Prescriber's guide

Introduction to the essentials

Bosentan Accord is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%) and PAH associated with congenital systemic-to-pulmonary shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

Because of the risks of liver injury and birth defects associated with Bosentan Accord treatment, the use of Bosentan Accord is restricted.

Before you prescribe Bosentan Accord

- Before prescribing Bosentan Accord, review the summary of product characteristics and discuss the risks of treatment with your patients, including the risks of hepatotoxicity, anaemia and teratogenicity.
- Order and review a liver function test (ALT/AST/bilirubin) and haemoglobin concentration and confirm that your female patients of childbearing potential are not pregnant. See the "definition of childbearing potential" on page 4.
- Agree to order and monitor monthly liver function, haemoglobin and, if applicable, pregnancy test.
- Educate (includes giving the patient an information booklet) and counsel females of childbearing potential on the need to use reliable methods of contraception during

treatment with bosentan and for 1 month after treatment discontinuation. See the table "Reliable methods of contraception" on page 5.

- Educate and counsel females of childbearing potential to notify you if they suspect they may be pregnant.

Monitor liver function, haemoglobin and pregnancy test results monthly

Liver function test, heamoglobin and pregnancy test must be measured prior to initiation of Bosentan Accord and monitored on monthly basis. Notify Accord and/or MHRA/local health authority of any pregnancies or adverse events, including liver injury.

Hepatotoxicity

The following pages contain important safety information about treatment with Bosentan Accord. You must be familiar with this information before prescribing Bosentan Accord.

Bosentan Accord may cause liver damage/hepatotoxicity

- In clinical studies, bosentan caused at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases.
- After prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis were observed in a setting of close monitoring.
- Because these changes are a marker for potential serious liver injury, liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.
- Elevations in aminotransferases require close attention. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.
- Discontinue Bosentan Accord if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin $\geq 2 \times$ ULN.

Liver enzyme elevations: experience and management

- Use of Bosentan Accord should generally be avoided in patients with elevated aminotransferases (>3 × ULN) at baseline because monitoring liver injury may be more difficult.
- It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.

- Changes in aminotransferases may occur early or late in treatment.
- There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of Bosentan Accord could not be excluded.

- For treatment and monitoring recommendations,

- For patients whose monthly LFTs are ≤3 × ULN, no change in monitoring schedule or dosage is required.
- For patients whose monthly LFTs are >3 × ULN, close monitoring and either dose reduction or treatment cessation are necessary.

Elevated monthly liver function test results do not preclude treatment with Bosentan Accord. The table below provides recommendations on managing Bosentan Accord patients with elevated liver function test results.

Bosentan Accord aminotransferase (ALT/AST) management

ALT/AST level	Treatment and monitoring recommendations
≤3 × ULN*	**Continue** to monitor; no change in monitoring schedule or dosage
>3 to ≤5 × ULN	**Confirm** by another test; **if confirmed, reduce the dose or interrupt** treatment and monitor LFT levels every 2 weeks **Continue or reintroduce**† **Bosentan Accord** if levels return to pretreatment levels
>5 to ≤8 × ULN	**Confirm** by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks **Consider** reintroduction† of therapy if LFTs return to pretreatment levels
>8 × ULN	**Stop** therapy; do not reintroduce

*Upper limit of normal.

†If Bosentan Accord is reintroduced it should be at the starting dose; aminotransferase levels should be checked within 3 days.

Discontinue Bosentan Accord if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity

Pregnancy must be excluded and prevented during treatment

- Bosentan Accord is very likely to cause major birth defects if used by pregnant females, based on animal data.
- To prevent pregnancy, females of childbearing potential must use 2 reliable methods of contraception during treatment and for 1 month after stopping Bosentan Accord.
- Concomitant administration of bosentan and hormonal contraceptives have effect on hepatic/intestinal enzyme CYP3A4 metabolism. This leads to reduce efficacy of hormonal contraceptive. Hencehormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives, should not be used as the sole means of contraception because they may not be effective in patients receiving Bosentan Accord.
- Monthly pregnancy tests should be obtained.
- Please remember that a patient receiving Bosentan Accord can transition into a female of childbearing potential during the course of therapy.

Definitions of childbearing potential

- Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.
- Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for

longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Bosentan Accord

- Females of childbearing potential using Bosentan Accord must use 2 reliable methods of contraception unless they have had a tubal sterilization or have a Copper T 380A IUD or LNg-20 IUS.

<table>
<tr><th>Methods to use alone</th><th>Hormone (choose 1 and use with a barrier method)

1.1.1</th><th>Barrier (use both OR choose 1 and use with a hormone method)</th></tr>
<tr><td rowspan="2">• Intrauterine devices (IUDs)
- Copper T 380A IUD
- LNg-20 IUS
(progesterone IUD)
• Tubal sterilization</td><td>• Estrogen and progesterone
- Oral contraceptives
- Transdermal patch
- Vaginal ring
• Progesterone only
- Injection
- Implant</td><td>• Male condom with spermicide
• Diaphragm with spermicide OR Cervical cap with spermicide</td></tr>
<tr><td colspan="2">A partner’s vasectomy still requires 1 additional method of contraception.</td></tr>
</table>

Reporting of suspected adverse reactions

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at http://www.medicinesauthority.gov.mt/adrportal,

and sent by post or email to;

Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
postlicensing.medicinesauthority@gov.mt