PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**VOLIBRIS**

ambrisentan tablets

5 mg and 10 mg

Endothelin Receptor Antagonist

GlaxoSmithKline Inc.
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Mississauga, ON
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RECENT MAJOR LABEL CHANGES

N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VOLIBRIS (ambrisentan tablets) 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.

VOLIBRIS is also indicated for initiation therapy in combination with tadalafil in adult PAH patients with WHO Functional class II or III symptoms.

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

1.1 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥ 65 years of age)

There is limited safety and effectiveness data in the geriatric population (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics).

2 CONTRAINDICATIONS

VOLIBRIS is contraindicated in:

- Patients with a known or suspected hypersensitivity to VOLIBRIS or any of the ingredients in the formulation (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Pregnancy (see 7.1.1 Pregnant Women).
- Breastfeeding (see 7.1.2 Breast-feeding).
- Patients with severe hepatic impairment (with or without cirrhosis) (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and 4 DOSAGE AND ADMINISTRATION).
- Patients with baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT)) >3x ULN (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and 4 DOSAGE AND ADMINISTRATION).
- Patients with idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should only be initiated by a physician experienced in the treatment of PAH.
- Assess liver function before starting VOLIBRIS (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and Monitoring and Laboratory Tests).
- VOLIBRIS 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 2 CONTRAINDICATIONS; 7.1.1 Pregnant Women).

- VOLIBRIS is contraindicated in patients with severe hepatic impairment and those with baseline AST or ALT >3x ULN. Patients with ALT/AST levels >2 x ULN were not included in a clinical trial studying co-administration of VOLIBRIS with tadalafil. VOLIBRIS should be used with caution in patients with moderate hepatic impairment (see 7 WARNINGS AND PRECAUTIONS; 10.3 Pharmacokinetics, and Special Populations and Conditions, Hepatic Insufficiency).
- Patients with PAH associated with connective tissue disease may require 10 mg VOLIBRIS for optimal efficacy. Consider increasing the dose to 10 mg VOLIBRIS providing the 5 mg dose is well tolerated (see 8 ADVERSE REACTIONS).

4.2 Recommended Dose and Dosage Adjustment

VOLIBRIS 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.

When used in initial combination with tadalafil, the dose of tadalafil should be uptitrated from 20 mg to 40 mg once daily 4 weeks after initiation and VOLIBRIS should be uptitrated from 5 mg to 10 mg after another 4 weeks, if well tolerated (see 14 CLINICAL TRIALS).

The maximum recommended daily dose is 10 mg.

When co-administered with cyclosporine A, the dose of VOLIBRIS should be limited to 5 mg once daily (see 9.4 Drug-Drug Interactions, Cyclosporine A).

VOLIBRIS can be administered with or without food.

Safety and efficacy of VOLIBRIS have not been established in patients under 18 years of age. Health Canada has not authorized an indication for pediatric use (see 16 NON-CLINICAL TOXICOLOGY).

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.

Renal metabolism and excretion of VOLIBRIS is minimal, so dose adjustment is unlikely to be required in patients with renal impairment.

4.5 Missed Dose

If a dose of VOLIBRIS 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.

5 OVERDOSAGE

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 VOLIBRIS, an overdosage of VOLIBRIS could potentially result in

hypotension. In the case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Route of Administration, Dosage Form /Strengths and Non-medicinal Ingredients

Route of Administration	Dosage Form / Strengths	Non-medicinal Ingredients
Oral	Tablet, 5 mg and 10 mg	Croscarmellose sodium, FD&C Red #40 Aluminum Lake, lactose monohydrate, lecithin, macrogol/polyethylene glycol 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, and titanium dioxide.

Packaging

VOLIBRIS 5 mg film-coated tablets are square, pale pink tablets engraved with 'GS' on one side and 'K2C' on the other.

VOLIBRIS 10 mg film-coated tablets are oval, deep pink tablets engraved with 'GS' on one side and 'KE3' on the other.

Each film-coated tablet contains ambrisentan and the following non-medicinal ingredients: croscarmellose sodium, FD&C Red #40 Aluminum Lake, lactose monohydrate, lecithin, macrogol/polyethylene glycol 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, and titanium dioxide.

VOLIBRIS tablets are available in blister packs of 30 tablets.

7 WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis

There are no human data available (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenesis and Mutagenesis).

Driving and Operating Machinery

There have been no studies to investigate the effect of VOLIBRIS 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.

Fluid retention

Peripheral edema (fluid retention) has been observed with endothelin receptor antagonists (ERAs) including VOLIBRIS. Peripheral edema may also be a clinical consequence of PAH. VOLIBRIS induced a dose-dependent increased incidence of mild to moderate peripheral edema (see 8 ADVERSE

REACTIONS).

Post-market reports confirm that fluid retention may occur within weeks after starting VOLIBRIS and, in some cases, has required intervention with a diuretic or hospitalization for fluid management or decompensated heart failure (see 8.2 Clinical Trial Adverse Reactions, Table 2). If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting VOLIBRIS.

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

Fluid retention/peripheral edema is more common during therapy with VOLIBRIS plus tadalafil than with either VOLIBRIS or tadalafil alone.

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 VOLIBRIS 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 VOLIBRIS, and stabilized thereafter. Anemia is more common during therapy with VOLIBRIS plus tadalafil than with either VOLIBRIS or tadalafil alone (see 8 ADVERSE REACTIONS).

Initiation of VOLIBRIS is not recommended for patients with clinically significant anemia (see 7 WARNINGS AND PRECAUTIONS, 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 VOLIBRIS. Monitor liver function as clinically indicated for patients with normal liver function or mild hepatic impairment. Initiation of VOLIBRIS 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. Patients with ALT/AST levels >2x ULN were not included in a clinical trial studying co-administration of VOLIBRIS with tadalafil. VOLIBRIS should be used with caution in patients with moderate hepatic impairment and monthly monitoring of ALT and AST is recommended (see 4 DOSAGE AND ADMINISTRATION, and 10 CLINICAL PHARMACOLOGY).

Although the incidence of aminotransferase abnormalities was low, the possibility of serum aminotransferase elevations associated with VOLIBRIS 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 VOLIBRIS. If patients develop clinically significant aminotransferase elevations or if aminotransferase elevations are accompanied by signs or symptoms of hepatic injury (e.g. jaundice), VOLIBRIS therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of VOLIBRIS 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 VOLIBRIS therapy, although the contribution of VOLIBRIS to these events is unclear.

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

Other ERAs have been associated with aminotransferase (AST, ALT) elevations, hepatotoxicity, and cases of liver failure (see 8 ADVERSE REACTIONS) In patients who develop hepatic impairment after VOLIBRIS initiation, the cause of liver injury should be fully investigated. Discontinue VOLIBRIS 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.

Monitoring and Laboratory Tests

Hemoglobin and Hematocrit

VOLIBRIS has been associated with reductions in hemoglobin concentrations and hematocrit. Initiation of VOLIBRIS 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 VOLIBRIS, 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 2). In monotherapy studies, the mean decrease in hemoglobin from baseline to the end of treatment for patients receiving VOLIBRIS in 12-week placebo-controlled studies was 0.8 g/dL Hemoglobin reductions were observed to persist for 4 years. In combination therapy studies, the incidence of anemia was increased when VOLIBRIS was dosed in combination with tadalafil (15%), compared to the incidence of anemia when ambrisentan or tadalafil were given as monotherapy (7% and 11%, respectively).

If a clinically significant decrease in hemoglobin or hematocrit is observed, and other causes have been excluded, discontinuation of VOLIBRIS 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 7 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 VOLIBRIS should be stopped.

