VOLIBRIS

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

VOLIBRIS 5 mg film-coated tablets

VOLIBRIS 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

VOLIBRIS 5 mg: Each tablet contains 5 mg ambrisentan. Contains sugar (95 mg of lactose monohydrate per tablet). Contains lecithin (soya) (E322) and Allura red AC Aluminium Lake (E129).

VOLIBRIS 10 mg: Each tablet contains 10 mg ambrisentan. Contains sugar (90 mg of lactose monohydrate per tablet). Contains lecithin (soya) (E322) and Allura red AC Aluminium Lake (E129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

VOLIBRIS 5 mg: Pale pink, square, convex film-coated tablet debossed with 'GS' on one side and 'K2C' on the other side.

VOLIBRIS 10 mg: Deep pink, oval, convex film-coated tablet debossed with 'GS' on one side and 'KE3' on the other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

VOLIBRIS is indicated for the treatment of pulmonary arterial hypertension (PAH):

- to improve exercise capacity, decrease the symptoms of PAH and delay clinical worsening
- in combination with tadalafil to reduce the risk of clinical failure (a composite of death, PAH hospitalisation, disease progression, and unsatisfactory clinical response), and to increase satisfactory clinical response and exercise ability.

4.2 Posology and method of administration:

Treatment should only be initiated by a medical practitioner experienced in the treatment of PAH.

Posology:

Recommended adult dosage:

VOLIBRIS as a single agent:

VOLIBRIS treatment should be initiated at a dose of 5 mg once daily.

Consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

VOLIBRIS used with tadalafil:

When used in combination with tadalafil, the VOLIBRIS dose should be titrated to 10 mg once daily.

Use with ciclosporin A:

When co-administered with ciclosporin A, the dose of VOLIBRIS should be limited to 5 mg once daily (see section 4.5).

Recommended paediatric and adolescent dosage:

Safety and efficacy of VOLIBRIS have not been established in patients under 18 years of age and therefore, the use of VOLIBRIS in these patients is not recommended.

Dosage instructions in special populations:

Elderly:

No dose adjustment is required in patients aged 65 years and over (see section 5.2).

Renal impairment:

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

Hepatic impairment:

VOLIBRIS has not been studied in subjects with severe hepatic impairment or with clinically significant elevated hepatic transaminases. However, hepatic impairment might be expected to increase exposure (C_{max} and AUC) to ambrisentan, since its main routes of metabolism are glucuronidation and, to a lesser extent, oxidation, with subsequent elimination in the bile. Therefore, VOLIBRIS is not recommended in this patient population (section 4.4 and 5.2).

Method of administration:

VOLIBRIS is for oral use and can be administered with or without food.

4.3 Contraindications:

VOLIBRIS is contraindicated in:

- patients with hypersensitivity to ambrisentan, or to any other ingredients
- pregnancy and lactation (see section 4.6)
- severe hepatic impairment (see section 4.4)
- idiopathic pulmonary fibrosis (IPF) with or without pulmonary hypertension.

4.4 Special warnings and precautions for use:

Hepatic impairment:

Hepatic enzyme elevations have been observed with VOLIBRIS (see section 5.2). Therefore, hepatic function should be evaluated prior to initiation of VOLIBRIS. If aminotransferases (alanine aminotransferase, ALT or aspartate aminotransferase, AST) are greater than 3 times upper limit of normal, initiation of VOLIBRIS is not recommended (see section 4.3).

In addition, monthly monitoring of aminotransferases is recommended. 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 auto-immune hepatitis are known to occur in PAH patients and auto-antibodies are frequently found in idiopathic pulmonary arterial hypertension (IPAH). Cases consistent with auto-immune hepatitis, including possible exacerbation of underlying auto-immune hepatitis, and hepatic injury have been reported with VOLIBRIS therapy.

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 medicines are not known. Management of auto-immune hepatitis in PAH patients should be optimised prior to initiation of VOLIBRIS and during VOLIBRIS therapy. If patients develop signs or symptoms of hepatitis or suffer exacerbation of existing auto-immune hepatitis VOLIBRIS should be discontinued.

Haematological changes:

Reductions in haemoglobin concentrations and haematocrit have been observed with VOLIBRIS and there have been cases where this has resulted in anaemia, sometimes requiring transfusion. In clinical trials, decreases in haemoglobin and haematocrit were observed within the first few weeks of therapy and generally stabilised thereafter.

The mean decrease in haemoglobin from baseline to the end of treatment for patients receiving VOLIBRIS in 12-week placebo-controlled studies was 0,8 g/dl.

