PRODUCT MONOGRAPH

[Pr]APO-AMBRISENTAN

Ambrisentan Tablets

5 mg and 10 mg

Endothelin Receptor Antagonist

APOTEX INC.
150 Signet Drive
Toronto, Ontario
Canada, M9L 1T9

Date of Revision:
May 3, 2018

Submission Control No: 202345

Table of Contents

[Pr]Apo-Ambrisentan

Ambrisentan Tablets

5 mg and 10 mg

Endothelin Receptor Antagonist

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet, 5 mg and 10 mg	5 mg: croscarmellose sodium, FD&C Red # 40, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sunset yellow aluminum lake 40% , talc and titanium dioxide. 10 mg: croscarmellose sodium, FD&C Red # 40 aluminum lake 38-42%, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

INDICATIONS AND CLINICAL USE

APO-AMBRISENTAN (ambrisentan) is indicated for treatment of idiopathic ('primary') pulmonary arterial hypertension (IPAH) and pulmonary arterial hypertension (PAH) associated with connective tissue disease in adult patients with WHO functional class II or III symptoms.

APO-AMBRISENTAN should only be used by clinicians experienced in the diagnosis and treatment of IPAH or PAH.

CONTRAINDICATIONS

APO-AMBRISENTAN (ambrisentan) is contraindicated in:

- Patients with a known or suspected hypersensitivity to ambrisentan or any of the ingredients in the formulation (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).
- Breastfeeding (see WARNINGS AND PRECAUTIONS, Special Populations, Nursing Women).
- Patients with severe hepatic impairment (with or without cirrhosis) (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and DOSAGE AND ADMINISTRATION).

- Patients with baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT)) >3x ULN (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and DOSAGE AND ADMINISTRATION).
- Patients with idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension.

WARNINGS AND PRECAUTIONS

General

There have been no studies to investigate the effect of ambrisentan on driving performance or the ability to operate machinery. Further, a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

Carcinogenesis and Mutagenesis

There are no human data available (see TOXICOLOGY, Carcinogenesis and Mutagenesis).

Hematologic

The development of drug-related decreases in hemoglobin concentration and hematocrit has been associated with administration of endothelin receptor antagonists and was observed in clinical studies with ambrisentan in monotherapy. There have been cases where this has resulted in anemia requiring transfusion. These decreases were generally observed within the first few weeks of treatment with ambrisentan, and stabilized thereafter. (see ADVERSE REACTIONS).

Initiation of APO-AMBRISENTAN is not recommended for patients with clinically significant anemia (see Monitoring and Laboratory Tests).

Hepatic/Biliary/Pancreatic

Liver function abnormalities have been associated with pulmonary arterial hypertension. Hepatic enzyme elevations potentially related to therapy have been observed with endothelin receptor antagonists (ERAs). Therefore, hepatic function should be evaluated prior to initiation of APO-AMBRISENTAN. Monitor liver function as clinically indicated for patients with normal liver function or mild hepatic impairment. Initiation of APO-AMBRISENTAN is contraindicated for patients with aminotransferase (alanine aminotransferase, ALT or aspartate aminotransferase, AST) concentrations greater than 3 times the upper limit of normal (>3x ULN) or patients with severe hepatic impairment. APO-AMBRISENTAN should be used with caution in patients with moderate hepatic impairment and monthly monitoring of ALT and AST is recommended (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY).

Although the incidence of aminotransferase abnormalities was low, the possibility of serum aminotransferase elevations associated with ambrisentan administration cannot be excluded. Therefore monthly monitoring of ALT and AST is recommended in particularly vulnerable patients such as those with moderate hepatic impairment or those with clinically significant right heart failure, pre-existing liver disease, previous elevations of aminotransferases due to medications or taking concurrent medications known to elevate aminotransferases who may be at increased risk for developing elevated aminotransferases on ambrisentan. If patients develop clinically significant aminotransferase elevations or if aminotransferase elevations are

accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of APO-AMBRISENTAN may be considered following resolution of hepatic enzyme abnormalities. Hepatic injury and autoimmune hepatitis are known to occur in PAH patients and autoantibodies are frequently found in IPAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, and hepatic injury have been reported with ambrisentan therapy, although the contribution of ambrisentan to these events is unclear.

Therefore, patients should be monitored for signs of hepatic injury and caution exercised when APO-AMBRISENTAN is used alone or concomitantly with other medicinal products known to be associated with hepatic injury as the additive effects of ambrisentan with these agents are not known. Management of autoimmune hepatitis in PAH patients should be optimized prior to initiation of APO-AMBRISENTAN and during ambrisentan therapy. If patients develop signs or symptoms of hepatitis, or suffer exacerbation of existing autoimmune hepatitis, APO-AMBRISENTAN should be discontinued.

Other ERAs have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure. In patients who develop hepatic impairment after APO-AMBRISENTAN initiation, the cause of liver injury should be fully investigated. Discontinue APO-AMBRISENTAN if elevations of liver aminotransferases are >3x ULN or if elevations are accompanied by bilirubin >2x ULN, or by signs or symptoms of liver dysfunction and other causes are excluded.

Fluid Retention

Peripheral edema (fluid retention) has been observed with ERAs including ambrisentan. Peripheral edema may also be a clinical consequence of PAH. Ambrisentan induced a dose-dependent increased incidence of mild to moderate peripheral edema (see ADVERSE REACTIONS).

Post-market reports confirm that fluid retention may occur within weeks after starting ambrisentan and, in some cases, has required intervention with a diuretic or hospitalization for fluid management or decompensated heart failure (see Clinical Trial Adverse Events, Table 1). If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting ambrisentan.

If clinically significant peripheral edema develops during therapy with APO-AMBRISENTAN, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as the use of APO-AMBRISENTAN or the existence of underlying heart failure. The possible need for specific treatment or discontinuation of APO-AMBRISENTAN therapy should also be evaluated.

Pulmonary Veno-Occlusive Disease

If patients develop acute pulmonary edema during initiation of APO-AMBRISENTAN, the possibility of pulmonary veno-occlusive disease should be considered.

Renal

APO-AMBRISENTAN has not been studied in individuals with renal impairment. Ambrisentan does not undergo significant renal metabolism or renal clearance (excretion), and therefore dose adjustment is unlikely to be required in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Sexual Function/Reproduction

The development of testicular tubular atrophy that was not reversible after 13 or 20 weeks has been observed in male rats at dose levels of 10 to 300 mg/kg/day, although reduced fertility and morphologic effects on sperm only occurred at 300 mg/kg/day and were reversible. The effect on male human fertility is not known (see CLINICAL TRIALS and TOXICOLOGY).

Special Populations

Pregnant Women: The use of APO-AMBRISENTAN is contraindicated in pregnant women. Animal studies in rats and rabbits have shown that ambrisentan is teratogenic with reports of increased incidences of fetal malformations and abnormalities following administration of ERAs including ambrisentan (see TOXICOLOGY, Pregnancy).

Women of child bearing potential should be advised of the risk of fetal harm if APO-AMBRISENTAN is taken during pregnancy. Pregnancy must be excluded before the start of treatment with APO-AMBRISENTAN and prevented thereafter by reliable contraception. Pregnancy tests during treatment with APO-AMBRISENTAN are recommended as clinically indicated.

Women of child bearing potential should be advised to contact their physician immediately if they become pregnant or suspect they may be pregnant. If pregnancy is to be continued, APO-AMBRISENTAN should be discontinued and alternative treatment should be initiated (see CONTRAINDICATIONS and TOXICOLOGY, Pregnancy).

Nursing Women: It is not known whether ambrisentan is excreted in human milk. Therefore breastfeeding is contraindicated in patients taking APO-AMBRISENTAN (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age): Safety and efficacy of APO-AMBRISENTAN have not been established in patients under 18 years of age. APO-AMBRISENTAN should therefore not be used in this age group.

Geriatrics (> 65 years of age): No dose adjustment is required in patients aged 65 years and over.

In clinical studies where ambrisentan was used in monotherapy, peripheral edema was reported as dose dependent, was more common and tended to be more severe in patients ≥65 years of age. (see ADVERSE DRUG REACTIONS, ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions and DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests

Hemoglobin and Hematocrit
Ambrisentan has been associated with reductions in hemoglobin concentrations and hematocrit. Initiation of APO-AMBRISENTAN is not recommended for patients with clinically significant anemia. It is recommended that hemoglobin and/or hematocrit levels are measured prior to the initiation of APO-AMBRISENTAN, again at one month, and periodically thereafter as clinically indicated.

