

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBRISENTAN TABLETS safely and effectively. See [full prescribing information](#) for AMBRISENTAN TABLETS.

AMBRISENTAN tablets, for oral use
Initial U.S. Approval: 2007

WARNING: EMBRYO-FETAL TOXICITY
See [full prescribing information](#) for complete **boxed warning**.

- Based on animal data ambrisentan tablets may cause fetal harm if used during pregnancy (4.1, 5.1, 8.1).
- Females of reproductive potential: Exclude pregnancy before the start of treatment. Use effective contraception prior to initiation of treatment, during treatment, and for one month after treatment with ambrisentan tablets (2.2, 4.1, 5.1, 8.1, 8.3).
- When pregnancy is detected, discontinue ambrisentan tablets as soon as possible (5.1).

RECENT MAJOR CHANGES

- Box Warning 4/2025
- Indications and Usage (1) 4/2025
- Dosage and Administration, Pregnancy Testing in Females of Reproductive Potential (2.2) 4/2025
- Warnings and Precautions for Use
Embryo-fetal Toxicity (5.1) 4/2025
Ambrisentan Risk Evaluation and Mitigation Strategy (REMS) (5.2) (removed) 4/2025

INDICATIONS AND USAGE

Ambrisentan tablets are an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adult patients:

To improve exercise ability and delay clinical worsening.

Studies establishing effectiveness included trials predominantly in patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%) (1).

DOSAGE AND ADMINISTRATION

- Initiate treatment at 5 mg once daily (2.1).
- Titrate at 4-week intervals as needed and tolerated (2.1).
- Do not split, crush, or chew tablets (2.1).

DOSAGE FORMS AND STRENGTHS

Tablet: 5 mg and 10 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1)
- Idiopathic Pulmonary Fibrosis (4.2)

WARNINGS AND PRECAUTIONS

- Fluid retention may require intervention (5.2).
- If patients develop acute pulmonary edema during initiation of therapy with ambrisentan tablets, consider underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.3).
- Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.4).
- Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.5).

ADVERSE REACTIONS

- Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Cyclosporine increases ambrisentan exposure; limit ambrisentan dose to 5 mg once daily (7).

USE IN SPECIFIC POPULATIONS

- Breastfeeding: Choose ambrisentan tablets or breastfeeding (8.2).
- Not recommended in patients with moderate or severe hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2025

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

Ambrisentan tablets are contraindicated for use during pregnancy because it may cause major birth defects if used by pregnant patients, based on studies in animals [see *Contraindications (4.1)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1)*].

Therefore, for females of reproductive potential, exclude pregnancy before the initiation of treatment with ambrisentan tablets. Advise use of effective contraception before initiation, during treatment, and for one month after treatment with ambrisentan tablets [see *Dosage and Administration (2.2)*, *Contraindications (4.1)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1, 8.3)*]. When pregnancy is detected, discontinue ambrisentan tablets as soon as possible (5.1).

1 INDICATIONS AND USAGE

Ambrisentan tablets are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adult patients:

- To improve exercise ability and delay clinical worsening.

Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

2 DOSAGE AND ADMINISTRATION

2.1 Adult Dosage

Initiate treatment at 5 mg once daily. At 4-week intervals, the dose of ambrisentan can be increased, as needed and tolerated, to ambrisentan 10 mg.

Do not split, crush, or chew tablets.

2.2 Pregnancy Testing in Females of Reproductive Potential

Exclude pregnancy before initiating treatment with ambrisentan tablets in females of reproductive potential [see *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1, 8.3)*].

3 DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg film-coated tablets for oral administration

- Each 5 mg tablet is pale pink, biconvex, beveled edged, arc square film-coated

tablet. Engraved “APO” on one side, “A5” on the other side.

- Each 10 mg tablet is deep pink, biconvex, oval film-coated tablet. Engraved “APO” on one side, “A10” on the other side.

4 CONTRAINDICATIONS

4.1 Pregnancy

Ambrisentan tablets may cause fetal harm when administered to a pregnant female. Ambrisentan tablets are contraindicated in females who are pregnant. Ambrisentan was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1), and *Use in Specific Populations* (8.1)].

4.2 Idiopathic Pulmonary Fibrosis

Ambrisentan tablets are contraindicated in patients with Idiopathic Pulmonary Fibrosis (IPF), including IPF patients with pulmonary hypertension (WHO Group 3) [see *Clinical Studies* (14.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-fetal Toxicity

Based on data from animal reproduction studies, ambrisentan tablets may cause fetal harm when administered during pregnancy and is contraindicated during pregnancy. The available human data for endothelin receptor antagonists do not establish the presence or absence of major birth defects related to the use of ambrisentan tablets. Advise patients who can become pregnant of the potential risk to a fetus. Obtain a pregnancy test prior to initiation of treatment with ambrisentan tablets. Advise patients who can become pregnant to use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with ambrisentan tablets. When pregnancy is detected, discontinue use as soon as possible [see *Dosage and Administration* (2.2), and *Use in Specific Populations* (8.1, 8.3)].

5.2 Fluid Retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg ambrisentan tablets compared to placebo [see *Adverse Reactions* (6.1)]. Most edema was mild to moderate in severity.

In addition, there have been postmarketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting ambrisentan tablets. Patients required intervention with a diuretic, fluid management, or, in some cases,

hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, 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.

5.3 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as ambrisentan, the possibility of PVOD should be considered, and if confirmed ambrisentan tablets should be discontinued.