Mean decreases from baseline (ranging from 0,9 to 1,2 g/dl) in haemoglobin concentrations persisted for up to 4 years of treatment with VOLIBRIS in the long-term open-label extension of the pivotal Phase 3 clinical studies.

It is recommended that haemoglobin is measured prior to initiation of VOLIBRIS, again at one month and periodically thereafter. Initiation of VOLIBRIS therapy is not recommended for patients with clinically significant anaemia. If a clinically significant decrease in haemoglobin is observed during therapy and other causes have been excluded, discontinuation of VOLIBRIS should be considered.

Fluid retention:

Peripheral oedema has been observed with VOLIBRIS. Peripheral oedema may also be a clinical consequence of PAH.

Most cases of peripheral oedema in clinical studies with VOLIBRIS were mild to moderate in severity.

Post-marketing reports of fluid retention occurring within weeks after starting VOLIBRIS have been received and, in some cases, have required intervention with a diuretic or hospitalisation for fluid management or decompensated heart failure.

If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting VOLIBRIS.

If clinically significant fluid retention develops during therapy with VOLIBRIS, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as VOLIBRIS or underlying heart failure, and the possible need for specific treatment or discontinuation of VOLIBRIS therapy.

Pulmonary veno-occlusive disease:

If patients develop acute pulmonary oedema during initiation of therapy with vasodilating medicines such as VOLIBRIS, the possibility of pulmonary veno-occlusive disease should be considered.

Excipients:

VOLIBRIS contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, the Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance, should not take VOLIBRIS (see section 2).

VOLIBRIS contains the azo colourant Allura red AC Aluminium Lake (E129), which can cause allergic reactions.

VOLIBRIS contains lecithin derived from soya. If a patient is hypersensitive to soya, VOLIBRIS must not be used.

4.5 Interaction with other medicines and other forms of interaction:

Ambrisentan is primarily metabolised by glucuronidation and to a lesser extent by oxidative metabolism, principally by CYP3A and to a lesser extent by CYP2C19.

Ambrisentan did not inhibit or induce phase I or II drug metabolising enzymes at clinically relevant concentrations in non-clinical studies, suggesting a low potential for ambrisentan to alter the profile of medicines metabolised by these pathways.

The potential for ambrisentan to induce CYP3A4 activity was explored in healthy volunteers, with results suggesting a lack of inductive effect of ambrisentan on the CYP3A4 isoenzyme.

- Ciclosporin: Steady-state co-administration of VOLIBRIS and ciclosporin A (an inhibitor of P-glycoprotein [P-gp] and organic anion transporting polypeptide [OATP]) resulted in a 2-fold increase in ambrisentan exposure in healthy volunteers. Therefore the dose of VOLIBRIS should be limited to 5 mg once daily when co-administered with ciclosporin A (see section 4.2). No clinically relevant effect of ambrisentan on ciclosporin A exposure was observed.
- Ketoconazole: Steady state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to VOLIBRIS.
- Rifampicin: Co-administration of rifampin (an inhibitor of OATP, a strong inducer of CYP3A and 2C19, and inducer of P-gp and uridine-diphospho-glucuronosyltransferases [UGTs]) was associated with a transient (approximately 2-fold) increase in ambrisentan exposure following initial doses in healthy volunteers. However, by day 7, steady state administration of rifampin had no clinically relevant effect on ambrisentan exposure. No dose adjustment of VOLIBRIS is required when co-administered with rifampin.
- Omeprazole: In PAH clinical studies, co-administration of VOLIBRIS and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan.
- Sildenafil: Co-administration of VOLIBRIS with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP3A4) in healthy volunteers, did not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or ambrisentan.
- Oral contraceptives: In a clinical study in healthy subjects, steady state dosing with VOLIBRIS 10 mg 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.

- Warfarin: Ambrisentan had no effects on the steady state pharmacokinetics and anti-coagulant activity of warfarin in a healthy volunteer study. Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in clinical studies of PAH patients, VOLIBRIS had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT) and international normalised ratio (INR).
- Digoxin: Steady-state administration of VOLIBRIS in healthy volunteers had no clinically relevant effects on the single-dose pharmacokinetics of digoxin, a substrate for P-gp.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

VOLIBRIS is contraindicated in pregnancy (see section 4.3).

Animal studies in rats and rabbits have shown that ambrisentan is teratogenic, which is a class effect of ERAs (endothelin receptor antagonists).

VOLIBRIS is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see section 4.3). Pregnancy must therefore be excluded before the initiation of treatment with VOLIBRIS and prevented thereafter by reliable methods of contraception. Pregnancy tests during treatment with VOLIBRIS are recommended as clinically indicated. Women of childbearing potential should be advised to contact their physician immediately if they become pregnant or suspect they may be pregnant.

