Information for healthcare professionals

Contents

Introduction

Please familiarise yourself with the complete Summary of Product Characteristics before prescribing or dispensing ambrisentan. This guide is only a summary of some of the most important information about ambrisentan.

Ambrisentan is an orally active, ETA-selective, endothelin receptor antagonist (ERA).

Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

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

Educational material for patients

When patients are initially prescribed ambrisentan, give them:

- The leaflet ***'Taking Volibris—what you need to know'***, which contains information and advice about taking ambrisentan. It also includes spaces for patients to record **appointments**, **blood test** results and pregnancy test results if appropriate, helping to ensure that they continue to be tested according to the recommended guidelines.
- The leaflet includes space for recording the doctor's and other **contact details**. Please fill these in before giving the booklet to the patient.
- It also includes space for recording the patient's **baseline test results**.

For male partners of women of childbearing potential who are taking ambrisentan, there is another leaflet, which is in the back pocket of the main patient leaflet.

- ***'Your partner is taking Volibris— what you need to know'***, which explains the importance of using reliable forms of contraception.

Important risk information

Teratogenicity

Animal studies have shown that ambrisentan is teratogenic. There is no evidence of whether it is teratogenic in humans and, therefore, ambrisentan is contraindicated in **pregnancy** and in women who are **breast feeding**.

Women of child-bearing potential

Ambrisentan is contraindicated in women of child-bearing potential who are not using reliable contraception.

This includes women with oligomenorrhea, women who are perimenopausal, and young females who have begun to menstruate (although ambrisentan is not indicated for use in patients aged under 18 years).

For a woman to be considered of non-child-bearing potential means any woman who meets at least one of the following criteria:

- aged at least 50 years and naturally amenorrhoeic for at least 1 year (amenorrhoea following cancer therapy does not rule out child-bearing potential)
- premature ovarian failure, confirmed by a specialist gynaecologist
- other documented impairment of oviductal or uterine function that would cause sterility
- previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, or uterine agenesis

If you have any doubt about an individual patient's child-bearing potential, or what contraceptive advice to give her, **seek expert advice** from a gynaecologist.

Women of child-bearing potential should not start to take ambrisentan unless:

- They are using reliable contraception (It is preferable that patients use 2 complimentary methods of contraception to avoid pregnancy, e.g.: double barrier method plus one other)
- They have had a pregnancy test with a negative result within three days of commencing treatment.

It is recommended that these women have **pregnancy tests** every month while they are taking ambrisentan and up to four weeks after stopping treatment.

It is important that women of child-bearing potential are specifically **counselled** about the importance of reliable contraception and the avoidance of pregnancy. It's preferable that patients use two complimentary methods of contraception e.g. double barrier method plus one other.

The following are generally **considered effective methods of contraception** (i.e. they have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label):

- oral contraceptive, either combined or progestogen alone
- injectable progestogen
- implants of etonogestrol or levonorgestrel
- oestrogenic vaginal ring
- percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) which has a failure rate of less than 1% as stated in the product label.
- male partner sterilisation (vasectomy with documentation of azoospermia)
- double barrier method: Male condom combined with female diaphragm with or without a vaginal spermicidal agent (foam/gel/film/cream/suppository)
- Abstinence from penile vaginal intercourse, when this is the female's preferred and usual lifestyle.

Regularly reiterate the importance of reliable contraception during therapy, and review contraceptive practice.

If a woman taking ambrisentan needs to change or stop the contraception she is using, she should:

- Tell the doctor who prescribes her contraception that she is taking ambrisentan
- Tell the doctor who prescribes her ambrisentan about any change to her contraception.

Provide female patients of child bearing potential the leaflet ***'Your partner is taking Volibris—what you need to know'*** to give to their partners. This leaflet can be found in the pocket at the back of the patient booklet.

Consider monthly (30-day) dispensing of ambrisentan.
Women taking ambrisentan should be advised of the risk of foetal harm.

Information about women of child-bearing potential continues overleaf…

If a woman becomes pregnant while taking ambrisentan

- She should be given an alternative treatment for her PAH
- If she continues the pregnancy, she should be referred to a specialist obstetrician for evaluation and advice.

Patients who think that they may be pregnant should be directed to speak with their doctor as soon as possible. A pregnancy test should be performed as soon as possible.

Please report all occurrences of pregnancy, and the outcome of the pregnancy. This includes cases detected within 1 month post-therapy. Please see the box at the bottom of page 7 for contact information.

Male fertility

In studies on animals, testicular tubular atrophy and impaired fertility have been linked to the long-term administration of ambrisentan.

