This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

# Prescriber Guide

## Important Safety Information You Need To Know When Prescribing Gonista® (Bosentan)

This Prescriber's Guide provides a summary of the most important safety information you should know about Bosentan and the following important risks associated with Bosentan treatment and how to minimise them:

- Hepatotoxicity
- Teratogenicity
- Decrease in haemoglobin concentration
- Pulmonary oedema associated with pulmonary veno-occlusive disease (pvod)
- Drug interactions possible to occur when using Bosentan

Before you prescribe Bosentan, you must familiarise yourself with the content of this educational guide as well as the full prescribing information.

### INTRODUCTION TO BOSENTAN

#### What is Gonista® (Bosentan)?

Gonista® tablets contain bosentan, which blocks a naturally occurring hormone called endothelin-1 (ET-1), which causes blood vessels to narrow. Gonista® therefore causes blood vessels to expand and belongs to the class of medicines called "endothelin receptor antagonists".

#### Indications

Gonista® (Bosentan) is used to treat:

- **Pulmonary arterial hypertension (PAH):** PAH is a disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels (the pulmonary arteries) that carry blood from the heart to the lungs. This pressure reduces the amount of oxygen that can get into the blood in the lungs, making physical activity more difficult. Gonista® widens the pulmonary arteries, making it easier for the heart to pump blood through them. This lowers the blood pressure and relieves the symptoms.

Gonista® is used to treat patients with class III PAH to improve exercise capacity (the ability to carry out physical activity) and symptoms. The 'class' reflects the seriousness of the disease: 'class III' involves marked limitation of physical activity. Some improvements have also been shown in patients with class II PAH. 'Class II' involves slight limitation of physical activity. The PAH for which Gonista® is indicated can be:

- primary (with no identified cause or familial);
- caused by scleroderma (also called systemic sclerosis, a disease where there is abnormal growth of the connective tissue that supports the skin and other organs);
- caused by congenital (inborn) heart defects with shunts (abnormal passageways) causing abnormal flow of blood through the heart and lungs.

- **Digital ulcers**: (sores on the fingers and toes) in adult patients with a condition called scleroderma. Gonista reduces the number of new finger and toe ulcers that appear.

## INFORMATION ABOUT POSSIBLE RISKS ASSOCIATED WITH THE USE OF BOSENTAN

### Teratogenicity:

Bosentan is teratogenic and embryotoxic in animals and its use is contraindicated in pregnant women and in women of child-bearing potential who are not using reliable methods of contraception. Before initiating Bosentan treatment in women of child-bearing potential:

- confirm absence of pregnancy
- ensure reliable contraception is initiated.

Prescribers and patients must be aware that since hormonal contraceptives methods, such as oral contraceptives, hormone injections, implants or transdermal patches, are not reliable due to the interaction between them and bosentan, hormonal contraception should not be used as the sole method of contraception. To prevent pregnancy, you need to advise patients to use a barrier method - such as a condom, diaphragm, or vaginal sponge - along with any of the hormonal contraceptive methods already in use.
It is also recommended to perform monthly pregnancy tests.

### Hepatotoxicity:

Bosentan is hepatotoxic and is contraindicated in patients with moderate to severe hepatic impairment (Child Pugh stages of Class B or C).

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Bosentan. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase. Elevations in liver aminotransferase levels (aspartate aminotransferase and/or alanine aminotransferase-AST/ALT) associated with Bosentan are dose dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment but may also occur late in treatment.

**The dose should be adjusted if hepatic aminotransferase levels rise above 3 times the Upper Limit of Normality (ULN) as mentioned in the table.**

| ALT/AST levels | Treatment and monitoring recommendations |
|---|---|
| > 3 and < 5 × ULN | Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate. |
| > 5 and < 8 × ULN | Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment. |
| > 8 × ULN | Treatment should be stopped and re-introduction of Bosentan should not be considered. There is no experience with re-introduction of Bosentan in these circumstances. |

**Haemoglobin Decrease:**

Bosentan has been associated with dose-related decreases in haemoglobin concentration. It is recommended that haemoglobin concentrations should be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment. In the post marketing period, cases of anaemia requiring red blood cell transfusion have been reported.

**Pulmonary Oedema Associated with Veno-Occlusive Disease:**

Bosentan may cause pulmonary oedema when used in patients with pulmonary veno-occlusive disease. The possibility of veno-occlusive lung disease should be considered in patients with PAH who show signs of pulmonary oedema during treatment with Bosentan.

**Possible Interactions:**

Interaction with oral contraceptives: Hormonal contraceptive methods such as oral contraceptives, hormone injections, implants, or transdermal patches, do not effectively prevent pregnancy in women who are being treated with Bosentan. To prevent pregnancy, you need to advise patients to use a barrier method - such as a condom, diaphragm, or vaginal sponge - along with any of the hormonal contraceptive methods already in use.

Interaction with sildenafil: Caution is advised in case of concomitant administration of sildenafil and Bosentan since there is a decrease in the bioavailability of sildenafil and an increase in Bosentan drug levels in the blood. Caution is advised in case of concomitant administration.

Interaction with antiretrovirals: When initiating treatment with lopinavir / ritonavir and other ritonavir-containing regimens for treatment of HIV concomitantly with Bosentan, it is necessary to adjust the dosage of Bosentan. Co-administration of Bosentan with cyclosporin A is contraindicated.

## ADVICE FOR PRESCRIBERS

- Healthcare professionals should refer to Bosentan Summary of Product Characteristics (SmPC) and to Bosentan Patient Information Leaflet (PIL) to ensure they are fully aware of every information when considering use of Bosentan in individual patients.
- Please Remember to Hand the Patient Card to the Patient at the Time of Prescription.
- Healthcare providers are asked to report any suspected adverse reactions.

### Call For Reporting:

Any suspected adverse reactions should be reported immediately to MS Pharma Saudi or to the National Pharmacovigilance and Drug Safety Centre.

- **Pharmacovigilance department at MS Pharma:**
  - Email: pharmacovigilance@mspharma.com
  - Website: www.mspharma.com
  - Phone No: + 966112790122 Ext. 6013

- **The National Pharmacovigilance Center (NPC): (Saudi food and drug authority)**
  - Email: npc.drug@sfda.gov.sa
  - Call Center: 19999
  - Website: https://ade.sfda.gov.sa/
  - QR Code: