Ambrisentan Film-coated Tablets

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VOLMARO 5 Film-coated Tablets

VOLMARO 10 Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VOLMARO 5: Each film coated tablet contains 5 mg ambrisentan.

VOLMARO 10: Each film coated tablet contains 10 mg ambrisentan.

Contains sugar (Lactose Monohydrate 95 mg and 90 mg lactose per 5 mg and 10 mg tablet, respectively)

For full list of excipients, see **section 6.1.**

3. PHARMACOLOGICAL FORM

Film coated Tablets

VOLMARO 5

Pale pink, square shaped, biconvex film coated tablets debossed with ‘CL’ on one side and ‘5’ on other side.

VOLMARO 10

Deep pink oval shaped biconvex film coated tablets, debossed with 'CL' on one side and '10' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VOLMARO is indicated for the treatment of:

- Pulmonary arterial hypertension (PAH), to improve exercise capacity, decrease the symptoms of PAH, and delay clinical worsening.

4.2 Posology and method of administration

Treatment with VOLMARO should only be initiated by a medical doctor experienced in the treatment of PAH.

Posology

Recommended adult dosage

VOLMARO 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 in combination with ciclosporin A

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

Special populations

Elderly patients

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 patient with renal impairment. There is limited experience with ambrisentan in individuals with severe renal impairment (creatinine clearance <30 mL/min), therapy should be initiated cautiously in this group and particular care taken if the dose is increased to 10 mg.

Hepatic impairment

VOLMARO has not been studied in individual 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, VOLMARO is not recommended in this patient population (see **section 4.4 and 5.2**)

Paediatric population

There are no data available on the use of VOLMARO in patients under 18 years of age and therefore, the use VOLMARO in these patients is not recommended.

Method of administration

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

4.3 Contraindications

VOLMARO is contraindicated in:

- patients with hypersensitivity to ambrisentan or any other ingredients of AMBRISENTAN CIPLA (**section 6.1**).
- pregnancy and lactation (see **section 4.6**)
- women of child-bearing potential who are not using reliable contraception
- patients with severe hepatic impairment (see **section 4.4**)
- patients with baseline value of hepatic aminotransferases [aspartate aminotransferases (AST) and /or alanine aminotransferases (ALT)] > values more than 3 times the upper limit of normal
- patients with 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 VOLMARO. (see **section 5.1**). Therefore, hepatic function should be evaluated prior to initiation of VOLMARO. If aminotransferases (alanine aminotransferase, ALT or aspartate aminotransferase, AST) are greater than 3 times upper limit of normal, Initiation of VOLMARO 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), VOLMARO therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of VOLMARO 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 VOLMARO therapy.

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

Haematological changes

Reductions in haemoglobin concentrations and haematocrit have been observed with VOLMARO and there have been cases where this has resulted In anaemia, sometimes requiring transfusion. It is recommended that haemoglobin and/or haematocrit levels are measured prior to initiation of VOLMARO again at one month and periodically thereafter. Initiation of VOLMARO therapy is not recommended for patients with clinically significant anaemia. If a clinically significant decrease in haemoglobin or haematocrit is observed during therapy and other causes have been excluded, dose reduction or discontinuation of treatment should be considered.

Fluid retention

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

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

Women of child-bearing age

VOLMARO treatment must not be initiated in women of child-bearing age unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist should be considered. Monthly pregnancy tests during treatment with ambrisentan are recommended (see **section 4.3** and **4.6**).

Pulmonary veno-occlussive disease

Cases of pulmonary oedema have been reported with vasodilating medicines, when used in patients with pulmonary veno-occlusive disease. If patients develop acute pulmonary oedema during initiation of therapy with vasodilating medicines such as VOLMARO, the possibility of pulmonary veno-occluslve disease should be considered.

Lactose intolerance

VOLMARO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

VOLMARO does not Inhibit or induce phase I or II drug metabolising enzymes at clinically relevant concentrations in non-clinical studies. A suggesting a low potential for VOLMARO to alter the profile of medicines metabolised by these pathways.

Ciclosporin A

Steady-state co-administration of VOLMARO and ciclosporin A, increases plasma concentrations of ambrisentan by about 2-fold and more than doubles the AUC; therefore, doses of VOLMARO should be limited to 5 mg once daily when co-administered with ciclosporin A (see **section 4.2**).

