VOLIBRIS®

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

VOLIBRIS® 5 mg film-coated tablets

VOLIBRIS® 10 mg film-coated tablets

COMPOSITION:

Each tablet contains 5 mg or 10 mg ambrisentan.

VOLIBRIS 5 mg and 10 mg tablets contain sugar (95 mg and 90 mg lactose per tablet, respectively) and the colourant, Allura Red AC Aluminium Lake.

Excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), macrogol/polyethylene glycol 3350, lecithin (soya) and Allura Red AC Aluminium Lake (E129).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Other hypotensives

PHARMACOLOGICAL CLASSIFICATION:

Pharmacodynamic properties:

Ambrisentan is an orally active, propanoic acid-class, endothelin receptor A (ET_A) selective, endothelin receptor antagonist (ERA). Endothelin 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 significant increase in mean cardiac index (+0,3 ℓ/min/m^2; 95 % CI: 0,15 to 0,51; p < 0,001), and a decrease in mean pulmonary artery pressure (-5,2 mmHg; 95 % CI: -7,6 to -2,9; p < 0,001), and mean pulmonary vascular resistance (-2,8 mmHg/ℓ/min; 95 % CI: -3,8 to -1,8; p < 0,001) for the combined ambrisentan group.

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 geometric 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**).**

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 *in vitro* plasma protein binding of ambrisentan was, on average, 98,8 % and independent of concentration over the range of 0,2-20 µg/ml. Ambrisentan is primarily bound to albumin (96,5 %) and to a lesser extent to α1-acid glycoprotein.

The distribution of ambrisentan into red blood cells is low, with a mean blood:plasma ratio of 0,57 and 0,61 in males and females, respectively.

Metabolism:

Ambrisentan is 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 (BSEP), respectively.

In vitro data have shown that at therapeutic concentrations, ambrisentan does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4. Additional *in vitro* studies showed that ambrisentan does not inhibit sodium-taurocholate co-transporter (NTCP), organic anion export pump (OATP) or bile salt export pump (BSEP).

Elimination:

Ambrisentan and its metabolites are eliminated primarily in the bile following hepatic and/or extra-hepatic metabolism. 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:

Age and gender:

Based on the results of a population pharmacokinetic analysis in healthy volunteers and patients with PAH, the pharmacokinetics of ambrisentan were not significantly influenced by gender or age (see DOSAGE AND DIRECTIONS FOR USE).

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 would 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.

Based on a final population pharmacokinetic model developed based on pharmacokinetic data from clinical trial subjects receiving ambrisentan, there was a significant relationship between ambrisentan CL/F and hepatic function as assessed by total bilirubin. However, the magnitudes of change in total bilirubin were relatively small.

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.

Based on a final population pharmacokinetic model developed based on pharmacokinetic data from clinical trial subjects receiving VOLIBRIS, there was a significant relationship between

ambrisentan CL/F and renal function as assessed by creatinine clearance (Cl_{cr}). However, the magnitudes of change in clearance of ambrisentan were relatively modest and are unlikely to be of clinical relevance.

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.

CONTRA-INDICATIONS:

VOLIBRIS is contra-indicated in patients with hypersensitivity to ambrisentan or any other ingredients.

VOLIBRIS is contra-indicated in pregnancy and lactation (see PREGNANCY AND LACTATION).

VOLIBRIS is contra-indicated in severe hepatic impairment (see WARNINGS AND SPECIAL PRECAUTIONS).

VOLIBRIS is contra-indicated in idiopathic pulmonary fibrosis (IPF) with or without pulmonary hypertension.

WARNINGS AND SPECIAL PRECAUTIONS:

Hepatic impairment:

Hepatic enzyme elevations have been observed with VOLIBRIS (see Pharmacodynamic properties). 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 CONTRA-INDICATIONS).

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 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 agents 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, although it occurred with greater frequency and severity in elderly patients.

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 agents such as VOLIBRIS, the possibility of pulmonary veno-occlusive disease should be considered.

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.

Contains lactose: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption or fructose intolerance, should not take this medicine (see COMPOSITION). Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:

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 does 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.

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 DOSAGE AND DIRECTIONS FOR USE). No clinically relevant effect of ambrisentan on ciclosporin A exposure was observed.

Steady state administration of ketoconazole (a strong inhibitor of CYP3A4) did not result in a clinically significant increase in exposure to VOLIBRIS.

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.

In PAH clinical studies, co-administration of VOLIBRIS and omeprazole (an inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan.

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.

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 oestradiol 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.

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).

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.

PREGNANCY AND LACTATION:

Pregnancy:

VOLIBRIS is contra-indicated in pregnancy (see CONTRA-INDICATIONS).

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

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 CONTRA-INDICATIONS). 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 child bearing potential should be advised to contact their physician immediately if they become pregnant.

Lactation:

It is not known whether ambrisentan is excreted in human milk. VOLIBRIS is not recommended for use by breastfeeding mothers (see CONTRA-INDICATIONS).

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.

DOSAGE AND DIRECTIONS FOR USE:

VOLIBRIS is for oral use and can be administered with or without food. Treatment should only be initiated by a medical practitioner experienced in the treatment of PAH.

Recommended adult dosage:

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.

Use with ciclosporin A:

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

Recommended paediatric and adolescent dosage:

There are no data available on the use of VOLIBRIS 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 Pharmacokinetics in special populations).

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 would 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 (see WARNINGS AND SPECIAL PRECAUTIONS and Pharmacokinetics in special populations).

SIDE EFFECTS:

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 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.

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)

Respiratory, thoracic and mediastinal disorders: dyspnoea

Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting VOLIBRIS therapy.

Gastrointestinal disorders: nausea and vomiting

Hepatobiliary disorders:

Common: hepatic transaminases increased

Unknown: hepatic injury, auto-immune hepatitis (see WARNINGS AND SPECIAL PRECAUTIONS)

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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.

IDENTIFICATION:

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.

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

VOLIBRIS 5 mg: 45/7.1.3/0106

VOLIBRIS 10 mg: 45/7.1.3/0107

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

21 April 2016

CCDS-7.0+IPF

VOLIBRIS is a registered trademark of Gilead Sciences, Inc. used under license by the **GSK** group of companies.

SKEDULERINGSTATUS:

S4

EIENDOMSNAAM EN DOSEERVORM:

VOLIBRIS® 5 mg filmbedekte tablette

VOLIBRIS® 10 mg filmbedekte tablette

SAMESTELLING:

Elke tablet bevat 5 mg of 10 mg ambrisentaan.

VOLIBRIS 5 mg en 10 mg tablette bevat suiker (onderskeidelik 95 mg en 90 mg laktose per tablet), en die kleurstof, Allure Red AC-aluminiumlak.

