Bosentan Tablets are indicated for the treatment of PAH in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included (2.1, 4.1, 8.1).

5.7 Decreases in Hemoglobin and Hematocrit

Treatment with bosentan can cause a dose-related decrease in hemoglobin and hematocrit. There have been postmarketing reports of decreases in hemoglobin associated with treatment with bosentan.

The overall mean decrease in hemoglobin concentration for adult bosentan-treated patients was 0.9 g/dL (change to end of 1-year treatment) and 1.6 g/dL (change to end of 2-year treatment) compared to placebo. For patients treated with bosentan for more than 2 years, the mean decreases in hemoglobin concentration were 0.7 g/dL at 3 years, 0.3 g/dL at 4 years, and 0.2 g/dL at 5 years. The mean decrease in hematocrit concentration was 0.4% at 1 year and 0.6% at 2 years.

5.5 Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease has been reported in patients treated with bosentan. In one case, bosentan was added to treatment after failed or inadequate alternative treatments. The patient developed worsening pulmonary vascular obstruction with right heart failure and progressive dyspnea requiring treatment with parenteral inotropic agents. The patient died 8 months after bosentan treatment was initiated. In the postmarketing period, there were multiple reports of worsening pulmonary vascular obstruction and right heart failure. Some of these patients required additional treatment with parenteral inotropic agents. One patient died 10 months after treatment initiation. In another case, bosentan was initiated after treatment with a thrombolytic agent and corticosteroids. The patient developed worsening pulmonary vascular obstruction and right heart failure 1 month after bosentan treatment was initiated. The patient died 3 months after treatment initiation. In all but one case, bosentan was added to treatment after failed or inadequate alternative treatments.

In patients treated for greater than or equal to 12 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 24 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 36 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue.

In patients treated for greater than or equal to 48 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 60 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 72 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 96 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 120 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 156 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 180 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 216 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 252 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 288 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 324 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 360 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 396 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 432 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 468 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 504 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 540 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 576 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 600 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 636 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue.

In patients treated for greater than or equal to 672 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 708 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 744 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 780 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 816 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 852 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 888 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 924 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 960 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue. In patients treated for greater than or equal to 996 months, the most common adverse events associated with bosentan treatment were nausea, headache, arthralgia, and fatigue.
**Pharmacodynamics**

- Inhibitors of the ET-1 receptor, bosentan tablets: Bosentan tablets are an oral medication for the treatment of pulmonary arterial hypertension (PAH) in patients 18 years and older. Bosentan is a nonselective ET-1 receptor antagonist, which means it blocks both the ET-1 type A and B receptors. This action helps to reduce blood pressure and improve blood flow to the lungs.

**Pharmacokinetics**

- Absorption: Bosentan is well absorbed after oral administration, with a bioavailability of about 50%.
- Distribution: Bosentan is widely distributed throughout the body and has a high plasma protein binding of greater than 98%, mainly to albumin.
- Metabolism: Bosentan is metabolized by the liver, primarily by the cytochrome P450 (CYP) 3A4 and CYP 2C9 pathways. The major metabolites are inactive.
- Excretion: The majority of the administered dose is excreted in the urine as inactive metabolites within 3 days of dosing.

**Adverse Reactions**

- The most common adverse reactions associated with bosentan tablets include:
  - headache
  - injection site reactions
  - upper respiratory tract infection
  - nasopharyngitis
  - injection site pain

**Contraindications**

- Contraindications to bosentan tablets include:
  - pregnancy
  - lactation
  - known hypersensitivity to bosentan or any of its components
  - severe hepatic impairment
  - severe renal impairment
  - hypoxemia
  - marked fluid retention

**Warnings and Precautions**

- Bosentan tablets should be used with caution in patients with cardiac, respiratory, or hepatic disease, or with a history of stroke or transient ischemic attack.
- Bosentan treatment should not be initiated in patients with NYHA Class III-IV heart failure, left ventricular ejection fraction less than 35%, on diuretics, ACE inhibitor, and other therapies.
- Patients with NYHA Class II or Class III heart failure should not be treated with bosentan tablets.

**Interactions**

- Bosentan tablets interact with many drugs, including those that are metabolized by CYP 3A4 or CYP 2C9.

**Dosage and Administration**

- The recommended dose of bosentan tablets is 125 mg twice daily, taken at least 3 hours apart. The dose may be increased to 250 mg twice daily after at least 5 days of treatment at the 125 mg twice daily dose.

**Special Populations**

- Use caution when administering bosentan tablets to pediatric patients, elderly patients, or patients with impaired liver or renal function.

**Pregnancy and Nursing**

- Bosentan tablets are contraindicated for use in pregnant women.

**Patient Counseling**

- Patients should be counseled about the risks and benefits of bosentan tablets.

**References**

- For more information, refer to the full prescribing information for bosentan tablets.

**Drug Interaction Summary**

- Bosentan tablets are primarily metabolized by CYP 3A4 and CYP 2C9. They are subject to significant drug interactions due to their multiple metabolic pathways.

**Additional Information**

- Bosentan tablets are available in 125 mg tablets, which are white to off-white, oblong-shaped tablets.
- Bosentan tablets are supplied in bottles of 60 tablets (NDC 0591-2512-60) with a child-resistant closure.

**Legal Information**

- This Medication Guide has been approved by the U.S. Food and Drug Administration.

**Manufacturing**

- Watanuska Pharma Private Ltd., Verna, Goa 403 722 India

**Distributed by**

- Actavis Pharma, Inc. Parsippany, NJ 07054 USA

**Revised**

- October 2018

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