Cipla Ambrisentan – information for prescribing doctors

Cipla Ambrisentan is an endothelin receptor agonist (ERA) and is indicated for the treatment of pulmonary arterial hypertension (PAH)[1]. Ambrisentan must not be used for the treatment of idiopathic pulmonary fibrosis (IPF) and must not be used in patients who have IPF with or without secondary pulmonary hypertension.

Cipla Ambrisentan should only be prescribed by a physician who is experienced in the treatment of PAH. Please familiarise yourself with the Product Information prior to initiating treatment for your patient. You should only prescribe this to patients who are able to comply with the safe use of Ambrisentan. You may need to provide comprehensive advice and to counsel your patient on the risks and safe use of Ambrisentan.

Patients should only receive 30 day's supply of Ambrisentan at a time, and blood tests should be checked prior to each supply.

Ambrisentan has some safety alerts that you need to be aware of. These include:

- Anaemia
- Hepatotoxicity
- Teratogenicity in animal studies

- ➢ As such, it is important to ensure a negative pre-treatment pregnancy test for women of child-bearing potential, and that a full blood count and liver function tests are done prior to starting treatment.
- ➢ Pregnancy tests in female patients of child-bearing potential and liver function tests in all patients should also be done on a monthly basis prior to the patient receiving the next medication supply, as a means to monitor these potential risks.
- ➢ Haemoglobin levels should be measured again at one month after starting treatment, then at 3 months and at clinically appropriate time frames thereafter.

Contraindications

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

Ambrisentan is contraindicated in pregnancy and in women who are breast feeding.

Ambrisentan is contraindicated in patients with severe hepatic impairment, with or without cirrhosis (baseline values of ALT and/or AST >3 x ULN).

Ambrisentan is NOT recommended for patients with clinically significant anaemia.

Pregnancy / Fertility

Ambrisentan may cause birth defects and is contraindicated in pregnancy (Pregnancy Category X).

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

Ambrisentan is contraindicated in women of child-bearing potential who are not using reliable forms of contraception. The use of contraception needs to continue for three months after stopping Ambrisentan.

- Women taking Ambrisentan need to have a negative pregnancy test each month prior to continuing treatment.
- Reliable forms of contraception are defined as methods with a failure rate of ≤ 1% per year

[1] Cipla Ambrisentan Approved Product Information.

when used consistently and correctly. These include:

- oral contraceptive, either combined or progestogen alone
- injectable progestogen
- implants of etonogestrel or levonorgestrel
- oestrogenic vaginal ring
- 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
- abstinence from penile vaginal intercourse, when this is the female's preferred and usual lifestyle.

If a female patient should become pregnant while she is taking Ambrisentan, she needs to stop Ambrisentan and be given an alternative medication for PAH. If she wishes to continue her pregnancy, she should be referred to an Obstetrician for evaluation and advice.

- Animal studies have shown that long term administration of Ambrisentan can lead to testicular tubular atrophy and impaired fertility in male animals. However, it is not known what effects it may have in humans. Male patients taking Ambrisentan should be made aware of this potential risk.

Anaemia

Decreases in haemoglobin concentration and haematocrit have been associated with ERAs, including Ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment; haemoglobin generally stabilised thereafter.

Patients taking Ambrisentan should have their haemoglobin levels measured prior to starting treatment, then at one and 3-months post treatment. Haemoglobin can be measured at clinically appropriate time frames thereafter.

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.

Hepatotoxicity

Liver function abnormalities have been associated with PAH. Cases consistent with hepatic injury and hepatic enzyme elevations potentially related to therapy have been observed with Ambrisentan. As such, patients need to have a liver function test to evaluate their alanine aminotransferase (ALT) and aspartate aminotransferase (AST) before they start taking Ambrisentan.

Do not start Ambrisentan treatment in patients with baseline values of ALT and/or AST > 3 × ULN. Ambrisentan is contraindicated in patients with baseline values of ALT and/or AST >3 x ULN.

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.

Adverse Reaction Reporting Obligations

All adverse drug reactions should be reported. In addition, anaemia, hepatotoxicity and pregnancy (for female patients or the partner of a male patient) are classified as events of interest. As such, there are specific questionnaires that you will be asked to complete to ensure that as much information about the risk/benefit of Ambrisentan can be collected and analysed.

Should your patient experience any adverse drug reactions related to Ambrisentan, or any of the events of interest, please kindly contact Cipla on the contact details provided in the text box below. Our Pharmacovigilance team will liaise with you and will request further information, as well as ask for you to complete a specific questionnaire related to an event of interest. Should a female patient or a partner of a male patient become pregnant during treatment with Ambrisentan, a Pregnancy follow up form including follow up for a birth outcome for the neonate and when the child is 12 months of age will be requested.

The following documents have been developed by Cipla to ensure the safe use of Ambrisentan. These should be given to the patient and also to give to their GP.

1. Consumer Medicines Information
2. Patient Information leaflet with blood test schedule aid
3. Information for male partners of a female patient

Should you require any further information, please contact Cipla Australia.

Reporting of related adverse drug reactions and events of interest

Please report any related drug reactions to Ambrisentan to Cipla using the contact details below. By reporting side effects, you can help provide more information on the safety of this medicine.

Contact Cipla at: drugsafety@cipla.com

or call: **1800 569 074**

You can also report these adverse drug reactions directly to the TGA on their website:

https://aems.tga.gov.au/privacy/