

## 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**

<b>WARNING: EMBRYO-FETAL TOXICITY</b> <i>See full prescribing information for complete boxed warning.</i>
<ul style="list-style-type: none"><li>Do not administer ambrisentan tablets to a pregnant female because it may cause fetal harm (4.1, 5.1, 8.1).</li><li>Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception (2.2, 8.3).</li><li>For all female patients, ambrisentan tablets are available only through a restricted program called the <b>PS-Ambrisentan Risk Evaluation and Mitigation Strategy (REMS)</b> (5.2).</li></ul>

**INDICATIONS AND USAGE**

Ambrisentan tablet is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- 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

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## FULL PRESCRIBING INFORMATION

**WARNING: EMBRYO-FETAL TOXICITY**

Do not administer ambrisentan tablets to a pregnant female because it may cause fetal harm. Ambrisentan tablet is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals [see *Contraindications* (4.1), *Warnings and Precautions* (5.1), and *Use in Specific Populations* (8.1)].

Exclude pregnancy before the initiation of treatment with ambrisentan tablets. Females of reproductive potential must use acceptable methods of contraception during treatment with ambrisentan tablets and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment [see *Dosage and Administration* (2.2) and *Use in Specific Populations* (8.3)].

Because of the risk of embryo-fetal toxicity, females can only receive ambrisentan tablets through a restricted program called the **PS-Ambrisentan REMS program** [see *Warnings and Precautions* (5.2)].

### 1 INDICATIONS AND USAGE

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

- 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%).

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 (5.3).
  - If patients develop acute pulmonary edema during initiation of therapy with ambrisentan tablets, consider underlying pulmonary venoocclusive disease and discontinue treatment if necessary (5.4).
  - Decreases in sperm count have been observed in patients taking endothelin receptor antagonists (5.5).
  - Decreases in hemoglobin have been observed within the first few weeks; measure hemoglobin at initiation, at 1 month, and periodically thereafter (5.6).
  - Most common adverse reactions (>3% compared to placebo) are peripheral edema, nasal congestion, sinusitis, and flushing (6.1).

**ADVERSE REACTIONS**

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

**HOW SUPPLIED/STORAGE AND HANDLING**

**HOW SUPPLIED/STORAGE AND HANDLING**

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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).

**HOW SUPPLIED/STORAGE AND HANDLING**

**PATIENT COUNSELING INFORMATION**

Revised: 3/2019

## 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

Initiate treatment with ambrisentan tablets in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy tests during treatment [see *Use in Specific Populations* (8.3)].

### DOSAGE FORMS AND STRENGTHS

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

- Each 5 mg tablet is pale pink square shaped biconvex film coated tablets debossed with "C" on one side and "386" on other side.
- Each 10 mg tablet is deep pink oval shaped biconvex film coated tablets debossed with "C" on one side and "387" on other side.

## 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 tablets were 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 *Warnings and Precautions* (5.1, 5.2) 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)].

## WARNINGS AND PRECAUTIONS

### 5.1 Embryo-fetal Toxicity

Ambrisentan tablets may cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. In females of reproductive potential, exclude pregnancy prior to initiation of therapy, ensure use of acceptable contraceptive methods, and obtain monthly pregnancy tests [see *Dosage and Administration* (2.2), and *Use in Specific Populations* (8.1, 8.3)].

Ambrisentan tablets are only available for females through a restricted program under a REMS [see *Warnings and Precautions* (5.2)].

### 5.2 PS-Ambrisentan REMS Program

For all females, ambrisentan tablets are available only through a restricted program called the PS-Ambrisentan REMS, because of the risk of embryo-fetal toxicity [see *Contraindications* (4.1), *Warnings and Precautions* (5.1), and *Use in Specific Populations* (8.1, 8.3)].

Notable requirements of the PS-Ambrisentan REMS program include the following:

- Prescribers must be certified with the program by enrolling and completing training.
- All females, regardless of reproductive potential, must enroll in the PS-Ambrisentan REMS program prior to initiating ambrisentan tablets. Male patients are not enrolled in the REMS.
  - Females of reproductive potential must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations* (8.3)].
- Pharmacies that dispense ambrisentan tablets must be certified with the program and must dispense to female patients who are authorized to receive ambrisentan tablets.

