Botecreel® (Bosentan)

Generic name:

Bosentan

Category:

Antihypertensive (pulmonary); Endothelin receptor antagonist

Mechanism of action:

Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension (PAH), suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors.

Pharmacokinetics:

After oral administration, C_{max} of bosentan are attained within 3 to 5 hours in healthy adult subjects. The exposure to bosentan after intravenous (IV) and oral administration is approximately 2-fold greater in adult patients with PAH than in healthy adult subjects. Steady state is reached within 3 to 5 days. The absolute bioavailability of bosentan in healthy volunteers is about 50% and is unaffected by food.

Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Bosentan is eliminated by biliary excretion following metabolism in the liver. The terminal elimination half-life is about 5 hours in healthy adult subjects.

Indications:

- Pulmonary Arterial Hypertension: bosentan is indicated for the treatment of PAH in patients with Word Health Organization class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.
- Treatment of PAH secondary to scleroderma.

Dosage and administration:

- Adults:

Pulmonary Arterial Hypertension; initial dosage: 62.5 mg twice daily for 4 weeks and then increased to the maintenance dosage. Maintenance dosage: 125 mg twice daily.

- Patients with low body weight: in patients with a body weight less than 40 kg but who are older than 12 years of age, the recommended initial and maintenance dosage is 62.5 mg twice daily.
- Tablets should be administered morning and evening with or without food.
- Discontinuation of therapy: there is limited experience with abrupt discontinuation of bosentan. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dosage reduction (62.5 mg twice daily for 3 to 7 days) should be considered.
- Safety and efficacy in children have not been established.

Contraindications:

- Pregnancy
- Concomitant use of bosentan and **cyclosporine**
- Concomitant use of bosentan and **glyburide**
- Hypersensitivity to bosentan or any component of the medication

Precautions:

- Hepatotoxicity: Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with bosentan. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $\geq 2 \times$ Upper Limit of Normal, treatment should be stopped.
- Hematologic changes: Treatment with bosentan can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.
- Fluid retention: there have been numerous post marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting bosentan. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

- Hepatic function impairment: avoid using bosentan in patients with moderate to severe liver impairment. In addition, generally avoid using bosentan in patients with elevated aminotransferases (greater than 3 times Upper Limit of Normal) because monitoring liver injury in these patients may be more difficult. There are no specific data to guide dosing in hepatically impaired patients; exercise caution in patients with mildly impaired liver function.

Pregnancy:

Category X

Lactation:

It is not known whether bosentan is excreted into human milk. Because many drugs are excreted in human milk, breast-feeding while taking bosentan is not recommended.

Drug interactions:

- **Cytochrome P450:** Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these enzymes may increase the plasma concentration of bosentan. Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A4 inhibitor (e.g., erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when bosentan is co-administered. Bosentan had no relevant inhibitory effect on any CYP isoenzymes tested (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). Consequently, bosentan is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

- **Hormonal contraceptives**: including oral, injectable, transdermal, and implantable forms, may not be reliable when bosentan is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking bosentan.

- **Cyclosporine A**: The concomitant administration of bosentan and cyclosporine A is contraindicated.

- **Glyburide:** An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of bosentan and glyburide is contraindicated, and alternative hypoglycemic agents should be considered.

- **Simvastatin and Other Statins**: the plasma concentrations of simvastatin and its metabolite decreased almost 50% when co-administered with bosentan. Bosentan is also expected to reduce plasma concentrations of other statins significantly metabolized by CYP3A4.

- **Warfarin**: co-administration decreased the plasma concentrations of S-warfarin and R-warfarin. Clinically relevant changes in INR or warfarin dose were not seen in patients with PAH during clinical trials.

Adverse reactions:

- Adverse reactions (greater than or equal to 3%): hypotension, palpitations, fatigue, headache, flushing, pruritus, abnormal hepatic function, dyspepsia, edema, nasopharyngitis.

Storage:

- Store below 30^0C, protect from moisture and light.
- Keep out of the reach of children.

Packaging:

- Botecreel® is available as 62.5 mg F.C tablets in box of 60 tablets.
- Botecreel® is available as 125 mg F.C tablets in box of 60 tablets.