Decreases in hemoglobin and/or hematocrit were observed as very common clinical trial adverse drug reactions (see Table 1). In monotherapy studies, the mean decrease in hemoglobin from baseline to the end of treatment for patients receiving ambrisentan in 12-week placebo-controlled studies was 0.8 g/dL Hemoglobin reductions were observed to persist for 4 years.

If a clinically significant decrease in hemoglobin or hematocrit is observed, and other causes have been excluded, discontinuation of ambrisentan should be considered.

Liver Function Tests
Liver transaminase levels should be measured prior to initiation of treatment and subsequently at monthly intervals in vulnerable patients, or generally in any patient as clinically indicated (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

If patients develop clinically significant elevations of transaminases greater than 3x ULN), or if transaminase elevations are accompanied by signs or symptoms of hepatic injury (such as nausea, vomiting, fever, abdominal pain, jaundice or unusual lethargy or fatigue) or if elevations are accompanied by increases in bilirubin 2xULN, treatment with APO-AMBRISENTAN should be stopped.

In patients without clinical symptoms of hepatic injury or jaundice, re-initiation of APO-AMBRISENTAN may be considered following resolution of hepatic enzyme abnormalities (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The safety of ambrisentan has been evaluated in Phase II and Phase III clinical studies totalling 483 patients with PAH who were treated with doses of 1, 2.5, 5, or 10 mg once daily, ranging in exposure from 1 day to 3.5 years. Overall, ambrisentan was well tolerated.

In placebo-controlled 12-week studies, the most commonly (≥10%) reported adverse drug reactions with ambrisentan were peripheral edema, headache, and nasal congestion (see Table 1).

In placebo-controlled phase III studies, the proportion of subjects who discontinued because of adverse events was similar across all treatment groups: 3.0% in the placebo group and 2.3% in the ambrisentan group.

In the placebo-controlled studies, six (4.5%) subjects in the placebo group died and 4 (1.5%)

subjects in the ambrisentan groups died. A higher proportion of subjects in the placebo group had at least one non-fatal serious adverse event (SAE) compared to the ambrisentan-treated patients. The most frequent SAEs for both the placebo and ambrisentan-treated patients were right ventricular failure (placebo, 6.1%; ambrisentan, 1.1%) and (worsening) pulmonary hypertension (placebo, 3.8 %; ambrisentan, 1.1 %). Treatment-related SAEs occurred with a similar frequency across all ambrisentan treatment groups.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Experience from Short-term Clinical Studies

The following safety data for ambrisentan were obtained from two Phase III 12-week placebo-controlled studies in subjects with PAH (ARIES-1 and ARIES-2). A total of 197 patients received ambrisentan at doses of 5 or 10 mg once daily and 132 patients received placebo.

The adverse drug reactions observed in ARIES-1 and ARIES-2 are summarized in Table 1.

Table 1 Adverse Drug Reactions for PAH Patients Receiving Ambrisentan in Short-Term Studies (ARIES-1 and ARIES-2, integrated analysis)

System Organ Class Preferred Term	**Placebo (N=132)** n (%)	**Ambrisentan 5 mg** (N=130) n (%)	**Ambrisentan 10 mg** (N=67) n (%)
Blood and lymphatic system disorders			
Anemia	2 (1.5)	2 (1.5)	2 (3.0)
Cardiac disorders			
Palpitations	3 (2.3)	5 (3.8)	3 (4.5)
Gastrointestinal disorders			
Constipation	2 (1.5)	4 (3.1)	4 (6.0)
Abdominal pain[a]	1 (0.8)	6 (4.6)	4 (6.0)
General disorders and administration site conditions			
Peripheral edema	14 (10.6)	24 (18.5)	19 (28.4)
Fluid retention[b]	4 (3.0)	4 (3.1)	4 (6.0)
Immune System Disorders			
Hypersensitivity[c]	0	1 (0.8)	0
Nervous system disorders			
Headache	18 (13.6)	20 (15.4)	13 (19.4)
Respiratory, thoracic and mediastinal disorders			

Nasal congestion	2 (1.5)	7 (5.4)	7 (10.4)
Nasopharyngitis	1 (0.8)	7 (5.4)	2 (3.0)
Sinusitis	0	4 (3.1)	3 (4.5)
Vascular disorders			
Flushing[d]	2 (1.5)	5 (3.8)	1 (1.5)

a) Includes Abdominal Pain Upper b) Includes Fluid Retention, Fluid Overload, and Local Swelling c) Includes Drug Hypersensitivity d) Includes Hot Flush.

Adverse drug reactions in short-term monotherapy trials were generally mild to moderate. The higher dose (10 mg) was associated with a higher incidence of peripheral edema, headache, nasal congestion, palpitations, constipation sinusitis, anemia, abdominal pain, and fluid retention. Peripheral edema was the most common adverse drug reaction observed with ambrisentan, and incidence rates varied with age. Among younger patients (<65 years), the incidence was 18% (28/155) among those receiving ambrisentan compared to 13% (13/104) receiving placebo. Among elderly patients (≥65 years), the incidence of peripheral edema was greater: 36% (15/42) among those receiving ambrisentan compared to 4% (1/28) receiving placebo. The results of such subgroup analyses must be interpreted cautiously.

Experience from Long-term Clinical Studies

The long-term safety (>3 months) of ambrisentan in monotherapy was evaluated in 383 patients with PAH in the ARIES-E study, a non-placebo controlled clinical trial extension of ARIES-1 and ARIES-2. Adverse drug reactions observed in long-term studies ARIES-E are summarized in Table 2.

Table 2 Adverse Drug Reactions for PAH Patients Receiving Ambrisentan in Long-term Studies (>3 months) ARIES-E

System Organ Class **Preferred Term**	**ARIES-E** **Ambrisentan Monotherapy** **N=383 n (%)**
Blood and lymphatic system disorders	
Anemia	52 (14)
Cardiac disorders	
Palpitations	50 (13)
Ear and labyrinth disorders	
Tinnitus	3 (<1)
Eye disorders	
Visual impairment[b]	13 (3)

System Organ Class Preferred Term	ARIES-E Ambrisentan Monotherapy N=383 n (%)
Gastrointestinal disorders	
Nausea	53 (14)
Vomiting	30 (8)
Constipation	33 (9)
Abdominal pain[c]	55 (14)
General disorders and administration site conditions	
Peripheral edema	168 (44)
Fluid retention[d]	24 (6)
Fatigue	47 (12)
Asthenia	20 (5)
Immune system disorders	
Hypersensitivity[e]	13 (3)
Nervous system disorders	
Headache	96 (25)
Dizziness	66 (17)
Respiratory, thoracic and mediastinal disorders	
Nasal congestion	48 (13)
Nasopharyngitis	58 (15)
Sinusitis	39 (10)
Dyspnoea[f]	64 (17)
Skin and subcutaneous tissue disorders	
Rash[g]	27 (7)
Vascular disorders	
Flushing[h]	23 (6)

b) Visual impairment includes Vision blurred and Visual disturbance. c) Abdominal pain includes Abdominal pain upper d) Fluid retention includes Fluid retention, Fluid overload, and Local swelling e) Hypersensitivity includes Drug hypersensitivity f) Dyspnea includes Dyspnea exertional. g) Rash includes Rash erythematous, Rash generalised, Rash macular, Rash papular, and Rash pruritic h) Flushing includes Hot flush.

Less Common Clinical Trial Adverse Drug Reactions

Adverse drug reactions including those which were less common in ambrisentan clinical trials are presented in Tables 1-2 (see Clinical Trial Adverse Drug Reactions).

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic Changes

In the placebo-controlled Phase III studies in patients with PAH, the mean changes from baseline (in patients receiving placebo, ambrisentan tablets 5 mg and 10 mg, respectively) were (+0.15, -0.77, -0.93) for hemoglobin and (+0.01%, -2%, -3%) for hematocrit. These changes were not dose-related in patients receiving ambrisentan tablets 5 mg and 10 mg. Marked decreases in

hemoglobin (> 15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of patients receiving ambrisentan and 4% of patients receiving placebo. Similar decreases in hemoglobin/hematocrit have been observed with other ERAs; the cause of the decrease is not fully understood, but it is not due to hemorrhage or hemolysis. Adverse events related to anemia, low hemoglobin or low hematocrit appeared to be more frequent with 10 mg ambrisentan than lower doses or placebo. Mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in hemoglobin concentrations persisted for up to 4 years of treatment with ambrisentan in the long-term open-label extension of the pivotal Phase III clinical studies.