Male patients should be informed of these findings. The effect of ambrisentan on human testicular function and male fertility is not known. In clinical studies, chronic administration of ambrisentan was not associated with a change in plasma testosterone.

Male patients who are particularly concerned about a potential effect on future fertility may wish to consider **storing a sample** of semen.

Liver function

Ambrisentan is contraindicated in patients with severe hepatic impairment (with or without cirrhosis), because it has not been studied in these patients.

Liver function abnormalities have been associated with PAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, hepatic injury and hepatic enzyme elevations potentially related to therapy have been observed with Volibris. Patients' hepatic aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) should be evaluated before they start taking ambrisentan.

Do not start ambrisentan treatment in patients with baseline values of ALT and/or AST >3× ULN, because it has not been studied in these patients.

Monthly monitoring of ALT and AST is recommended. You should also monitor patients clinically for signs or symptoms of liver injury.

Patients with raised liver enzymes

If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if ALT and/or AST elevation is accompanied by signs or symptoms of liver injury (e.g. jaundice), **discontinue ambrisentan therapy**. Monitor these patients closely.

If these patients have no clinical symptoms of hepatic injury or of jaundice, consider starting ambrisentan again, once hepatic enzyme abnormalities have been resolved. Consider seeking specialist hepatology advice.

Educate patients about the importance of monthly monitoring and the possible signs and symptoms of liver injury.

Consider monthly (30-day) dispensing of ambrisentan.

Please report clinically significant elevations of ALT and/or AST, or any other liver related adverse events, to GSK or to the SFDA. Please see the box at the bottom of page 14 for contact information.

Haemoglobin concentration

Decreases in haemoglobin concentration and haematocrit have been associated with ERAs, including ambrisentan, whether used as monotherapy. Most of these decreases were detected during the first 4 weeks of treatment; haemoglobin generally stabilised thereafter. In the Volibris post-marketing period, cases of anaemia requiring blood transfusion have also been reported.

Initiation of ambrisentan is not recommended for patients with clinically significant anaemia.

Patients taking ambrisentan should have their haemoglobin and/or haematocrit levels measured regularly—for example, at 1 month, at 3 months, and periodically thereafter, in line with clinical practice.

If tests show a clinically significant decrease in haemoglobin or haematocrit, and other causes have been excluded, consider reducing the dose of ambrisentan, or stopping treatment.

Please report clinically significant decreases in haemoglobin or haematocrit and adverse events to GSK or to the SFDA. Please see the box at the bottom of page 14 for contact information.

Idiopathic Pulmonary Fibrosis

Volibris is contraindicated in patients with idiopathic pulmonary fibrosis (IPF), with or without secondary pulmonary hypertension.

A study of 492 patients (ambrisentan N=329, placebo N=163) with idiopathic pulmonary fibrosis (IPF), 11% of which had secondary pulmonary hypertension (WHO group 3), has been conducted, but was terminated early when it was determined that the primary efficacy endpoint could not be met (ARTEMIS-IPF study). Ninety events (27%) of IPF progression (including respiratory hospitalisations) or death were observed in the ambrisentan group compared to 28 events (17%) in the placebo group.

Additional safety information

In patients with severe renal impairment, be cautious about starting treatment with ambrisentan.

Peripheral oedema has been observed with ERAs, including ambrisentan whether used as monotherapy. In clinical studies with ambrisentan, most cases of peripheral oedema were mild to moderate in severity. There have been post-marketing reports of **fluid retention** occurring within weeks after starting ambrisentan; in some cases, it has been necessary to administer a diuretic, or to hospitalise the patient for fluid management.

If a patient develops clinically significant peripheral oedema, with or without associated weight gain, carry out further evaluation to determine the cause—for example, ambrisentan or underlying heart failure. Assess the possible need for specific treatment, or the need to discontinue ambrisentan.

Ambrisentan has been associated with adverse events of symptomatic hypotension as with other ERA's.

Adverse drug reactions associated with ambrisentan include side effects characteristic of ERAs:

- headache, flushing, palpitations, upper respiratory tract symptoms (e.g. nasal congestion, sinusitis, and pharyngitis)
- Gastrointestinal complaints, such as constipation and abdominal pain.

Hypersensitivity reactions (e.g. angioedema, rash) were uncommon in short term clinical trials, and were common in longer term trials.

Post-marketing safety surveillance

It is believed that the major risks and potential risks associated with ambrisentan have been identified by the clinical development programme.

However, as with any medicine, the safety profile of ambrisentan in clinical practice may change as the numbers of patients exposed to ambrisentan increases.

It is, therefore, important that you promptly report any suspected adverse reactions to ambrisentan, to assist in more fully characterising the product's safety profile.

