan after previously discontinuing bosentan and/or sitaxsentan treatment because of liver function test abnormalities.[36] In this study, the primary outcome measure was defined as the incidence of serum aminotransferase levels >3 times the ULN at week 12.[37]

- Ambrisentan was generally well tolerated in patients with PAH in the short-term ARIES-1 and -2 trials, with most adverse events of mild to moderate intensity.[17,21] The overall incidence of adverse events did not differ significantly between treatment

groups. Peripheral oedema, headache and nasal congestion were the most common adverse events with ambrisentan (figure 2),[21] and nasal congestion was the only adverse event that was dose-dependent.[17]

- Premature discontinuations during the 12-week ARIES-1 and -2 trials were reported in 7.6% of patients in the combined ambrisentan dosage groups versus 15.9% in the placebo treatment groups.[21] At least one serious adverse event occurred in 9.6% of patients in the ambrisentan group versus 16.7% of patients in the placebo groups. Hospitalizations for PAH occurred in 9 ambrisentan recipients versus 11 recipients of placebo, and 5 ambrisentan recipients met early escape criteria versus 11 placebo recipients. Six patients (4.5%) died in the placebo group and 4 (1.5%) died in the combined ambrisentan groups; the deaths were not thought to be treatment-related by the study investigators.[21]

- Mean haemoglobin concentrations were reduced by 0.8 g/dL in ambrisentan recipients at week 12 compared with an increase of 0.2 g/dL for placebo recipients; however, the degree of change was not related to ambrisentan dosage in the ARIES-1 and -2 trials.[21]

- In the 12-week ARIES-1 and -2 trials, no ambrisentan recipients experienced increases from baseline in liver function tests. Moreover, no ambrisentan recipients developed serum aminotransferase levels >3 times the ULN versus 2.3% in placebo groups.[21]

- The frequency of adverse events seen in the randomized trials was maintained in the ARIES-E extension trial (quantitative data not shown).[28] Two patients experienced an elevation in serum aminotransferase levels >3 times the ULN in the AMB-220-E trial that required treatment discontinuation.[35] However, the incidence of elevated aminotransferase levels >3 times the ULN in ARIES-E was similar to that for placebo in ARIES-1 and -2 (quantitative data not shown).[28]

- An open-label, phase II trial in which 36 patients with PAH discontinuing bosentan (86%), sitaxsentan (6%) or both therapies (8%) because of elevated serum aminotransferases were treated with 12 weeks of ambrisentan 2.5–10 mg once daily,

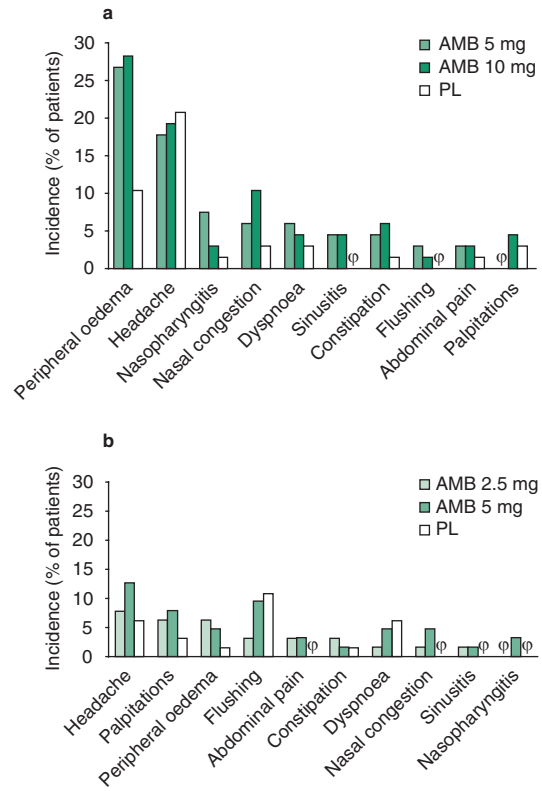


Fig. 2. Tolerability of oral ambrisentan (AMB) in patients with pulmonary arterial hypertension. Data presented are the incidence of adverse events in patients receiving AMB (all dosages combined) with an incidence >3% and ≥1% higher than in patients from placebo (PL) groups in randomized, double-blind, PL-controlled, multicentre, phase III trials.[21] (**a**) ARIES-1 patients received AMB 5 mg (n = 67), AMB 10 mg (n = 67) or PL (n = 67) once daily for 12 weeks, (**b**) ARIES-2 patients received AMB 2.5 mg (n = 64), AMB 5 mg (n = 63) or PL (n = 65) once daily for 12 weeks. φ = incidence of 0%.

revealed no recurrence of liver function abnormality that required discontinuation of ambrisentan treatment (although one patient had a temporary dose reduction to stabilize aminotransferase levels).[36] Moreover, no further liver function abnormalities were observed in patients continuing to receive ambrisentan for up to 2 years.[38]

- At high concentrations, ambrisentan is clastogenic in mammalian *in vitro* cell culture, and teratogenic in animal studies.[17] Currently, there are no studies in humans.

5. Dosage and Administration

In adult patients with PAH, initial therapy with ambrisentan (which may be administered without regard to food) may be started at a dosage of 5 mg once daily and, if the dosage is tolerated, it may be increased to 10 mg once daily.[17] Ambrisentan carries black box warnings stating that liver aminotransferases must be monitored monthly and treatment discontinued if levels reach >5 times the ULN when accompanied with bilirubin levels >2 times the ULN or if other liver dysfunction symptoms are apparent. Furthermore, treatment is contraindicated in pregnancy, as ambrisentan may cause fetal harm and, therefore, two reliable methods of contraception must be used.[17]

As with other ET receptor antagonists, ambrisentan has been associated with reductions in haemoglobin and haematocrit concentrations in clinical trials. Haemoglobin concentrations must be assessed prior to commencing treatment and measured at 1 month and periodically thereafter. Discontinuation of treatment is recommended if clinically significant reductions in haemoglobin levels are observed. Local prescribing information should be consulted for other contraindications, warnings or recommended dosage adjustments in special patient groups.

6. Ambrisentan: Current Status

Ambrisentan is approved in the US,[17] Canada, the EU[39] and other countries worldwide for the treatment of patients with PAH (WHO group I) classified as WHO functional class II or III. Two large, well designed, short-term, phase III trials have shown that oral ambrisentan 5 or 10 mg once daily is effective in increasing exercise capacity and reducing the incidence of clinical worsening of patients with PAH. This therapeutic efficacy was maintained at 48 weeks in a phase III extension trial where ambrisentan was generally well tolerated. Ambrisentan is associated with a low incidence of drug-drug interactions and liver function abnormalities, and requires only once-daily administration. Patients with PAH who discontinued treatment with other ET receptor antagonists (bosentan or sitaxsentan) because of elevated serum aminotransferases were effectively treated with ambrisentan without a recurrence of liver function abnormalities in a small, open-label, phase II trial of up to 2 years' duration.

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