Further information is available at www.PSAmbrisentanREMS.com.

### 5.3 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 were 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.

### 5.4 Pulmonary Edema with Pulmonary Veno-occlusive Disease (PVOD)

In 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.

### 5.5 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 tablets may have an adverse effect on spermatogenesis. Counsel patients about potential effects on fertility [see *Use in Specific Populations* (8.6) and *Nonclinical Toxicology* (13.1)].

### 5.6 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, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving ambrisentan 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 (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 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.

## 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* (5.3)]
- Pulmonary Edema with PVOD [see *Warnings and Precautions* (5.4)]
- Decreased Sperm Count [see *Warnings and Precautions* (5.5)]
- Hematological Changes [see *Warnings and Precautions* (5.6)]

### 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 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 6 days to 102 days.

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

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

	Placebo (N=132)	Ambrisentan (N=261)	
Adverse Reaction	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 (14%; 29/205) or placebo (13%; 13/104), and was greater in elderly patients (≥65 years) receiving ambrisentan (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. Other 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. 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* (5.6)] heart failure (associated with fluid retention), symptomatic hypotension, and hypersensitivity (e.g., angioedema, rash).

Elevations of liver aminotransferases (ALT, AST) were associated 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)].

## 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)].

## USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Based on data from animal reproduction studies, ambrisentan tablets may cause fetal harm when administered to a pregnant woman and is contraindicated during pregnancy. There are limited data on ambrisentan tablets use in pregnant women. 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 hµg/mL) in rats and ≥7 mg/kg/day (24.7 hµg/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 hµg/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/m<sup>2</sup> 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/m<sup>2</sup>.

### 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 tablets, 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

#### Pregnancy Testing

Female patients of reproductive potential must have a negative pregnancy test prior to initiation of treatment, monthly pregnancy test during treatment, and pregnancy test 1 month after stopping treatment with ambrisentan tablets. Advise patients to contact their healthcare provider if they become pregnant or suspect they may be pregnant. Perform a pregnancy test if pregnancy is suspected for any reason. For positive pregnancy tests, counsel patient on the potential risk to the fetus and patient options [see *Boxed Warning and Dosage and Administration* (2.2)].

#### Contraception

Female patients of reproductive potential must use acceptable methods of contraception during treatment with ambrisentan tablets and for 1 month after stopping treatment with ambrisentan tablets. Patients may choose one highly effective form of contraception (intrauterine device [IUD], contraceptive implant, or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see *Boxed Warning*].

#### 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 tablets 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 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 tablets are not recommended in patients with moderate or severe hepatic impairment. There is no information on the use of ambrisentan tablets 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 tablet initiation, the cause of liver injury should be fully investigated. Discontinue ambrisentan tablets if elevations of liver aminotransferases are >5 x ULN or if elevations are accompanied by bilirubin >2 x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

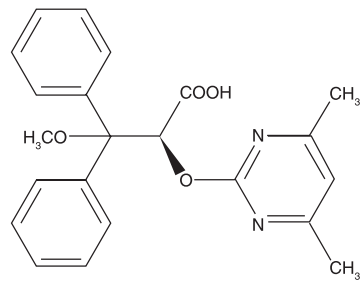
## OVERDOSAGE

There is no experience with overdose of ambrisentan tablets. 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 overdose could potentially result in hypotension that may require intervention.

## DESCRIPTION

Ambrisentan is an endothelin receptor antagonist that is selective for the endothelin type-A (ET<sub>A</sub>) 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<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> and a molecular weight of 378.42. 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 off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state ambrisentan is very stable, is not hygroscopic, and is not light sensitive.

Ambrisentan is 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, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink ambrisentan tablet contains 5 mg of ambrisentan. Each oval, deep pink ambrisentan tablet contains 10 mg of ambrisentan. Ambrisentan tablets are unscored.

## CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ET<sub>A</sub> and ET<sub>B</sub>, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ET<sub>A</sub> are vasoconstriction and cell proliferation, while the predominant actions of ET<sub>B</sub> are vasodilation, angioproliferation, 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



## What should I tell my doctor before taking ambrisentan tablets?

### Before you take ambrisentan tablets, tell your doctor if you:

- have been told that you have a low red blood cell level (anemia)
- have liver problems
- have any other medical conditions

**Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.** Ambrisentan tablets and other medicines may affect each other, causing side effects. Do not start any new medicines until you check with your doctor.