Clinical Chemistry Changes
A number of patients (19%) showed an increase of γGT (>3x ULN). The clinical significance is not known.

Post-Marketing Adverse Drug Reactions
In addition to adverse drug reactions identified from clinical studies, the following adverse drug reactions were identified during post-approval use of ambrisentan. Because these events have been reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiac Disorders
Fluid retention and heart failure associated with fluid retention occurring within weeks after starting ambrisentan therapy have been reported post-marketing. In some cases, these events have required intervention with a diuretic or hospitalization for fluid management or decompensated heart failure.

Blood and Lymphatic System Disorders
Anemia requiring transfusion.

Hepatobiliary Disorders
Cases of increased hepatic transaminases (AST and ALT >3x ULN), autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury of unclear aetiology (including increased blood bilirubin >2x ULN) have been reported during ambrisentan therapy. The incidence of liver events was similar in patients with left ventricular dysfunction.

DRUG INTERACTIONS

Overview
Studies with human liver tissue indicate that ambrisentan is metabolized by uridine 5'-diphosphate glucuronosyltransferases (UGTs) 1A9S, 2B7S, and 1A3S, CYP3A4 and CYP2C19. *In vitro* studies suggest that ambrisentan is a substrate of Organic Anion Transport Protein (OATP). *In vitro* studies also show ambrisentan is a substrate but not an inhibitor of P-glycoprotein (P-gp).

In vitro data show that ambrisentan at concentrations up to 300mcM does not markedly inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Further, *in vitro* studies using cell-lines transfected with the human transporter genes showed that ambrisentan does not inhibit P- gp, breast cancer receptor protein (BCRP), multi-drug resistance related protein 2 (MRP2), or bile salt export pump (BSEP)

at concentrations up to 100mcM. Ambrisentan showed weak *in vitro* inhibition of OATP1B1, OATP1B3 and sodium- taurocholate co-transporter (NTCP) with IC_{50} values of 47mcM, 45mcM, and approximately 100mcM, respectively. *In vitro* studies in rat and human hepatocytes showed no evidence for ambrisentan inhibition of NTCP, OATP, BSEP and MRP2. Furthermore, ambrisentan did not induce MRP2, P-gp or BSEP protein expression in rat hepatocytes. Taken together, the *in vitro* data suggest that ambrisentan, at clinically relevant concentrations, would not be expected to have an effect on UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 or transport via BSEP, BCRP, P-gp, MRP2, OATP1B1/3, or NTCP.

Drug-Drug Interactions

Table 3 Established or Potential Drug-Drug Interactions

Drug interaction	Level of evidence	Effect	Clinical comment
Cyclosporine A	CT	The effects of repeat dosing of cyclosporine A (100 – 150 mg twice daily) on the steady-state pharmacokinetics of ambrisentan (5 mg once daily), and the effects of repeat dosing of ambrisentan (5 mg once daily) on the steady-state pharmacokinetics of cyclosporine A (100 – 150 mg twice daily) were studied in healthy volunteers. The C_{max} and $AUC_{(0-\tau)}$ of ambrisentan increased (48% and 121%, respectively) in the presence of multiple doses of cyclosporine A. The apparent plasma $t_{1/2}$ of ambrisentan in the presence of cyclosporine increased by 38% as compared to ambrisentan alone (from 8.36h to 11.5h). No important differences in the median t_{max} were observed. However, multiple doses of ambrisentan had no clinically relevant effect on cyclosporine A exposure. It should be noted that the apparent mean $t_{1/2}$ value of cyclosporine A increased by 32% from 4.79h (cyclosporine A alone) to 6.33h in the presence of ambrisentan.	The dose of ambrisentan should be limited to 5 mg once daily when co-administered with cyclosporine A (see DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment). No dose adjustment of cyclosporine A is warranted.
Ketoconazole	CT	Steady-state administration of ketoconazole increased the AUC_{∞} and C_{max} of ambrisentan by 35% and 20%, respectively. The clinical significance of these changes is not known.	Patients on 10 mg of ambrisentan while on ketoconazole should be monitored closely for any signs of adverse effects.
Digoxin	CT	The effects of repeat dosing of ambrisentan (10 mg) on the pharmacokinetics of single dose digoxin were studied in 15 healthy volunteers. Multiple doses of ambrisentan resulted in slight but significant increases in digoxin $AUC_{(0\text{-last})}$ (16%) and trough	No dose adjustment of digoxin is warranted. However, given the narrow therapeutic index of digoxin, caution and monitoring are recommended.

Drug interaction	Level of evidence	Effect	Clinical comment
		concentrations, and a 29% increase in digoxin C_{max}. The increase in digoxin exposure (by 9% of $AUC_{(0-\infty)}$) observed in the presence of multiple doses of ambrisentan was not considered clinically relevant.	
Oral contraceptives	CT	In a clinical study in healthy volunteers, steady-state dosing with ambrisentan 10 mg once daily did not significantly affect the single-dose pharmacokinetics of the ethinyl estradiol and norethindrone components of a combined oral contraceptive. Based on this pharmacokinetic study, ambrisentan would not be expected to significantly affect exposure to oestrogen- or progestogen-based contraceptives. The effects of 12 days dosing with ambrisentan (10 mg once daily) on the pharmacokinetics of a single dose of oral contraceptive containing ethinyl estradiol (35 µg) and norethindrone (1 mg) were studied in healthy female volunteers. The C_{max} and $AUC_{(0-\infty)}$ were slightly decreased for ethinyl estradiol (8% and 4%, respectively), and slightly increased for norethindrone (13% and 14 %, respectively). These changes in exposure to ethinyl estradiol or norethindrone were small and are unlikely to be clinically significant.	No dose adjustment is warranted.
Strong 2C19 inhibitor (omeprazole)	CT	In clinical studies of patients with PAH, co-administration of ambrisentan and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan.	No dose adjustment is warranted.
Rifampin	CT	The effects of acute and repeat dosing of rifampin (600 mg once daily) on the steady-state pharmacokinetics of ambrisentan (10 mg once daily) were studied in healthy volunteers. Following initial doses of rifampin, a transient increase in ambrisentan $AUC_{(0-\tau)}$ (121% and 116% after first and second doses of rifampin, respectively) was observed. Apparent plasma $t_{1/2}$ of ambrisentan decreased by 50% from 8.28h to 4.59h when co-administered with rifampin. However, there was no clinically relevant effect on ambrisentan exposure by day 8, following administration of multiple doses of rifampin.	No dose adjustment of ambrisentan is warranted upon concomitant administration with rifampin.
Warfarin	CT	In healthy volunteers receiving warfarin, daily doses of ambrisentan (10 mg) did not have a clinically relevant effect on prothrombin time (PT), International Normalized Ratio (INR), or the	No dose adjustment is warranted.

Drug interaction	Level of evidence	Effect	Clinical comment
		pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate). In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of ambrisentan did not result in a clinically relevant change in PT, INR or anticoagulant dose (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).	

CT, Clinical Trial

Drug-Food Interactions

APO-AMBRISENTAN can be taken with or without food (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Drug-Herb Interactions

Interactions with herbal products have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Treatment should only be initiated by a physician experienced in the treatment of PAH.
- Assess liver function before starting APO-AMBRISENTAN (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and Monitoring and Laboratory Tests).
- Safety and efficacy of APO-AMBRISENTAN have not been established in patients under 18 years of age. APO-AMBRISENTAN should therefore not be used in this age group.
- No dose adjustment is required in patients aged 65 years and over. In clinical monotherapy studies, peripheral edema was reported as dose dependent and more common in patients ≥65 years of age.
- APO-AMBRISENTAN treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and providing they are using a reliable method of contraception (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).
- APO-AMBRISENTAN is contraindicated in patients with severe hepatic impairment and those with baseline AST or ALT >3x ULN. APO-AMBRISENTAN should be used with caution in patients with moderate hepatic impairment (see WARNINGS AND PRECAUTIONS; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, and Special Populations and Conditions, Hepatic Insufficiency).
- Renal metabolism and excretion of ambrisentan is minimal, so dose adjustment is unlikely to be required in patients with renal impairment.