Hulpstowwe: laktosemonohidraat, mikrokristallyne sellulose, natriumkruiskarmellose, magnesiumstearaat, polivinielalkohol, talk, titaandioksied (E171), makrogol/poliëtileenglikol 3350, lesitien (soja) en Allure Red AC-aluminiumlak (E129).

FARMAKOLOGIESE KLASSIFIKASIE:

A 7.1.3 Ander hipotensiewe middels

FARMAKOLOGIESE KLASSIFIKASIE:

Farmakodinamiese eienskappe:

Ambrisentaan is ’n oraal aktiewe endotelienreseptorantagonis (ERA) van die propanoësuurklas wat selektief vir die endotelienreseptor A (ET_A) is. Endotelien speel ’n belangrike rol in die patofisiologie van pulmonêre arteriële hipertensie (PAH).

- Ambrisentaan blokkeer die ET_A-reseptorsubtipe wat oorwegend op die vaskulêre gladdespierselle en hartmiosiete voorkom. Dit verhoed aktivering van tweedeboodskapperstelsels bemiddel deur endotelien wat tot vasokonstriksie en proliferasie van gladdespierselle lei.

- Dit word verwag dat die selektiwiteit van ambrisentaan vir die ET_A- bo die ET_B-reseptore na verwagting produksie van die vasodilatore stikstofoksied en prostasiklien bemiddel deur die ET_B-reseptor sal behou.

Indringende hemodinamiese parameters van pasiënte met PAH (n=29) is in 'n Fase 2-studie by basislyn en na 12 weke beoordeel. Behandeling met ambrisentaan het tot 'n beduidende toename in die gemiddelde hartindeks gelei (+0,3 ℓ/min/m^2; 95 % BI: 0,15 tot 0,51; $p < 0,001$), en 'n afname in gemiddelde druk in die pulmonêre arterie (-5,2 mmHg, 95 % BI: -7,6 tot -2,9; $p < 0,001$), en gemiddelde pulmonêre vaskulêre weerstand (-2,8 mmHg/ℓ/min; 95 % BI: -3,8 tot -1,8; $p < 0,001$) vir die gekombineerde ambrisentaangroep.

In pasiënte met PAH is getoon dat afnames in B-tipe natriuretiese peptied (BNP) gelyktydig verbeterings in hemodinamika en 6-minute loopafstand (6MWD) gee. Ontleding van die gekombineerde resultate van twee Fase 3 plasebogekontroleerde studies het getoon dat plasmakonsentrasies van BNP gedaal het in pasiënte wat ambrisentaan vir 12 weke ontvang het. Die geometriese gemiddelde plasmakonsentrasie van BNP was 11 % hoër in die plasebogroep, en het gedaal met 29 % in die groep met 2,5 mg, 30 % in die groep met 5 mg en 45 % in die groep met 10 mg ($p < 0,001$ vir elke dosisgroep).

Farmakokinetiese eienskappe:

Absorpsie:

In pasiënte met PAH word die maksimum plasmakonsentrasies (C_{maks}) tipies ongeveer 2 uur na orale toediening bereik. In gesonde vrywilligers, onder beide vastende en gevoede toestande, word blootstelling aan ambrisentaan nie beduidend deur voedsel beïnvloed nie en dus kan ambrisentaan met of sonder kos geneem word. C_{maks} en area onder die plasmakonsentrasie-tydkurwe (AOK) verhoog in die terapeutiese doseerreeks volgens die dosis.

Gelykvlakke word oor die algemeen na 4 dae van herhaalde dosering bereik.

Verspreiding:

In vitro was gemiddeld 98,8 % van die ambrisentaan aan plasmaproteïene gebind en dit was oor 'n gebied van 0,2-20 µg/ml onafhanklik van die konsentrasie. Ambrisentaan is hoofsaaklik aan albumien (96,5 %) gebind en tot 'n mindere mate aan α1-suurglikoproteïen.
Die verspreiding van ambrisentaan in rooibloedselle is laag, met 'n gemiddelde verhouding van bloed tot plasma van 0,57 en 0,61 in mans en in vroue, onderskeidelik.

Metabolisme:

Ambrisentaan word deur verskeie UGT-ensieme (UGT1A9S, UGT2B7S en UGT1A3S) geglukuronideer om ambrisentaan-glukuronied te vorm.
Ambrisentaan ondergaan ook oksidatiewe metabolisme, hoofsaaklik deur CYP3A4 en tot 'n mindere mate deur CYP3A5 en CYP2C19, om 4-hidroksimetielambrisentaan te vorm, wat verder na 4-hidroksimetielambrisentaanglukuronied geglukuronideer word.
In plasma bedra die AOK van 4-hidroksimetielambrisentaan ongeveer 4 % van die AOK van moederverbinding ambrisentaan.
Verder is die bindende affiniteit van 4-hidroksimetielambrisentaan vir die menslike ET_A-reseptor meer as 100 keer laer as dié van ambrisentaan. Daarom word nie verwag dat 4-hidroksimetielambrisentaan tot farmakologiese aktiwiteit van ambrisentaan sal bydra nie.
In vitro-studies met behulp van rot- en menslike hepatosietkulture het getoon dat ambrisentaan 'n moontlike substraat vir die hepatiese instromingstransporter OATP en vir die uitstromingstransporter P-gp is, maar nie vir die hepatiese instromings- of uitstromingsbane, naamlik natrium-taurocholaat kotransporterproteïen (NTCP) of galsoutuitvoerpomp (BSEP), onderskeidelik nie.
In vitro-data het getoon dat ambrisentaan by terapeutiese konsentrasies nie UGT1A1, UGT1A6, UGT1A9, UGT2B7 of sitochroom P450-ensieme 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 rem nie. Verdere *in vitro*-studies het getoon dat ambrisentaan nie die natrium-taurocholaat kotransporter (NTCP), organiese anioonuitvoerpomp (OATP) of galsoutuitvoerpomp (BSEP) rem nie.

Uitskeiding:

Ambrisentaan en sy metaboliete word na hepatiese en/of ekstra-hepatiese metabolisme primêr in die gal uitgeskei. In die feses word 40 % van die dosis as die moederverbinding ambrisentaan en 21 % as 4-hidroksimetielambrisentaan herwin. Ongeveer 22 % van die toegediende dosis word na orale toediening in die urien herwin met 3,3 % as onveranderde ambrisentaan en die res as glukuroniedmetaboliete. Die eliminasie halfleeftyd in plasma by gelykvlakke het gewissel van 13,6 tot 16,5 uur in gesonde vrywilligers en van 12,9 tot 17,9 uur in pasiënte met PAH.