Lactation:

It is not known whether ambrisentan is excreted in human milk. Mothers on VOLIBRIS should not breastfeed their infants (see section 4.3).

Fertility:

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of VOLIBRIS. The effect on male human fertility is not known.

4.7 Effects on ability to drive and use machines:

There have been no studies to investigate the effect of VOLIBRIS on driving performance or the ability to operate machinery. A detrimental effect on such activities is not anticipated from the known safety profile.

4.8 Undesirable effects:

Experience from pivotal clinical studies:

The safety of VOLIBRIS was evaluated during clinical trials in more than 480 patients with PAH. Adverse drug reactions (ADRs) from clinical trial data are listed below by system organ class and frequency.

Frequencies are placebo corrected and defined as common (≥ 1/100, < 1/10) and uncommon (≥ 1/1 000, < 1/100). Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice.

Blood and lymphatic system disorders:

Common: anaemia (decreases in haemoglobin and/or haematocrit)

Immune system disorders:

Uncommon: hypersensitivity (e.g., angioedema, rash)

Nervous system disorders:

Common: headache

Cardiac disorders:

Common: palpitations

Vascular disorders:

Common: flushing

Respiratory, thoracic and mediastinal disorders:

Common: nasal congestion (the incidence was dose-related), sinusitis, nasopharyngitis

Gastrointestinal disorders:

Common: abdominal pain, constipation

General disorders and administration site disorders:

Common: fluid retention, peripheral oedema.

Experience from long-term clinical studies:

The long-term safety (>3 months) of VOLIBRIS was evaluated in more than 500 patients with PAH. Adverse reactions from non-placebo controlled clinical trial data are listed below. Frequencies are defined as very common (≥1/10) and common (≥1/100, <1/10).

Blood and lymphatic system disorders:

Very common: anaemia (decreases in haemoglobin and/or haematocrit)

Immune system disorders:

Common: hypersensitivity (including medicine hypersensitivity)

Nervous system disorders:

Very common: dizziness, headache

Cardiac disorders:

Very common: palpitations

Vascular disorders:

Very common: flushing (including hot flush)

Respiratory, thoracic and mediastinal disorders:

Very common: nasal congestion, sinusitis, nasopharyngitis, dyspnoea (including dyspnoea exertional)

Gastrointestinal disorders:

Very common: abdominal pain (including upper and lower), nausea

Common: vomiting, constipation

Skin and subcutaneous tissue disorders:

Common: rash (rash erythematous, rash generalised, rash macular, rash popular, rash pruritic)

General disorders and administration site conditions:

Very common: fatigue, fluid retention (including fluid overload), peripheral oedema

Common: asthenia

Eye disorders:

Common: visual impairment (including vision blurred).

Experience from a clinical study with VOLIBRIS used in combination with tadalafil:

The 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). The adverse reactions observed were generally consistent with the safety profile of VOLIBRIS used alone. The following adverse reactions were seen more frequently in the combination of VOLIBRIS with tadalafil than with either medicine alone:

Gastrointestinal disorders:

Very common: vomiting.

In addition, the following adverse reaction was observed:

Ear and labyrinth disorders:

Common: tinnitus.

Post-marketing experience:

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

Blood and lymphatic system disorders: anaemia requiring transfusion

Cardiac disorders: heart failure (associated with fluid retention)

Vascular disorders: hypotension

Hepatobiliary disorders: hepatic transaminases increased

hepatic injury, auto-immune hepatitis (see section 4.4).

Cases of auto-immune hepatitis, including cases of exacerbation of auto-immune hepatitis, and hepatic injury of unclear aetiology have been reported during VOLIBRIS therapy.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of VOLIBRIS is important. It allows continued monitoring of the benefit/risk balance of VOLIBRIS. Healthcare providers are asked to report any suspected adverse reactions to: SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms and signs: 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 its mechanism of action, an overdose of VOLIBRIS also could potentially result in hypotension.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A 7.1.3 Other hypotensives.

Ambrisentan is an orally active, selective antagonist, endothelin receptor A (ET_A) (ERA). Endothelin which plays a significant role in the pathophysiology of pulmonary arterial hypertension (PAH).

- Ambrisentan blocks the ET_A receptor subtype, localised predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.
- The selectivity of ambrisentan for the ET_A over the ET_B receptor is expected to retain ET_B receptor mediated production of the vasodilators nitric oxide and prostacyclin.