Recommended Dose and Dosage Adjustment

APO-AMBRISENTAN should be initiated at a dose of 5 mg once daily. Additional benefit may

be obtained by increasing the dose to 10 mg once daily. Patients with PAH associated with connective tissue disease may require 10 mg ambrisentan for optimal efficacy. Consider increasing the dose to 10 mg ambrisentan providing the 5 mg dose is well tolerated (see ADVERSE REACTIONS).

The maximum recommended daily dose is 10 mg.

When co-administered with cyclosporine A, the dose of APO-AMBRISENTAN should be limited to 5 mg once daily (see DRUG INTERACTIONS, Drug-Drug Interactions, Cyclosporine A).

APO-AMBRISENTAN can be administered with or without food.

Missed Dose

If a dose of APO-AMBRISENTAN is missed, the patient should be advised to take it as soon as they remember, and then continue with the next dose at the regular interval. Two doses should not be taken at the same time to make up for a missed dose.

OVERDOSAGE

There is currently no experience with overdosage of ambrisentan. No specific antidote is available. In healthy volunteers, single doses of 50 and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea, and nasal congestion.

Due to the mechanism of action of ambrisentan, an overdosage of APO-AMBRISENTAN could potentially result in hypotension. In the case of pronounced hypotension, active cardiovascular support may be required.

For management of a suspected drug overdose contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ambrisentan is an orally active, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. Selective inhibition of the ET_A receptor inhibits phospholipase C-mediated vasoconstriction and protein kinase C-mediated cell proliferation, while preserving nitric oxide and prostacyclin production, cyclic GMP- and cyclic AMP-mediated vasodilation, and endothelin-1 (ET-1) clearance that is associated with the endothelin type B (ET_B) receptor.

Pharmacodynamics

Cardiopulmonary Hemodynamics

Invasive hemodynamic parameters were assessed in patients with pulmonary arterial

hypertension (PAH) at baseline and after 12 weeks (n=29) in a Phase II study. The cardiac index for treatment with ambrisentan 5 mg and 10 mg was increased by 0.5 L/min/m^2 (95% CI: -0.01 to 0.95; p=0.0518) and 0.4 L/min/m^2 (95% CI: -0.02 to 0.76; p=0.0560), respectively. The mean pulmonary artery pressure for treatment with ambrisentan 5 mg and 10 mg were -4.3 mmHg (95% CI: -8.0 to -0.6; p=0.0272) and -13.3 mmHg (95% CI: -26.1 to -0.6; p=0.0460), respectively. The mean pulmonary vascular resistance for treatment with ambrisentan 5 mg and 10 mg were - 3.5 mmHg/L/min (95% CI: -6.0 to -0.94; p=0.0131) and -4.3 mmHg/L/min (95% CI: -11.3 to 2.7; p=0.1179), respectively. There was no significant reduction in mean right atrial pressure.

B-type Natriuretic Peptide
Two Phase III placebo-controlled studies demonstrated that plasma concentrations of BNP in patients who received ambrisentan for 12 weeks decreased by 29% in the 2.5 mg, 30% in the 5 mg, and 45% in the 10 mg group ($p < 0.001$ for each dose group) and increased by 11% in the placebo group.

Cardiac Electrophysiology
In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either ambrisentan 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 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of ambrisentan increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. The effect of concomitant therapy of ambrisentan with metabolic inhibitors of ambrisentan (i.e. ketoconazole, cyclosporine A) on QT prolongation is unknown (see DRUG INTERACTIONS).

Pharmacokinetics

Absorption: Ambrisentan is absorbed rapidly in humans. The absolute bioavailability of ambrisentan is not known. After oral administration, maximum plasma concentrations (C_{max}) of ambrisentan typically occurs between 1 and 2 hours post dose under both fasted and fed conditions. C_{max} and area under the plasma concentration-time curve (AUC) increase dose proportionally over the therapeutic dose range. Steady-state is generally achieved following 4 days of repeat dosing.

A food-effect study involving administration of ambrisentan to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 12% while the AUC remained unchanged. This decrease in peak concentration is not clinically significant, and therefore ambrisentan can be taken with or without food.

Distribution: Ambrisentan is highly plasma protein bound. The *in vitro* plasma protein binding of ambrisentan was, on average, 99% and independent of concentration over the range of 0.2 - 20 mcg/mL. Ambrisentan is primarily bound to albumin (96.5%) and to a lesser extent to $alpha_1$-acid glycoprotein.

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

Metabolism: Ambrisentan is primarily glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S, and UGT1A3S) to form ambrisentan glucuronide (13%). To a lesser extent, ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to an even lesser extent by CYP3A5 and CYP2C19 to form 4- hydroxymethyl ambrisentan (21%) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5%). The binding affinity of 4-hydroxymethyl ambrisentan for the human endothelin receptor is 65-fold less than ambrisentan. Therefore at concentrations observed in the plasma (approximately 20% relative to parent ambrisentan), 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

Interaction of ambrisentan with UGTs, cytochromes and drug transporters have been studied *in vitro* (see DRUG INTERACTIONS, Drug-Drug Interactions).

Excretion: Ambrisentan and its metabolites are primarily found in the feces following hepatic and/or extra-hepatic metabolism. Approximately 22% of the administered dose is recovered in the urine following oral administration with 3.3% being unchanged ambrisentan. The half-life after multiple dosing is approximately 15 hours (range 13.6 to 16.5 hours) in healthy volunteers and 9 to 15 hours in PAH patients. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively.

Special Populations and Conditions

Pediatrics: Safety and efficacy of APO-AMBRISENTAN have not been established in patients under 18 years of age.

Geriatrics: Based on the results of a population pharmacokinetic analysis in healthy volunteers and patients with PAH, the pharmacokinetics of ambrisentan were not significantly influenced by age (see DOSAGE AND ADMINISTRATION).

Gender: Based on the results of a population pharmacokinetic analysis in healthy volunteers and patients with PAH, the pharmacokinetics of ambrisentan were not significantly influenced by gender.

Hepatic Insufficiency: The pharmacokinetics of ambrisentan in patients with severe hepatic impairment or with clinically significant elevated hepatic transaminases has not been studied. However, since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment might be expected to increase exposure (C_{max} and AUC) of ambrisentan, however the magnitude of this and any effect on safety and efficacy has not been evaluated. Therefore, APO-AMBRISENTAN is contraindicated in patients with severe hepatic impairment or levels of ALT/AST >3x ULN. APO-AMBRISENTAN should be used with caution in patients with moderate hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: No pharmacokinetic studies have been conducted in renally impaired patients. However, the renal excretion of ambrisentan is minimal, therefore renal impairment should not significantly increase exposure to ambrisentan.

STORAGE AND STABILITY

Store at room temperature 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-AMBRISENTAN 5 mg film-coated tablets are pale pink, biconvex, beveled edged, arc square coated tablets, engraved “APO” on one side, “A5”on the other side.

APO-AMBRISENTAN 10 mg film-coated tablets are deep pink, oval coated tablets, engraved “APO” on one side, “A10”on the other side.

Each film-coated tablet contains the following non-medicinal ingredients:

APO-AMBRISENTAN 5 mg: croscarmellose sodium, FD&C Red # 40, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sunset yellow aluminum lake 40%, talc and titanium dioxide.

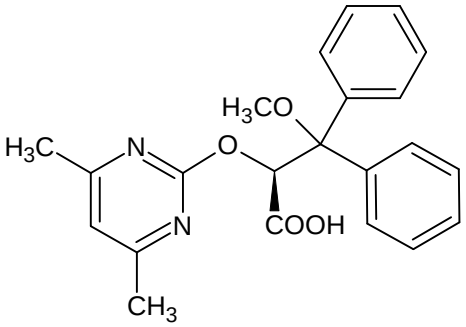
APO-AMBRISENTAN 10 mg: croscarmellose sodium, FD&C Red # 40 aluminum lake 38-42% , lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

APO-AMBRISENTAN tablets are available in blister packs of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name	:	ambrisentan
Chemical name	:	(+)-(2*S*)-2-[(4,6-dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid (2S)-2-[(4,6-Dimethylpyrimidin-2-yl)oxy]-3-methoxy-3,3-diphenylpropanoic acid
Molecular formula and molecular mass	:	$C_{22}H_{22}N_2O_4$, 378.42 g/mol
Structural formula	:	
Physicochemical properties	:	Ambrisentan is a white to yellow crystalline powder. 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.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 25 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of ambrisentan was measured and compared following a single oral dose (1 x 10 mg tablet) of APO-AMBRISENTAN (ambrisentan) 10 mg tablet (Apotex Inc.) and VOLIBRIS® (ambrisentan) 10 mg tablet (GlaxoSmithKline Inc.).