5.4 Decreased Sperm Counts

Decreased sperm counts have been observed in human and animal studies with another endothelin receptor antagonist and in animal fertility studies with ambrisentan. Ambrisentan may have an adverse effect on spermatogenesis [see *Use in Specific Populations* (8.6) and *Nonclinical Toxicology* (13.1)].

5.5 Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with ambrisentan. These decreases were observed within the first few weeks of treatment with ambrisentan tablets and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving ambrisentan tablets in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving ambrisentan tablets (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

In the long-term open-label extension of the two pivotal clinical studies, mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment.

There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion.

Measure hemoglobin prior to initiation of ambrisentan tablets, at one month, and periodically thereafter. Initiation of ambrisentan tablets therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing ambrisentan tablets.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Embryo-fetal Toxicity [see *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1)]
- Fluid Retention [see *Warnings and Precautions* (5.2)]
- Pulmonary Edema with PVOD [see *Warnings and Precautions* (5.3)]
- Decreased Sperm Count [see *Warnings and Precautions* (5.4)]
- Hematologic Changes [see *Warnings and Precautions* (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data for ambrisentan tablets are presented from two 12-week, placebo-controlled studies (ARIES-1 and ARIES-2) in patients with pulmonary arterial hypertension (PAH). The exposure to ambrisentan in these studies ranged from 1 day to 4 years (N=357 for at least 6 months and N=279 for at least 1 year).

In ARIES-1 and ARIES-2, a total of 261 patients received ambrisentan tablets at doses of 2.5 mg, 5 mg, or 10 mg once daily and 132 patients received placebo. The adverse reactions that occurred in >3% more patients receiving ambrisentan tablets than receiving placebo are shown in [Table 1](#).

Table 1 Adverse Reactions with Placebo-Adjusted Rates >3% in ARIES-1 and ARIES-2

Adverse Reaction	Placebo (N=132)	Ambrisentan tablets (N=261)	
	n (%)	n (%)	Placebo-adjusted (%)
Peripheral edema	14 (11)	45 (17)	6
Nasal congestion	2 (2)	15 (6)	4
Sinusitis	0 (0)	8 (3)	3
Flushing	1 (1)	10 (4)	3

Most adverse drug reactions were mild to moderate and only nasal congestion was dose-dependent.

Few notable differences in the incidence of adverse reactions were observed for patients by age or sex. Peripheral edema was similar in younger patients (<65 years) receiving ambrisentan tablets (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving ambrisentan tablets (29%; 16/56) compared to placebo (4%; 1/28). The results of such subgroup analyses must be interpreted cautiously.

The incidence of treatment discontinuations due to adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for ambrisentan (2%; 5/261 patients) and placebo (2%; 3/132 patients). The incidence of patients with serious adverse events other than those related to PAH during the clinical trials in patients with PAH was similar for placebo (7%; 9/132 patients) and for ambrisentan (5%; 13/261 patients).

During 12 week controlled clinical trials, the incidence of aminotransferase elevations >3 x upper limit of normal (ULN) were 0% on ambrisentan and 2.3% on placebo. In practice, cases of hepatic injury should be carefully evaluated for cause.

Use in Patients with Prior Endothelin Receptor Antagonist (ERA) Related Serum Liver Enzyme Abnormalities

In an uncontrolled, open-label study, 36 patients who had previously discontinued endothelin receptor antagonists (ERAs: bosentan, an investigational drug, or both) due to aminotransferase elevations >3 x ULN were treated with ambrisentan tablets. Prior elevations were predominantly moderate, with 64% of the ALT elevations <5 x ULN, but 9 patients had elevations >8 x ULN. Eight patients had been re-challenged with bosentan and/or the investigational ERA and all eight had a recurrence of aminotransferase abnormalities that required discontinuation of ERA therapy. All patients had to have normal aminotransferase levels on entry to this study. Twenty-five of the 36 patients were also receiving prostanoid and/or phosphodiesterase type 5 (PDE5) inhibitor therapy. Two patients discontinued early (including one of the patients with a prior 8 x ULN elevation). Of the remaining 34 patients, one patient experienced a mild aminotransferase elevation at 12 weeks on ambrisentan tablets 5 mg that resolved with decreasing the dosage to 2.5 mg, and that did not recur with later escalations to 10 mg. With a median follow up of 13 months and with 50% of patients increasing the dose of ambrisentan tablets to 10 mg, no patients were discontinued for aminotransferase elevations. While the uncontrolled study design does not provide information about what would have occurred with re-administration of previously used ERAs or show that ambrisentan led to fewer aminotransferase elevations than would have been seen with those drugs, the study indicates that ambrisentan may be tried in patients who have experienced asymptomatic aminotransferase elevations on other ERAs after aminotransferase levels have returned to normal.

6.2 Postmarketing Experience

The following adverse reactions were identified during post-approval use of ambrisentan tablets. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate reliably the frequency or to establish a causal relationship to drug exposure: anemia requiring transfusion [see *Warnings and Precautions* (5.5)] heart failure (associated with fluid retention), symptomatic hypotension, and hypersensitivity (e.g., angioedema, rash).

Elevations of liver aminotransferases (ALT, AST) have been reported with ambrisentan use; in most cases alternative causes of the liver injury could be identified (heart failure, hepatic congestion, hepatitis, alcohol use, hepatotoxic medications). Other endothelin receptor antagonists have been associated with elevations of aminotransferases, hepatotoxicity, and cases of liver failure [see *Adverse Reactions* (6.1)].