In patients without clinical symptoms of hepatic injury or jaundice, re-initiation of VOLIBRIS may be considered following resolution of hepatic enzyme abnormalities (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Pulmonary Veno-Occlusive Disease

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

Renal

VOLIBRIS has not been studied in individuals with renal impairment. VOLIBRIS 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 10.3 Pharmacokinetics).

Reproductive Health: Female and Male Potential

Fertility

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of ERAs, including ambrisentan (see 16 NON-CLINICAL TOXICOLOGY). The effect on male human fertility is not known (see 14 CLINICAL TRIALS and 16 NON-CLINICAL TOXICOLOGY).

Teratogenic Risk

Teratogenicity is a class effect of ERAs. Animal studies in rats and rabbits have shown that VOLIBRIS is teratogenic with reports of increased incidences of fetal malformations and abnormalities following administration. (see 16 NON-CLINICAL TOXICOLOGY).

Sensitivity/Resistance

VOLIBRIS contains the azo colouring agent FD&C Red #40 Aluminum Lake which may cause allergic-type reactions.

7.1 Special Populations

7.1.1 Pregnant Women

The use of VOLIBRIS is contraindicated in pregnant women. Animal studies in rats and rabbits have shown that VOLIBRIS is teratogenic with reports of increased incidences of fetal malformations and abnormalities following administration of ERAs including VOLIBRIS (see 16 NON-CLINICAL TOXICOLOGY).

Women of child bearing potential should be advised of the risk of fetal harm if VOLIBRIS is taken during pregnancy. Pregnancy must be excluded before the start of treatment with VOLIBRIS and prevented thereafter by reliable contraception. Pregnancy tests during treatment with VOLIBRIS 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, VOLIBRIS should be discontinued and alternative treatment should be initiated (see 2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY, Pregnancy).

7.1.2 Breast-feeding

It is unknown if VOLIBRIS is excreted in human milk. Therefore breastfeeding is contraindicated in patients taking VOLIBRIS (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics (< 18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 16 NON-CLINICAL TOXICOLOGY).

7.1.4 Geriatrics (> 65 years of age)

No dose adjustment is required in patients aged 65 years and over.

In clinical studies where VOLIBRIS 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. In a subsequent clinical study (AMBITION), incidence of edema for patients on ambrisentan monotherapy was 19% in patients <55 years, and 28% for those ≥55 years of age (see 8 ADVERSE REACTIONS, 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions and 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of VOLIBRIS 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, VOLIBRIS was well tolerated.

In placebo-controlled 12-week studies, the most commonly (≥10%) reported adverse drug reactions with VOLIBRIS were peripheral edema, headache, and nasal congestion (see Table 2).

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 VOLIBRIS group.

In the placebo-controlled studies, six (4.5%) subjects in the placebo group died and 4 (1.5%) subjects in the VOLIBRIS groups died. A higher proportion of subjects in the placebo group had at least one non-fatal serious adverse event (SAE) compared to the VOLIBRIS-treated patients. The most frequent SAEs for both the placebo and VOLIBRIS-treated patients were right ventricular failure (placebo, 6.1%; VOLIBRIS, 1.1%) and (worsening) pulmonary hypertension (placebo, 3.8 %; VOLIBRIS, 1.1 %). Treatment-related SAEs occurred with a similar frequency across all VOLIBRIS treatment groups.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Experience from Short-term Clinical Studies

The following safety data for VOLIBRIS 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 VOLIBRIS 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 2.

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

System Organ Class Preferred Term	**Placebo** **(N=132)** n (%)	**VOLIBRIS** **5 mg** (N=130) n (%)	**VOLIBRIS** **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)
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[c]	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 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 VOLIBRIS, and incidence rates varied with age. Among younger patients (<65 years), the incidence was 18% (28/155) among those receiving VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS 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. The long-term safety of VOLIBRIS used in combination with tadalafil was evaluated in 302 patients with PAH in a double-blind, active-controlled clinical trial (>3 months; median exposure 534 days), AMBITION. The adverse drug reactions observed were generally consistent with the safety profile of VOLIBRIS used alone. Adverse drug reactions observed in long-term studies ARIES-E and AMBITION are summarized in Table 3.

Table 3 Adverse Drug Reactions for PAH Patients Receiving VOLIBRIS in Long-term Studies (>3 months), AMBITION and ARIES-E data

System Organ Class Preferred Term	ARIES-E Ambrisentan Monotherapy N=383 n (%)	AMBITION Combination Therapy (ITT) N=302 n (%)	AMBITION Ambrisentan Monotherapy (ITT) N=152 n (%)	AMBITION Tadalafil Monotherapy (ITT) N=151 n (%)
Blood and lymphatic system disorders				
Anemia	52 (14)	44 (15)	11 (7)	17 (11)
Cardiac disorders				
Palpitations	50 (13)	33 (11)	23 (15)	20 (13)
Eye disorders				
Visual impairment[a]	13 (3)	22 (7)	8 (5)	7 (5)
Gastrointestinal disorders				
Nausea	53 (14)	45 (15)	23 (15)	23 (15)
Vomiting	30 (8)	35 (12)	13 (9)	13 (9)
Constipation	33 (9)	16 (5)	10 (7)	6 (4)
Abdominal pain[b]	55 (14)	17 (6)	14 (9)	15 (10)
General disorders and administration site conditions				
Peripheral edema	168 (44)	135 (45)	58 (38)	43 (28)
Fluid retention[c]	24 (6)	34 (11)	16 (11)	18 (12)
Fatigue	47 (12)	34 (11)	22 (14)	20 (13)
Asthenia	20 (5)	8 (3)	4 (3)	9 (6)
Immune system disorders				
Hypersensitivity[d]	13 (3)	5 (2)	1 (<1)	2 (1)
Nervous system disorders				
Headache	96 (25)	125 (41)	51 (34)	53 (35)

System Organ Class Preferred Term	ARIES-E Ambrisentan Monotherapy N=383 n (%)	AMBITION Combination Therapy (ITT) N=302 n (%)	AMBITION Ambrisentan Monotherapy (ITT) N=152 n (%)	AMBITION Tadalafil Monotherapy (ITT) N=151 n (%)
Dizziness	66 (17)	56 (19)	30 (20)	22 (15)
Respiratory, thoracic and mediastinal disorders				
Nasal congestion	48 (13)	58 (19)	25 (16)	17 (11)
Nasopharyngitis	58 (15)	51 (17)	31 (20)	23 (15)
Sinusitis	39 (10)	22 (7)	10 (7)	11 (7)
Dyspnoea[e]	64 (17)	55 (18)	31 (20)	31 (21)
Skin and subcutaneous tissue disorders				
Rash[f]	27 (7)	28 (9)	8 (5)	9 (6)
Vascular disorders				
Flushing[g]	23 (6)	46 (15)	22 (14)	16 (11)

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

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 VOLIBRIS.

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.

Experience from a Clinical Study with VOLIBRIS Used in Combination with Tadalafil

As described above in Experience from Long Term Clinical Studies, the long-term safety of VOLIBRIS used in combination with tadalafil was evaluated in a double-blind, active-controlled clinical trial, AMBITION. The adverse drug reactions observed were generally consistent with the safety profile of VOLIBRIS used alone (see Table 3). Table 4 below presents the adverse reactions seen more frequently in the combination of VOLIBRIS with tadalafil than with either drug alone.

Table 4 Adverse Drug Reactions for PAH Patients Receiving VOLIBRIS in AMBITION Long-term Study (>3 months) with ≥2% Higher Incidence in the Combination Therapy Arm versus either of the Monotherapy Arms by Decreasing Incidence in Combination Arm

Preferred Term	AMBITION Combination Therapy (ITT) N=302 n (%)	AMBITION Ambrisentan Monotherapy (ITT) N=152 n (%)	AMBITION Tadalafil Monotherapy (ITT) N=151 n (%)
Peripheral edema	135 (45)	58 (38)	43 (28)
Headache	125 (41)	51 (34)	53 (35)
Nasal congestion	58 (19)	25 (16)	17 (11)
Dizziness	56 (19)	30 (20)	22 (15)
Flushing[a]	46 (15)	22 (14)	16 (11)
Anemia	44 (15)	11 (7)	17 (11)
Vomiting	35 (12)	13 (9)	13 (9)
Rash[b]	28 (9)	8 (5)	9 (6)
Visual impairment[c]	22 (7)	8 (5)	7 (5)
Tinnitus	8 (3)	1 (<1)	0 (0)

a) Flushing includes Hot flush. b) Rash includes Rash erythematous, Rash generalised, Rash macular, Rash papular, and Rash pruritic. c) Visual impairment includes Vision blurred.

In the AMBITION study, the incidence of peripheral edema in elderly patients (≥65 years) was 44% (44/101), 37% (18/49) and 29% (16/56) in the VOLIBRIS + tadalafil, VOLIBRIS monotherapy and tadalafil monotherapy groups respectively, compared to 45% (91/201), 39% (40/103) and 28% (27/95) in younger patients (<65 years).

8.3 Less Common Clinical Trial Adverse Reactions

The following less common clinical trial adverse reaction occurred in PAH patients receiving VOLIBRIS in phase III 12-week placebo-controlled studies in subjects with PAH (ARIES-1 and ARIES-2):

Immune system disorders: Hypersensitivity

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematologic Changes

In the placebo-controlled Phase III studies in patients with PAH, the mean changes from baseline (in patients receiving placebo, VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS 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. The incidence of anemia was increased when VOLIBRIS was dosed in combination with tadalafil (15% adverse event frequency), compared to the incidence of anemia when ambrisentan or tadalafil were given as monotherapy (7% and 11%, respectively). Adverse events related to anemia, low

hemoglobin or low hematocrit appeared to be more frequent with 10 mg VOLIBRIS 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 VOLIBRIS 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.

8.5 Post-Market Adverse Reactions

In addition to adverse drug reactions identified from clinical studies, the following adverse drug reactions were identified during post-approval use of VOLIBRIS. Events of 'unknown' frequency have been reported voluntarily from a population of unknown size, therefore estimates of frequency cannot be made.

Cardiac Disorders

Fluid retention and heart failure associated with fluid retention occurring within weeks after starting VOLIBRIS 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 (see 7 WARNINGS AND PRECAUTIONS), including cases of exacerbation of autoimmune hepatitis, and hepatic injury of unclear etiology (including increased blood bilirubin >2x ULN) have been reported during VOLIBRIS therapy. In the AMBITION study, in a subset of patients without left ventricular dysfunction, the incidence of liver adverse events (primarily increased levels of liver enzymes) occurred in 7% of patients of the VOLIBRIS plus tadalafil combination therapy group, versus in 2% and 5% of patients in the VOLIBRIS monotherapy and tadalafil monotherapy groups, respectively. The incidence of liver events was similar in patients with left ventricular dysfunction.

Vascular Disorders

Hypotension: In the AMBITION study, in a subset of patients without left ventricular dysfunction, the rates of adverse events potentially indicative of hypotension (hypotension, dizziness, syncope, presyncope, vasodilatation, blood pressure decreased, orthostatic hypotension, dizziness exertional, dizziness postural, hypovolemic shock) and the rates of the adverse event of hypotension itself were: 32% and 8% in the VOLIBRIS+tadalafil arm, compared to 27% and 7% in the ambrisentan, and 27% and 7% in the tadalafil monotherapy arms. Including patients with left ventricular dysfunction, the rates of adverse events potentially indicative of hypotension and hypotension itself were: 30% and 8% in the VOLIBRIS+tadalafil arm, compared to 29% and 7% in the ambrisentan, and 30% and 8% in the tadalafil monotherapy arms.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

In vitro data show that VOLIBRIS at concentrations up to 300microM 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 VOLIBRIS 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 100microM. VOLIBRIS showed weak *in vitro* inhibition of OATP1B1, OATP1B3 and sodium-taurocholate co-transporter (NTCP) with IC_{50} values of 47μmicroM, 45microM, and approximately 100microM, respectively. *In vitro* studies in rat and human hepatocytes showed no evidence for ambrisentan inhibition of NTCP, OATP, BSEP and MRP2. Furthermore, VOLIBRIS did not induce MRP2, P-gp or BSEP protein expression in rat hepatocytes. Taken together, the *in vitro* data suggest that VOLIBRIS, 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.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 5 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 VOLIBRIS (5 mg once daily), and the effects of repeat dosing of VOLIBRIS (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 VOLIBRIS increased (48% and 121%, respectively) in the presence of multiple doses of cyclosporine A. The apparent plasma $t_{1/2}$ of VOLIBRIS in the presence of cyclosporine increased by 38% as compared to VOLIBRIS alone (from 8.36h to 11.5h). No important differences in the median t_{max} were observed. However, multiple doses of VOLIBRIS 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 VOLIBRIS.	The dose of VOLIBRIS should be limited to 5 mg once daily when co-administered with cyclosporine A (see 4.2 Recommended Dose and Dosage Adjustment). No dose adjustment of cyclosporine A is warranted.

Drug interaction	Level of evidence	Effect	Clinical comment
Phosphodiesterase inhibitors (Sildenafil; Tadalafil)	CT	In healthy volunteers, co-administration of VOLIBRIS with a phosphodiesterase inhibitor, (either sildenafil or tadalafil) did not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or VOLIBRIS. The effects of steady-state VOLIBRIS (10 mg once daily) on the pharmacokinetics of a single dose of tadalafil, and the effects of steady-state tadalafil (40 mg once daily) on the pharmacokinetics of a single dose of VOLIBRIS were studied in 23 healthy volunteers. VOLIBRIS did not have any clinically relevant effects on the pharmacokinetics of tadalafil. Similarly, co-administration with tadalafil did not affect the pharmacokinetics of VOLIBRIS. In healthy volunteers receiving a single dose of sildenafil (20 mg), daily doses of VOLIBRIS (10 mg) did not have a clinically relevant effect on the pharmacokinetics of sildenafil or the active metabolite, n-desmethyl sildenafil. Similarly, daily doses of sildenafil (20 mg tid) did not have a clinically relevant effect on the pharmacokinetics of a single dose of VOLIBRIS (10 mg) (see , 10.3 Pharmacokinetics).	The co-administration of VOLIBRIS with tadalafil was studied in a multicenter, double-blind, active-controlled study. See 7 WARNINGS AND PRECAUTIONS, 8 ADVERSE REACTIONS, 4 DOSAGE AND ADMINISTRATION, and 14 CLINICAL TRIALS
Ketoconazole	CT	Steady-state administration of ketoconazole increased the AUC_{∞} and C_{max} of VOLIBRIS by 35% and 20%, respectively. The clinical significance of these changes is not known.	Patients on 10 mg of VOLIBRIS while on ketoconazole should be monitored closely for any signs of adverse effects.