Farmakokinetika in spesiale populasies:

Ouderdom en geslag:

Op grond van die resultate van ’n farmakokinetiese ontleding van ’n populasie gesonde vrywilligers en pasiënte met PAH is gevind dat die farmakokinetika van ambrisentaan nie beduidend deur geslag of ouderdom beïnvloed word nie (sien DOSIS EN GEBRUIKSAANWYSINGS).

Swak lewerfunksie:

Die farmakokinetika van ambrisentaan is nie in proefpersone met erge swak lewerfunksie of met klinies betekenisvolle hoë vlakke hepatiese transaminases bestudeer nie. Tog sou verwag word dat swak lewerfunksie blootstelling (C_{maks} en AOK) aan ambrisentaan verhoog, omdat die hoofroete van metabolisme glukuronidering is en tot ’n mindere mate oksidasie, met die daaropvolgende uitskeiding in die gal. Die grootte van hierdie effek en impak op veiligheid en doeltreffendheid is nie bepaal nie. Ambrisentaan word gevolglik nie vir hierdie pasient-populasie aanbeveel nie.

Gebaseer op ’n finale ontwikkelde farmakokinetiese model van farmakokinetiese data van ’n populasie proefpersone wat ambrisentaan in kliniese proewe ontvang het, was daar ’n beduidende verband tussen die CL/F van ambrisentaan en lewerfunksie soos beoordeel uit die totale konsentrasie bilirubien. Die mate van verandering in totale konsentrasie bilirubien was egter relatief klein.

Swak nierfunksie:

Die farmakokinetika van ambrisentaan is nie in proefpersone met swak nierfunksie bestudeer nie. Renale metabolisme en uitskeiding van ambrisentaan is egter minimaal sodat dit onwaarskynlik is dat swak nierfunksie blootstelling aan ambrisentaan aansienlik sal verhoog.

Gebaseer op 'n finale ontwikkelde farmakokinetiese model van farmakokinetiese data van 'n populasie proefpersone wat VOLIBRIS in kliniese proewe ontvang het, was daar 'n beduidende verband tussen ambrisentaan CL/F en nierfunksie soos beoordeel uit kreatinienopruiming (Cl_{cr}). Die mate van verandering in opruiming van ambrisentaan was relatief klein en dit is onwaarskynlik dat dit van kliniese betekenis is.

INDIKASIES:

VOLIBRIS is aangedui vir die behandeling van pulmonêre arteriële hipertensie (PAH), om oefeningskapasiteit te verbeter, om die simptome van PAH te verminder en om kliniese agteruitgang te vertraag.

KONTRA-INDIKASIES:

VOLIBRIS is teenaangedui vir pasiënte met hipersensitiwiteit teenoor ambrisentaan of enige van die ander bestanddele.

VOLIBRIS is teenaangedui tydens swangerskap en laktasie (kyk SWANGERSKAP EN LAKTASIE).

VOLIBRIS is teenaangedui vir pasiënte met erge swak lewerfunksie (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).

VOLIBRIS is teenaangedui vir pasiënte met idiopatiese pulmonêre fibrose (IPF) met of sonder pulmonêre hipertensie.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:

Swak lewerfunksie:

Stygings in die vlakke van lewerensieme is met VOLIBRIS waargeneem (kyk Farmakodinamiese eienskappe). Daarom moet lewerfunksie voor aanvang van VOLIBRIS beoordeel word. As die vlakke van aminotransferases (alanienaminotransferase, ALT of aspartaataminotransferase, AST) meer as 3 keer die boonste grens van normaal is, word aanvang van behandeling met VOLIBRIS nie aanbeveel nie (kyk KONTRA-INDIKASIES).

Daarbenewens word maandelikse monitering van aminotransferases aanbeveel. As pasiënte klinies betekenisvolle hoë vlakke van aminotransferases ontwikkel of as hoë vlakke aminotransferase met tekens of simptome van lewerskade (bv. geelsug) gepaardgaan, moet VOLIBRIS gestaak word.

Hervatting van VOLIBRIS vir pasiënte sonder kliniese simptome van lewerskade of geelsug kan na opklaring van abnormaliteite in lewerensieme oorweeg word.

Dit is bekend dat lewerskade en outo-immuun hepatitis in pasiënte met PAH voorkom en outo-teenliggame word dikwels met IPAH gevind. Gevalle ooreenstemmend aan outo-immuun hepatitis, waaronder moontlike verergering van onderliggende outo-immuun hepatitis en lewerskade, is met behandeling met VOLIBRIS aangemeld.

Daarom moet pasiënte vir tekens van lewerskade gemonitor word en VOLIBRIS moet versigtig alleen gebruik word of saam met ander medisinale produkte wat bekend is daarvoor dat hulle met lewerskade gepaardgaan omdat die additiewe effekte van VOLIBRIS saam met hierdie middels nie bekend is nie. Bestuur van outo-immuun hepatitis in pasiënte met PAH moet voor aanvang van behandeling met VOLIBRIS en gedurende behandeling met VOLIBRIS ge-optimiseer word. As pasiënte tekens of simptome van hepatitis ontwikkel, of verergering van bestaande outo-immuun hepatitis ervaar, moet VOLIBRIS gestaak word.

Hematologiese veranderings:

Daling in die konsentrasies van hemoglobien en hematokrit is met VOLIBRIS waargeneem, en daar was gevalle waar dit tot bloedarmoede gelei het, waarvoor bloedoortapping soms nodig was. In kliniese proewe is ’n daling in hemoglobienvlakke en hematokrit in die eerste paar weke van behandeling waargeneem en oor die algemeen het dit daarna gestabiliseer.

Die gemiddelde daling in hemoglobienvlakke vanaf basislyn tot aan die einde van behandeling vir pasiënte wat VOLIBRIS in plasebogekontroleerde studies oor 12 weke gekry het, was 0,8 g/dl. Gemiddelde dalings in hemoglobienkonsentrasie vanaf die basislyn (wat gewissel het van 0,9 tot 1,2 g/dl) het vir tot 4 jaar van die behandeling met VOLIBRIS voortgeduur in die oop voortsetting van die deurslaggewende Fase 3 kliniese studies oor die lang termyn.
Dit word aanbeveel dat hemoglobienvlakke voor aanvang van VOLIBRIS gemeet word en weer na een maand en van tyd tot tyd daarna. Begin van behandeling met VOLIBRIS word nie vir pasiënte met klinies betekenisvolle anemie aanbeveel nie. As 'n klinies beduidende daling in hemoglobienvlakke tydens behandeling waargeneem word en ander oorsake is uitgesluit, moet staking van VOLIBRIS oorweeg word.