7 DRUG INTERACTIONS

Multiple dose coadministration of ambrisentan and cyclosporine resulted in an approximately 2 fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when coadministered with cyclosporine [see *Clinical Pharmacology* ([12.3](#))].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, ambrisentan may cause fetal harm, including birth defects and fetal death, when administered to a pregnant woman and is contraindicated during pregnancy. There are limited data on ambrisentan use in pregnant women. Available data from postmarketing reports and published literature over decades of use with endothelin receptor antagonists in the same class as ambrisentan tablets have not identified an increased risk of major birth defects; however, these data are limited. Methodological limitations of these postmarketing reports and published literature include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and missing data. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal endothelin receptor antagonist use. In animal reproduction studies, ambrisentan was teratogenic in rats and rabbits at doses which resulted in exposures of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day [see *Animal Data*]. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential hazard to a fetus [see *Contraindications* ([4.1](#)), *Warnings and Precautions* ([5.1](#))].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Ambrisentan was teratogenic at oral dosages of ≥ 15 mg/kg/day (AUC 51.7 h•mcg/mL) in rats and ≥ 7 mg/kg/day (24.7 h•mcg/mL) in rabbits; it was not studied at lower dosages. These dosages are of 3.5 and 1.7 times, respectively, the human dose of 10 mg per day (14.8 h•mcg/mL) based on AUC. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

A preclinical study in rats has shown decreased survival of newborn pups (mid and high dosages) and effects on testicle size and fertility of pups (high dosage) following maternal treatment with ambrisentan from late gestation through weaning. The mid and high dosages were 51 x, and 170 x (on a mg/m² body surface area basis) the maximum

oral human dose of 10 mg and an average adult body weight of 70 kg. These effects were absent at a maternal dosage 17 x the human dose based on mg/m².

8.2 Lactation

Risk Summary

It is not known whether ambrisentan is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in breastfed infants from ambrisentan, a decision should be made whether to discontinue breastfeeding or discontinue ambrisentan tablets, taking into account the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Based on data from animal reproductive toxicity studies, ambrisentan may cause fetal harm, including birth defects and fetal death, when administered to a pregnant patient and is contraindicated during pregnancy [see *Contraindications (4.1)*, *Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify that patients who can become pregnant are not pregnant prior to initiating ambrisentan. The patient should contact their physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient should discuss the risks to the pregnancy and the fetus.

Contraception

Patients who can become pregnant who are using ambrisentan should use effective contraception prior to initiation of treatment, during treatment, and for one month after discontinuation of treatment with ambrisentan to prevent pregnancy [see *Warnings and Precautions (5.1)*].

Infertility

Males

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months, and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data [see *Nonclinical Toxicology (13.1)*] from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as ambrisentan have an adverse effect on spermatogenesis. Counsel patients about the potential effects on fertility [see *Warnings and Precautions (5.5)*].

8.4 Pediatric Use

Safety and effectiveness of ambrisentan tablets in pediatric patients have not been established.

Juvenile Animal Data

In juvenile rats administered ambrisentan orally once daily during postnatal day 7 to 26, 36, or 62, a decrease in brain weight (–3% to –8%) with no morphologic or neurobehavioral changes occurred after breathing sounds, apnea, and hypoxia were observed, at exposures approximately 1.8 to 7.0 times human pediatric exposures at 10 mg, based on AUC.

8.5 Geriatric Use

In the two placebo-controlled clinical studies of ambrisentan tablets, 21% of patients were ≥ 65 years old and 5% were ≥ 75 years old. The elderly (age ≥ 65 years) showed less improvement in walk distances with ambrisentan tablets than younger patients did, but the results of such subgroup analyses must be interpreted cautiously. Peripheral edema was more common in the elderly than in younger patients.

8.6 Renal Impairment

The impact of renal impairment on the pharmacokinetics of ambrisentan has been examined using a population pharmacokinetic approach in PAH patients with creatinine clearances ranging between 20 and 150 mL/min. There was no significant impact of mild or moderate renal impairment on exposure to ambrisentan [see *Clinical Pharmacology* (12.3)]. Dose adjustment of ambrisentan tablets in patients with mild or moderate renal impairment is therefore not required. There is no information on the exposure to ambrisentan in patients with severe renal impairment.

The impact of hemodialysis on the disposition of ambrisentan has not been investigated.

8.7 Hepatic Impairment

Pre-existing Hepatic Impairment

The influence of pre-existing hepatic impairment on the pharmacokinetics of ambrisentan has not been evaluated. Because there is *in vitro* and *in vivo* evidence of significant metabolic and biliary contribution to the elimination of ambrisentan, hepatic impairment might be expected to have significant effects on the pharmacokinetics of ambrisentan [see *Clinical Pharmacology* (12.3)]. Ambrisentan is not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of ambrisentan in patients with mild pre-existing impaired liver function; however, exposure to ambrisentan may be increased in these patients.

Elevation of Liver Transaminases

Other endothelin receptor antagonists (ERAs) have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure [see *Adverse Reactions* (6.1, 6.2)]. In patients who develop hepatic impairment after ambrisentan tablets initiation, the cause of liver injury should be fully investigated. Discontinue ambrisentan tablets if elevations of liver aminotransferases are $>5 \times$ ULN or if elevations are accompanied by bilirubin $>2 \times$ ULN, or by signs or symptoms of liver

dysfunction and other causes are excluded.