Drug interaction	Level of evidence	Effect	Clinical comment
Digoxin	CT	The effects of repeat dosing of VOLIBRIS (10 mg) on the pharmacokinetics of single dose digoxin were studied in 15 healthy volunteers. Multiple doses of VOLIBRIS resulted in slight but significant increases in digoxin $AUC_{(0\text{-last})}$ (16%) and trough concentrations, and a 29% increase in digoxin C_{max}. The increase in digoxin exposure (by 9% of $AUC_{(0\text{-}\infty)}$) observed in the presence of multiple doses of VOLIBRIS was not considered clinically relevant.	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
Oral contraceptives	CT	In a clinical study in healthy volunteers, steady-state dosing with VOLIBRIS 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, VOLIBRIS would not be expected to significantly affect exposure to oestrogen- or progestogen- based contraceptives. The effects of 12 days dosing with VOLIBRIS (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 VOLIBRIS and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of VOLIBRIS.	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 VOLIBRIS (10 mg once daily) were studied in healthy volunteers. Following	No dose adjustment of VOLIBRIS is warranted upon concomitant administration with rifampin.

Drug interaction	Level of evidence	Effect	Clinical comment
		initial doses of rifampin, a transient increase in VOLIBRIS $AUC_{(0-\tau)}$ (121% and 116% after first and second doses of rifampin, respectively) was observed. Apparent plasma $t_{1/2}$ of VOLIBRIS decreased by 50% from 8.28h to 4.59h when co-administered with rifampin. However, there was no clinically relevant effect on VOLIBRIS exposure by day 8, following administration of multiple doses of rifampin.	
Warfarin	CT	In healthy volunteers receiving warfarin, daily doses of VOLIBRIS (10 mg) did not have a clinically relevant effect on prothrombin time (PT), International Normalized Ratio (INR), or the pharmacokinetics of S-warfarin (CYP2C9 substrate) or R-warfarin (CYP3A4 substrate). In patients with PAH receiving warfarin-type anticoagulants, concomitant administration of VOLIBRIS did not result in a clinically relevant change in PT, INR or anticoagulant dose (see 10.3 Pharmacokinetics).	No dose adjustment is warranted.

CT, Clinical Trial

9.5 Drug-Food Interactions

VOLIBRIS can be taken with or without food (see 10.3 Pharmacokinetics).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

VOLIBRIS (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.

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.

10.2 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 VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS 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.

In patients with PAH who received combination therapy with VOLIBRIS and tadalafil in the AMBITION study, greater decreases from baseline in N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) were observed relative to VOLIBRIS monotherapy (geometric least-squares mean percent decreases of 67% versus 56%, respectively; $p = 0.0111$) or versus tadalafil monotherapy (44% decrease; $p < 0.0001$).

The decrease in NT-pro-BNP was observed early (Week 4) and was sustained through Week 24.

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either VOLIBRIS 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. VOLIBRIS 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of VOLIBRIS increased mean QTc at t_{max} by 5 ms with an upper 95% confidence limit of 9 ms. The effect of concomitant therapy of VOLIBRIS with metabolic inhibitors of ambrisentan (i.e. ketoconazole, cyclosporine A) on QT prolongation is unknown (see 9 DRUG INTERACTIONS).

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 μM 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 VOLIBRIS, including the effects on serum amino transferases. Patients who received VOLIBRIS in ARIES-1 and ARIES-2 remained on their current dose at enrolment into ARIES-E, whereas patients who received placebo were randomized to VOLIBRIS 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 VOLIBRIS monotherapy during these time periods.

Survival

In ARIES-E, patients who were treated with VOLIBRIS (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 VOLIBRIS 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 VOLIBRIS and cannot be used to determine the long-term effect of VOLIBRIS on mortality.

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.

10.3 Pharmacokinetics

Absorption

VOLIBRIS (ambrisentan) is absorbed rapidly in humans. The absolute bioavailability of VOLIBRIS is not known. After oral administration, maximum plasma concentrations (C_{max}) of VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS can be taken with or without food.

Distribution

VOLIBRIS (ambrisentan) is highly plasma protein bound. The *in vitro* plasma protein binding of VOLIBRIS was, on average, 99% and independent of concentration over the range of 0.2 - 20 μg/mL. VOLIBRIS is primarily bound to albumin (96.5%) and to a lesser extent to alpha$_1$-acid glycoprotein.

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

Metabolism

VOLIBRIS (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 VOLIBRIS with UGTs, cytochromes and drug transporters have been studied *in vitro* (see 9.4 Drug-Drug Interactions).

Elimination

VOLIBRIS (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 VOLIBRIS 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 VOLIBRIS were not significantly influenced by age (see 4 DOSAGE AND ADMINISTRATION)

Gender

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

Hepatic Insufficiency

The pharmacokinetics of VOLIBRIS 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 VOLIBRIS are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment might be expected to increase exposure (C_{max} and AUC) of VOLIBRIS, however the magnitude of this and any effect on safety and efficacy has not been evaluated. Therefore, VOLIBRIS is contraindicated in patients with severe hepatic impairment or levels of ALT/AST >3x ULN. Patients with ALT/AST levels >2 x ULN were not included in a clinical trial studying co-administration of VOLIBRIS with tadalafil. VOLIBRIS should be used with caution in patients with moderate hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, and 4 DOSAGE AND ADMINISTRATION).

Renal Insufficiency

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

11 STORAGE, STABILITY AND DISPOSAL

Store between 15-30°C.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

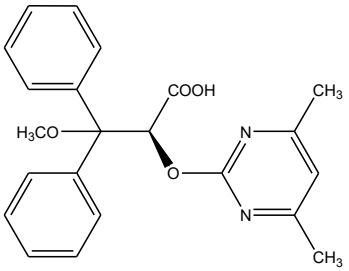
Drug Substance

Proper name: ambrisentan

Chemical name: (+)-(2*S*)-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

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 Summary of the Design and Patient Demographics in Pivotal Clinical Trials of VOLIBRIS (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, multinational	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, multinational	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%)
AMBITION	Phase III/IV, randomized, double blind, active-controlled, multicentre, multinational	ambrisentan 10 mg + tadalafil 40 mg, ambrisentan 10 mg, or tadalafil 40 mg taken orally q.d.. Ambrisentan was initiated at 5 mg for 8 weeks and tadalafil at 20 mg for 4 weeks, up-titrated if tolerated	Combination ambrisentan + tadalafil: n=302 Ambrisentan monotherapy: n=152 Tadalafil monotherapy: n=151	55.7 (18-75)	Male: 144 (24 %) Female: 461 (76 %)	IPAH*: 330 (54.6%) Non-IPAH: 274 (45.4%)

*IPAH = idiopathic PAH

VOLIBRIS 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 6. In both studies, VOLIBRIS 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.

VOLIBRIS in Combination with Tadalafil for the Treatment of PAH

The effect of initial combination therapy with VOLIBRIS and tadalafil was investigated in a multicenter, double-blind, active-controlled study that compared the combination of VOLIBRIS and tadalafil to VOLIBRIS or tadalafil monotherapy in patients with WHO functional class II–III PAH. The study enrolled 610 patients; 605 patients received at least one dose of study drug and 500 met the criteria for the primary efficacy analysis. Patients were randomized 2:1:1 to once daily VOLIBRIS 10 mg + tadalafil 40 mg, VOLIBRIS 10 mg, or tadalafil 40 mg. VOLIBRIS was initiated at 5 mg for 8 weeks and tadalafil at 20 mg for 4 weeks, then each was up-titrated if tolerated. In the primary efficacy analysis, 226 patients (89%) treated with VOLIBRIS + tadalafil had an up-titration of the tadalafil dose from 20 to 40 mg, and 220 (87%) patients had an up-titration of the VOLIBRIS dose from 5 mg to 10 mg.

The primary study endpoint was time to first clinical failure event. Secondary endpoints were change in NT-pro-BNP, percentage of patients with satisfactory clinical response, and change from baseline 6MWD, all assessed at Week 24 (see 10 CLINICAL PHARMACOLOGY).