Ambrisentan (1x 10 mg) From measured data Geometric Mean[#] Arithmetic Mean (CV %)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_T (ng•h/mL)	5565.0 5701.9 (24)	5401.6 5551.0 (25)	103.03	99.86 - 106.29
AUC_I (ng•h/mL)	5923.5 6151.2 (25)	5776.1 5925.2 (24)	102.55	99.13 – 106.10
C_{max} (ng/mL)	781.4 812.2 (29)	753.9 766.5 (19)	103.65	96.40 - 111.44
T_{max}[§] (h)	1.97 (55)	1.81 (45)		
$T_{1/2}$[§] (h)	19.94 (54)	19.90 (57)		

* APO-AMBRISENTAN (ambrisentan) 10 mg tablets (Apotex Inc.)

† VOLIBRIS® (ambrisentan) 10 mg tablets (GlaxoSmithKline Inc.) was purchased in Canada.

Based on Geometric Least Squares Means.

§ Expressed as arithmetic means (CV%) only.

Pivotal Trials for Treatment of Pulmonary Arterial Hypertension Study demographics and trial design

Table 4 Summary of the Design and Patient Demographics in Clinical Trials of Ambrisentan Tablets in Patients with Pulmonary Arterial Hypertension (PAH)

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number randomized)	Mean age (range)	Sex	PAH Etiology n (%)
ARIES-1	Phase III, randomized, double-blind, placebo-controlled, multicentre,	5 mg and 10 mg tablets taken orally q.d. for 12 weeks	Placebo: n=67 5 mg: n=67 10 mg: n=67	50.1 (17-82)	Male: 33 (16.4%) Female: 168 (83.6%)	IPAH*: 126 (62.7%) Non-IPAH: 75 (37.3%)
ARIES-2	Phase III, randomized, double-blind, placebo-controlled, multicentre,	2.5 mg and 5 mg tablets taken orally q.d. for 12 weeks	Placebo: n=65 2.5 mg: n=64 5 mg: n=63	50.9 (20-81)	Male: 49 (25.5%) Female: 143 (74.5%)	IPAH*: 125 (65.1%) Non-IPAH: 67 (34.9%)

*IPAH = idiopathic PAH

Ambrisentan Monotherapy for the Treatment of PAH

Two randomised, double-blind, multi-centre, placebo controlled, Phase III pivotal studies were conducted (ARIES-1 and ARIES-2). The design and patient demographics are shown in Table 4. In both studies, ambrisentan was added to patients' supportive/background medication, which may have included a combination of digoxin, anticoagulants, diuretics, oxygen and vasodilators (calcium channel blockers, ACE inhibitors). The primary study endpoint was 6-minute walk distance (6MWD). In addition, clinical worsening, WHO functional class, Borg Dyspnea Index and SF-36® Health Survey were assessed.

Non-IPAH was predominately associated with connective tissue disease, and a few percent associated with anorexigen use or HIV infection. The majority of patients had WHO functional Class II (38%) or Class III (55%) symptoms.

Study results

The primary endpoint defined for these studies was improvement in exercise capacity assessed by change from baseline in 6MWD at 12 weeks. In both studies, treatment with ambrisentan resulted in a statistically significant improvement in 6MWD for each dose of ambrisentan as shown in Table 5. The improvement in exercise capacity was evident after 4 weeks of treatment and was maintained at week 12 of the double-blind treatments as illustrated in Figure 1.

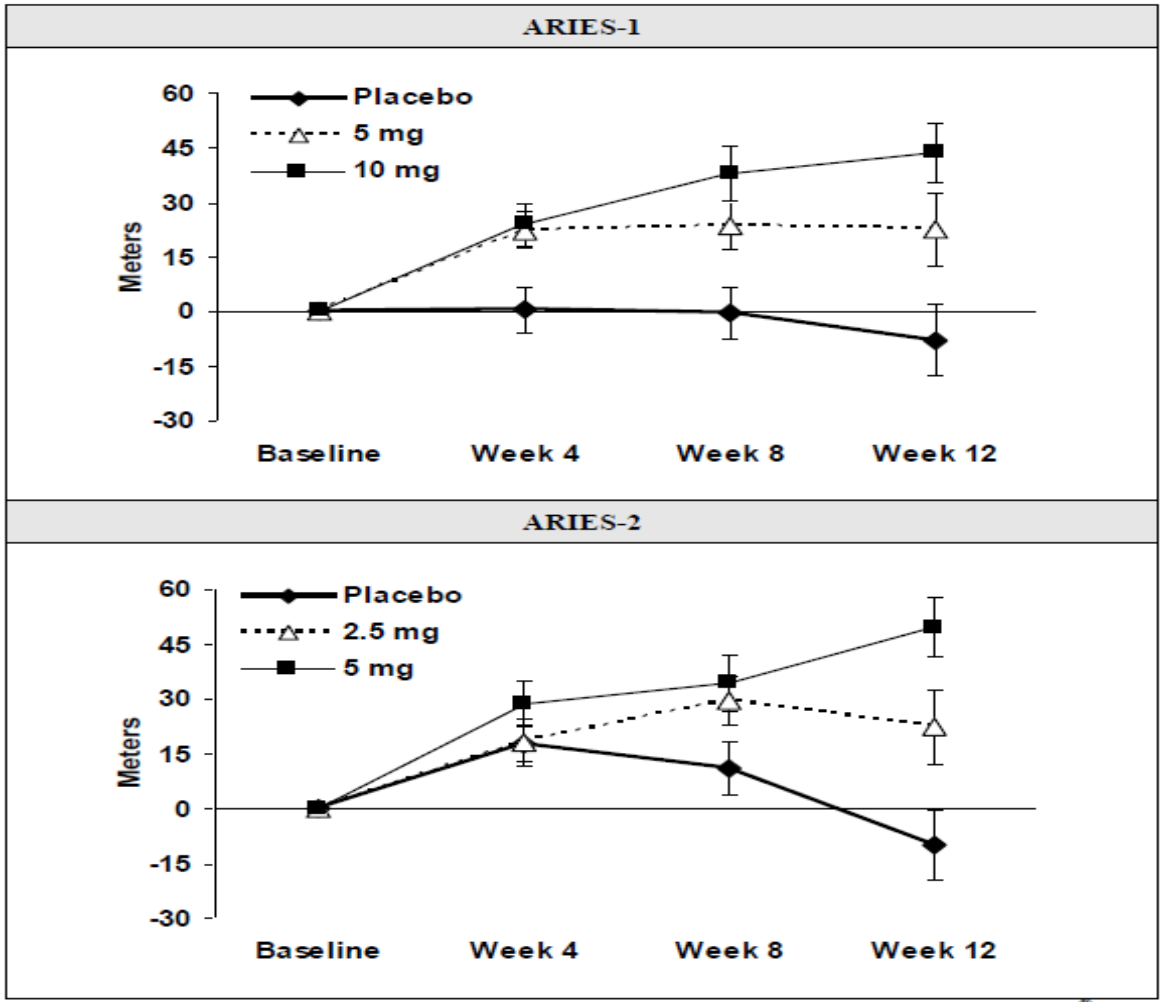
Table 5 Changes from Baseline in 6-minute Walk Distance (metres) at Week 12 in Phase III studies (Idiopathic and Non-Idiopathic PAH Patients: see also Table 9)

	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	341.9 ± 73.47	339.6 ± 76.68	341.5 ± 78.28	342.7 ± 85.93	347.3 ± 83.81	355.3 ± 84.45
Mean change from baseline	-7.8 ± 78.88	22.8 ± 82.98	43.6 ± 65.91	-10.1 ± 93.79	22.2 ± 82.67	49.4 ± 75.36
Median change from baseline	0.5	21.1	32.5	-3.5	27.5	40.0
Placebo adjusted mean change from baseline		30.6	51.4		32.3	59.4
95% CI		2.9, 58.3	26.6, 76.2		1.5, 63.1	29.6, 89.3
p-value†		0.008	<0.001		0.022	<0.001

Mean ± standard deviation

† p-values are Wilcoxon rank sum test comparisons of ambrisentan to placebo at Week 12 stratified by idiopathic PAH and non-idiopathic PAH patients

Figure 1 Mean Change in 6-minute Walk Distance (Phase III Studies) in Idiopathic and Non-Idiopathic PAH Patients



Mean change from baseline in 6-minute walk distance in the placebo and ambrisentan groups

Values are expressed as mean ± standard error of mean.

