BOZPAH Tablets

(Bosentan Monohydrate)

بوزپا گولیاں

(بوسنٹان مونو ھائیڈریٹ)

COMPOSITION:
Each film coated tablet contains:
Bosentan monohydrate equivalent to Bosentan ... 62.5mg or 125mg.
NQ Specs.

CLINICAL PHARMACOLOGY: Mechanism of Action: Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissues of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ETA and ETB. Bosentan has a slightly higher affinity for ETA receptors than for ETB receptors.
Pharmacokinetics: It is not known whether Bosentan's pharmacokinetics is influenced by gender, body weight, race, or age.
Absorption: In healthy subjects, the absolute bioavailability of Bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3-5 hours.
Distribution: Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes. A volume of distribution (V_{ss}) of about 18 litres was determined after an intravenous dose of 250mg.
Biotransformation and elimination: After a single intravenous dose of 250mg, the clearance was 8.2L/h. The terminal elimination half-life ($t_{½}$) is 5.4 hours. Upon multiple dosing, plasma concentrations of Bosentan decrease gradually to 50%-65% of those seen after single dose administration. This decrease is probably due to auto-induction of metabolising liver enzymes. Steady-state conditions are reached within 3-5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes, CYP2C9 and CYP3A4. Less than 3% of an administered oral dose is recovered in urine. Bosentan forms three metabolites and only one of these is pharmacologically active. This metabolite is mainly excreted unchanged via the bile. In adult patients, the exposure to the active metabolite is greater than in healthy subjects. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

INDICATIONS: BOZPAH (Bosentan) Tablet is indicated for the treatment of idiopathic pulmonary arterial hypertension, familial pulmonary arterial hypertension, pulmonary arterial hypertension (PAH) associated with scleroderma or pulmonary arterial hypertension associated with congenital systemic to pulmonary shunts including Eisenmenger's physiology in patients with WHO Class III or IV symptoms. **BOZPAH** (Bosentan) Tablet is indicated for the treatment of systemic sclerosis with ongoing digital ulcer disease (to reduce number of new digital ulcers).

CONTRA-INDICATIONS: Bosentan is contra-indicated in patients with:
- Hypersensitivity to the active substance or to any of the excipients.
- Moderate to severe hepatic impairment, i.e., Child-Pugh class B or C.
- Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal.
- Concomitant use of cyclosporine.
- Pregnancy.
- Women of child-bearing potential who are not using reliable methods of contraception.

DOSAGE AND ADMINISTRATION: General: BOZPAH (Bosentan) Tablet treatment should be initiated at a dose of 62.5mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125mg b.i.d. Doses above 125mg b.i.d. does not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered in morning and evening with or without food. If **BOZPAH** (Bosentan) Tablet is re-introduced, it should be at the starting dose; aminotransferase levels should be checked within 3 days.
Use in Women of Child-bearing Potential: BOZPAH (Bosentan) Tablet treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception.
Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of **BOZPAH** (Bosentan) Tablet is small and does not require dosing adjustment.
Dosage Adjustment in Geriatric Patients: Caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.
Dosage Adjustment in Hepatically Impaired Patients: Caution should be exercised in patients with mildly impaired liver function. **BOZPAH** (Bosentan) Tablet should generally be avoided in patients with moderate or severe liver impairment.
Dosage Adjustment in Children: Safety and efficacy in pediatric patients have not been established.
Dosage Adjustment in Patients with Low Body Weight: In patients with a body weight below 40kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5mg b.i.d.
Discontinuation of Treatment: To avoid the potential for clinical deterioration, gradual dose reduction (62.5mg b.i.d. for 3 to 7 days) should be considered.
Dose for Systemic sclerosis with ongoing digital ulcer disease: Initially 62.5mg twice daily increased after 4 weeks to 125mg twice daily.

OVERDOSAGE: The most common side effect was headache of mild to moderate intensity. Massive overdosage may result in pronounced hypotension requiring active cardiovascular support.

PRECAUTIONS:
Haematologic Changes: Treatment with Bosentan caused a dose-related decrease in haemoglobin and haematocrit. Haemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. The overall mean decrease in haemoglobin concentration for Bosentan-treated patients was 0.9g/dL (change to end of treatment). If a marked decrease in haemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

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Fluid retention: Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.
Pulmonary Veno-Occlusive Disease (PVOD): Signs of pulmonary edoema occur when Bosentan is administered in patients with pulmonary arterial hypertension, the possibility of associated PVOD should be considered and Bosentan should be discontinued.
Pregnancy & Lactation: Bosentan is contra-indicated to the pregnant women as teratogenicity is a class effect of these drugs. Breast feeding while taking Bosentan is not recommended.
Pediatric Use: Safety and efficacy in pediatric patients have not been established.
Drug Interactions: 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 CYP3A4 inhibitor (such as ketoconazole, itraconazole, or ritonavir) with Bosentan will likely lead to large increases in plasma concentrations of Bosentan. Co-administration of such combinations of a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor with Bosentan is not recommended. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Bosentan is co-administered. Bosentan had no relevant inhibitory effect on any CYP isozyme in-vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). Consequently, Bosentan is not expected to increase the plasma concentrations of drugs metabolised by these enzymes.

ADVERSE EFFECTS:

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Common	Anaemia, haemoglobin decrease
	Not known	Anaemia or haemoglobin decreases requiring red blood cell transfusion
	Uncommon	Thrombocytopenia
	Uncommon	Neutropenia, leukopenia
Immune system disorders	Common	Hypersensitivity reactions (including dermatitis, pruritus and rash)
	Rare	Anaphylaxis and/or angioedema
Nervous system disorders	Very common	Headache
	Common	Syncope
Cardiac disorders	Common	Palpitations
Vascular disorders	Common	Flushing
	Common	Hypotension
Respiratory, thoracic and mediastinal disorders	Common	Nasal congestion
Gastrointestinal disorders	Common	Gastroesophageal reflux disease Diarrhoea
Hepatobiliary disorders	Very common	Abnormal liver function test
	Uncommon	Aminotransferase elevations associated with hepatitis (including possible exacerbation of underlying hepatitis) and/or jaundice
	Rare	Liver cirrhosis, liver failure
Skin and subcutaneous disorders	Common	Erythema
General disorders and administration site conditions	Very common	Edoema, fluid retention

WARNINGS: Potential Liver Injury: 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. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. The combination of hepatocellular injury (increases in aminotransferases of >3×ULN) and increase in total bilirubin (≥3×ULN) is a marker for potential serious liver injury. 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 ≥2×ULN, treatment should be stopped. There is no experience with the re-introduction of Bosentan in these circumstances.
Pre-existing Liver Impairment: Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Bosentan should generally be avoided in patients with moderate or severe liver impairment. In addition, Bosentan should generally be avoided in patients with elevated aminotransferases (>3×ULN) because monitoring liver injury in these patients may be more difficult.

INSTRUCTIONS: Store below 30°C. Protect from heat, light and moisture. Keep out of the reach of children.

PRESENTATION: BOZPAH (Bosentan) Tablet 62.5mg and 125mg are available in pack sizes of 10 tablets.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
NABIQASIM INDUSTRIES (PVT) LTD.
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