**Especially tell your doctor if you take the medicine cyclosporine (Gengraf, Neoral, Sandimmune).** Your doctor may need to change your dose of ambrisentan tablets.

### How should I take ambrisentan tablets?

- Ambrisentan tablets will be mailed to you by a certified pharmacy. Your doctor will give you complete details.
- Take ambrisentan tablets exactly as your doctor tells you to take it. Do not stop taking ambrisentan tablets unless your doctor tells you to stop.
- You can take ambrisentan tablets with or without food.
- Do not split, crush or chew ambrisentan tablets.
- It will be easier to remember to take ambrisentan tablets if you take it at the same time each day.
- If you take more than your regular dose of ambrisentan tablets, call your doctor right away.
- If you miss a dose, take it as soon as you remember that day. Take your next dose at the regular time. Do not take two doses at the same time to make up for a missed dose.

### What should I avoid while taking ambrisentan tablets?

- **Do not get pregnant** while taking ambrisentan tablets. (See the serious birth defects section of the Medication Guide above called “**What is the most important information I should know about ambrisentan tablets?**”) If you miss a menstrual period, or think you might be pregnant, call your doctor right away.
- **It is not known if ambrisentan passes into your breast milk. You should not breastfeed** if you are taking ambrisentan tablets. Talk to your doctor about the best way to feed your baby if you take ambrisentan tablets.

**What are the possible side effects of ambrisentan tablets?**

### Ambrisentan tablets can cause serious side effects including:

- See “**What is the most important information I should know about ambrisentan tablets?**”
- **Swelling all over the body** (fluid retention) can happen within weeks after starting ambrisentan tablets. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking ambrisentan tablets. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.
- **Decreased sperm count.** Decreased sperm counts have happened in some men taking a medicine that is like ambrisentan tablets. A decreased sperm count may affect the ability to father a child. Tell your doctor if being able to have children is important to you.
- **Low red blood cell levels** (anemia) can happen during the first weeks after starting ambrisentan tablets. If this happens, you may need a blood transfusion. Your doctor will do blood tests to check your red blood cells before starting ambrisentan tablets. Your doctor may also do these tests during treatment with ambrisentan

tablets.

### The most common side effects of ambrisentan tablets include:

- swelling of hands, legs, ankles and feet (peripheral edema)
- stuffy nose (nasal congestion)
- inflamed nasal passages (sinusitis)
- hot flashes or getting red in the face (flushing)

**Some medicines that are like ambrisentan tablets can cause liver problems. Tell your doctor if you get any of these symptoms of a liver problem while taking ambrisentan tablets:**

- loss of appetite
- nausea or vomiting
- fever
- achiness
- generally do not feel well
- pain in the upper right stomach (abdominal) area
- yellowing of your skin or the whites of your eyes
- dark urine
- itching

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of ambrisentan tablets. For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store ambrisentan tablets?

Store ambrisentan tablets at room temperature between 68°F to 77°F (20°C to 25°C), in the package it comes in.

### Keep ambrisentan tablets and all medicines out of the reach of children.

### General information about the safe and effective use of ambrisentan tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ambrisentan tablets for a condition for which it was not prescribed. Do not give ambrisentan tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ambrisentan tablets. If you would like more information, ask your doctor. You can ask your doctor or pharmacist for information about ambrisentan tablets that is written for health professionals.