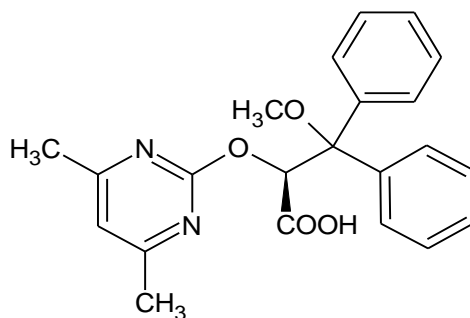
10 OVERDOSAGE

There is no experience with overdosage of ambrisentan. The highest single dose of ambrisentan tablets administered to healthy volunteers was 100 mg, and the highest daily dose administered to patients with PAH was 10 mg once daily. In healthy volunteers, single doses of 50 mg and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion. Massive overdosage could potentially result in hypotension that may require intervention.

11 DESCRIPTION

Ambrisentan, an endothelin receptor antagonist that is selective for the endothelin type-A (ETA) receptor. The chemical name of ambrisentan is (+)-(2S)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid. It has a molecular formula of $C_{22}H_{22}N_2O_4$ and a molecular weight of 378.42 g/mol. It contains a single chiral center determined to be the (S) configuration and has the following structural formula:

Figure 1 Ambrisentan Structural Formula



Ambrisentan is a white to yellow powder. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is freely soluble in THF, sparingly soluble in ethyl acetate, slightly soluble in ethanol, practically insoluble in n-hexane and water. Ambrisentan is not hygroscopic.

Ambrisentan tablets are available as 5 mg and 10 mg film-coated tablets for once daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red # 40 aluminum lake 38-42% (10 mg only), FDC Red # 40 (5 mg only), polyethylene glycol, polyvinyl alcohol, Sunset yellow aluminum lake 40% (5 mg only), talc and titanium dioxide. Each pale pink ambrisentan tablet contains 5 mg of ambrisentan. Each deep pink ambrisentan tablet contains 10 mg of ambrisentan.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET_A and ET_B, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET_A are vasoconstriction and cell proliferation, while the predominant actions of ET_B are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high-affinity ($K_i=0.011$ nM) ET_A receptor antagonist with a high selectivity for the ET_A versus ET_B receptor (>4000-fold). The clinical impact of high selectivity for ET_A is not known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either ambrisentan tablets 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. Ambrisentan tablets 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of ambrisentan tablets increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving ambrisentan tablets 5–10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

12.3 Pharmacokinetics

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects is dose proportional. The absolute bioavailability of ambrisentan is not known. Ambrisentan is absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. *In vitro* studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4% relative to parent ambrisentan AUC. The *in vivo* inversion of S-ambrisentan to R-ambrisentan is negligible. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

Drug Interactions

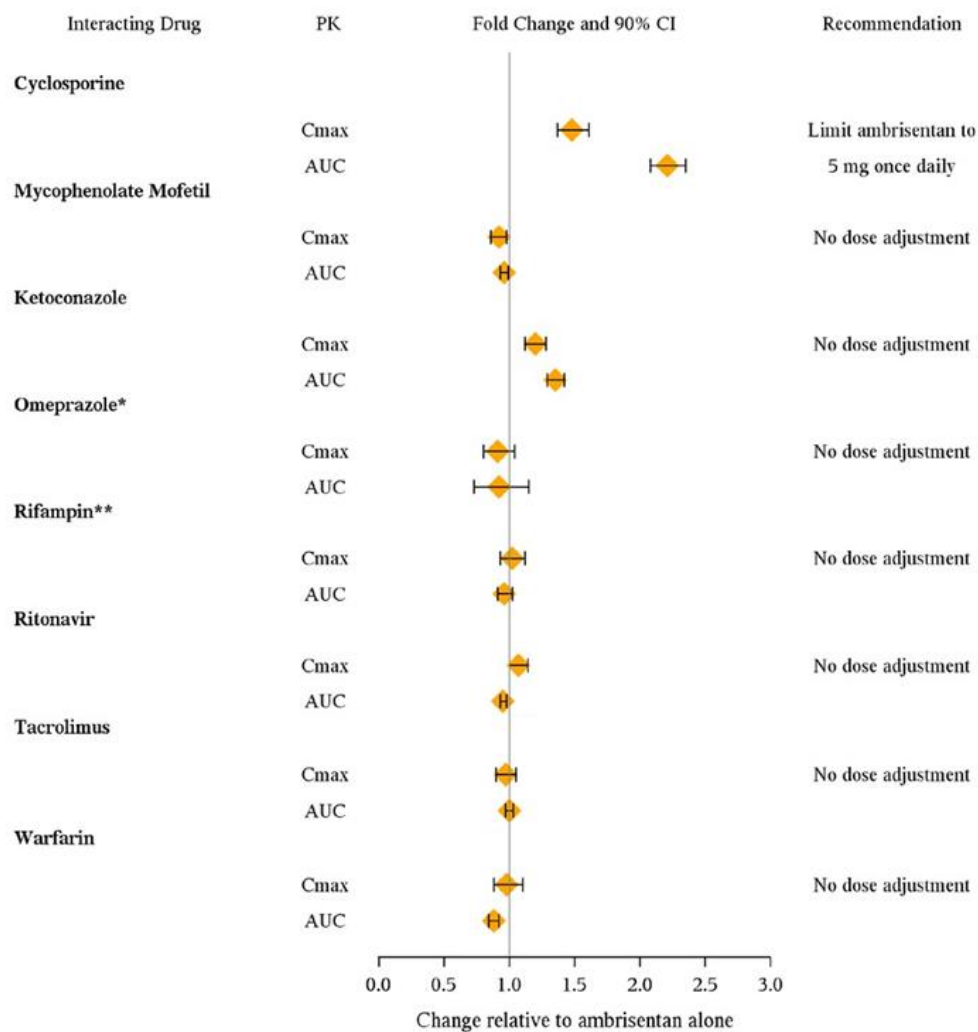
In Vitro Studies

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S. *In vitro* studies suggest that ambrisentan is a substrate of the Organic Anion Transporting Polypeptides OATP1B1 and OATP1B3, and P-glycoprotein (P-gp). Drug interactions might be expected because of these factors; however, a clinically relevant interaction has been demonstrated only with cyclosporine [see *Drug Interactions* (7)]. *In vitro* studies found ambrisentan to have little to no inhibition of human hepatic transporters. Ambrisentan demonstrated weak dose-dependent inhibition of OATP1B1, OATP1B3, and NTCP (IC₅₀ of 47 mcM, 45 mcM, and approximately 100 mcM, respectively) and no transporter-specific inhibition of BSEP, BRCP, P-gp, or MRP2. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