Patients enrolled in the study had idiopathic PAH (53%), heritable PAH (3%), or PAH associated with connective tissue diseases, congenital heart disease, HIV infection, or drugs or toxins (APAH, 44%). Median time from diagnosis to first study drug administration was 22 days. Approximately 31% and 69% of patients were in WHO functional class II and III, respectively. The mean patient age was 54.4 years (32% were ≥65 years old). Most patients were white (90%) and female (78%); 46% were North American. For the primary efficacy analysis, median exposure to combination treatment was 534 days.

14.2 Study Results

Results of VOLIBRIS Monotherapy for the Treatment of PAH

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 VOLIBRIS resulted in a statistically significant improvement in 6MWD for each dose of VOLIBRIS as shown in Table 7. 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 **Error! Reference source not found.**.

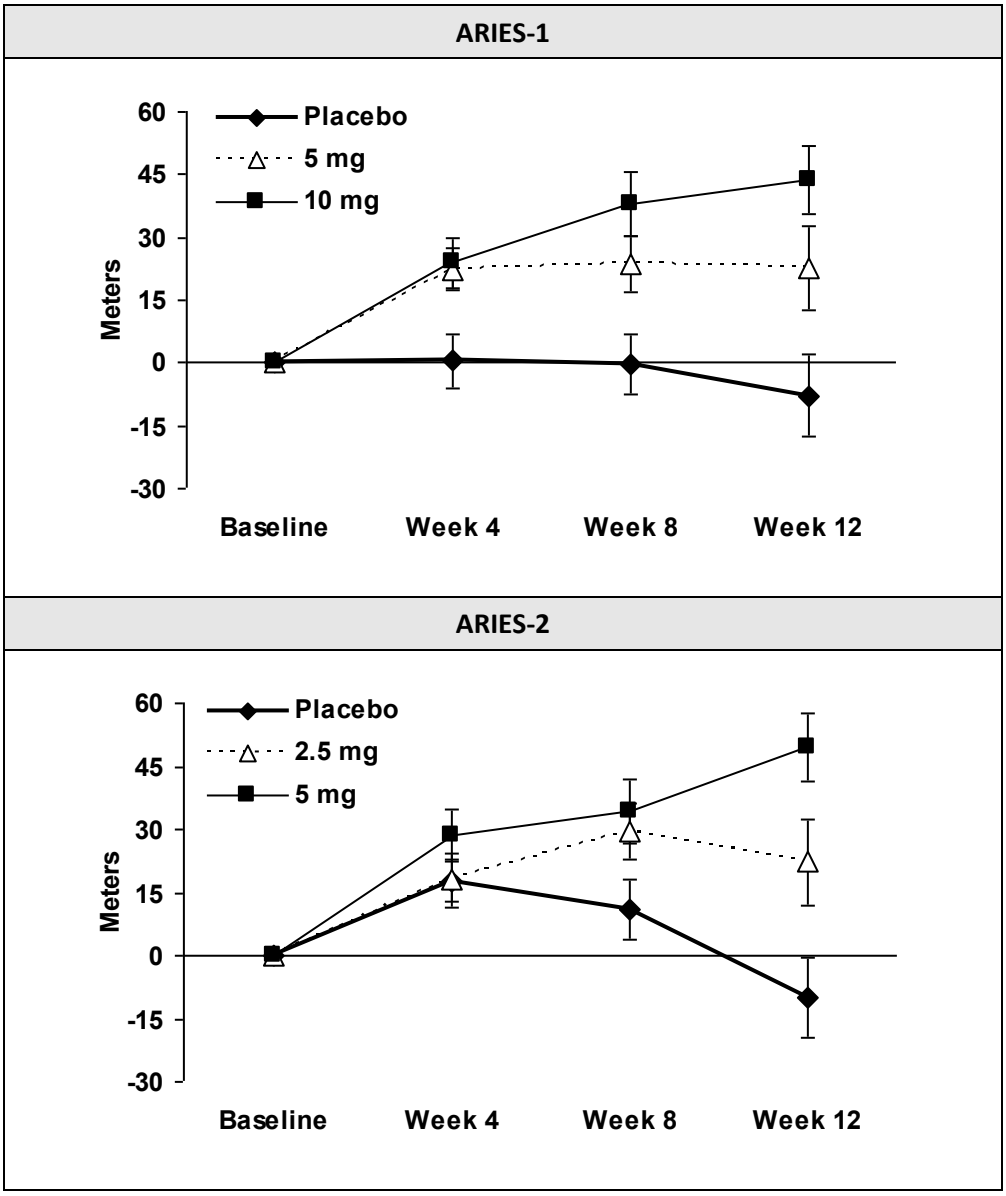
Table 7 Changes from Baseline in 6-minute Walk Distance (metres) at Week 12 in Phase III studies (Idiopathic and Non-Idiopathic PAH Patients: see also Table 11)

	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 VOLIBRIS 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 VOLIBRIS 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 VOLIBRIS led to statistically significant improvements in BDI at week 12 (Table 8). Improvements in the physical functioning scale (SF-36) were also observed, however, were not statistically significant.

Table 8 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

VOLIBRIS 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 9).

Table 9 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 VOLIBRIS compared to placebo after 12 weeks treatment (Table 10). Improvement in secondary endpoints also supported efficacy in both WHO functional class II and class III patients.

Table 10 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	**VOLIBRIS 5 mg**	**VOLIBRIS 10 mg**	**Placebo**	**VOLIBRIS 2.5 mg**	**VOLIBRIS 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 11.

Table 11 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**	**VOLIBRIS 5 mg**	**VOLIBRIS 10 mg**	**Placebo**	**VOLIBRIS 2.5 mg**	**VOLIBRIS 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

Results of VOLIBRIS in Combination with Tadalafil for the Treatment of PAH

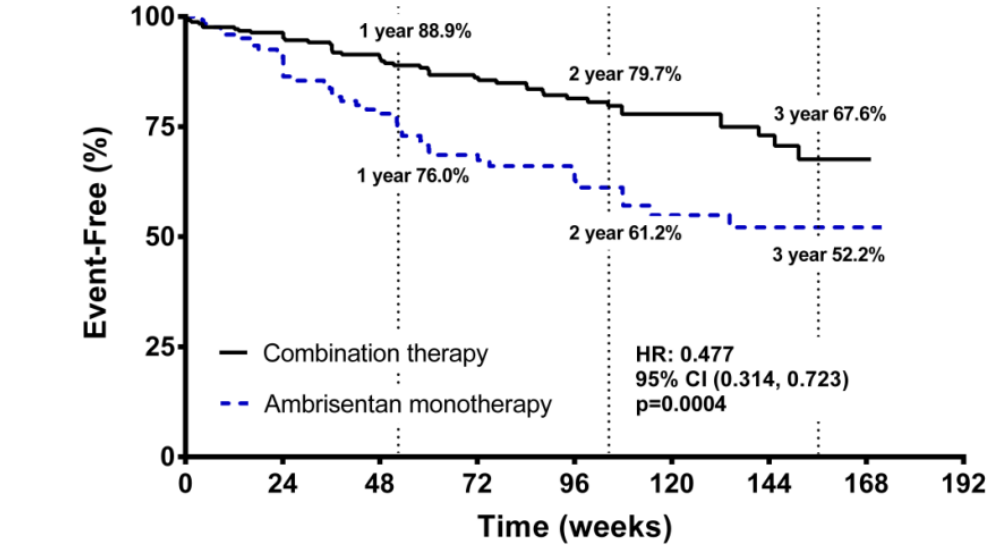
Time to Clinical Failure

Time to clinical failure of PAH was a composite endpoint defined as time to the first occurrence of death (all-cause), hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. Hospitalization for worsening PAH was defined as any hospitalization for worsening PAH, lung or heart/lung transplant, atrial septostomy, or initiation of parenteral prostanoid therapy. Disease progression was defined as >15% decrease from baseline in 6MWD combined with WHO functional class III or IV symptoms (at 2 consecutive post-baseline visits separated by ≥14 days). Unsatisfactory long term clinical response was defined as any reduction in 6MWD below baseline combined with an assessment of functional class III status measured at visits 6 months apart.