In addition, **all cases of pregnancy** should be reported to GSK. Please see the box at the bottom of page 14 for contact information.

Abbreviated Prescribing Information for use in Saudi Markets based on the latest registered Prescribing Information Ref: EU v21 and prepared to meet the requirements of the GSK International Pharmaceutical Promotional and Marketing Policy.

Volibris film-coated tablets. Ambrisentan 5 mg & 10 mg

THERAPEUTIC INDICATIONS Volibris is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. **POSOLOGY AND METHOD OF ADMINISTRATION** Volibris is to be taken orally, it is recommended that the tablet is swallowed whole and it can be taken with or without food at a dose of 5 mg once daily. Some additional efficacy has been observed with 10 mg ambrisentan in patients with class III symptoms, however an increase in peripheral oedema has also been observed. Patients with PAH associated with connective tissue disease may require 10 mg ambrisentan for optimal efficacy. It should be confirmed that the 5 mg dose is well tolerated before considering an increase in dose to 10 mg ambrisentan in these patients. Limited data suggest that the abrupt discontinuation of ambrisentan is not associated with rebound worsening of PAH. When co-administered with cyclosporine A, the dose of ambrisentan should be limited to 5 mg once daily and the patient should be carefully monitored. **Special Populations:** Elderly: No dose adjustment is required in patients over the age of 65 years, Renal Impairment: No dose adjustment is required, There is limited experience with severe renal impairment (creatinine clearance <30 ml/min); therapy should be initiated cautiously in this subgroup. Hepatic Impairment: Ambrisentan has not been studied in individuals with hepatic impairment (with or without cirrhosis). Ambrisentan must not be initiated in patients with severe hepatic impairment, or clinically significant elevated hepatic aminotransferases (greater than 3 times the Upper Limit of Normal (>3xULN), Paediatric Population: The safety and efficacy of ambrisentan in children and adolescents aged below 18 years has not been established. **CONTRAINDICATIONS** Hypersensitivity to the active substance, to soya, or to any of the excipients, Pregnancy, Women of child-bearing potential who are not using reliable contraception, Breast-feeding, Severe hepatic impairment (with or without cirrhosis), Baseline values of hepatic aminotransferases >3xULN, Idiopathic pulmonary fibrosis (IPF), with or without secondary pulmonary hypertension **WARNINGS PRECAUTIONS:** Ambrisentan's Efficacy has not been studied in WHO Functional Class I, and has not also been established in Class IV, Liver Function:- Liver function abnormalities have been associated with PAH. Cases consistent with autoimmune hepatitis, including possible exacerbation of underlying autoimmune hepatitis, hepatic injury and hepatic enzyme elevations potentially related to therapy have been observed with ambrisentan. Therefore hepatic aminotransferases (ALT and AST) should be evaluated prior to initiation of ambrisentan and treatment should not be initiated in patients with baseline values of ALT and/or AST>3xULN. Haemoglobin Concentration: - Reductions in haemoglobin concentrations and haematocrit have been associated with endothelin receptor antagonists (ERAs) including ambrisentan, Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. Fluid Retention: - Peripheral oedema has been observed with ERAs including ambrisentan. Women of child bearing potential: - Volibris 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. Pulmonary veno-occlusive disease: Cases of pulmonary oedema have been reported with vasodilating medicinal products, such as ERAs, when used in patients with pulmonary veno-occlusive disease. Concomitant use with other medicinal products: Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin. Excipients: Volibris tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Volibris tablets contain the azo colouring agent Allura red AC Aluminium Lake (E129), which can cause allergic reactions. Volibris tablets contain lecithin derived from soya. If a patient is hypersensitive to soya, ambrisentan must not be used **Drug INTERACTION:** Cyclosporine A: Multiple doses of ambrisentan had no effect on cyclosporine A exposure, and no dose adjustment of cyclosporine A is warranted. Rifampicin: - Patients on ambrisentan therapy should be closely monitored when starting treatment with rifampicin. Other targeted PAH treatments: The efficacy and safety of ambrisentan when co-administered with other treatments for PAH has not been specifically studied. Phosphodiesterase inhibitor: Co-administration of ambrisentan 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: ambrisentan would not be expected to significantly affect exposure to oestrogen- or progestogen-based contraceptives. Warfarin: Ambrisentan had no effects on Warfarin. Ketoconazole: no significant interactions. Effect of ambrisentan on xenobiotic transporters: no clinically relevant effect. **Fertility, PREGNANCY AND LACTATION**: - Pregnancy Category X, is contraindicated in pregnancy, Breast feeding: breast-feeding is contraindicated in patients taking Ambrisentan, Male Fertility:-The effect on male human fertility is not known but a deterioration of spermatogenesis cannot be excluded. Chronic administration of ambrisentan was not associated with a change in plasma testosterone in clinical studies. **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:** Ambrisentan has minor or moderate influence on the ability to drive and use machines. **UNDESIRABLE EFFECTS:** Very common: Headache (including sinus headache, migraine), Peripheral oedema, fluid retention. Common: Anaemia, Dizziness, Cardiac failure, Palpitation, hypotension, flushing, epistaxis, dyspnoea, Upper respiratory (e.g. nasal, sinus) congestion, sinusitis, nasopharyngitis, rhinitis, abdominal pain, constipation, Nausea, vomiting, diarrhoea, Hepatic transaminases increased, chest pain/discomfort, Asthenia and fatigue. Uncommon: hypersensitivity reactions, syncope, hepatic injury, autoimmune hepatitis. **OVERDOSE:** There is no experience in PAH patients of ambrisentan at daily doses greater than 10 mg. In healthy volunteers, single doses of 50 and 100 mg (5 to 10 times the maximum recommended dose) were associated with headache, flushing, dizziness, nausea and nasal congestion. Due to the mechanism of action, an overdose of ambrisentan could potentially result in hypotension. In the case of pronounced hypotension, active cardiovascular support may be required. No specific antidote is available.