In Vivo Studies

The effects of other drugs on ambrisentan pharmacokinetics and the effects of ambrisentan on the exposure to other drugs are shown in [Figure 2](#) and [Figure 3](#), respectively.

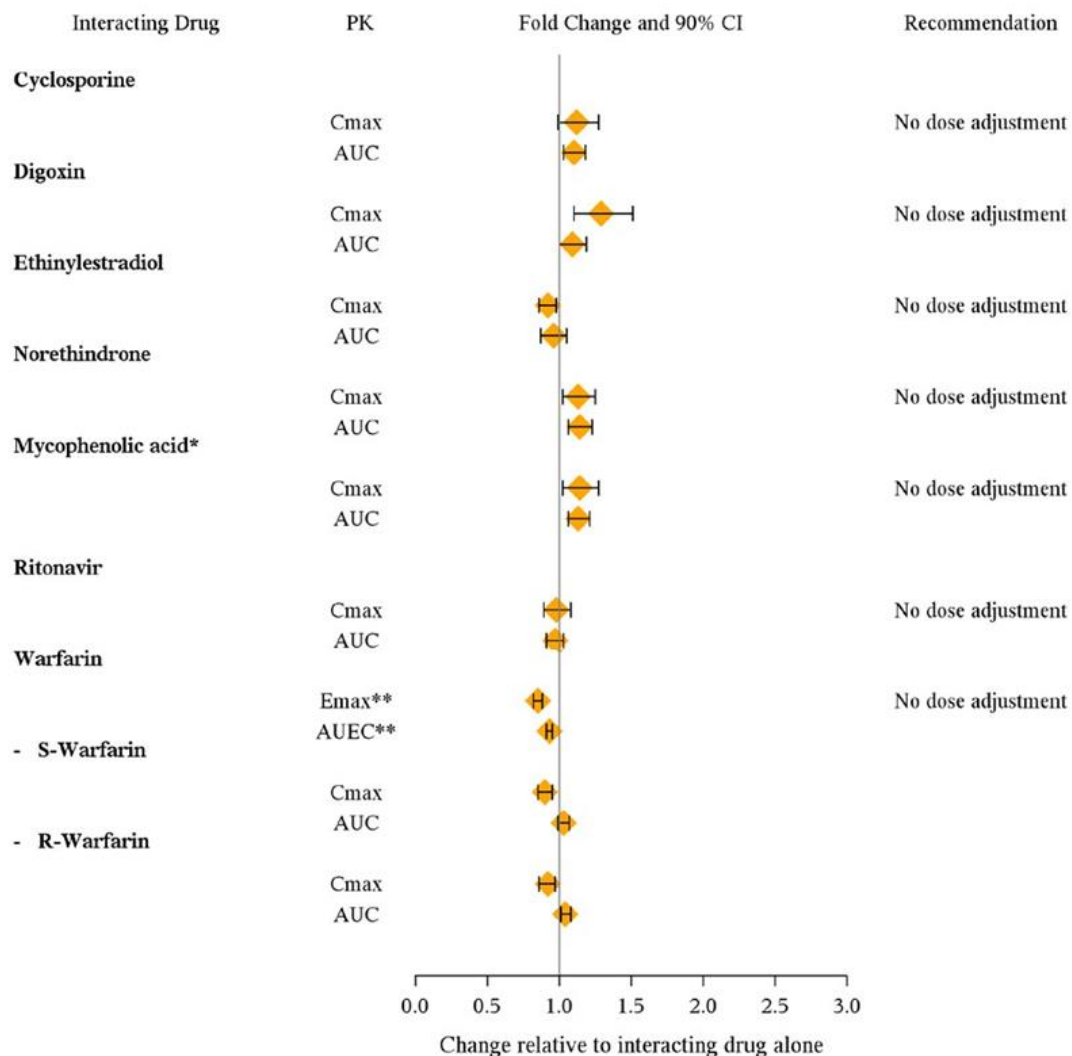
Figure 2 Effects of Other Drugs on Ambrisentan Pharmacokinetics



* Omeprazole: based on population pharmacokinetic analysis in PAH patients

** Rifampin: AUC and C_{max} were measured at steady-state. On Day 3 of coadministration a transient 2-fold increase in AUC was noted that was no longer evident by Day 7. Day 7 results are presented.

