SIDE EFFECTS

Serious side effects of Ambrisentan include:

- Serious birth defects.
- Swelling all over the body (fluid retention) can happen within weeks after starting Ambrisentan. Tell your doctor right away if you have any unusual weight gain, tiredness, or trouble breathing while taking Ambrisentan. These may be symptoms of a serious health problem. You may need to be treated with medicine or need to go to the hospital.
- Sperm count reduction. Reduced sperm counts have been observed in some men taking a drug similar to Ambrisentan, an effect which might impair their ability to father a child. Tell your doctor if remaining fertile is important to you.
- Low red blood cell levels (anemia) can happen during the first weeks after starting Ambrisentan. Your doctor will do blood tests to check your red blood cells before starting Ambrisentan. Your doctor may also do these tests during treatment with Ambrisentan.

The most common side effects of Ambrisentan are:

- Swelling of hands, legs, ankles and feet (peripheral edema)
- Stuffy nose (nasal congestion)
- Inflamed nasal passages (sinusitis)
- Hot flashes or getting red in the face (flushing)
- Feeling your heart beat (palpitations)
- Red and sore throat and nose
- Stomach pain
- Constipation
- Shortness of breath
- Headache

Some medicines that are like Ambrisentan can cause liver problems. Tell your doctor if you get any of these symptoms of a liver problem while taking Ambrisentan:

- loss of appetite
- nausea or vomiting
- fever
- achiness
- generally do not feel well
- pain in the upper right stomach (abdominal) area
- yellowing of your skin or the whites of your eyes
- dark urine
- itching

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of Ambrisentan. For more information, ask your doctor or pharmacist.

HOW SUPPLIED

Ambrisentan 5 mg & 10 mg tablets are available as 1x10 PVC/PVDC blister pack.

STORAGE

Store below 25 °C.
Protect from light and moisture.
TM Trade mark under registration
Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
Bollaram, Sangareddy District - 502 325,
Telangana, INDIA.

B31237-02

AMBRISENTAN TABLETS IP 5/10 mg

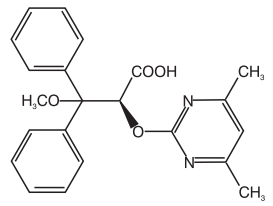
COMPOSITION

Each film coated tablet contains

Pulmonext 5 पल्मोनेक्सट ५
Ambrisentan IP..... 5 mg
Colours: Titanium dioxide IP & Ponceau 4 R Lake

Pulmonext 10 पल्मोनेक्सट १०
Ambrisentan IP.....10 mg
Colours: Titanium dioxide IP & Ponceau 4 R Lake

Chemical Name:(+)-(2S)
-2-[(4,6-dimethylpyrimidin-2-yl)oxy]
-3 methoxy-3,3-diphenylpropanoic acid.
Empirical formula: $C_{22}H_{22}N_2O_4$
Molecular weight: 378.42
Structural formula:



INDICATIONS AND USAGE

Ambrisentan is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II–III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

DOSAGE AND ADMINISTRATION

Initiate treatment at 5 mg once daily with or without food, and consider increasing the dose to 10 mg once daily if 5 mg is tolerated.

Treat women of childbearing potential only after a negative pregnancy test and treat only women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests

Not recommended in patients with moderate or severe hepatic impairment.

CLINICAL PHARMACOLOGY

Mechanism of Action

Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ETA and ETB, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ETA are vasoconstriction and cell proliferation, while the predominant actions of ETB are vasodilation, antiproliferation, and ET-1 clearance.

In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH.

Ambrisentan is a high affinity (Ki=0.011 nM) ETA receptor antagonist with a high selectivity for the ETA versus ETB receptor (>4000-fold). The clinical impact of high selectivity for ETA is not known.

Pharmacodynamics

Cardiac Electrophysiology

In a randomized, positive- and placebo-controlled, parallel-group study, healthy subjects received either Ambrisentan 10 mg daily followed by a single dose of 40 mg, placebo followed by a single dose of moxifloxacin 400 mg, or placebo alone. Ambrisentan 10 mg daily had no significant effect on the QTc interval. The 40 mg dose of Ambrisentan increased mean QTc at tmax by 5 ms with an upper 95% confidence limit of 9 ms. For patients receiving Ambrisentan 5–10 mg daily and not taking metabolic inhibitors, no significant QT prolongation is expected.