### What are the ingredients in ambrisentan tablets?

#### Active ingredient: ambrisentan

**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, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 3/2019

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

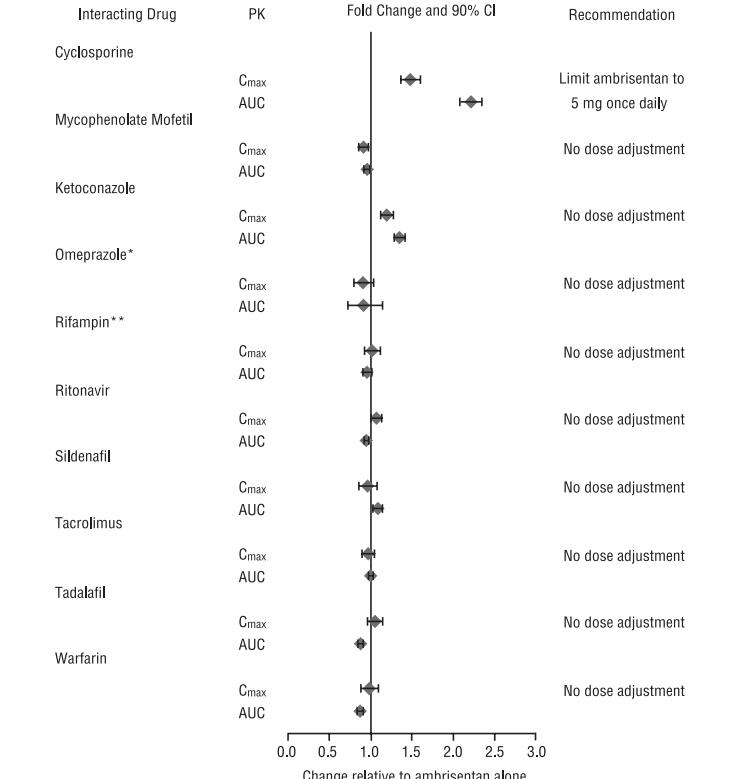
##### In Vitro Studies

Studies with human liver tissue indicate that ambrisentan is metabolized by CYP3A, CYP2C19, and uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9, 2B7, and 1A3. *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 (IC<sub>50</sub> of 47 μM, 45 μM, and approximately 100 μM, respectively) and no transporter-specific inhibition of BSEP, BCRP, P-gp, or MRP2. Ambrisentan does not inhibit or induce drug metabolizing enzymes at clinically relevant concentrations.

##### In Vivo Studies

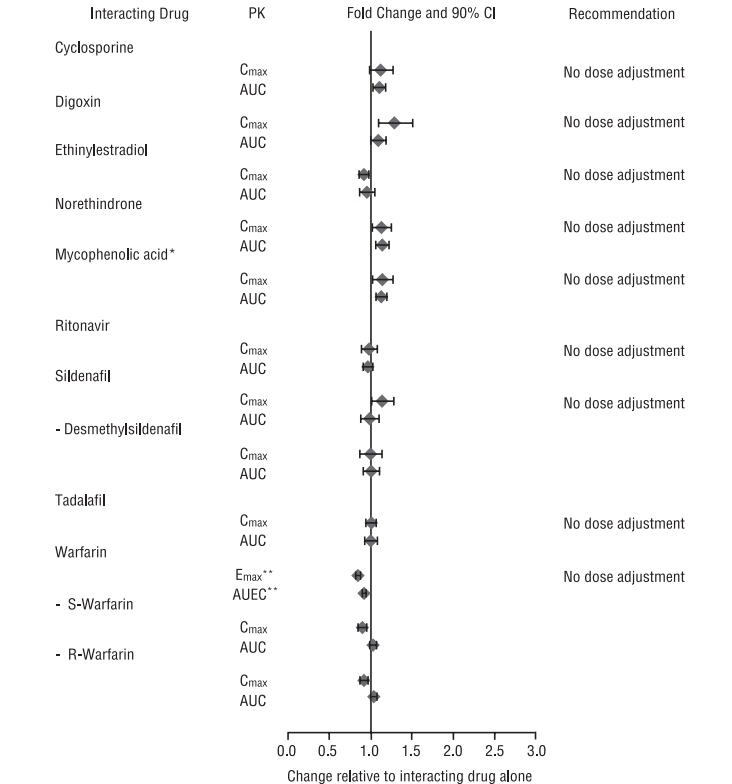
The effects of other drugs on ambrisentan pharmacokinetics and the effects of ambrisentan on the exposure to other drugs are shown in Figure 2 and Figure 3, respectively.

Figure 2 Effects of Other Drugs on Ambrisentan Pharmacokinetics



\* Omeprazole: based on population pharmacokinetic analysis in PAH patients  
\*\* Rifampin: AUC and C<sub>max</sub> 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/m<sup>2</sup> 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 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 eprostenoil, 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<sup>®</sup> 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.