Figure 3 Effects of Ambrisentan on Other Drugs



* Active metabolite of mycophenolate mofetil

** GMR (95% CI) for INR

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Oral carcinogenicity studies of up to two years duration were conducted at starting doses of 10, 30, and 60 mg/kg/day in rats (8 to 48 times the maximum recommended human dose [MRHD] on a mg/m² basis) and at 50, 150, and 250 mg/kg/day in mice (28 to 140 times the MRHD). In the rat study, the high- and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51 because of effects

on survival. The high-dose males and females were taken off drug completely in weeks 69 and 93, respectively. The only evidence of ambrisentan-related carcinogenicity was a positive trend in male rats, for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in the mid-dose group (high-dose group excluded from analysis), and the occurrence of mammary fibroadenomas in males in the high-dose group. In the mouse study, high-dose male and female groups had their doses lowered to 150 mg/kg/day in week 39 and were taken off drug completely in week 96 (males) or week 76 (females). In mice, ambrisentan was not associated with excess tumors in any dosed group.

Positive findings of clastogenicity were detected, at drug concentrations producing moderate to high toxicity, in the chromosome aberration assay in cultured human lymphocytes. There was no evidence for genetic toxicity of ambrisentan when tested *in vitro* in bacteria (Ames test) or *in vivo* in rats (micronucleus assay, unscheduled DNA synthesis assay).

The development of testicular tubular atrophy and impaired fertility has been linked to the chronic administration of endothelin receptor antagonists in rodents. Testicular tubular degeneration was observed in rats treated with ambrisentan for two years at doses ≥ 10 mg/kg/day (8-fold MRHD). Increased incidences of testicular findings were also observed in mice treated for two years at doses ≥ 50 mg/kg/day (28-fold MRHD). Effects on sperm count, sperm morphology, mating performance, and fertility were observed in fertility studies in which male rats were treated with ambrisentan at oral doses of 300 mg/kg/day (236-fold MRHD). At doses of ≥ 10 mg/kg/day, observations of testicular histopathology in the absence of fertility and sperm effects were also present.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (PAH)

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted in 393 patients with PAH (WHO Group 1). The two studies were identical in design except for the doses of ambrisentan tablets and the geographic region of the investigational sites. ARIES-1 compared once-daily doses of 5 mg and 10 mg ambrisentan tablets to placebo, while ARIES-2 compared once-daily doses of 2.5 mg and 5 mg ambrisentan tablets to placebo. In both studies, ambrisentan tablets or placebo was added to current therapy, which could have included a combination of anticoagulants, diuretics, calcium channel blockers, or digoxin, but not epoprostenol, treprostinil, iloprost, bosentan, or sildenafil. The primary study endpoint was 6-minute walk distance. In addition, clinical worsening, WHO functional class, dyspnea, and SF-36® Health Survey were assessed.

Patients had idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%), HIV infection (3%), or anorexigen use (1%). There were no patients with PAH associated with congenital heart disease.

Patients had WHO functional class I (2%), II (38%), III (55%), or IV (5%) symptoms at baseline. The mean age of patients was 50 years, 79% of patients were female, and 77% were Caucasian.

Submaximal Exercise Ability

Results of the 6-minute walk distance at 12 weeks for the ARIES-1 and ARIES-2 studies are shown in [Table 3](#) and [Figure 4](#).

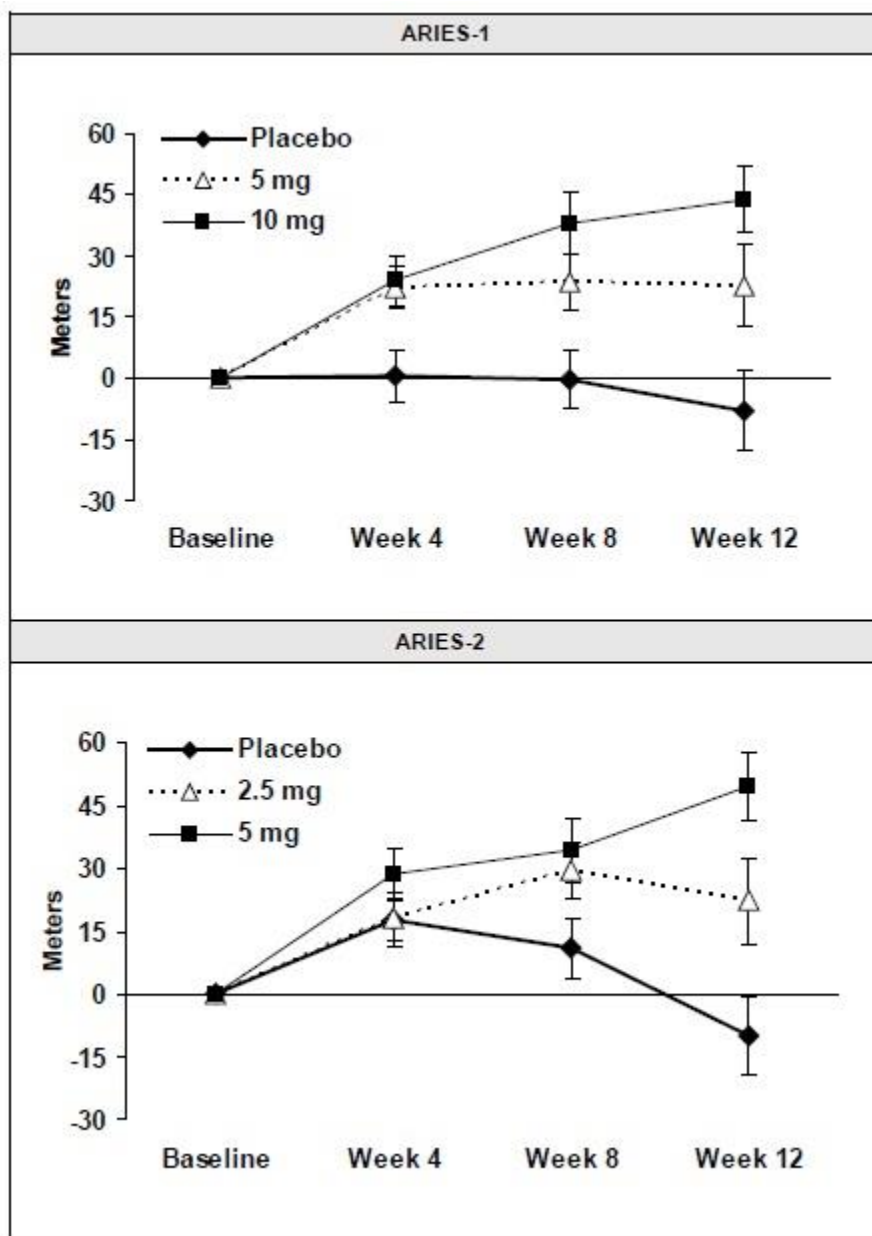
Table 3 Changes from Baseline in 6-Minute Walk Distance (meters) (ARIES-1 and ARIES-2)