Vloeistofretensie:

Perifere edeem is met VOLIBRIS waargeneem. Perifere edeem kan ook 'n kliniese effek van PAH wees.
Die meeste gevalle van perifere edeem in kliniese studies met VOLIBRIS was lig tot matig in graad, hoewel dit met 'n groter frekwensie en graad in bejaarde pasiënte voorgekom het.
Daar is na bemarking verslae ontvang van vloeistofretensie wat binne weke ná die aanvang van VOLIBRIS voorgekom het en, in sommige gevalle, was intervensie met 'n diuretikum of hospitalisasie vir vloeistofbestuur of gedekompenseerde hartversaking nodig. As pasiënte bestaande vloeistofoorlading het, moet dit voor die begin van behandeling met VOLIBRIS soos klinies toepaslik bestuur word.
Indien klinies beduidende vloeistofretensie, met of sonder gepaardgaande gewigstoename, tydens behandeling met VOLIBRIS ontwikkel, moet verdere evaluering gedoen word om die oorsaak, soos VOLIBRIS of onderliggende hartversaking, en die moontlike behoefte aan spesifieke behandeling of staking van behandeling met VOLIBRIS te bepaal.

Pulmonêre veno-okklusiewe siekte:

As pasiënte akute pulmonêre edeem tydens aanvang van behandeling met vasodilatore soos VOLIBRIS ontwikkel, moet die moontlikheid van pulmonêre veneuse-okklusie oorweeg word.

Vermoë om te bestuur en masjinerie te gebruik: Daar was geen studies om die effek van VOLIBRIS te ondersoek op die vermoë om motor te bestuur of om masjinerie te hanteer nie. Uit die bekende veiligheidsprofiel word geen nadelige effek op sulke aktiwiteite verwag nie.

Bevat laktose: Pasiënte met die skaars oorerflike probleem van onverdraagbaarheid van galaktose bv. galaktosemie, die Lapp-laktasetekort of wanabsorpsie van glukose/galaktose of onverdraagbaarheid van fruktose, moet nie hierdie medisyne gebruik nie (kyk SAMESTELLING). Laktose mag ’n effek hê op die kontrole van glisemie in pasiënte met diabetes mellitus.

INTERAKSIES:

Ambrisentaan word hoofsaaklik deur glukuronidering en tot ’n mindere mate deur oksidatiewe metabolisme gemetaboliseer, hoofsaaklik deur CYP3A en tot ’n mindere mate deur CYP2C19. Teen klinies relevante konsentrasies het ambrisentaan in nie-kliniese studies nie fase I of II-geneesmiddelmetaboliserende ensieme gerem of geïnduseer nie, wat dui op ’n lae potensiaal vir ambrisentaan om die profiel te verander van medisyne wat deur hierdie roetes gemetaboliseer word.

Die potensiaal vir ambrisentaan om aktiwiteit van CYP3A4 te induseer is in gesonde vrywilligers ondersoek, en die resultate toon geen induserende effek van ambrisentaan op die CYP3A4-isoënsiem nie.

Gelyktydige toediening van VOLIBRIS en siklosporien A (’n remmer van P-glikoproteïen [P-gp] en organiese-anioontransportpolipeptied [OATP]) by gelykvlakke aan gesonde vrywilligers het gelei tot ’n 2-voudige toename in blootstelling aan ambrisentaan, en daarom moet die dosis van VOLIBRIS tot 5 mg een keer per dag beperk word as dit saam met siklosporien A toegedien word (kyk DOSIS EN GEBRUIKSAANWYSINGS). Geen klinies relevante effek van ambrisentaan op blootstelling aan siklosporien A is waargeneem nie.

Toediening van ketokonasool (’n sterk remmer van CYP3A4) by gelykvlakke het nie tot ’n klinies beduidende toename in blootstelling aan VOLIBRIS gelei nie.

Gelyktydige toediening van rifampien (’n remmer van OATP, ’n sterk induseerder van CYP3A en 2C19 en induseerder van P-gp en uridiendifosfoglukuronosiel-transferases [UGTs]) aan gesonde vrywilligers het na die aanvangsdosisse met ’n verbygaande toename (ongeveer 2-voudig) in blootstelling aan ambrisentaan gepaardgegaan. Teen dag 7 het toediening van rifampien by gelykvlakke egter geen klinies relevante effek op blootstelling aan ambrisentaan gehad nie. Geen aanpassing in die dosis van VOLIBRIS is nodig as dit saam met rifampien gebruik word nie.

In kliniese studies van PAH het gelyktydige toediening van VOLIBRIS en omeprasool (’n remmer van CYP2C19) nie ’n beduidende invloed op die farmakokinetika van ambrisentaan nie.

Gelyktydige toediening van VOLIBRIS saam met ’n fosfodiësteraseremmer, óf sildenafiel óf tadalafiel (albei substrate van CYP3A4), aan gesonde vrywilligers het nie ’n beduidende invloed op die farmakokinetika van die fosfodiësteraseremmer of ambrisentaan nie.

In ’n kliniese studie met gesonde proefpersone het dosering met VOLIBRIS 10 mg by gelykvlakke nie ’n beduidende invloed op die farmakokinetika van enkeldosisse van etinielestradiol en noretindroon as komponente van gekombineerde orale voorbehoedmiddels nie. Op grond van hierdie farmakokinetiese studie word nie verwag dat ambrisentaan blootstelling aan estrogeen- of progestogeen gebaseerde voorbehoedmiddels beduidend sal beïnvloed nie.

In ’n studie met gesonde vrywilligers het ambrisentaan geen effek gehad op die farmakokinetika en antikoagulantaktiwiteit van warfarien by gelykvlakke nie. Warfarien het ook geen klinies betekenisvolle effek op die farmakokinetika van ambrisentaan nie. Verder het VOLIBRIS in kliniese studies met PAH-pasiënte geen algehele effek op die weeklikse dosis van warfarien-tipe antikoagulante, protrombientyd (PT) en internasionale genormaliseerde verhouding (INR) gehad nie.

Toediening van VOLIBRIS by gelykvlakke aan gesonde vrywilligers het geen klinies relevante uitwerking op die farmakokinetika van enkele dosisse van digoksien, ’n substraat vir P-gp, nie.

SWANGERSKAP EN LAKTASIE:

Swangerskap:

VOLIBRIS is teenaangedui tydens swangerskap (kyk KONTRA-INDIKASIES).

Dierstudies met rotte en konyne het getoon dat ambrisentaan teratogenies is, wat 'n effek van die klas ERA's is.