Pharmacokinetics

The pharmacokinetics of ambrisentan (S-ambrisentan) in healthy subjects are dose proportional.

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The absolute bioavailability of ambrisentan is not known. Ambrisentan is absorbed with peak concentrations occurring approximately 2 hours after oral administration in healthy subjects and PAH patients. Food does not affect its bioavailability. In vitro studies indicate that ambrisentan is a substrate of P-gp. Ambrisentan is highly bound to plasma proteins (99%). The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well characterized. In plasma, the AUC of 4-hydroxymethyl ambrisentan accounts for approximately 4% relative to parent ambrisentan AUC. The in vivo inversion of S-ambrisentan to R-ambrisentan is negligible. The mean oral clearance of ambrisentan is 38 mL/min and 19 mL/min in healthy subjects and in PAH patients, respectively. Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours.

CONTRAINDICATIONS

Pregnancy Category X

Ambrisentan may cause fetal harm when administered to a pregnant woman. Ambrisentan was teratogenic at oral doses of ≥ 15 mg/kg/day in rats and ≥ 7 mg/kg/day in rabbits; it was not studied at lower doses. In both species, there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid.

Teratogenicity is a class effect of endothelin receptor antagonists. There are no data on the use of Ambrisentan in pregnant women

Ambrisentan is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Pregnancy must be excluded before the initiation of treatment with Ambrisentan and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception. If the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNg 20 IUS for pregnancy prevention, no additional contraception is needed

WARNINGS AND PRECAUTIONS

Fluid Retention

Peripheral edema is a known class effect of endothelin receptor antagonists, and is also a clinical consequence of PAH and worsening PAH. In the placebo-controlled studies, there was an increased incidence of peripheral edema in patients treated with doses of 5 or 10 mg Ambrisentan compared to placebo . Most edema was mild to moderate in severity, and it occurred with greater frequency and severity in elderly patients.

In addition, there have been post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting Ambrisentan. Patients required intervention with a diuretic, fluid management, or, in some cases, hospitalization for decompensating heart failure.

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

Decreased Sperm Counts

In a 6-month study of another endothelin receptor antagonist, bosentan, 25 male patients with WHO functional class III and IV PAH and normal baseline sperm count were evaluated for effects on testicular unction. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with bosentan. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Bosentan was discontinued and after 2 months the sperm count had returned to baseline levels. In 22 patients who completed 6 months of treatment, sperm count remained within the normal range and no changes in sperm morphology, sperm motility, or hormone levels were observed. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Ambrisentan have an adverse effect on spermatogenesis.

Hematological Changes

Decreases in hemoglobin concentration and hematocrit have followed administration of other endothelin receptor antagonists and were observed in clinical studies with Ambrisentan. These decreases were observed within the first few weeks of treatment with Ambrisentan, and stabilized thereafter. The mean decrease in hemoglobin from baseline to end of treatment for those patients receiving Ambrisentan in the 12-week placebo-controlled studies was 0.8 g/dL.

Marked decreases in hemoglobin (>15% decrease from baseline resulting in a value below the lower limit of normal) were observed in 7% of all patients receiving Ambrisentan (and 10% of patients receiving 10 mg) compared to 4% of patients receiving placebo. The cause of the decrease in hemoglobin is unknown, but it does not appear to result from hemorrhage or hemolysis.

Measure hemoglobin prior to initiation of Ambrisentan, at one month, and periodically thereafter. Initiation of Ambrisentan therapy is not recommended for patients with clinically significant anemia. If a clinically significant decrease in hemoglobin is observed and other causes have been excluded, consider discontinuing Ambrisentan.

Pulmonary Veno-occlusive Disease

If patients develop acute pulmonary edema during initiation of therapy with vasodilating agents such as Ambrisentan, the possibility of pulmonary veno-occlusive disease should be considered, and if confirmed Ambrisentan should be discontinued.

DRUG INTERACTIONS

Multiple dose co-administration of ambrisentan and cyclosporine resulted in an approximately 2-fold increase in ambrisentan exposure in healthy volunteers; therefore, limit the dose of ambrisentan to 5 mg once daily when co-administered with cyclosporine.

USE IN SPECIFIC POPULATIONS