Symptoms of PAH were assessed using Borg Dyspnea Index (BDI), WHO functional class and SF-36® Health Survey physical functioning scale. Treatment with ambrisentan led to statistically significant improvements in BDI at week 12 (Table 6). Improvements in the physical functioning scale (SF-36®) were also observed, however, were not statistically significant.

Table 6 Summary of Secondary Endpoints from Study ARIES-1 and ARIES-2 at 12 Weeks (Population ITT)

		ARIES-1			ARIES-2		
		Placebo	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Placebo**	**Ambrisentan 2.5 mg**	**Ambrisentan 5 mg**
Change in Borg Dyspnea Index (BDI)	Change from baseline to Week 12	0.0 (-0.55, 0.54)	-0.3 (-0.79, 0.16)	-0.9 (-1.3, -0.41)	0.8 (0.17, 0.54)	-0.2 (-0.74, 0.34)	-0.4 (-0.87, 0.14)
	Comparison vs placebo, point estimate (95% CI)		-0.3 (-1.0, 0.4) p=0.316 -	-0.9 (-1.6, -0.2) p=0.002 +		-1.0 (-1.9, -0.2) p=0.046 +	-1.2 (-2.0, -0.4) p=0.040 +
Change in WHO Class, N (%)	Improved	16 (23.9%)	19 (28.4%)	20 (29.9%)	11 (16.9%)	10 (15.6%)	9 (14.3%)
	Deteriorated	11 (16.4%)	1 (1.5%)	3 (4.5%)	12 (18.5%)	3 (4.7%)	2 (3.2%)
	Comparison with placebo[1]		p=0.0726 -	p=0.0957 -		p= 0.2058 -	p=0.1872 -
Change in SF-36 Physical component summary	Change from baseline, Mean (SD)	1.82 (9.25)	1.88 (8.68)	4.79 (7.90)	-0.15 (7.29)	3.78 (7.63)	2.97 (7.79)
	Comparison with placebo		p=0.992 -	p=0.056 -		0.005 +	0.052 -

[1] Based on analysis of 7-point change from baseline scale

+ statistically significant result, - not statistically significant

Ambrisentan delayed clinical worsening (the measure included a benefit for both death and hospitalization for PAH), although this did not reach a level of statistical significance. Time to clinical worsening of PAH was defined as the time from randomization to the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study discontinuation due to the addition of other PAH therapeutic agents, or study discontinuation due to two or more early escape criteria (see Table 7).

Table 7 Summary of Clinical Worsening of PAH Events from Study ARIES-1 and ARIES-2 at 12 Weeks (Population ITT)

Treatment Group **Event n (%)**	ARIES-1			ARIES-2		
	Placebo (N=67)	**Ambrisentan 5 mg (N=67)**	**Ambrisentan 10 mg (N=67)**	**Placebo (N=65)**	**Ambrisentan 2.5 mg (N=64)**	**Ambrisentan 5 mg (N=63)**
Death	2 (3.0)	1 (1.5)	1 (1.5)	3 (4.6)	2 (3.1)	0 (0.0)
Lung transplantation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalization for PAH	2 (3.0)	2 (3.0)	2 (3.0)	9 (13.8)	3 (4.7)	2 (3.2)
Atrial septostomy	0 (0.00)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Study discontinuation due to addition PAH treatment	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)

Escape criteria	3 (4.5)	0 (0.0)	2 (3.0)	7 (10.8)	2 (3.1)	1 (1.6)
Total subjects with ≥1 events	6 (9.0)	3 (4.5)	3 (4.5)	14 (21.5)	3 (4.7)	3 (4.8)
p-value (ambrisentan vs placebo)*		0.4925	0.4925		0.008	0.008

*Fisher exact test comparison to placebo

In the ARIES studies, those patients with WHO functional class II symptoms at baseline had a mean BDI of 2.98, a mean 6MWD of 375 m; 47% had a 6MWD of more than 400 m. Those with WHO functional class III symptoms had a mean BDI of 4.38 and a mean 6MWD of 330 m at baseline.

In patients with class II and class III symptoms, increases in mean 6MWD were observed with 5 mg and 10 mg ambrisentan compared to placebo after 12 weeks treatment (Table 8). Improvement in secondary endpoints also supported efficacy in both WHO functional class II and class III patients.

Table 8 Improvement in 6MWD at Week 12 in Phase III Studies in patients with WHO Functional Class II symptoms or WHO Functional Class III symptoms (Population ITT)

		ARIES-1			ARIES-2		
		Placebo	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Placebo**	**Ambrisentan 2.5 mg**	**Ambrisentan 5 mg**
WHO Class II	Change in 6MWD from baseline to Week 12, mean (95% CI)	-0.3 (-19.3, 18.7)	+26.6 (-1.0, 54.2)	+43.4 (17.6, 69.2)	-7.3 (-45.9, 31.4)	+37.0 (9.1,64.9)	+61.4 (31.3, 91.5)
	Placebo-Adjusted improvement in 6MWD, mean (95% CI)		27.0 (-4.8, 58.7) p=0.0460	43.7 (12.8, 74.7) p=0.0072		+44.2 (-1.1, 89.6) p=0.0624	+68.6 (21.5, 115.8) p=0.0104
WHO Class III	Change in 6MWD from baseline to Week 12, mean (95% CI)	-15.2 (-45.0, 14.5)	+18.7 (-5.8, 43.3)	+42.2 (21.0, 63.4)	-15.2 (-48.3, 17.8)	+6.2 (-26.2, 38.7)	+38.3 (11.7, 64.9)
	Placebo-Adjusted improvement in 6MWD, mean (95% CI)		+34.0 (-4.1, 72.1) p=0.0624	+57.4 (20.5, 94.3) p=0.0187		21.4 (-24.8, 67.7) p=0.4500	53.5 (11.2, 95.8) p=0.0217

A summary of the 6-Minute Walk Distance (6MWD) change from baseline to Week 12 is provided in Table 9.

Table 9 Summary of 6-Minute Walk Distance Change from Baseline to Week 12 by PAH Stratification using LOCF (Population: ITT)

		ARIES-1			ARIES-2		
Treatment Group		**Placebo**	**Ambrisentan 5 mg**	**Ambrisentan 10 mg**	**Placebo**	**Ambrisentan 2.5 mg**	**Ambrisentan 5 mg**
IPAH							
Change from baseline to Week 12	N	43	42	41	42	42	41
	Mean (SD)	-6.3 (82.14)	36.6 (85.42)	50.6 (58.22)	-20.6 (101.23)	35.7 (67.97)	55.1 (86.58)
Comparison versus placebo	Point estimate		42.9	56.9		56.3	75.7
	p-value[1]		0.0053	0.0011		0.005	<0.001
Non-IPAH							
Change from baseline to Week 12	N	24	25	26	23	22	22
	Mean (SD)	-10.6 (74.32)	-0.4 (74.69)	32.4 (76.38)	9.1 (76.77)	-3.5 (102.10)	38.6 (47.96)
Comparison versus placebo	Point estimate		10.2	43.0		-12.6	29.5
	p-value[1]		0.4965	0.0487		1.000	0.170

[1]Wilcoxon rank sum test stratified by IPAH and non-IPAH subjects

Hepatic Safety

Hepatic function was assessed in clinical studies. In ARIES 1 and 2, there were no cases of aminotransferase abnormalities >3x the upper limit of normal (ULN) in 262 patients receiving ambrisentan compared with three cases (out of 132) in patients receiving placebo (2.3%). The cumulative incidence of serum aminotransferase abnormalities >3x ULN in all Phase II and III (including extension) studies was 3.5% (17 of 483 subjects over a mean exposure duration of 79.5 weeks). In the ARIES-E open label long term extension study of ARIES-1 and ARIES-2 (N=383), the 2 year risk of developing serum aminotransferase elevations >3x ULN in patients treated with ambrisentan was 3.9%.