Invasive haemodynamic parameters were assessed in patients with PAH at baseline and after 12 weeks (n=29) in a Phase 2 study. Treatment with ambrisentan resulted in a statistically significant increase in mean cardiac index and a decrease in mean pulmonary artery pressure and mean pulmonary vascular resistance. In patients with PAH, reductions in B-type natriuretic peptide (BNP)

have been shown to parallel improvements in haemodynamics and 6-minute walk distance (6MWD). Combined analysis of results from two Phase 3 placebo-controlled studies, demonstrated that plasma concentrations of BNP decreased in patients who received ambrisentan for 12 weeks. The mean plasma concentration of BNP increased by 11 % in the placebo group, and decreased by 29 % in the 2,5 mg, 30 % in the 5 mg, and 45 % in the 10 mg groups ($p < 0,001$ for each dose group).

In patients with PAH who received first-line combination therapy with VOLIBRIS and tadalafil, a greater decrease from baseline in N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) relative to pooled monotherapy was observed (geometric least-squares mean percent decreases of 67 % versus 50 %, respectively; $p<0,0001$). Similar results were observed for the comparisons of combination therapy versus VOLIBRIS monotherapy group (56 % decrease; $p=0,0111$) and tadalafil monotherapy group (44 % decrease; $p<0,0001$). The decrease in NT-pro-BNP was observed early (Week 4) and was sustained through Week 24.

5.2 Pharmacokinetic properties:

Absorption:

In patients with PAH, the maximum plasma concentrations (C_{max}) typically occur around 2 hours after oral administration. In healthy volunteers, under both fasted and fed conditions, ambrisentan exposure does not change significantly with food intake and therefore ambrisentan can be taken with or without food. 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.

Distribution:

The plasma protein binding of ambrisentan was, 98,8 %. Ambrisentan is primarily bound to albumin (96,5 %).

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 glucuronidated by several UGT enzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide.

Ambrisentan also undergoes oxidative metabolism, mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19, to form 4-hydroxymethyl ambrisentan, which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide.

In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4 % relative to parent ambrisentan AUC.

Furthermore, the binding affinity of 4-hydroxymethyl ambrisentan for the human ET_A receptor is more than 100-fold less than ambrisentan. Therefore, 4-hydroxymethyl ambrisentan is not expected to contribute to pharmacological activity of ambrisentan.

In vitro studies using rat and human hepatocyte cultures have demonstrated that ambrisentan is a possible substrate for the hepatic influx transporter OATP and for the efflux transporter P-gp, but not for the hepatic influx or efflux sodium-taurocholate co-transporter protein (NTCP) or bile salt export pump, respectively.

The *in vitro* data suggest, 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.

Elimination:

Ambrisentan and its metabolites are eliminated primarily in the bile. In the faeces, 40 % of the dose is recovered as parent ambrisentan and 21 % as the 4-hydroxymethyl ambrisentan. Approximately 22 % of the administered dose is recovered in the urine following oral administration with 3,3 % being unchanged ambrisentan and the remainder as glucuronide metabolites. Steady-state plasma elimination half-life ranged from 13,6 to 16,5 hours in healthy volunteers and from 12,9 to 17,9 hours in patients with PAH.

Pharmacokinetics in special populations:

The pharmacokinetics of ambrisentan are not influenced by gender or age.

Hepatic impairment:

The pharmacokinetics of ambrisentan have not been studied in subjects with severe hepatic impairment or with clinically significant elevated hepatic transaminases. However, hepatic impairment might be expected to increase exposure (C_{max} and AUC) to ambrisentan, since its main routes of metabolism are glucuronidation and, to a lesser extent by oxidation, with subsequent elimination in the bile. The magnitude of this effect and any impact on safety and efficacy, have not been evaluated. Therefore, ambrisentan is not recommended in this patient population.

Renal impairment:

The pharmacokinetics of ambrisentan have not been studied in subjects with renal impairment. However, renal metabolism and excretion of ambrisentan is minimal, so renal impairment is unlikely to significantly increase exposure to ambrisentan.

5.3 Preclinical safety data:

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Tablet core:

Lactose monohydrate

Microcrystalline cellulose

Croscarmellose sodium

Magnesium stearate.

Film coat:

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Macrogol/polyethylene glycol 3350

Lecithin (soya)

Allura Red AC Aluminium Lake (E129).

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

60 months.

6.4 Special precautions for storage:

Store at or below 30 °C.

Keep out of reach of children.

6.5 Nature and contents of container:

VOLIBRIS tablets are packed into opaque PVC/PVdC and aluminium foil blister strips containing 10 tablets each. Three blister strips are packed into a carton giving a 30 tablet pack.

6.6 Special precautions for disposal and other handling:

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS:

VOLIBRIS 5 mg: 45/7.1.3/0106

VOLIBRIS 10 mg: 45/7.1.3/0107

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

21 April 2016

10. DATE OF REVISION OF THE TEXT:

22 November 2023

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