Bosentan Accord Prescriber's Guide

This guide provides important safety information about Bosentan Accord regarding the risk of liver injury and birth defects. Information is provided concerning the monitoring of liver function, treatment management and prevention of pregnancy.

Introduction

Bosentan Accord is indicated for the treatment of pulmonary arterial hypertension (PAH) to improve exercise ability and to reduce the deterioration of clinical symptoms. Studies undertaken to establish the effectiveness of treatment have mainly included 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 walking 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 the disease progresses.

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

Before you prescribe Bosentan Accord

- Before prescribing Bosentan Accord, you must review the summary of product characteristics and discuss the risks of treatment with your patients, including the

risks of hepatotoxicity, anaemia and teratogenicity. Full prescribing information is contained in the approved summary of product characteristics, which can be found on the Medicines and Healthcare products Regulatory Agency (MHRA) website, the Electronic Medicines Compendium or the Accord website.

- You must order and review a blood test to assess both liver function (ALT/AST/bilirubin) and haemoglobin concentration. Also you should confirm that your female patients of childbearing potential are not pregnant.
- You must order and monitor tests to assess the following on a monthly basis: liver function, haemoglobin and, if applicable, a test for pregnancy. You must inform your patients about the importance of monthly testing and ensure that the results are obtained and reviewed.
- You should educate females of childbearing potential on the need to use reliable methods of contraception during treatment with bosentan and for 1 month after treatment discontinuation. The patient should be referred to the patient leaflet and patient alert card.
- You must instruct females of childbearing potential to notify you immediately if they suspect they may be pregnant.

Monitor liver function, haemoglobin and pregnancy test results monthly

Liver function, haemoglobin and pregnancy testing must be carried out prior to initiation of Bosentan Accord, and monitored on a monthly basis. You should notify Accord medical information and / or the MHRA of any pregnancies or adverse events, including liver injury.

Safety profile: Liver Warnings

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 a 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 and close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed.
- 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 monitoring is required thereafter. In addition, liver function must be measured 2 weeks after any dose increase.
- 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 is contraindicated in patients with elevated aminotransferases (>3 × ULN) at baseline, because monitoring of liver injury may be more difficult.
- Use of Bosentan Accord is contraindicated in Child-Pugh Class B or C, i.e. moderate to severe hepatic impairment.
- It is important to strictly adhere to the monthly monitoring schedule whilst the patient is being treated with bosentan, the reasons for this are:
    - Changes in aminotransferases may occur early or late in treatment.
    - There have been rare post-marketing reports of liver failure and unexplained hepatic cirrhosis. The contribution of bosentan could not be excluded as a potential cause of these reports.

For treatment and monitoring recommendations please refer to Table 1 "Management of liver aminotransferase levels (ALT and AST) in patients using Bosentan Accord"

- 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. Table 1 provides recommendations on managing Bosentan Accord patients with elevated liver function test results.

Bosentan Accord aminotransferase (ALT/AST) management

Table 1. Management of liver aminotransferase levels (ALT and AST) in patients using Bosentan Accord

ALT/AST level	**Treatment and monitoring recommendations**
≤3 × ULN*	**Continue** to monitor, without changing the monitoring schedule or dosage
>3 to ≤5 × ULN	**Confirm** by a second liver test. **If confirmed,** a decision should be made on an individual basis to continue Bosentan Accord, possibly at **a reduced dose, or to interrupt treatment.** Monitoring of aminotransferase levels should be continued at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, **continuation or re-introduction Bosentan Accord** according to the conditions described below† should be considered.
>5 to ≤8 × ULN	**Confirm** by a second liver test. **If confirmed,** treatment should be stopped and aminotransferase levels monitored at least every 2 weeks. **Consider** reintroduction of Bosentan Accord according to the conditions described below† if aminotransferase levels return to pre-treatment values
>8 × ULN	**Stop** treatment. Re-introduction of Bosentan Accord is not to be considered.

*Upper limit of normal.

† *Re-introduction of treatment*

Re-introduction of treatment with Bosentan Accord should only be considered if the potential benefits of treatment with Bosentan Accord outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2 of the summary of product characteristics.

Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.

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

Safety profile: Pregnancy warnings

Teratogenicity

Pregnancy must be excluded and prevented during treatment

- Animal studies with Bosentan have shown reproductive toxicity. Bosentan Accord may cause major birth defects if used by pregnant females. Therefore its use is contraindicated during pregnancy and in females of childbearing potential who are not using reliable methods of contraception.
- Pregnancy should be excluded prior to initiating Bosentan Accord in females of childbearing potential
- To prevent pregnancy, females of childbearing potential must use 2 reliable methods of contraception during treatment and for 1 month after stopping Bosentan Accord.
- Due to a Pharmacokinetic interaction, Bosentan Accord may render hormonal contraceptives ineffective. Therefore, hormonal 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 carried out.
- Please remember that a patient receiving Bosentan Accord can transition into a female of childbearing potential during the course of therapy.

Further information on the use of Bosentan Accord is available in the summary of product of product characteristics, which can be found on the MHRA website, the Electronic Medicines Compendium or the Accord website

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, at : www.mhra.gov.uk/yellowcard.

Adverse reactions can also be reported to Accord Healthcare Ltd at the company contact point below.

Company contact point:

Address
Actavis UK Ltd, a subsidiary of Accord Healthcare Ltd, Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK
Medical Information Direct Line
+44 (0)1271 385 257
Medical Information e-mail
medinfo@accord-healthcare.com