Healthcare professional guide

Risk of central venous catheter related blood stream infections and sepsis associated with the intravenous route of administration of ***Treprostinil Tillomed*** Solution for Infusion

This healthcare professional training guide is a mandatory part of the approval of Treprostinil Tillomed Solution for Infusion. This document is part of the additional risk-minimisation measures implemented to reduce the risk of occurrence of catheter-related blood stream infections when Treprostinil Tillomed Solution for Infusion is administered by intravenous continuous infusion via an external infusion pump and a central venous catheter (CVC).

The other risk minimisation measures include: a patient brochure and a patient questionnaire. Copies of all these materials are available via https://www.tillomed.de/index.html, as well as on https://www.hpra.ie/homepage/medicines/safety-information/educational-material

Prescribers should also read the currently approved Summary of Product Characteristics (SmPC) for this product available via the https://www.tillomed.de/index.html.

Summary of key messages:

- Due to the risk of central venous catheter-related blood stream infection the subcutaneous route is the preferred mode of delivery for treprostinil infusion therapy.
- Continuous intravenous infusion should be reserved for those patients that are stabilised on subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable.
- For patients requiring treatment with a continuous intravenous infusion of treprostinil delivered via an indwelling central venous catheter the risk of blood stream infection and sepsis can be minimised by adopting best practice guidelines which are outlined in this health professional guide.
- The clinical team responsible for the care of the patient should complete the short patient questionnaire with the patient at initiation of treatment, after they have been on treatment for at least 3-6 months, and if the patient experiences the adverse event of catheter associated blood stream infection.
  The questionnaire will assess the ease with which patients are able to apply the risk minimisation activities and identify any particular difficulties that they experience.

  Completed questionnaires should be sent via email to PVUK@tillomed.co.uk, or via post at: 220 Butterfield, Great Marlings, Luton, LU2 8DL.

ABOUT THE DRUG:

Class of drug and indication:

Treprostinil is a prostacyclin analogue indicated for idiopathic or hereditary Pulmonary Arterial Hypertension (PAH) to improve tolerance to physical stress and reduce disease symptoms in New York Heart Association (NYHA) Class III patients.

How is it administered?

Due to the risks of the range of potential Gram-negative and Gram-positive organisms that can infect patients with permanent central venous catheters or indwelling central venous catheters, including severe circulatory infections, subcutaneous infusion (undiluted) is the preferred mode of application. Continuous intravenous infusion should be reserved for patients stabilised on a subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable.

The treatment should be initiated and monitored only by clinicians experienced in the treatment of pulmonary hypertension

Considerations when selecting patients for IV treprostinil therapy

It is administered intravenously by continuous infusion through a surgical central venous indwelling catheter or temporarily by means of a peripheral venous cannula using an infusion pump developed for intravenous drug administration.

- When deciding on treprostinil therapy, one should consider that a chronic infusion is highly likely to continue for a long time. For this reason, the willingness and responsibility of the patient for an indwelling catheter and an infusion device must be carefully examined.

- Circulatory infections associated with central venous catheters and sepsis have been reported in patients receiving treprostinil intravenous infusion. These risks are attributable to the drug delivery system.

- The treating physician must ensure that the patient is fully instructed in the operation of the selected infusion set.

ABOUT THE RISK:

Important identified risk for the attention of treating doctors and healthcare professional-

Central venous catheter-related blood stream infections and sepsis associated with the intravenous route of administration (risk attributable to drug delivery system)

Proposed mechanism of this risk:

Several interrelated factors have been proposed to participate in the pathogenesis of catheter associated blood stream infections. The catheter itself can be involved in 4 different pathogenic pathways including colonisation of the catheter tip and cutaneous tract with skin flora; colonisation of the catheter lumen caused by contamination; hematogenous seeding of the catheter from another infected site; and contamination of the lumen of the catheter with infusate.

Reference: *Gahlot R, Nigam C, Kumar V, Yadav G. Anupurba S. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci. 2014;4(2):162–167*

RISK MINIMISATION

Reference: *Doran AK, Ivy DD, Barst RJ, et al. Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract Suppl. 2008;(160):5-9. doi:10.1111/j.1742-1241.2008.01811.x*

To minimise the risk of catheter associated circulatory infections:

For patients that require treatment with a continuous intravenous infusion of treprostinil delivered via an indwelling central venous catheter, the risk of blood stream infection and sepsis can be minimised by adopting best practice guidelines, which include:

General principles

- Use of a cuffed and tunnelled central venous catheter (CVC) with a minimum number of ports
- Introduction of the CVC in compliance with sterile barrier techniques
- Use of proper hand hygiene and aseptic techniques when the catheter is inserted, replaced, accessed, repaired or when the catheter insertion site is examined and/or dressed
- A sterile gauze (change every two days) or a sterile transparent semi- permeable wound dressing (change at least every seven days) should be used to cover the insertion site of the catheter
- The dressing should be replaced whenever it becomes damp, loosened, or soiled or after examination of the site
- Topical antibiotic ointments or creams should not be applied as they may promote fungal infections and antibiotic resistant bacteria.
- Do not submerge the catheter or catheter site in water. Showering should be permitted if precautions can be taken to reduce the likelihood of introducing organisms into the catheter (e.g., if the catheter and connecting device are protected with an impermeable cover during the shower).

Duration of use of the diluted treprostinil solution:

- The maximum period of use of the diluted product should not exceed 24 hours.

The use of an inline filter (0.2 micron)

- 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 other recommendations which are potentially important in preventing waterborne circulatory infections with Gram negative bacteria relate to catheter hub handling. These include:

- ***The use of a split septum closed hub system***
    - The use of a closed-hub system (preferably a split septum rather than a mechanical valve device), ensures that the lumen of the catheter is sealed each time the infusion system is disconnected. This reduces the risk of microbial contamination of the lumen
    - The split-septum closed hub device should be replaced every 7 days.
- ***Infusion system - Luer lock inter-connections***
    - The risk of contamination with water-borne Gram-negative organisms is likely to be increased if a Luer lock inter-connection is wet at the time of exchanging either the infusion line or the closed hub. Therefore:
        - swimming and submersion of the infusion system at the site of connection with the catheter hub should be discouraged

- at the time of replacing the closed-hub device, there should not be any water visible in the Luer lock connection threads
- the infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement

HARD COPIES OF ADDITIONAL RISK MINIMISATION MATERIALS:

If you require hard copies of the materials (healthcare professional guide, patient brochure, patient questionnaire) or additional information, please contact the Tillomed Pharma GmbH via the contact details below.

ADVERSE EVENT REPORTING:

Adverse events should be reported.
Reporting forms and information can be found at:
HPRA Pharmacovigilance
Website: www.hpra.ie

Adverse events should also be reported to Tillomed Pharma GmbH at

Tel: +44 (0) 1480 402400

E-mail: PVUK@tillomed.co.uk

Please be informed that, upon reporting a central venous catheter-related blood stream infections or sepsis, the MAH will contact you to complete the event of special interest form. Completed questionnaires should be sent via email to: PVUK@tillomed.co.uk, or via post at: 220 Butterfield, Great Marlings, Luton, LU2 8DL.

CONTACT FOR ADVISORY:

For further information or enquiry please contact Tillomed Pharma GmbH Medical Information Department at:

Tel: +44 (0) 1480 402400

E-mail: PVUK@tillomed.co.uk