Patients treated with VOLIBRIS + tadalafil experienced a significant reduction in risk of clinical failure versus patients treated with VOLIBRIS monotherapy (p=0.0004) or tadalafil monotherapy (p=0.0045). The reduction in risk of a clinical failure event was 52% (HR= 0.48, 95% CI: 0.31, 0.72) on combination therapy versus VOLIBRIS monotherapy, and 47% (HR=0.53, 95% CI: 0.34, 0.83) versus tadalafil

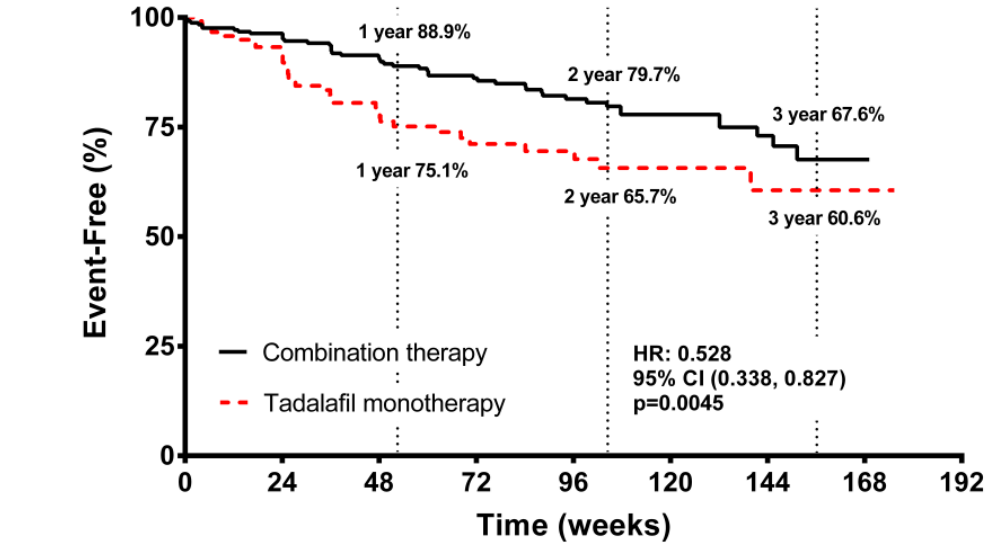
monotherapy. The Kaplan-Meier plots of time to clinical failure for combination therapy versus each monotherapy are shown in Figure 2; the summary of primary endpoint events is shown in Table 12.

Figure 2 **Time to Clinical Failure, VOLIBRIS + Tadalafil Combination Therapy versus VOLIBRIS or Tadalafil Monotherapy (Adjudicated) in the AMBITION Study**



Number at risk:

Combination:	253	229	186	145	106	71	36	4
Ambrisentan mono:	126	104	81	57	39	23	14	3



Number at risk:

Combination:	253	229	186	145	106	71	36	4
Tadalafil mono:	121	105	74	51	38	26	11	2

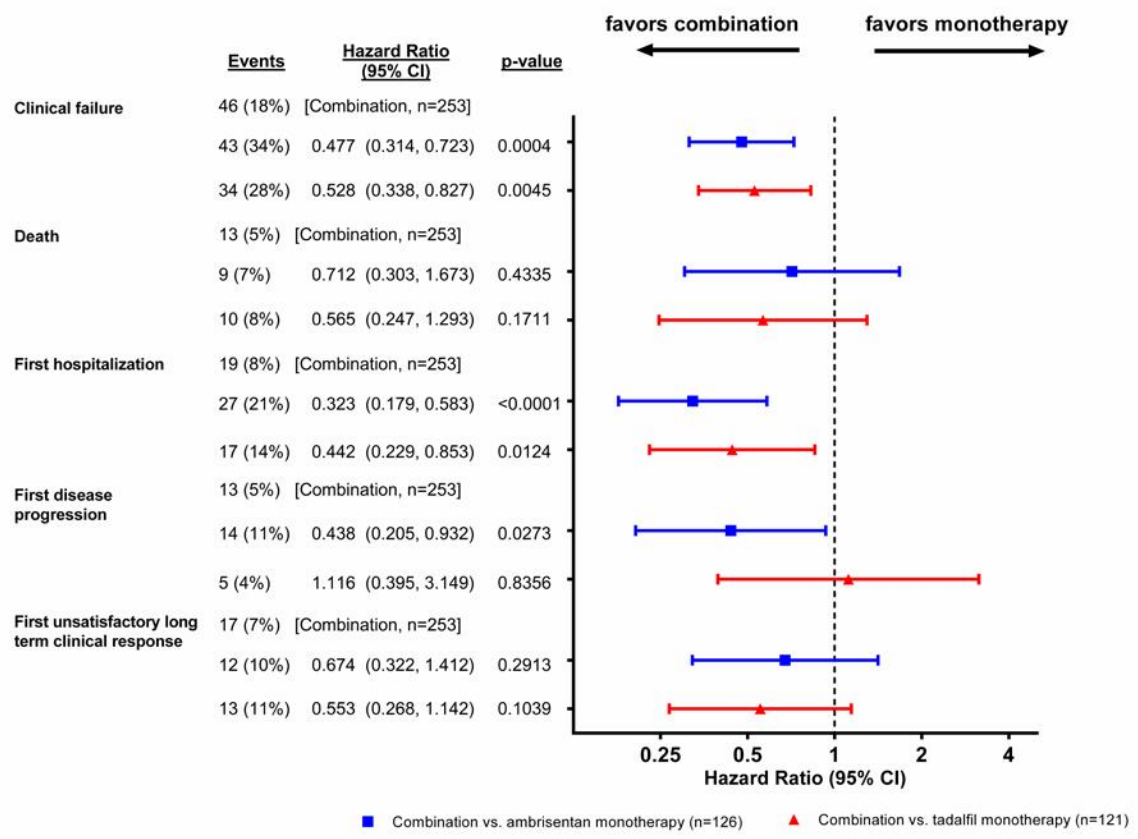
Time from randomization to first clinical failure with Kaplan-Meier estimates of the proportions of failures; p-values shown are the log-rank comparisons of VOLIBRIS + tadalafil combination therapy to the individual monotherapy.

Table 12 Summary of Primary Endpoint Events (Adjudicated) in the AMBITION Study

	VOLIBRIS + Tadalafil (N=253) n (%)	**VOLIBRIS Monotherapy (N=126) n (%)**	**Tadalafil Monotherapy (N=121) n (%)**
Component as First Clinical Failure Event			
Death (All-Cause)	9 (4%)	2 (2%)	6 (5%)
Hospitalization for Worsening PAH	10 (4%)	18 (14%)	12 (10%)
Disease Progression	10 (4%)	12 (10%)	4 (3%)
Unsatisfactory Long-term Clinical Response	17 (7%)	11 (9%)	12 (10%)

The results for analyses of time to adjudicated clinical failure and to the first of each component of clinical failure are shown in Figure 3.