Ketoconazole

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

Rifampicin

No dose adjustment of VOLMARO is required when co-administered with rifampicin. Patients on VOLMARO therapy should be closely monitored when starting treatment with rifampicin.

Other targeted PAH treatments

Co-administration of VOLMARO and omeprazole (an Inhibitor of CYP2C19) did not significantly affect the pharmacokinetics of ambrisentan. Therefore, caution is recommended in the case of co-administration with other treatments for PAH (e.g. prostanoids and soluble guanylate cyclase stimulators).

Phosphodiesterase inhibitors

Co-administration of VOLMARO with a phosphodiesterase inhibitor, either sildenafil or tadalafil (both substrates of CYP3A4) does not significantly affect the pharmacokinetics of the phosphodiesterase inhibitor or ambrisentan (see **section 5.2**).

Oral contraceptives

Steady-state dosing with VOLMARO 10 mg once daily does not significantly affect the single-dose pharmacokinetics of the ethinyl oestradiol and norethindrone components of a combined oral contraceptive. Based on the pharmacokinetic studies, 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 anticoagulant activity of warfarin in a healthy volunteer study. Warfarin also had no clinically significant effects on the pharmacokinetics of ambrisentan. In addition, in patients, ambrisentan had no overall effect on the weekly warfarin-type anticoagulant dose, prothrombin time (PT) and international normalised ratio (INR).

Digoxin

Steady-state administration of VOLMARO 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

Women of Childbearing Potential

VOLMARO treatment must not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. Monthly pregnancy tests during treatment with ambrisentan are recommended.

Pregnancy

VOLMARO is contraindicated in pregnancy (see **section 4.3**). Animal studies have shown that ambrisentan is teratogenic. Women receiving ambrisentan must be advised of the risk of foetal harm and alternative therapy initiated if pregnancy occurs.

VOLMARO 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 VOLMARO and prevented thereafter by reliable methods of contraception. Pregnancy tests during treatment with VOLMARO are recommended as clinically indicated. Women of childbearing potential should be advised to contact their doctor immediately if they become pregnant.

Breastfeeding

It is not known whether ambrisentan is excreted in human breast milk. Therefore, breastfeeding is contraindicated in patients taking VOLMARO, (see **section 4.3**).

Fertility

The development of testicular tubular atrophy in male animals has been linked to the chronic administration of VOLMARO. The effect on male human fertility is not known, but a deterioration of spermatogenesis cannot be excluded.

4.7 Effects on ability to drive and use machines

VOLMARO has minor or moderate influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of ambrisentan (such as hypotension, dizziness, asthenia, fatigue) should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (see **section**

4.8). Patients should be aware of how they might be affected by ambrisentan before driving or using machines.

4.8 Undesirable effects

a) Summary of the safety profile

Peripheral oedema, fluid retention and headache (including sinus headache, migraine) were the most common adverse reactions observed with VOLMARO. The higher dose of 10 mg was associated with a higher incidence of these adverse reactions, and peripheral oedema tended to be more severe in patients ≥ 65 years (see **section 4.4**).

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders

Frequent: Anaemia (decreased haemoglobin and/or haematocrit).

Immune system disorders

Less frequent: Hypersensitivity reactions (e.g. angioedema, rash, pruritis).

Nervous system disorders

Frequent: headache (including sinus headache, migraine); dizziness.

Eye disorders

Less frequent: Blurred vision, visual impairment.

Ear and labyrinth disorders

Frequent: Tinnitus

Rare: Sudden hearing loss.

Cardiac disorders

Frequent: Palpitations, heart failure (associated with fluid retention).

Vascular disorders

Less frequent: Hypotension, flushing, syncope.

Respiratory, thoracic, and mediastinal disorders

Frequent: Nasal congestion, sinusitis, nasopharyngitis, rhinitis, upper respiratory congestion, dyspnoea, epistaxis.

Gastrointestinal disorders

Frequent: Abdominal pain, constipation, nausea, vomiting, diarrhoea.

Hepatobiliary disorders

Frequent: Increased hepatic transaminases.