DETAILED PHARMACOLOGY

Ambrisentan is a specific, competitive endothelin receptor antagonist, with ET_A receptor selectivity. This pharmacologic property is the primary mode of action of ambrisentan.

Pharmacological activity of ambrisentan has been evaluated in a series of assays and animal models.

Primary Pharmacodynamics: *In vitro* studies using membrane preparations from human ventricular myocytes, showed that ambrisentan is an endothelin antagonist with a K_i of 16 pM against ET_A receptors. The selectivity of ambrisentan for ET_A receptors over ET_B receptors is about 4000-fold. The relative affinity of the R-enantiomer was markedly weaker as compared to the value for the S-enantiomer.

In vivo studies have been performed in a rat model of endothelin-induced hypertension. Ambrisentan dose-dependently (1, 3, or 10 mg/kg p.o.) reduced the increases in arterial pressure resulting from endothelin (Big ET-1) infusion.

No studies were performed on the pharmacodynamic effects of ambrisentan in animal models of pulmonary hypertension.

Secondary Pharmacodynamics: When tested for specificity using a battery (100) of receptors and ion channels, ambrisentan at 10 mcM was not active (< 50% inhibition). The R-enantiomer and 4-hydroxymethyl metabolite of ambrisentan were also inactive in a similar specificity panel.

In normotensive rats, oral administration of 300 mg/kg of ambrisentan or intravenous administration of 100 mg/kg ambrisentan caused initial increases in arterial pressure and heart rate that were followed by sustained reductions in these cardiovascular parameters.

In normotensive dogs, oral administration of 1, 10, and 100 mg/kg of ambrisentan caused dose-dependent reductions in arterial pressure that were not compensated for by increased heart rate.

Safety Pharmacology: Safety pharmacology studies were conducted to examine the effect of ambrisentan on the central and peripheral nervous system, cardiovascular and respiratory, gastrointestinal and renal systems, as well as cardiac conductivity (hERG cell current and guinea pig papillary muscle), uterine smooth muscle contractility, blood coagulation and spleen cell mitogenicity.

There was no evidence of overt central or peripheral effects in mice and rats after intravenous and oral administration of doses up to 100 mg/kg and 300 mg/kg, respectively.

The results from these safety pharmacology tests indicate that high concentrations of ambrisentan produced little to no effects in *in vitro*, *ex vivo* and in whole animal models and suggests minimal risk for off-target biological effects; however, large single doses of ambrisentan could lower arterial pressure and have the potential for causing hypotension and symptoms related to vasodilation. In addition, in rats, ambrisentan (single i.v. or oral doses) reduced renal sodium, chloride and calcium excretion rates in a dose-dependent manner.

No pharmacodynamic drug interaction studies were performed.

Long-term Treatment

Eligible Patients from the two pivotal studies, ARIES-1 and ARIES-2, were enrolled into an open-label extension study: ARIES-E. The main purpose of ARIES-E was to evaluate the incidence and severity of adverse events associated with long-term exposure to ambrisentan, including the effects on serum amino transferases. Patients who received ambrisentan in ARIES-1 and ARIES-2 remained on their current dose at enrolment into ARIES-E, whereas patients who received placebo were randomized to ambrisentan 2.5 mg, 5 mg or 10 mg once daily (N=383). Patients could be up-titrated or down-titrated and could receive prostanoid drugs approved for PAH therapy as needed in the course of ARIES-E (13% of patients required prostanoid therapy).

Of the 96 patients on 2.5 mg, 190 on 5 mg and 97 on 10 mg at randomization, 82%, 68% and 49% remained in the study at 1, 2 and 3 years, respectively and 91%, 83%, 79% of these patients were on ambrisentan monotherapy during these time periods.

Survival

In ARIES-E, patients who were treated with ambrisentan (2.5 mg, 5 mg, or 10 mg once daily), 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 as mentioned above. A dose-response relationship was not observed. These uncontrolled observations do not allow comparison with a group not given ambrisentan and cannot be used to determine the long-term effect of ambrisentan on mortality.

Safety

In general, no new or unexpected adverse events were observed during the long-term extension of ARIES-1 and ARIES-2 which had lasted 12 weeks. Of the 67 (18%) deaths during the extension study, six serious adverse reactions observed in four patients (N=32; 13%) were considered by the investigators to be causally related to ambrisentan.

An adverse event led to permanent discontinuation of 85 (22%) patients due mainly to worsening of pulmonary hypertension (5.2%) and right ventricular failure. Sixteen (4%) subjects had ALT and/or AST elevation >3 times the upper limit of normal which led to discontinuation of only one patient. Decrease in hemoglobin persisted for the full duration of treatment. Patients on warfarin or other anticoagulants had no clinically relevant changes in *mean* PT or INR.

Efficacy

In general, benefits observed during the placebo-controlled trials, ARIES-1 and ARIES- 2, were maintained in the majority of the patients remaining in ARIES-E during the full period of observation.

TOXICOLOGY

Repeat Dose Toxicity: The principal findings in repeat dose toxicity studies in mice and rats with ambrisentan are in part attributed to exaggerated pharmacology and include effects in the nasal cavity and testes. Repeat dose studies in the dog reveal ambrisentan to be well tolerated with findings limited to fundic glandular atrophy and clinical signs of audible breathing and gastrointestinal disturbance. Deaths or findings resulting in early sacrifice of animals attributed to oral administration of ambrisentan occurred in repeat-dose toxicity studies in rats at ≥ 100 mg/kg/day and in dogs at 1500 mg/kg/day. An increased mortality rate also occurred in 2-year carcinogenicity studies in rats at 30/20 and 60/40 mg/kg/day (initial daily dose of 30 mg/kg/day subsequently lowered to 20 mg/kg/day, and 60 mg/kg/day subsequently lowered to 40 mg/kg/day) and mice at 250/150 mg/kg/day (initial daily dose of 250 mg/kg/day subsequently lowered to 150 mg/kg/day).

Inflammation and changes in the nasal cavity epithelium and/or turbinates has been seen with chronic administration of ambrisentan and other endothelin receptor antagonists (ERAs) to rodents and, to a lesser extent, dogs.

Carcinogenesis and Mutagenesis: The genotoxicity of ambrisentan was assessed in a comprehensive battery of *in vitro* and *in vivo* studies. Ambrisentan was clastogenic in human lymphocytes *in vitro* both in the presence and absence of metabolic activation. Ambrisentan was not mutagenic to *Salmonella typhimurium*, did not elicit unscheduled DNA synthesis in rat liver, and was not clastogenic in an *in vivo* micronucleus study conducted in male rats.

There was no evidence of carcinogenic potential in 2 year oral daily dosing studies in rats and mice. There was a small increase in mammary fibroadenomas, a benign tumor, in male rats at the highest dose only.

Fertility: The development of testicular tubular atrophy and sterility in male animals has been linked to the chronic administration of ERAs, including ambrisentan, to rodents. Testicular tubular atrophy was observed at all dose levels (10 to 300 mg/kg/day) in oral fertility studies with male rats that was not reversible after 13 or 20 weeks following cessation of dosing. Reduced fertility and morphologic effects on sperm only occurred at 300 mg/kg/day and were reversible. No effects on sperm count or sperm motility were observed. Testicular tubular atrophy (focal/multifocal or diffuse) was also observed in repeat dose studies in rats and mice. There were no significant effects on fertility or embryofetal development in female rats dosed up to the time of implantation.

Pregnancy: Teratogenicity is a class effect of ERAs. The effect of ambrisentan on embryo-fetal development has been assessed in rats and rabbits after oral dose administration on gestation days 6-17 and 6-18, respectively. In both species, abnormalities of the lower jaw, tongue, and/or palate were consistently observed at all dose levels. Additionally, interventricular septal defects, trunk vessel defects, thyroid and thymus abnormalities, ossification of the basisphenoid bone, and the occurrence of the umbilical artery located on the left side of the urinary bladder instead of the right side and heart and associated blood vessel abnormalities were seen in the rabbit study.

REFERENCES

1. Galie N, Badesch D, Oudiz R, Simonneau G, McGoon MD, Keogh AM et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. 2005;46(3):529-535.

2. Galie N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo- controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation. 2008;117(23):3010-3019.

