Re: Treposuvi solution for infusion and the risk of central venous catheter-related bloodstream infections and sepsis

Dear Doctor,

Treposuvi solution for infusion has been approved for the treatment of idiopathic or hereditary pulmonary arterial hypertension (PAH) to improve exercise tolerance and symptoms in adult patients with New York Heart Association (NYHA) classification III diseases. It should be initiated and monitored by specialists experienced in the treatment of pulmonary hypertension.

Central venous catheter associated blood stream infections and sepsis have been reported in patients receiving treprostinil by intravenous infusion. These risks are attributable to the drug delivery system. A Centres for Disease Control retrospective survey of seven centers in the United States that used intravenous treprostinil for the treatment of PAH found an incidence rate for catheter-related bloodstream infections of 1.10 events per 1000 catheter days. Clinicians should be aware of the range of possible Gram-negative and Gram-positive organisms that may infect patients with long-term central venous catheters.

Treposuvi can be administered by continuous subcutaneous or intravenous infusion, but due to the risks associated with chronic use of indwelling central venous catheters, including serious blood stream infections, subcutaneous infusion (undiluted) is the preferred method of administration. Continuous intravenous infusion should be reserved for patients who have been stabilised with a subcutaneous infusion of treprostinil and who become intolerant of subcutaneous administration, and in whom these risks are considered acceptable.

Minimising the risk of catheter-related blood stream infections

To minimise the risk of catheter-related bloodstream infections in patients receiving treprostinil via intravenous infusion, we would like to draw your attention to the following. This advice is in accordance with the current best practice guidelines for the prevention of catheter-related blood stream infections, and includes:

<u>General Principles</u>

- Use of a cuffed and tunnelled central venous catheter (CVC) with a minimum number of ports.
- Insertion of the CVC using sterile barrier techniques

- Use of proper hand hygiene and aseptic techniques if the catheter is inserted, replaced, repaired or accessed, or when the catheter insertion site is examined, connected and/or dressed.
- Use of a sterile gauze (changed every two days) or a sterile, transparent, semi-permeable dressing (changed at least every seven days) to cover the catheter entry site.
- The dressing should be changed whenever it gets wet, loosened or soiled, or after examining the entry site.
- Topical antibiotic ointments or creams should not be used, as they promote fungal infections and antimicrobial-resistant bacteria.

Duration of use of the diluted Treposuvi solution

- The diluted product must not be used for longer than 24 hours.

Use of in-line 0.2 micron filter

- A 0.2 micron filter must be placed between the infusion tubing and the catheter hub and replaced every 24 hours at the time of changing the infusion reservoir.

Two further recommendations that are potentially important for the prevention of water-borne Gram-negative blood stream infections relate to management of the catheter hub. These include:

<u>Use of a split septum closed hub system</u>

- The use of a closed hub system (preferably with a split septum and not a mechanical valve device) ensures that the catheter lumen is sealed each time the infusion system is disconnected. This prevents the risk of exposure to microbial contamination.
- The split-septum closed-hub device should be changed every seven days.

<u>Infusion system luer lock inter-connections</u>

The risk of contamination with water-borne, Gram-negative organisms is likely to be increased if a luer lock connection is wet when changing the infusion line or the closed hub. Therefore:

- Swimming or submersion of the infusion system at the site of connection with the catheter hub should be discouraged.
- There must not be any visible water in the Luer Lock connection threads when replacing the closed hub device.
- The infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement.

Please refer to the SmPC for further information on the risk of catheter-related blood stream infections.

An educational program for Treposuvi, to minimise the risk of catheter-related bloodstream infections, has been developed and approved by the HPRA. It comprises the following:

- Training presentation for healthcare professionals
- Patient Brochure
- Patient Questionnaire

We are committed to monitoring the incidence of bloodstream infections associated with central lines in connection with IV treprostinil therapy. As a result, we would be grateful if you could inform our pharmaceutical safety department immediately of any suspected cases of catheter-associated infections of the bloodstream, which have occurred in any patient of yours treated with IV treprostinil. Please use the enclosed form ("Treposuvi event of special interest – bloodstream infection") to do so. Any dosage errors or pump/infusion tube malfunctions should also be reported.

Please report all adverse reactions in connection with Treposuvi solution for infusion to Orpha-Devel Handels und Vertriebs GmbH, Wintergasse 85/1B, 3002 Purkersdorf, Austria.

Fax: +43 1 503 7244 41, Email: drugsafety@aoporphan.com

Adverse reactions can also be reported via HPRA Pharmacovigilance, website: www.hpra.ie

Thank you for your cooperation, which helps us to guarantee the ongoing safety of patients with PAH who are treated with Treposuvi.

Kind regards,

Medical Department

Appendices:

- Information booklets about Treposuvi (patient brochure, patient questionnaire)
- "Treposuvi event of special interest – bloodstream infection" form
- Summary of Product Characteristics for Treposuvi (1 mg/ml solution for infusion)