Figure 3 Analysis of Adjudicated Events in the AMBITION Study



Efficacy of initial combination treatment with VOLIBRIS + tadalafil on time to clinical failure was seen across the following subgroups of interest: etiology of PAH (IPAH/HPAH and non-IPAH, Baseline WHO FC (II, III), region (North America, rest of world (predominantly European subjects)), Baseline age group (< 65, ≥ 65 years), Baseline age group above or below study median age, sex, and Baseline 6MWD above or below study median 6MWD. Each subgroup analysis showed a reduction in risk with combination therapy relative to the individual monotherapies in all subgroups, with the exception of the male subgroup, in which reduction in risk was not observed with combination therapy relative to tadalafil monotherapy. This may be a statistical artifact due to the relatively low number of male participants (n=122) in the study.

Supportive analyses of time to first adjudicated clinical worsening event (death, hospitalization for worsening PAH, and disease progression) were performed. Patients treated with VOLIBRIS + tadalafil had a lower risk of having a first adjudicated clinical worsening event at any time from baseline to final assessment visit compared with patients treated with VOLIBRIS or tadalafil monotherapy. These risk reductions amounted to a statistically significant 56% in comparison with ambrisentan monotherapy (HR=0.443, 95% CI: 0.279, 0.704, p=0.0004), and a statistically non-significant 39% in comparison with tadalafil monotherapy (HR=0.611, 95% CI: 0.364, 1.028, p=0.0607).

Clinical Response

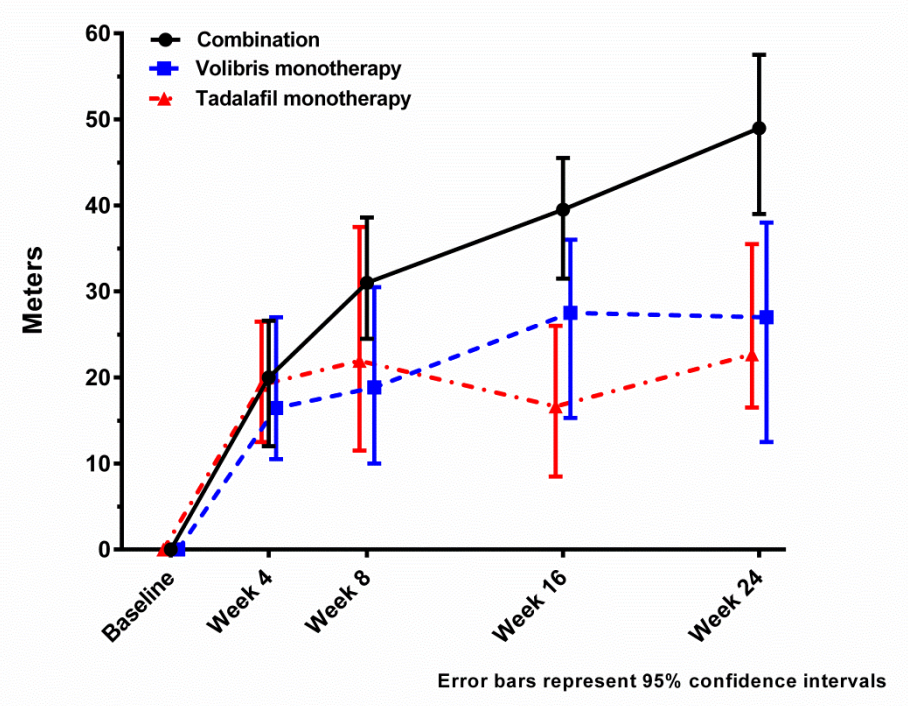
Satisfactory clinical response at Week 24 was a composite secondary endpoint defined as ≥10% improvement in 6MWD compared to baseline, improvement to or maintenance of WHO functional class

I or II symptoms, and no events of clinical worsening prior to or at the Week 24 visit. The percentage of patients achieving satisfactory clinical response at Week 24 in the combination therapy group (39%) was significantly greater than in the tadalafil monotherapy group (27%, p=0.0321, odds ratio 1.723, 95% CI: 1.047, 2.833). The difference in satisfactory clinical response between combination therapy and VOLIBRIS monotherapy (31%, p=0.1518, odds ratio 1.424, 95% CI: 0.878, 2.308) was not statistically significant.

Exercise Ability

The observed improvement from baseline in median 6MWD at Week 24 was higher with combination therapy (from 357.0 m to 414.0 m) than with VOLIBRIS monotherapy (from 368.5 m to 407.0 m) or with tadalafil monotherapy (from 363.3 m to 392.0 m). Statistical analysis using imputed data showed that the difference between median change in the combination therapy group (49.0m, 95% CI: 39.0, 57.5) and the VOLIBRIS monotherapy group (27.0 m, 95% CI: 12.5, 38.0) was statistically significant (p=0.0005), and so was the difference with the tadalafil monotherapy group (22.7 m, 95% CI: 16.5, 35.5; p=0.003).

Figure 4 **Median Change from Baseline in 6-Minute Walk Distance (meters) in the AMBITION Study**



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 VOLIBRIS 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 VOLIBRIS was 3.9%. In the AMBITION study, in a subset of patients without left ventricular dysfunction, the incidence of serum aminotransferase (ALT and/or AST) abnormalities >3x ULN when VOLIBRIS was used in combination with tadalafil was 4% (10 of 253 patients), versus 2% (2 of 126 patients) when VOLIBRIS was used in monotherapy, versus 3% (3 of 121 patients when tadalafil was used in monotherapy. Incidence rates were similar when considering populations with left ventricular dysfunction.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The principal findings in repeat dose toxicity studies in mice and rats with VOLIBRIS (ambrisentan) are in part attributed to exaggerated pharmacology and include effects in the nasal cavity and testes. Repeat dose studies in the dog reveal VOLIBRIS 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 VOLIBRIS occurred in repeat-dose toxicity studies in rats at $\geq$ 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 have been seen with chronic administration of VOLIBRIS and other endothelin receptor antagonists (ERAs) to rodents and, to a lesser extent, dogs.

Carcinogenicity

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.

Genotoxicity

The genotoxicity of VOLIBRIS was assessed in a comprehensive battery of *in vitro* and *in vivo* studies. VOLIBRIS was clastogenic in human lymphocytes *in vitro* both in the presence and absence of metabolic activation. VOLIBRIS 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.

Reproductive and Developmental Toxicity

The development of testicular tubular atrophy and sterility in male animals has been linked to the chronic administration of ERAs, including VOLIBRIS, 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.

Teratogenicity is a class effect of ERAs. The effect of VOLIBRIS 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.

Juvenile Toxicity In a juvenile rat study, oral administration of ambrisentan once daily during postnatal day (PND) 7 to 62 decreased brain weight -4% in males and females with no brain morphologic effects at 20 mg/kg/day, after a period of breathing sounds which occurred at doses of 4 mg/kg/day and above (1.5 to 6.4 times higher than the maximum recommended human adult dose of 10 mg, based on AUC). In two separate respiratory function juvenile rat studies, 20 mg/kg/day of ambrisentan administered on PND 7 to 26 or PND 7 to 36 evoked decreases in brain weight (-3% to -8%), and also caused breathing sounds (a singular audible click), irregular respiratory function, apnea and hypoxia starting 10 days after dosing, and continuing two days after treatment stopped, with no detection of these effects at one month after dose interruption. There were no neurobehavioral changes observed at the end of treatment and one month after dose interruption, and a morphometric assessment of changes to the pharynx and larynx was inconclusive. Although the mechanisms by which ambrisentan reduces brain weight of juvenile rats have not been fully elucidated, it is plausible that this effect is mediated by chronic hypoxia that may be associated with mechanically induced apnea originating from pharyngeal dysmorphogenesis occurring during postnatal pharyngeal development. The clinical relevance of this finding in humans is unknown; however, this postnatal time frame would likely correlate to human pharyngeal development from 0 to 3 years of age. Safety and efficacy of VOLIBRIS have not been established in patients under 18 years of age. VOLIBRIS should therefore not be used in this age group.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVOLIBRIS

ambrisentan tablets

Read this carefully before you start taking **VOLIBRIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VOLIBRIS**.

