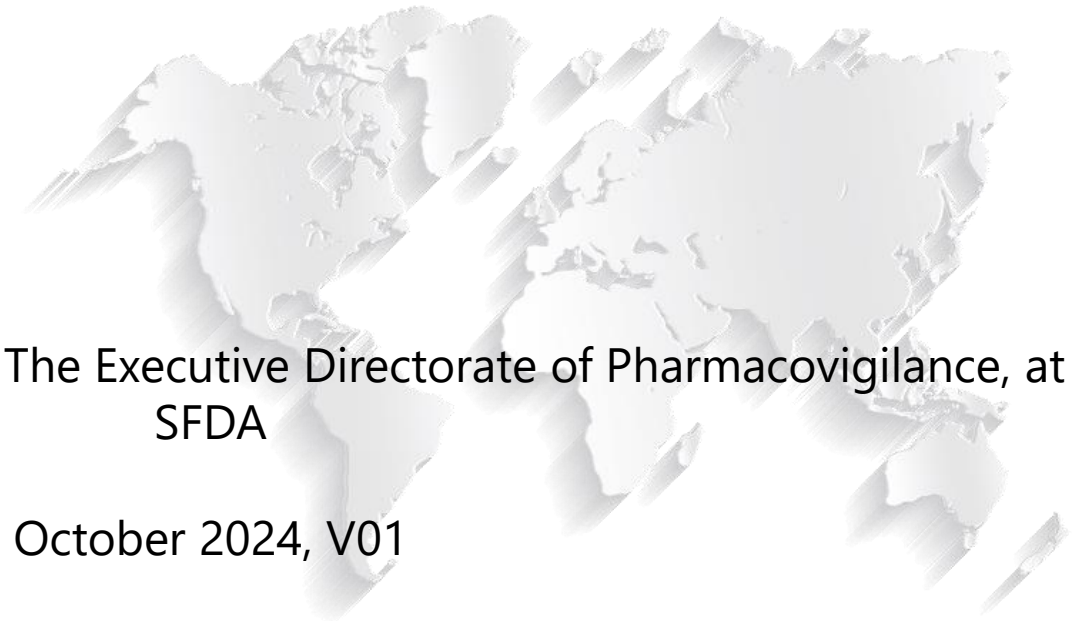
Training for healthcare professionals in the safe handling of intravenous (IV) Trisuva® (Treprostinil) and the prevention (of catheter-related bloodstream infections (CRBI



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

October 2024, V01

Main components of this training unit

- Background of the risk of CRBI
- Practical techniques to minimise CRBI
- The treprostinil license
- Detecting and reporting of suspected CRBI, dosage errors and pump/infusion tube malfunctions
- The transition from SC to IV treprostinil
- Summary
- Recommended readings

BI = bloodstream infection;
CRBI = catheter-related bloodstream infection;
CVC = central venous catheter

The risk of catheter-related bloodstream infections (CRBI)

CRBI and IV prostanoids: A retrospective study by the CDC

	Days of medication (total)	CRBI rate per 1,000 days of medication
IV epoprostenol	201,158	0.43
IV treprostinil	51,183	1.11
Total[1]	**252,341**	**0.57**

- Retrospective study of records from patients at seven large centres in the USA, who received IV prostanoids (epoprostenol or treprostinil) between 2003 and 2006
- Higher rate of CRBIs observed in IV treprostinil patients in comparison with epoprostenol patients

BI = bloodstream infection; CDC = Centers for Disease Control; CRBI = catheter-related bloodstream infection; IV = intravenous; MMWR = mortality and morbidity weekly report

1. Barst et al. MMWR Morb Mortal Wkly Rep. 2007;56:170-172;

The incidence of CRBI in connection with use of CVC

- In patients who regularly receive IV treatment via CVC, around five CRBI occur per 1,000 catheter days in the USA[1]
- This results in 80,000 CRBI yearly[2]

Rate of CRBI per 1,000 catheter days (Range)

Total IV treatment via CVC: Range 0.3 to 9.1 [3-5]

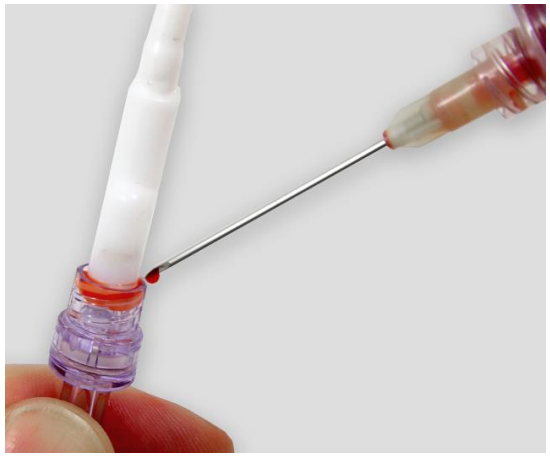
PAH IV treatment via CVC: Range 0.1 to 1.1 [6,7]

CRBI = catheter-related bloodstream infection; CVC = central venous catheter; IV = intravenous; PAH = pulmonary arterial hypertension

1. National Nosocomial Infections Surveillance System. *Am J Infect Control*. 2004;32:470-485; 2. O'Grady et al. *MMWR Recomm Rep*. 2002;51(RR-10):1-29; 3. van Hoff et al. *J Clin Oncol*. 1990;8:1255-1262; 4. Decker et al. *Pediatr Clin North Am.* 1988;35:579–612; 5. Moureau et al. *J Vasc Interv Radiol*. 2002;13:1009–1101; 6. Akagi et al. *Circ J*. 2007;71:559-564; 7. Barst et al. *MMWR Morb Mortal Wkly Rep*. 2007;56:170-172