Abbreviated Prescribing Information was prepared on 21st December 2016

Pre-prescription checklist for Healthcare Professionals

This checklist is provided to help you ensure that all necessary important actions have been taken before you prescribe ambrisentan.

Before prescribing ambrisentan, please familiarise yourself with:

- the complete Summary of Product Characteristics
- the supplementary educational materials ***'Information for healthcare professionals'***
- The educational materials provided for patients.

Consider the following before prescribing ambrisentan:

Ambrisentan is contraindicated (see SPC section 4.3) in:

- hypersensitivity to the active substance, to soya or to any of the excipients (see also SPC sections 4.4 and 6.1)
- severe hepatic impairment (with or without cirrhosis) (see also SPC section 4.2)
- baseline values of hepatic aminotransferases (aspartate aminotransferases [AST] and/or alanine aminotransferases [ALT]) >3× ULN (see also SPC sections 4.2 and 4.4)
- pregnancy (animal studies have shown ambrisentan to be teratogenic) (see also SPC section 4.6)
- lactation (see also SPC section 4.6)
- Women of child-bearing potential who are not using reliable contraception (see also SPC sections 4.4 and 4.6).
- patients with idiopathic pulmonary fibrosis with or without secondary pulmonary hypertension

Ambrisentan should be initiated with caution in patients with severe renal impairment (creatinine clearance <30 ml/min).

Initiation of ambrisentan is not recommended for patients with clinically significant anaemia.

Ambrisentan is not recommended for use in patients below 18 years of age, due to a lack of data on safety and efficacy

Continued overleaf...

Before prescribing ambrisentan

✔ Provide the supplementary educational booklet to the patient
✔ Enter your contact details in the booklet
✔ Enter the patients baseline information in the booklet
✔ Discuss important information regarding the use of ambrisentan with the patient
✔ Obtain pre-therapy haemoglobin/haematocrit – enter results in patient booklet
    ✔ Counsel the patient on importance of periodic on-therapy measurement of haemoglobin/haematocrit
✔ Obtain pre-therapy ALT/AST - enter results in patient booklet
    ✔ Counsel the patient on importance of monthly on-therapy aminotransferase testing
    ✔ Counsel the patient on signs/symptoms of possible liver injury

Female patients:
✔ Assess child-bearing potential of the patient
If there is any doubt about child-bearing potential, or what contraceptive advice should be given, consultation with an expert should be considered.

If the patient is of child-bearing potential:
✔ Obtain pre-therapy pregnancy test – enter results in patient booklet
✔ Counsel patient on importance of avoidance of pregnancy
✔ Agree on reliable methods of contraception
✔ Highlight the card in the back of the patient booklet to be given to their partners

Male patients:
✔ Male patients should be advised of potential risk of testicular tubular atrophy based on animal studies with ambrisentan. The effect in humans is not known.
✔ Male patients who are particularly concerned about a potential effect on future fertility may wish to consider storing a sample of semen

To report Product Complaint/s or Adverse Event/s associated with the use of GSK product/s, please contact us via sa.aermi-saudi@gsk.com or by calling Saudi Arabia (+966 1 26536666)."
Or you can report to the SFDA through:
– Toll free phone: 800249000
– Fax: +966112057662
– E-mail: npc.drug@sfda.gov.sa
– Online: https://ade.sfda.gov.sa/