VOLIBRIS sal heel waarskynlik ernstige geboortedefekte veroorsaak indien swanger vroue dit gebruik, omdat hierdie effek konsekwent gesien is toe dit aan diere gegee is (kyk KONTRA-INDIKASIES). Swangerskap moet dus voor die aanvang van behandeling met VOLIBRIS uitgesluit word en daarna met betroubare metodes van voorbehoeding voorkom word. Swangerskaptoetse word soos klinies aangedui tydens behandeling met VOLIBRIS aanbeveel. Vroue wat swanger kan raak, moet aangeraai word om hulle dokter onmiddellik te skakel as hulle swanger raak.

Laktasie:

Dit is nie bekend of ambrisentaan in borsmelk uitgeskei word nie. VOLIBRIS word nie aanbeveel vir gebruik deur borsvoedende moeders nie (kyk KONTRA-INDIKASIES).

Fertiliteit:

Die ontwikkeling van atrofie van testikelbuise in manlike diere word met chroniese toediening van VOLIBRIS verbind. Die effek op manlike vrugbaarheid by mense is nie bekend nie.

DOSIS EN GEBRUIKSAANWYSINGS:

VOLIBRIS is vir orale gebruik en kan met of sonder kos geneem word. Behandeling moet net ingestel word deur 'n mediese praktisyn met ervaring in die behandeling van PAH.

Aanbevole volwasse dosis:

Behandeling met VOLIBRIS moet teen 'n dosis van 5 mg een keer per dag begin.

Oorweeg verhoging van die dosis tot 10 mg een keer per dag as 5 mg verdra word.

Gebruik saam met siklosporien A:

Wanneer dit saam met siklosporien A gebruik word, moet die dosis van VOLIBRIS tot 5 mg een keer per dag beperk word (kyk INTERAKSIES).

Aanbevole pediatriese en adolessentdosis:

Daar is geen inligting beskikbaar oor die gebruik van VOLIBRIS deur pasiënte jonger as 18 jaar nie en dus word die gebruik van VOLIBRIS deur hierdie pasiënte nie aanbeveel nie.

Doseeraanwysings vir spesiale populasies:

Bejaardes:

Geen aanpassing in die dosis is nodig vir pasiënte van 65 jaar en ouer nie (kyk Farmakokinetika in spesiale populasies).

Swak nierfunksie:

Metabolisme en uitskeiding van ambrisentaan deur die niere is minimaal, sodat aanpassing in die dosis vir pasiënte met swak nierfunksie waarskynlik nie nodig is nie.

Swak lewerfunksie:

VOLIBRIS is nie in proefpersone met erge swak lewerfunksie of met klinies betekenisvolle hoë vlakke hepatiese transaminases bestudeer nie. Tog sou verwag word dat swak lewerfunksie blootstelling (C_{maks} en AOK) aan ambrisentaan verhoog, omdat die hoofroete van metabolisme glukuronidering is en tot 'n mindere mate oksidasie, met die daaropvolgende uitskeiding in die gal. Daarom word VOLIBRIS nie vir hierdie pasiëntbevolking aanbeveel nie (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS en Farmakokinetika in spesiale populasies).

NEWE-EFFEKTE:

Die veiligheid van VOLIBRIS is in kliniese proewe met meer as 480 pasiënte met PAH beoordeel.

Nadelige geneesmiddelreaksies (NGR's/"ADRs") uit die data van kliniese proewe word hier onder volgens sisteem-orgaanklas en frekwensie gegee.

Frekwensies word gedefinieer as algemeen (≤ 1/100, < 1/10) of minder algemeen (≤ 1/1 000, < 1/100). Die kategorieë van frekwensies van nadelige reaksie gebaseer op ervaring in kliniese proewe kan dalk nie die frekwensie van nadelige reaksies in normale kliniese praktyk weerspieël nie.

Versteurings van bloed en limfatiese stelsel:

Algemeen: bloedarmoede (dalings in hemoglobienvlakke en/of hematokrit)

Versteurings van immuunstelsel:

Minder algemeen: hipersensitiwiteit (bv. angio-edeem, uitslag)

Versteurings van senustelsel:

Algemeen: hoofpyn

Versteurings van die hart:

Algemeen: palpitasies

Vaskulêre versteurings:

Algemeen: gloede

Respiratoriese, toragiese en mediastinale versteurings:

Algemeen: toe neus (die voorkoms is dosisverwant), sinusitis, nasofaringitis

Gastro-intestinale versteurings:

Algemeen: buikpyn, hardlywigheid

Algemene versteurings en versteurings by die plek van toediening:

Algemeen: vloeistofretensie, perifere edeem.

Ervaring na bemarking:

Benewens nadelige reaksies wat in kliniese studies geïdentifiseer is, is die volgende nadelige reaksies van VOLIBRIS tydens gebruik na goedkeuring gesien. Omdat hierdie effekte vrywillig uit 'n bevolking van onbekende grootte aangemeld is, kan beramings van die frekwensie nie gemaak word nie.

Versteurings van bloed en limfatiese stelsel: anemie waarvoor bloedoortapping nodig was

Versteurings van die hart: hartversaking (wat met vloeistofretensie verband hou)

Respiratoriese, toragiese en mediastinale versteurings: dispnee

Gevalle van verslegtende dispnee van onduidelik etiologie is kort ná die begin van behandeling met VOLIBRIS aangemeld.

Gastro-intestinale versteurings: naarheid en braking

Hepatobiliêre versteurings:

Algemeen: styging in lewertransaminases

Onbekend: lewerskade, outo-immuun hepatitis (kyk WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS)

Gevalle van outo-immuun hepatitis, waaronder gevalle van verergering van outo-immuun hepatitis en lewerskade van onduidelike etiologie is tydens behandeling met VOLIBRIS aangemeld.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:

Simptome en tekens: In gesonde vrywilligers het enkele dosisse van 50 en 100 mg (5 tot 10 keer die maksimum aanbevole dosis) met hoofpyn, gloede, duiseligheid, naarheid en toe neus gepaardgegaan.

As gevolg van die werkingsmeganisme kan ’n oordosis VOLIBRIS ook potensieel tot hipotensie lei.

Behandeling: Aktiewe kardiovaskulêre ondersteuning kan in geval van uitgesproke hipotensie nodig wees. Daar is nie ’n spesifieke teenmiddel nie.

IDENTIFIKASIE:

VOLIBRIS 5 mg: Bleekpienk, vierkantige, konvekse filmbedekte tablet met “GS“ op een kant en “K2C“ op die ander kant gedebosseleer.

VOLIBRIS 10 mg: Dieppienk, ovaal, konvekse filmbedekte tablet met “GS“ op een kant en “KE3“ op die ander kant gedebosseleer.

AANBIEDING:

VOLIBRIS-tablette is verpak in stulpstroke van ondeursigtige PVC/PVdC en aluminiumfoelie met 10 tablette elk. Drie stulpstroke is verpak in ’n karton om ’n pak met 30 tablette te gee.