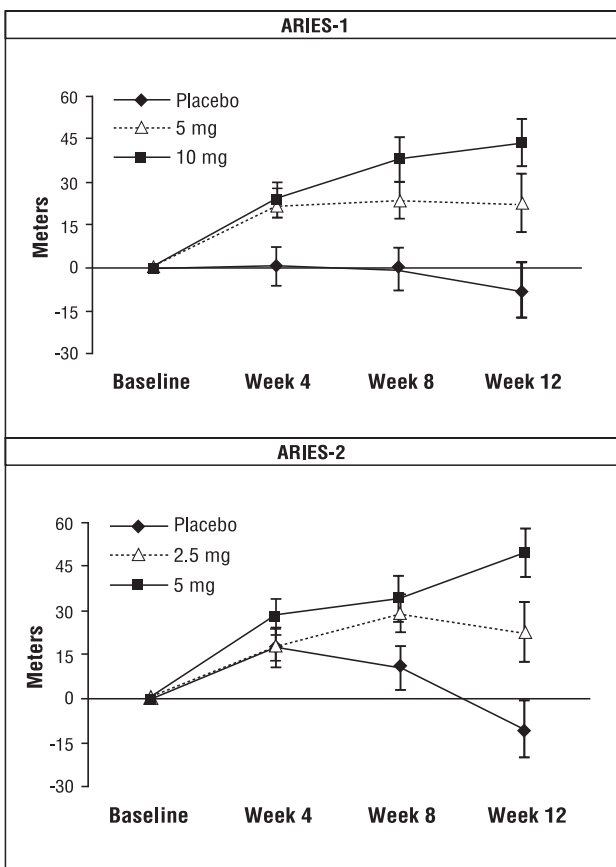
Table 3 Changes from Baseline in 6-Minute Walk Distance (meters) (ARIES-1 and ARIES-2)

	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*	-	0.008	<0.001	-	0.022	<0.001

Mean ± standard deviation

\* 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 tablet groups.

Values are expressed as mean ± 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 tablets 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 tablet 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

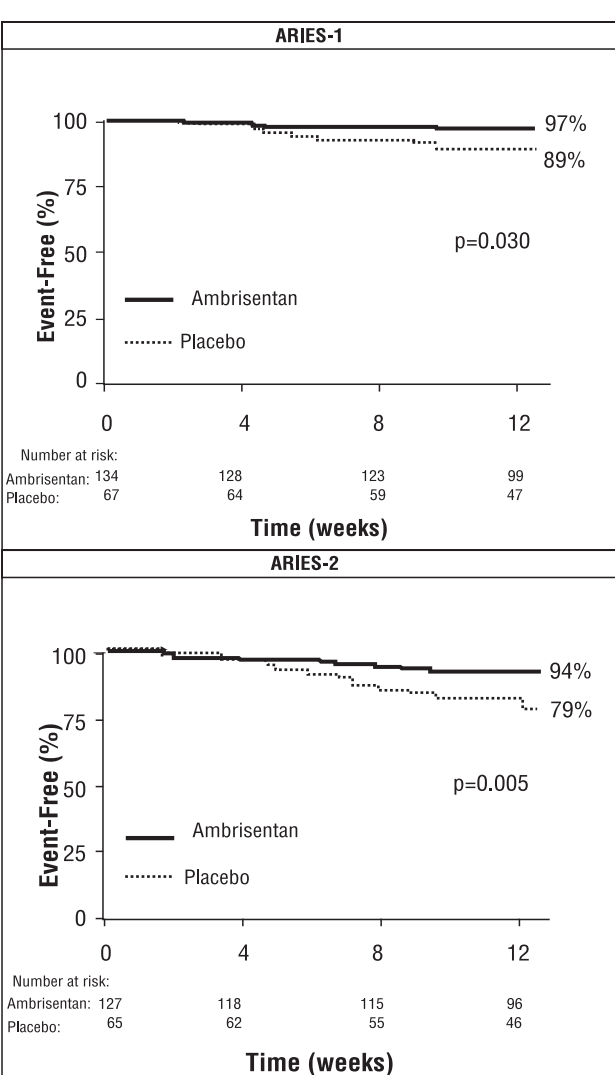
Intention-to-treat population.

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 tablets 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 tablets 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 (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 tablets 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 tablets 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 tablets (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 tablets. 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)*).