What is VOLIBRIS used for?

VOLIBRIS is used in adults to treat high blood pressure in the pulmonary arteries. They are blood vessels that carry blood away from the heart to the lungs. VOLIBRIS can be used as an initiation therapy in combination with tadalafil.

How does VOLIBRIS work?

VOLIBRIS 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.

What are the ingredients in VOLIBRIS?

Medicinal ingredients: ambrisentan

Non-medicinal ingredients: croscarmellose sodium, FD&C Red #40 Aluminum Lake, lactose monohydrate, lecithin, macrogol/polyethylene glycol 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, talc, and titanium dioxide.

VOLIBRIS comes in the following dosage forms:

Tablets: 5 mg and 10 mg

Do not use VOLIBRIS if:

- you are pregnant, are planning to become pregnant, or could become pregnant because you are not using reliable birth control (see Other warnings you should know about).
- you are breastfeeding or plan to breastfeed your baby.
- you are allergic to ambrisentan or to any of the other ingredients in VOLIBRIS. VOLIBRIS contains lactose, lecithin (soya) and FD&C Red #40 Aluminum Lake (a colouring agent).
- you have liver disease or abnormal liver test results.
- have a lung condition called Idiopathic Pulmonary Fibrosis (IPF). The symptoms of this condition include:
    - Shortness of breath
    - Dry cough
    - Fatigue
    - Joint or muscle pain

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VOLIBRIS. Talk about any health conditions or problems you may have, including if you:

- have swelling

- have a low amount of red blood cells (anemia)
- have or ever had liver problems

Other warnings you should know about:

VOLIBRIS can cause serious side effects, including:

- **Peripheral edema** (swelling of the legs or hands caused by fluid retention) : This may happen within weeks after starting VOLIBRIS. You are at a higher risk of experiencing it if you:
    - take VOLIBRIS with tadalafil
    - take high doses of VOLIBRIS
    - are 65 years of age or older

  Tell your healthcare professional if you experience swelling in your hands or legs while taking VOLIBRIS.

- **Anemia** (decreased number of red blood cells): This may happen within weeks after starting VOLIBRIS. You are at a higher risk of experiencing it if you take VOLIBRIS with tadalafil. Tell your healthcare professional if you experience signs of anemia while taking VOLIBRIS.

- **Liver problems:** Stop taking VOLIBRIS and tell your healthcare professional **right away** if you experience:
    - signs and symptoms of liver problems
    - Worsening of liver disease.

- **Allergic reactions**: VOLIBRIS contains FD&C Red#40 Aluminum Lake, a colouring agent that may cause allergic reactions. If you experience signs of an allergic reaction while taking VOLIBRIS, stop taking it and tell your healthcare professional **right away**.

See the Serious side effects and what to do about them table, below, for more information on these and other serious side effects.

Driving and operating machinery:

- It is not known whether VOLIBRIS affects your ability to drive or use machines.
- You should not drive or use machines until you know how VOLIBRIS affects you.
- If you ever feel sleepy or unwell, do not drive or use machines, and tell your healthcare professional.

Male fertility: During animal studies, reduced fertility was observed in male rats taking ambrisentan, the active ingredient in VOLIBRIS. If you are a man taking VOLIBRIS, it is possible that VOLIBRIS may lower your sperm count. Talk to your healthcare professional if you wish to father a child, or have any questions or concerns about this.

Pregnancy:

- VOLIBRIS should **not** be used during pregnancy. Taking it during pregnancy may cause injury to your baby.

- If you are a woman who could become pregnant, your healthcare professional will ask you to take a pregnancy test before you start taking VOLIBRIS and regularly while you are taking VOLIBRIS.
- Use a highly effective birth control method while taking VOLIBRIS. If you discover that you are pregnant while taking VOLIBRIS, contact your healthcare professional as soon as possible.

Breastfeeding: It is not known whether VOLIBRIS can pass into breastmilk. VOLIBRIS should not be used during breastfeeding.

Children and adolescents (under 18 years of age): VOLIBRIS is not to be used in children and adolescents under 18 years of age.

Laboratory tests and monitoring: Your healthcare professional will do tests, including blood tests, before you start VOLIBRIS and regularly during treatment. These tests will check:

- The amount of red blood cells in your body.
- That your liver is working properly.
- If you are pregnant.

Depending on your test results, your healthcare professional may adjust your dose, stop or discontinue your treatment with VOLIBRIS.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VOLIBRIS:

- Cyclosporine A – used to treat certain autoimmune diseases and to prevent rejection of organ transplants
- Sildenafil, tadalafil – used to treat erectile dysfunction or high blood pressure in the lungs
- Ketoconazole – used to treat fungal skin infections
- Digoxin – used to treat heart conditions

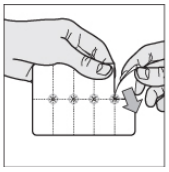
How to take VOLIBRIS:

Take VOLIBRIS:

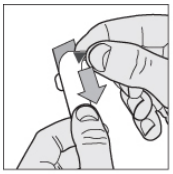
- exactly as your healthcare professional tells you.
- with or without food.

Instructions on how to remove a tablet from the blister packaging

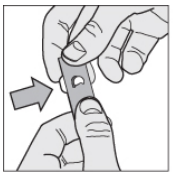
1. Tear along the cutting lines to separate one “pocket” from the strip.



2. Starting at the coloured corner, lift the outer layer and peel it back over the pocket.



3. Gently push one end of the tablet out through the foil layer.



Usual dose:

- The initial dose of VOLIBRIS is 5 mg, once a day. Your healthcare professional may decide to increase your dose to 10 mg, once a day.
- If you take VOLIBRIS with tadalafil, your healthcare professional will usually start your dose at 5 mg once a day and increase it to 10 mg once a day after 8 weeks.
- The maximum recommended daily dose is 10 mg.
- If you take cyclosporine A, do not take more than 5 mg of VOLIBRIS, once per day.

Overdose:

If you think you, or a person you are caring for, have taken too much VOLIBRIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take VOLIBRIS, take the missed dose as soon as you remember, then continue with the next dose at your usual time. Do not take a double dose to make up for the one that you missed.

What are possible side effects from using VOLIBRIS?

These are not all the possible side effects you may have when taking VOLIBRIS. If you experience any side effects not listed here, tell your healthcare professional.

If you take VOLIBRIS with tadalafil, you may be more likely to experience some of these side effects.

Side effects may include:

- Headache
- Stuffy nose
- Sore throat
- Constipation
- Pain in the abdomen
- Problems with sinuses
- Feeling sick
- Vomiting
- Feeling weak or tired
- Skin rash
- Hot flashes
- Ringing in the ears
- Changes in vision, including blurry vision

If any of these affects you severely, tell your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff		✓	
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Flushing (redness of the skin)		✓	
Dyspnea (shortness of breath)		✓	
Dizziness		✓	
Palpitations: fast and/or irregular heart beat		✓	
COMMON			
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.		✓	
RARE			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness, loss of appetite		✓	
UNKNOWN			
Heart failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.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.

Storage:

Store between 15-30°C.

Keep out of reach and sight of children.

If you want more information about VOLIBRIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.gsk.ca, or by calling 1-800-387-7374.

This leaflet was prepared by GlaxoSmithKline Inc.

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