BEWARINGSAANWYSINGS:

Bewaar by of benede 30 °C.

Hou buite bereik van kinders.

REGISTRASIENOMMER:

VOLIBRIS 5 mg: 45/7.1.3/0106

VOLIBRIS 10 mg: 45/7.1.3/0107

NAAM EN BESIGHEIDSADRES VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT:

GlaxoSmithKline South Africa (Edms) Bpk

Hawkinslaan 39

Epping Industrie 1, 7460

DATUM VAN PUBLIKASIE VAN HIERDIE VOUBILJET:

21 April 2016

VOLIBRIS is ’n geregistreerde handelsmerk van Gilead Sciences, Ingelyf, gebruik onder lisensie van die **GSK**-maatskappygroep.

Patient Information Leaflet

SCHEDULING STATUS:

S4

PROPRIETARY NAME, STRENGTH AND PHARMACEUTICAL FORM:

VOLIBRIS® 5 mg film-coated tablets

VOLIBRIS® 10 mg film-coated tablets

Ambrisentan

Read all of this leaflet carefully before you start taking VOLIBRIS.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- VOLIBRIS has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

WHAT VOLIBRIS CONTAINS:

The active substance is ambrisentan.

Each tablet contains 5 mg or 10 mg ambrisentan.

VOLIBRIS 5 mg and 10 mg tablets contain sugar (95 mg and 90 mg lactose per tablet, respectively) and the colourant, Allura Red AC Aluminium Lake.

The inactive ingredients are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), macrogol/polyethylene glycol 3350, lecithin (soya) and Allura Red AC Aluminium Lake (E129).

WHAT VOLIBRIS IS USED FOR:

VOLIBRIS is used to treat pulmonary arterial hypertension (PAH). PAH is high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. In people with PAH, these arteries get narrower, so the heart has to work harder to pump blood through them. This causes people to feel tired, dizzy and short of breath.

VOLIBRIS widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure and relieves the symptoms.

VOLIBRIS has not been studied in patients under 18 years old.

BEFORE YOU TAKE VOLIBRIS:

Do not take VOLIBRIS:

- if you are allergic to ambrisentan or to any of the inactive ingredients
- if you have severe liver problems
- if you have scarring of the lungs, of unknown cause (idiopathic pulmonary fibrosis)
- if you are pregnant or breastfeeding your baby.

Take special care with VOLIBRIS:

- if you have anaemia (a reduced number of red blood cells)
- if you have liver disease
- if you have swelling (oedema).

Tell your doctor, who will decide whether VOLIBRIS is suitable for you.

You will need regular blood tests:

Before you start taking VOLIBRIS and at regular intervals while you are taking it, your doctor will take blood to check:

- whether you have anaemia (a reduced number of red blood cells)
- whether your liver is working properly.

It is important that you have these regular blood tests for as long as you are taking VOLIBRIS.

Pregnancy and breastfeeding:

If you are pregnant or breastfeeding your baby, please consult your doctor, pharmacist or other healthcare professional for advice, before taking VOLIBRIS.

Pregnancy: VOLIBRIS may harm unborn babies, conceived before, during or soon after treatment.

If it is possible you could become pregnant, use a reliable form of birth control (contraception) while you're taking VOLIBRIS. Talk to your doctor about this.

Don't take VOLIBRIS if you are pregnant or planning to become pregnant. If you become pregnant or think that you may be pregnant while you're taking VOLIBRIS, see your doctor immediately.

If you are a woman who could become pregnant, your doctor will ask you to take a pregnancy test before you start taking VOLIBRIS and regularly while you are taking VOLIBRIS.

Do not take VOLIBRIS if you are pregnant, if you are planning to become pregnant, or if you could become pregnant because you are not using reliable birth control (contraception). If this applies to you, tell you doctor and do not take VOLIBRIS.

Breastfeeding: It is not known if VOLIBRIS is transferred to breast milk. Don't breastfeed while you are taking VOLIBRIS. Talk to your doctor about this.

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

Driving and using machinery:

VOLIBRIS is unlikely to produce an effect on the ability to drive and use machines.

Important information about some of the ingredients of VOLIBRIS:

VOLIBRIS contains lactose which may have an effect on the control of your blood sugar if you have diabetes mellitus. Patients with the rare hereditary conditions of lactose/fructose or galactose intolerance should not take VOLIBRIS.

Using other medicines and VOLIBRIS:

Always tell your healthcare professional if you are taking any other medicine. (This includes complementary or traditional medicines.)

Your doctor may need to adjust your dose of VOLIBRIS if you start taking ciclosporin A (a medicine used after transplant or to treat psoriasis). Tell your doctor or pharmacist if you are taking this medicine.

HOW TO USE VOLIBRIS:

Always take VOLIBRIS exactly as your doctor has told you to. Check with your doctor or pharmacist if you are not sure.

The usual dose of VOLIBRIS is one 5 mg tablet, once a day. Your doctor may decide to increase your dose to 10 mg, once a day.

If you take ciclosporin A, do not take more than one 5 mg tablet of VOLIBRIS, once a day.

You can take VOLIBRIS with or without food.

If you take more VOLIBRIS than you should:

If you accidentally take too much VOLIBRIS, ask your doctor or pharmacist for advice.

If you forget to take VOLIBRIS:

If you forget a dose of VOLIBRIS, just take the tablet as soon as you remember, then carry on as before.

Do not take two doses at the same time to make up for a forgotten dose.

Do not stop taking VOLIBRIS without your doctor’s advice.

POSSIBLE SIDE EFECTS:

VOLIBRIS can cause side effects. Not all side effects reported for VOLIBRIS are included in this leaflet. Should your general health worsen, or if you experience any untoward effects while taking VOLIBRIS, please consult your doctor, pharmacist or other healthcare professional for advice.

Liver function: VOLIBRIS may affect the levels of your liver enzymes which may cause damage to your liver. Your doctor will be doing regular blood tests to ensure that this does not happen. Signs that your liver may not be working properly include loss of appetite, feeling sick (nausea), being sick (vomiting), high temperature (fever), pain in your stomach, yellowing of your skin or the whites of your eyes (jaundice), dark-coloured urine and itching of your skin. If you notice any of these signs, tell your doctor immediately.

Anaemia (a reduced number of red blood cells): Anaemia can cause tiredness, weakness, shortness of breath and generally feeling unwell. Your doctor will be doing regular blood tests to ensure that this does not happen. If you notice any of these signs, tell your doctor immediately. In some instances, a blood transfusion may be required.

Allergic reactions: You may notice a rash or itching and swelling (usually of the face, lips, tongue or throat), which may cause difficulty in breathing or swallowing.
Tell your doctor straight away if you get these effects, or if they happen suddenly after taking VOLIBRIS.

Frequent side effects:

- swelling (oedema), especially of the ankles and feet
- headache
- a runny or blocked nose, red and sore throat, congestion of pain in the sinuses
- constipation
- pain in your stomach
- flushing (redness of the skin)
- palpitations (fast or irregular heartbeats).

Other side effects:

The frequency of the following side effects is not known:

- heart failure (associated with swelling/oedema)
- worsening shortness of breath shortly after starting VOLIBRIS
- nausea (feeling sick) and vomiting (being sick)
- liver injury
- inflammation of the liver caused by the body's own defences (auto-immune hepatitis).

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

STORING AND DISPOSING OF VOLIBRIS:

Store all medicines out of sight of children.

Store at or below 30 °C .

Do not use VOLIBRIS after the expiry date shown on the pack.

Return all unused medicines to your pharmacist. Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

PRESENTATION OF VOLIBRIS:

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.

IDENTIFICATION OF VOLIBRIS:

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.

REGISTRATION NUMBER:

VOLIBRIS 5 mg: 45/7.1.3/0106

VOLIBRIS 10 mg: 45/7.1.3/0107

NAME AND ADDRESS OF REGISTRATION HOLDER:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

DATE OF PUBLICATION:

21 April 2016

CCDS-7.0+IPF

VOLIBRIS is a registered trademark of Gilead Sciences, Inc. used under license by the **GSK** group of companies.

Pasiëntinligtingsbrosjure

SKEDULERINGSTATUS:

S4

EIENDOMSNAAM, STERKTE EN DOSEERVORM:

VOLIBRIS® 5 mg filmbedekte tablette

VOLIBRIS® 10 mg filmbedekte tablette

Ambrisentaan

Lees hierdie hele brosjure noukeurig deur voordat jy begin om VOLIBRIS te gebruik.

- Hou hierdie brosjure. Dit mag nodig wees dat jy dit weer moet lees.
- As jy nog vrae het, moet jy jou dokter of apteker asseblief vra.
- VOLIBRIS is vir jou persoonlik voorgeskryf en jy moet nie jou medisyne aan ander mense gee nie. Dit kan hulle skaad, selfs al is hulle simptome dieselfde as joune.

WAT VOLIBRIS BEVAT:

Die aktiewe bestanddeel is ambrisentaan.

Elke tablet bevat 5 mg of 10 mg ambrisentaan.

VOLIBRIS 5 mg en 10 mg tablette bevat suiker (onderskeidelik 95 mg en 90 mg laktose per tablet), en die kleurstof, Allure Red AC-aluminiumlak.

Die onaktiewe bestanddele is laktosemonohidraat, mikrokristallyne sellulose, natriumkruiskarmellose, magnesiumstearaat, polivinielalkohol, talk, titaandioksied (E171), makrogol/poliëtileenglikol 3350, lesitien (soja) en Allure Red AC-aluminiumlak (E129).

WAARVOOR VOLIBRIS GEBRUIK WORD:

VOLIBRIS word gebruik vir pulmonêre arteriële hipertensie (PAH). PAH is hoë bloeddruk in die bloedvate (die pulmonêre slagare) wat bloed vanaf die hart na die longe vervoer. In mense met

PAH word hierdie slagare nouer, sodat die hart harder moet werk om bloed deur hulle te pomp. Dit veroorsaak dat mense moeg, duiselig en kort van asem voel.

VOLIBRIS verwyd die pulmonêre slagare en maak dit makliker vir die hart om bloed deur hulle te pomp. Dit verlaag die bloeddruk en verlig die simptome.

VOLIBRIS is nie in pasiënte jonger as 18 jaar bestudeer nie.

VOORDAT JY VOLIBRIS GEBRUIK:

Jy moet VOLIBRIS nie gebruik nie:

- as jy allergies teenoor ambrisentaan of enige van die onaktiewe bestanddele is
- as jy ernstige lewerprobleme het
- as jy letsels van onbekende oorsaak in die longe het (idiopatiese pulmonêre fibrose)
- as jy swanger is of jou baba borsvoed.

Wees besonder versigtig met VOLIBRIS:

- as jy bloedarmoede het (min rooibloedselle)
- as jy 'n lewersiekte het
- as jy swelling (edeem) het.

Sê vir jou dokter wat sal besluit of VOLIBRIS vir jou geskik is.

Jy moet gereelde bloedtoetse ondergaan:

Voordat jy begin om VOLIBRIS te drink en met gereelde tussenposes terwyl jy dit gebruik sal jou dokter bloed trek om die volgende na te gaan:

- of jy bloedarmoede het (min rooibloedselle)
- of jou lewer behoorlik werk.

Dit is belangrik dat jy hierdie gereelde bloedtoetse ondergaan vir so lank as wat jy VOLIBRIS neem.

Swangerskap en borsvoeding:

As jy swanger is of jou baba borsvoed, moet jy asseblief jou dokter, apteker of ander gesondheidsorgkundige om advies vra voordat jy VOLIBRIS gebruik.

Swangerskap: VOLIBRIS kan ongebore babas skaad wat voor, tydens of kort na behandeling verwek word.

As dit moontlik is dat jy kan swanger raak, moet jy 'n betroubare vorm van geboortebeperking (voorbehoeding) gebruik terwyl jy VOLIBRIS neem. Praat met jou dokter hieroor.

Jy moet VOLIBRIS nie gebruik as jy swanger is of as jy beplan om swanger te raak nie. As jy swanger raak of dink dat jy dalk swanger is terwyl jy VOLIBRIS drink, moet jy jou dokter dadelik spreek.

As jy 'n vrou is wat swanger kan raak, sal jou dokter jou vra om 'n swangerskaptoets te doen voordat jy begin om VOLIBRIS te neem en gereeld terwyl jy VOLIBRIS neem.

Moenie VOLIBRIS drink as jy swanger is, as jy beplan om swanger te raak, of as jy swanger kan raak omdat jy nie betroubare geboortebeperking (voorbehoeding) gebruik nie. As dit op jou van toepassing is, sê vir jou dokter en moenie VOLIBRIS neem nie.

Borsvoeding: Dit is nie bekend of VOLIBRIS in borsmelk uitgeskei word nie. Moenie borsvoed terwyl jy VOLIBRIS neem nie. Praat met jou dokter hieroor.

VOLIBRIS kan spermtelling verlaag: As jy 'n man is wat VOLIBRIS gebruik, is dit moontlik dat VOLIBRIS jou spermtelling kan verlaag. Praat met jou dokter as jy enige vrae of probleme hiermee het.