3. Harrison B, Magee MH, Mandagere A, Walker G, Dufton C, Henderson LS, et al. Effects of rifampicin (rifampin) on the pharmacokinetics and safety of ambrisentan in healthy subjects: a single-sequence, open-label study. Clin Drug Investig. 2010;30(12):875-885.

4. Oudiz RJ, Galie N, Olschewski H, Torres F, Frost A, Ghofrani HA, et al. Long-term ambrisentan therapy for the treatment of pulmonary arterial hypertension. J Am Coll Cardiol. 2009;54(21):1971-1981.

5. Richards DB, Spence R, Mandagere A, Henderson LS, Magee MH. Effects of multiple doses of ambrisentan on the pharmacokinetics of a single dose of digoxin in healthy volunteers. J Clin Pharmacol. 2011;51(1):102-106.

6. Richards DB, Walker GA, Mandagere A, Magee MH, Henderson LS. Effect of ketoconazole on the pharmacokinetic profile of ambrisentan. J Clin Pharmacol. 2009;49(6):719-724.

7. Spence R, Mandagere A, Richards DB, Magee MH, Dufton C, Boinpally R. Potential for pharmacokinetic interactions between ambrisentan and cyclosporine. Clin Pharmacol Ther. 2010;88(4):513-520.

8. Spence R, Mandagere A, Walker G, Dufton C, Boinpally R. Effect of steady-state ambrisentan on the pharmacokinetics of a single dose of the oral contraceptive norethindrone (norethisterone) 1 mg/ethinylestradiol 35 microg in healthy subjects: an open-label, single-sequence, single-centre study. Clin Drug Investig. 2010;30(5):313-324.

9. Walker G, Mandagere A, Dufton C, Venitz J. The pharmacokinetics and pharmacodynamics of warfarin in combination with ambrisentan in healthy volunteers. Br J Clin Pharmacol. 2009;67(5):527-534.

10. Product Monograph- VOLIBRIS® (ambrisentan tablets) 5 mg and 10 mg. GlaxoSmithKline Inc. Date of revision: June 23, 2016 and Submission Control No: 182566.

PART III: CONSUMER INFORMATION

[Pr]Apo-Ambrisentan
Ambrisentan Tablets
5 mg and 10 mg

This leaflet is part III of a three-part "Product Monograph" published when APO-AMBRISENTAN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-AMBRISENTAN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
APO-AMBRISENTAN is used in adults to treat high blood pressure in the pulmonary arteries (pulmonary arterial hypertension).

What it does:
APO-AMBRISENTAN is an endothelin receptor antagonist (ERA).
It reduces high blood pressure by relaxing the pulmonary arteries. This makes it easier for the heart to pump blood to the lungs.

Tests your doctor will do before treatment:
- a blood test to check that your liver is working properly and to check for anemia (reduction in red blood cells).
- a pregnancy test.

When it should not be used:
Do not take APO-AMBRISENTAN if you:
- are allergic to ambrisentan or any ingredients in the tablet (see What the nonmedicinal ingredients are).
- are pregnant, are planning to become pregnant, or could get pregnant because you are not using reliable birth control (contraception) (see WARNINGS AND PRECAUTIONS).
- are breastfeeding
- have liver disease or abnormal liver test results. Your doctor will decide if this medicine is suitable for you.
- have a lung condition called idiopathic pulmonary fibrosis (IPF) that makes it hard to breathe, along with a dry cough, and sometimes, joint pain or swelling.

What the medicinal ingredient is:
ambrisentan

What the nonmedicinal ingredients are:
APO-AMBRISENTAN 5 mg: croscarmellose sodium, FD&C Red # 40 , lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sunset yellow aluminum lake 40% talc and titanium dioxide.

APO-AMBRISENTAN 10 mg: croscarmellose sodium, FD&C Red # 40 aluminum lake 38-42%, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

What dosage forms it comes in:
5 mg and 10 mg film-coated tablets

WARNINGS AND PRECAUTIONS

Warnings and Precautions
APO-AMBRISENTAN may harm your unborn baby if you take it while pregnant. Before you use APO-AMBRISENTAN talk to your doctor or pharmacist if you:
- **are pregnant or thinking of becoming pregnant.**
- **could become pregnant because you are not using reliable birth control (contraceptive) methods.**
- **are breastfeeding.**

Before Treatment
BEFORE you use APO-AMBRISENTAN talk to your doctor or pharmacist if you:
- have or ever had liver problems
- have a low number of red blood cells (anemia)
- have swelling (edema)

If you are a man taking APO-AMBRISENTAN, it is possible that APO-AMBRISENTAN may lower your sperm count. Talk to your doctor if you have any questions or concerns about this.

During treatment:
Some patients taking APO-AMBRISENTAN were found to have abnormal liver function (increase in liver enzymes) and some patients developed anemia (reduction in red blood cells). Because these findings may not cause symptoms you can feel or observe yourself, your doctor will do regular blood tests to check for any changes in your liver function and for anemia.

Liver function:
If your doctor decides it is needed this blood test will be done every month or more frequently.

If you develop abnormal liver function, your doctor may decide to stop treatment with APO-AMBRISENTAN. When your blood test results for liver function return to normal, your doctor may decide to restart treatment with APO-AMBRISENTAN.

Anemia:
This blood test will be done after 1 month and periodically after that.

If you develop anemia, your doctor may decide to perform further tests to investigate the cause.

Pediatrics (< 18 years of age): Safety and efficacy of APO-AMBRISENTAN under 18 years of age have not been established, and should therefore not be used in this age group.

Pregnancy:
If you become pregnant or think you may be pregnant while you're taking APO-AMBRISENTAN, see your doctor immediately. APO-AMBRISENTAN may harm your unborn baby if you take it while you are pregnant. If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking APO-AMBRISENTAN and regularly while you are taking APO-AMBRISENTAN. You will also have to use a reliable method of birth control.

Driving and using machines:
It is not known whether APO-AMBRISENTAN affects your ability to drive or use machines. Don't drive or operate machines if you're feeling unwell.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-AMBRISENTAN:

- cyclosporine A (an autoimmune drug typically used in organ transplants),
- digoxin (a heart drug),
- rifampin (an anti-bacterial drug typically used in lung infections),
- ketoconazole (an anti-fungal drug typically used in skin infections),
- warfarin (typically used to prevent clotting),
- omeprazole (typically used to treat indigestion),
- oral contraceptives (birth control).

PROPER USE OF THIS MEDICATION

Do not stop taking APO-AMBRISENTAN without discussion with your doctor or your pharmacist.

Usual dose:
The usual dose of APO-AMBRISENTAN is 5 mg, once a day. Your doctor may decide to increase your dose to 10 mg, once a day. The maximum recommended daily dose is 10 mg.

If you take cyclosporine A, do not take more than 5 mg of APO-AMBRISENTAN, once a day.

You can take APO-AMBRISENTAN with or without food.

Overdose:

If you think you have taken too much APO-AMBRISENTAN contact your doctor, pharmacist, hospital emergency department or regional Poison Control Centre immediately even if there are no symptoms.

Missed Dose:

If you forget to take a dose of APO-AMBRISENTAN, just take the tablet as soon as you remember, then continue with the next dose at your usual time. Don't take two tablets at the same time to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- headache
- nasal congestion (runny or blocked nose), red and sore throat, sinusitis
- constipation, abdominal pain, nausea, vomiting
- flushing (redness of the skin),
- fluid retention (edema)
- feeling tired or weak
- palpitations (fast or irregular heartbeat)
- vision changes, (blurry or other changes to vision)
- ringing in the ears (tinnitus)

Some patients taking APO-AMBRISENTAN may have symptoms related to low blood pressure, like dizziness or fainting.

If any of these affects you severely, tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Common	Swelling (edema), especially in the ankles and feet	√		
	Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
	Flushing (redness of the skin)	√		
	Worsening shortness of breath shortly after		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	starting APO-AMBRISENTAN			
	Dizziness	√		
	Palpitations: fast and/or irregular heart beat		√	
Common	**Allergic Reaction:** rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Rare	**Liver Disorder:** yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite			√
Not Known	**Heart Failure:** shortness of breath, extreme tiredness and swelling in the ankles and legs		√	
	Chest pain and/or discomfort		√	

This is not a complete list of side effects. For any unexpected effects while taking APO-AMBRISENTAN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature 15°C to 30°C.
Keep out of reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: May 3, 2018