Pertensio (Bosentan)

Prescriber's Guide

Version: 1

Date: 09/2018

Pertensio 62.5mg & 125mg
Film-Coated Tablet
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The following pages contain important safety information about Pertensio regarding the risk of hepatotoxicity, Teratogenicity, Decrease in haemoglobin concentration. You must be familiar with this information before prescribing Pertensio.

Introduction:

Pertensio (Bosenta) is indicated for the reatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III.

Efficacy has been shown in:

- Primary (idiopathic and heritable) pulmonary arterial hypertension
- Pulmonary arterial hypertension secondary to scleroderma without significant interstitial pulmonary disease
- Pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology"

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 Pertensio treatment, the use of this medicine is restricted

Safety profile: Liver Warnings

Hepatotoxicity:

- In clinical studies, Pertensio 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.
- Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In addition, liver function must be measured 2 weeks after any dose increase.
- In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (more than 12 months) therapy with Pertensio in patients with multiple comorbidities and drug therapies.
- There have also been reports of liver failure. The contribution of Pertensio in these cases could not be excluded.
- Elevations in aminotransferases require close attention. Generally, avoid using Pertensio in patients with elevated aminotransferases (greater than 3 times the ULN) at baseline because monitoring for hepatotoxicity may be more difficult.
- Stop treatment with Pertensio if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (eg, abdominal pain, fever, jaundice, nausea, unusual lethargy or fatigue, vomiting) or increases in bilirubin 2 times the ULN or greater

Before you prescribe Pertensio

- Before prescribing Pertensio you must review the summary of product characteristics and discuss the risks of treatment with your patients, including the risks of hepatotoxicity, teratogenicity, anaemia, and fluid retention/peripheral edema.
- 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 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 Pertensio 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 and pregnancy test results monthly

Liver function and pregnancy testing must be carried out prior to initiation of Pertensio and monitored on a monthly basis.

Liver enzyme elevations: experience and management

- Use of Pertensio is contraindicated in patients with elevated aminotransferases (>3 × ULN) at baseline, because monitoring of liver injury may be more difficult.
- Use of Pertensio 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 Pertensio, 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 Pertensio 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 Pertensio "

- 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 should be considered.

Table 1 provides recommendations on managing Pertensio patients with elevated liver function test results.

Pertensio aminotransferase (ALT/AST) management

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

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Pertensio. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.
Recommendations in case of ALT/AST elevations

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 × ULN	The result should be confirmed by a second liver test; if confirmed, a decision should be made on an individual basis to continue Pertensio, possibly at a reduced dose, or to stop Pertensio administration. Monitoring of aminotransferase levels should be continued at least every 2 weeks. If the aminotransferase levels return to pre-treatment values continuing or re-introducing Pertensio according to the conditions described below should be considered.
> 5 and ≤ 8 × ULN	The result should be confirmed by a second liver test; if confirmed, treatment should be stopped and aminotransferase levels monitored at least every 2 weeks. If the aminotransferase levels return to pre-treatment values re-introducing Pertensio according to the conditions described below should be considered.
> 8 × ULN	Treatment must be stopped and re-introduction of Pertensio is not to be considered.

In the case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Pertensio is not to be considered.

<u>Re-introduction of treatment</u>

Re-introduction of treatment with Pertensio should only be considered if the potential benefits of treatment with Pertensio 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 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.

ULN = Upper Limit of Normal

Safety profile: Pregnancy warnings

Teratogenicity

Pregnancy must be excluded and prevented during treatment.

- Pertensio is likely to cause major birth defects if used by pregnant women based on animal data. Therefore, its use is contraindicated during pregnancy and in females of childbearing potential who are not using reliable methods of contraception.
- Pregnancy must be excluded before the start of treatment with Pertensio in females of childbearing potential
- Throughout treatment and for 1 month after stopping Pertensio, women of childbearing potential must use 2 reliable methods of contraception unless the patient has an intrauterine device (IUD) or tubal sterilization in which case no other contraception is needed.
- Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives, should not be used as the sole means of contraception because these may not be effective in patients receiving Pertensio.

✓ If there is any doubt about what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended.

✓ Because of possible hormonal contraception failure during Pertensio treatment, and also bearing in mind the risk that pulmonary hypertension severely deteriorates with pregnancy, monthly pregnancy tests during treatment with Pertensio are recommended to allow early detection of pregnancy.

✓ Please remember that a patient receiving Pertensio can transition into a female of childbearing potential during the course of therapy

Hematologic effects:

- Dose-related decreases in hematocrit/hemoglobin may be observed, usually within the first few weeks of therapy with subsequent stabilization of levels by 4 to 12 weeks of treatment.
- Monitor hemoglobin prior to treatment initiation, after 1 and 3 months, and every 3 months thereafter. Significant decreases in hemoglobin require further evaluation to determine the cause and specific management.

Fluid retention/peripheral edema:

- Development of peripheral edema due to treatment and/or disease state (pulmonary arterial hypertension) may occur.
- There have also been postmarketing reports of fluid retention requiring treatment (eg, diuretics, fluid management, hospitalization) for heart failure.
- If clinically significant fluid retention develops (with or without weight gain), further evaluation is necessary to determine cause and appropriate treatment or discontinuation of therapy.
- Use with caution in patients with underlying heart failure due to potential complications from fluid retention. In a scientific statement from the American Heart Association, bosentan has been determined to be an agent that may exacerbate underlying myocardial dysfunction (magnitude: major) (AHA [Page 2016])

Drug Interaction:

Interaction with oral contraceptives: Hormonal contraceptive methods such as oral contraceptives, hormone injections, implants, or transdermal patches, do not safely 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: Concomitant administration of sildenafil and bosentan decreases the bioavailability of sildenafil and increases bosentan drug levels in 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.
Remember that co-administration of bosentan with cyclosporin A is contraindicated. Please consult the the Summary of Product Characteristics and the Patient leaflet for the rest of the interactions.

Further information on Pertensio

For further information on Pertensio please read the Summary of Product Characteristics here attached Should you have any questions or need additional prescriber guide, our scientific information's department remains at your disposal.

Call of reporting

As a reminder, there is a need to report any suspected adverse reactions to the National Pharmacovigilance and Drug Safety Centre or Pharmacovigilance department in SPIMACO, according to the following

Calling: 19999
By e-mail: npc.drug@sfda.gov.sa
Or by fax: +966 11 2057662
Or by online: https://ade.sfda.gov.sa

Pharmacovigilance department in Spimaco
QPPV: Arwa Alsayil
E-mail : Arwa.alsayil@spimaco.sa
Fax no. : +966 11 252 3300
Phone: +966 11 252 3393