Motorbestuur en gebruik van masjinerie:

Dit is onwaarskynlik dat VOLIBRIS 'n effek sal hê op die vermoë om motor te bestuur of masjinerie te gebruik.

Belangrike inligting oor sommige van die bestanddele van VOLIBRIS:

VOLIBRIS bevat laktose wat ’n effek op die kontrole van jou bloedsuiker mag hê indien jy aan diabetes mellitus ly. Pasiënte met die raar oorerflike toestand van onverdraagbaarheid van laktose/fruktose of galaktose moet nie VOLIBRIS neem nie.

Die gebruik van ander medisyne en VOLIBRIS:

Sê altyd vir jou gesondheidsorgkundige as jy enige ander medisyne gebruik. (Dit sluit aanvullende of tradisionele medisyne in.)

Jou dokter moet dalk jou dosis VOLIBRIS aanpas as jy begin om siklosporien A te gebruik (’n middel wat ná oorplanting gebruik word of om psoriase te behandel). Sê vir jou dokter of apteker as jy hierdie medisyne tans gebruik.

HOE OM VOLIBRIS TE GEBRUIK:

Gebruik VOLIBRIS altyd presies soos wat jou dokter aan jou gesê het. Raadpleeg jou dokter of apteker as jy nie seker is nie.

Die normale dosis VOLIBRIS is een tablet van 5 mg een keer per dag. Jou dokter kan besluit om jou dosis na 10 mg per dag te verhoog.

As jy siklosporien A gebruik, moet jy nie meer as een tablet van 5 mg VOLIBRIS een keer per dag neem nie.

Jy kan VOLIBRIS met of sonder voedsel neem.

As jy meer VOLIBRIS geneem het as wat jy moes:

Indien jy per ongeluk te veel VOLIBRIS neem, vra vir jou dokter of apteker om advies.

As jy vergeet om VOLIBRIS te neem:

As jy ’n dosis van VOLIBRIS vergeet het, neem die tablet so gou as wat jy onthou, en gaan dan voort soos voorheen.

Moenie twee dosisse op dieselfde tyd drink om vir die vergete dosis op te maak nie.

Jy moet nie sonder jou dokter se advies ophou om VOLIBRIS te gebruik nie.

MOONTLIKE NEWE-EFFEKTE:

VOLIBRIS kan newe-effekte veroorsaak. Nie al die newe-effekte wat vir VOLIBRIS aangemeld is, is in hierdie brosjure opgeneem nie. As jou algemene gesondheidstoestand vererger of as jy newe-effekte ervaar terwyl jy VOLIBRIS gebruik, moet jy jou dokter, apteker of ander gesondheidsorgkundige om advies raadpleeg.

Lewerfunksie: VOLIBRIS kan die vlakke van jou lewerensieme beïnvloed wat skade aan jou lewer kan veroorsaak. Jou dokter sal gereelde bloedtoetse doen om te verseker dat dit nie gebeur nie. Tekens dat jou lewer dalk nie behoorlik werk nie, is onder meer verlies aan eetlus, voel naar (naarheid), bring op (braking), hoë temperatuur (koors), pyn op die maag, geel verkleuring van die vel of die wit van die oë (geelsug), donker gekleurde urien en gejeuk van die vel. As jy enige van hierdie simptome opmerk, moet jy dadelik vir jou dokter sê.

Anemie (min rooibloedselle - bloedarmoede): Bloedarmoede kan moegheid, swakheid en kortasemheid veroorsaak en maak dat mens oor die algemeen siek voel. Jou dokter sal gereelde bloedtoetse doen om te verseker dat dit nie gebeur nie. As jy enige van hierdie simptome opmerk, moet jy dadelik vir jou dokter sê. In sommige gevalle, kan ’n bloedoortapping nodig wees.

Allergiese reaksies: Jy kan ’n veluitslag of jeuk en swelling (gewoonlik van die gesig, lippe, tong of keel) opmerk wat probleme met asemhaling of sluk veroorsaak.
Sê dadelik vir jou dokter as jy hierdie effekte kry, of as dit skielik voorkom nadat VOLIBRIS geneem is.

Frekwente newe-effekte:

- swelling (edeem), veral van die enkels en voete
- hoofpyn
- ’n loopneus of toe neus, rooi en seer keel, kongestie en pyn in die sinusse

- hardlywigheid
- maagpyn
- gloede (rooiheid van die vel)
- palpitasies (vinnige of onreëlmatige hartklop).

Ander newe-effekte:

Die frekwensie van die volgende newe-effekte is nie bekend nie:

- hartversaking (wat met swelling/edeem gepaardgaan)
- verslegtende kortasemheid kort nadat met VOLIBRIS begin is
- naarheid (mislike gevoel) en braking (opbring)
- lewerskade
- inflammasie van die lewer veroorsaak deur die liggaam se eie verdedigingstelsel (outo-immuun hepatitis).

As jy enige newe-effekte opmerk wat nie in hierdie brosjure genoem word nie, moet jy jou dokter of apteker asseblief daarvan sê.

BERGING EN WEGDOENING VAN VOLIBRIS:

Hou alle medisyne buite sig van kinders.

Bewaar by of benede 30 °C.

Moenie VOLIBRIS na die vervaldatum op die pakkie gebruik nie.

Gee alle ongebruikte medisyne terug aan jou apteker. Ongebruikte medisyne moet nie in dreinering- of rioolstelsels (bv. toilette) gegooi word nie.

AANBIEDING VAN VOLIBRIS:

VOLIBRIS-tablette is verpak in stulpstroke van ondeursigtige PVC/PVdC en aluminiumfoelie met 10 tablette elk. Drie stulpstroke is verpak in ’n karton om ’n pak met 30 tablette te gee.

IDENTIFIKASIE VAN VOLIBRIS:

VOLIBRIS 5 mg: Bleekpienk, vierkantige, konvekse filmbedekte tablet met “GS“ op een kant en “K2C“ op die ander kant gedebosseleer.

VOLIBRIS 10 mg: Dieppienk, ovaal, konvekse filmbedekte tablet met “GS“ op een kant en “KE3“ op die ander kant gedebosseleer.

REGISTRASIENOMMER:

VOLIBRIS 5 mg: 45/7.1.3/0106

VOLIBRIS 10 mg: 45/7.1.3/0107

NAAM EN ADRES VAN REGISTRASIEHOUER:

GlaxoSmithKline South Africa (Edms) Bpk

Hawkinslaan 39

Epping Industrie 1, 7460

DATUM VAN PUBLIKASIE:

21 April 2016

VOLIBRIS is ’n geregistreerde handelsmerk van Gilead Sciences, Ingelyf, gebruik onder lisensie van die **GSK**-maatskappygroep**.**