	ARIES-1			ARIES-2		
	Placebo (N=67)	5 mg (N=67)	10 mg (N=67)	Placebo (N=65)	2.5 mg (N=64)	5 mg (N=63)
Baseline	342 ± 73	340 ± 77	342 ± 78	343 ± 86	347 ± 84	355 ± 84
Mean change from baseline	-8 ± 79	23 ± 83	44 ± 63	-10 ± 94	22 ± 83	49 ± 75
Placebo-adjusted mean change from baseline	-	31	51	-	32	59
Placebo-adjusted median change from baseline	-	27	39	-	30	45
p-value ^a	-	0.008	<0.001	-	0.022	<0.001

Mean ± standard deviation

a p-values are Wilcoxon rank sum test comparisons of ambrisentan tablets to placebo at Week 12 stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients

Figure 4 Mean Change in 6-Minute Walk Distance (ARIES-1 and ARIES-2)



Mean change from baseline in 6-minute walk distance in the placebo and ambrisentan groups. Values are expressed as mean \pm standard error of the mean.

In both studies, treatment with ambrisentan tablets resulted in a significant improvement in 6-minute walk distance for each dose of ambrisentan tablets and the improvements increased with dose. An increase in 6-minute walk distance was observed after 4 weeks of treatment with ambrisentan tablets, with a dose-response observed after 12 weeks of treatment. Improvements in walk distance with ambrisentan were smaller for elderly patients (age ≥ 65) than younger patients and for patients with secondary PAH than for patients with idiopathic or heritable PAH. The results of such subgroup analyses must be interpreted cautiously.

Clinical Worsening

Time to clinical worsening of PAH was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents, or study withdrawal due to early escape. Early escape was defined as meeting two or more of the following criteria: a 20% decrease in the 6-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. The clinical worsening events during the 12-week treatment period of the ambrisentan clinical trials are shown in [Table 4](#) and [Figure 5](#).

Table 4 Time to Clinical Worsening (ARIES-1 and ARIES-2)

	ARIES-1		ARIES-2	
	Placebo (N=67)	Ambrisentan tablets (N=134)	Placebo (N=65)	Ambrisentan tablets (N=127)
Clinical worsening, no. (%)	7 (10%)	4 (3%)	13 (22%)	8 (6%)
Hazard ratio	-	0.28	-	0.30
p-value, Log-rank test	-	0.030	-	0.005

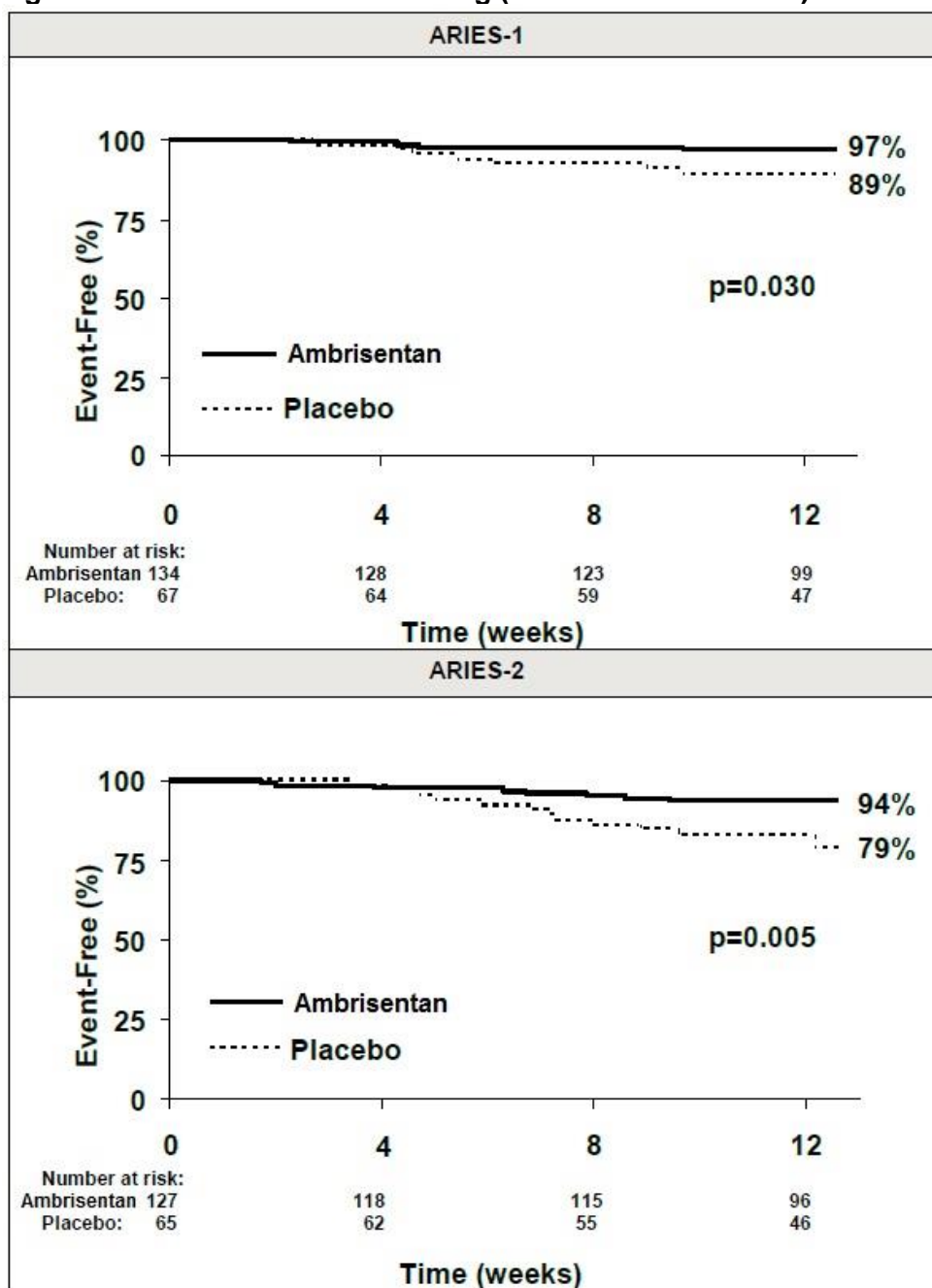
Intention-to-treat population.