Less Frequent: Hepatic injury, autoimmune hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Rash

General disorders and administration site conditions

Frequent: Fluid retention, peripheral oedema, chest pain/ discomfort, asthenia, fatigue.

Post-marketing experience

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

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 ambrisentan therapy.

Gastrointestinal disorders: nausea and vomiting.

Hepatobiliary disorders

Common: hepatic transaminases increased

Unknown: 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 has been reported during ambrisentan therapy.

c) Description of selected adverse reactions

Decreased haemoglobin

In the post-marketing period, cases of anaemia requiring blood cell transfusion have been reported (see **section 4.4**). The frequency of decreased haemoglobin (anaemia) was higher with 10 mg ambrisentan.

Reporting of suspected adverse reactions

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

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 VOLMARO also could potentially result in hypotension, active cardiovascular support may be required. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 7.1.3 Other hypotensives

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 is a potent (Ki 0.016 nM) and highly selective ET_A antagonist (approximately 4000-fold more selective for ET_A as compared to ET_B).
- 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 vasodilator's nitric oxide and prostacyclin.

5.2 Pharmacokinetic properties

Absorption

Ambrisentan is absorbed rapidly in humans. After oral administration, maximum plasma concentrations (C_{max}) of ambrisentan typically occur around 1,5 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.

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

Ambrisentan is highly plasma protein bound. The *in vitro* plasma protein binding of ambrisentan was, on average, 98,8 % and independent of concentration over the range of 0,2 – 20 microgram/mL. Ambrisentan is primarily bound to albumin (96,5 %) and to a lesser extent to alpha$_1$-acid glycoprotein.

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

Biotransformation

Ambrisentan is a non-sulphonamide (propanoic acid) ERA.

Ambrisentan is glucuronidated via several UGT isoenzymes (UGT1A9S, UGT2B7S and UGT1A3S) to form ambrisentan glucuronide (13 %). Ambrisentan also undergoes oxidative metabolism mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 to form 4-hydroxymethyl ambrisentan (21 %) which is further glucuronidated to 4-hydroxymethyl ambrisentan glucuronide (5 %).

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

Furthermore, the binding affinity of 4-hydroxymethyi 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 data have shown that at therapeutic concentrations, ambrisentan does not inhibit UGT1A1, UGT1A6, UGT1A9, UGT2B7 or cytochrome P450 enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4. Additional *in vitro* studies have shown 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-hydroxymethyf 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 **section 4.2**).

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.

There is 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.

There is a significant relationship between ambrisentan CL/F and renal function as assessed by creatinine clearance (Clcr). However, the magnitudes of change in clearance of ambrisentan were relatively modest and are unlikely to be of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients include:

Croscarmellose sodium (Ac-Di-Sol),

lactose monohydrate (Lactopress granulated),

magnesium stearate (Vegetable grade),

microcrystalline cellulose (Avicel PH 102),

Opadry II complete film coating system: 85G94065 Pink/ 85G94101 Red:

polyvinyl alcohol (E1203),

Talc (E553b),

Titanium dioxide (E171),

Macrogol / PEG 4000 (E1521),

Lecithin (Soya) (E322),

Allura red AC Aluminium Lake (E129).

6.2 Incompatibilities

N/A

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

VOLMARO 5: Blister pack of 10`s and 3 x 10`s film coated tablets packed in a 270 gsm CFB board type 4 plain carton.

The blister pack is composed of Lidding Peel – Push Aluminium Foil 206 mm, 50 gsm paper and 0.25 / 206 mm PVC / 60 gsm PVDC coated white opaque film.

VOLMARO 10: Blister pack of 10`s and 3 x 10`s film coated tablets packed in a 270 gsm CFB board type 4 plain carton.

The blister pack is composed of Lidding Peel – Push Aluminium Foil 206 mm, 50 gsm paper and 0.25 / 206 mm PVC / 60 gsm PVDC coated white opaque film.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9,

Parc du Cap,

Mispel Street,

Belville,

7530,

customer care number: 080 2226662

8. REGISTRATION NUMBER(S)

VOLMARO 5: 52/7.1.3/0604.602

VOLMARO 10: 52/7.1.3/0605.603

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 July 2021

10. DATE OF REVISION OF THE TEXT

30 March 2022