Note: Patients may have had more than one reason for clinical worsening.

Nominal p-values

There was a significant delay in the time to clinical worsening for patients receiving ambrisentan compared to placebo. Results in subgroups such as the elderly were also favorable.

Figure 5 Time to Clinical Worsening (ARIES-1 and ARIES-2)



Time from randomization to clinical worsening with Kaplan-Meier estimates of the proportions of patients without events in ARIES-1 and ARIES-2.

p-values shown are the log-rank comparisons of ambrisentan to placebo stratified by idiopathic or heritable PAH and non-idiopathic, non-heritable PAH patients.

14.3 Long-term Treatment of PAH

In long-term follow-up of patients who were treated with ambrisentan tablets (2.5 mg, 5 mg, or 10 mg once daily) in the two pivotal studies and their open-label extension (N=383), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 93%, 85%, and 79%, respectively. Of the patients who remained on ambrisentan for up to 3 years, the majority received no other treatment for PAH. These uncontrolled observations do not allow comparison with a group not given ambrisentan tablets and cannot be used to determine the long-term effect of ambrisentan on mortality.

14.4 Adverse Effects in Idiopathic Pulmonary Fibrosis (IPF)

A randomized controlled study in patients with IPF, with or without pulmonary hypertension (WHO Group 3), compared ambrisentan (N=329) to placebo (N=163). The study was terminated after 34 weeks for lack of efficacy, and was found to demonstrate a greater risk of disease progression or death on ambrisentan. More patients taking ambrisentan tablets died (8% vs. 4%), had a respiratory hospitalization (13% vs. 6%), and had a decrease in FVC/DLCO (17% vs. 12%) [see *Contraindications* (4.2)].

16 HOW SUPPLIED/STORAGE AND HANDLING

Ambrisentan film-coated tablets are supplied as follows:

Each 5 mg tablet is pale pink, biconvex, beveled edged, arc square film-coated tablet. Engraved “APO” on one side, “A5” on the other side.

Bottles of 30 tablets	NDC 60505-4552-3
Blisters of 10 (1 x 10 blister pack)	NDC 60505-4552-0
Blisters of 30 (3 x 10 blister pack)	NDC 60505-4552-1

Each 10 mg tablet is deep pink, biconvex, oval film-coated tablet. Engraved “APO” on one side, “A10” on the other side.

Bottles of 30 tablets	NDC 60505-4553-3
Blisters of 10 (1 x 10 blister pack)	NDC 60505-4553-0
Blisters of 30 (3 x 10 blister pack)	NDC 60505-4553-1

Store at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see *USP Controlled Room Temperature*]. Store ambrisentan tablets in its original packaging.

Dispense in a tight container [see USP].

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Embryo-fetal Toxicity

Instruct patients on the risk of fetal harm when ambrisentan tablets are used in pregnancy [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.1)]. Instruct females of reproductive potential to immediately contact their physician if they suspect they may be pregnant. Educate and counsel patients who can become pregnant about the need to use effective contraception prior to treatment with ambrisentan tablets, during treatment, and for one month after treatment discontinuation [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.1, 8.3)]. Patients who can become pregnant should have a negative pregnancy test prior to treatment with ambrisentan tablets [see *Dosage and Administration* (2.2), *Contraindications* (4.1), *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1, 8.3)].

Counsel patients who can become pregnant about pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

Hepatic Effects

Advise patients of the symptoms of potential liver injury and instruct them to report any of these symptoms to their physician.

Hematological Change

Advise patients of the importance of hemoglobin testing.

Other Risks Associated with ambrisentan tablets

Instruct patients that the risks associated with ambrisentan tablets also include the following:

- Decreases in sperm count
- Fluid overload

Administration

Advise patients not to split, crush, or chew tablets.

APOTEX INC.
AMBRISENTAN TABLETS
5 mg and 10 mg

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, Florida
USA 33326

Rev. 9