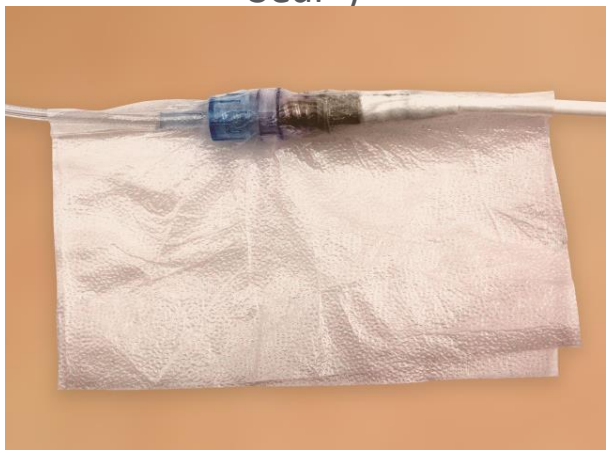
Occurrence of pathogens in the central venous catheter

Dye follows the course of the thread[1]



Contamination occurs upon removal[2]

A connection covered with a plastic barrier (for example: GLAD Press'n Seal®)



GLAD Press'n Seal® is an example of a sealable plastic wrap, which can be used to protect the catheter hub connection from water-borne contaminations[2]

1. Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829; 2. Doran. Health Matters; Herbst 2008. http://www.phassociation.org/Document.Doc?id=226. Accessed in May 2010

Pulmonary Hypertension Association: Guidelines of catheter care and the prevention of CVC- related blood stream infections

Possible entry sites of bloodstream infections

- CVC entry site on the skin
- Catheter hub and tube connections
- Prostaglandin bottles and containers

CVC = central venous catheter

Pulmonary Hypertension Association: Guidelines of catheter care and the prevention of CVC- related blood stream infections

The guidelines for CRBI prevention of the Society for Pulmonary Hypertension should be followed [1]

- Protecting the catheter hub is crucial
- Avoiding contact with water is important
- Please take care of the type of dressing at the insertion site, and observe the site

BI = bloodstream infection; CRBI = catheter-related bloodstream infection; CVC = central venous catheter

1. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Practical techniques to minimise CRBI

Important patient training & general principles

- Patients must understand the risks associated with the treatment and be aware of the role they can play themselves in the minimisation of such risks. It is the duty of the responsible clinical team to train patients in the following areas:
  - **Hand hygiene** – the significance of good hand hygiene with relevant cleaning agents as well as easy and effective techniques to maintain asepsis during preparation of infusions.
  - **Area preparation** – The need to always carefully prepare the environment at home before changing the container solution and the tube must be discussed.
  - **Maintenance and observation of** the insertion site of the catheter into the skin and the frequency of changing the gauze or the transparent wound dressing must be regularly monitored and maintained.
  - **The importance of maintaining dry connection hubs** and the use of waterproof bandages or wrapping when bathing and showering. Swimming must be greatly discouraged.
  - **Awareness of signs and symptoms** of suspected CRBI and the procedure for reporting them to healthcare specialists.

Important patient training & general principles

- An information brochure has been prepared to help you with explaining these key points to patients. It is important that you check that the patients have understood this brochure after you instructed them verbally.

0.2 micron inline filter

- Eliminates bacteria, fungi, moulds and foreign particles from the infusion tube
- During a study performed by the originator, the catheter tube was deliberately contaminated in order to assess the filter efficiency
- There were no signs of contamination in the fluid samples taken after the filter, which had been cultivated for disease pathogens

Closed hub system with split septum

- The catheter hub is the most common source of central venous catheter infections.[1,2]
- Closed hub systems became available at the end of the 1980s.
- A needle-free setup with a split septum is preferred over a mechanical valve device because it ensures that the lumen of the catheter is sealed each time the infusion system is disconnected which reduces the risk of microbial contamination of the lumen.
- If a mechanical valve device is used, it should have a flat, smooth surface for disinfection before use.[3]
- Closed hub devices provide direct access to the fluid route for medication delivery, but also are self-sealing in case of detachment. (Comment: Closed hub devices do not prevent backflow; a clamp on a Hickman line is therefore required before removing the infusion tube).
- The split-septum closed hub device should be replaced every 7 days.

1. Sitges-Serra et al. JPEN J Parenter Enteral Nutr. 1984;8:668-672
2. Sitges-Serra et al. Surgery. 1985;97:355-357
3. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Closed hub systems with split septum decrease the risk of bloodstream infections

- Akagi et al. demonstrated the efficacy of closed hub systems[1]
- 20 PAH patients (24 cases) were evaluated:
  - Closed hub (n=13)
  - Unclosed hub (n=11)
- Catheter-related bloodstream infection:
  - Closed hub: 0.10 per 1,000 catheter days
  - Unclosed hub: 0.89 per 1,000 catheter days

BI = bloodstream infection; IV = intravenous;
PAH = pulmonary arterial hypertension

1. Akagi et al. Circ J. 2007;71:559-564

Hub protection in Children's Hospital Denver

- CRBI were evaluated in patients receiving IV prostanoid treatment before and after the introduction of the closed hub system
- The data collection comprised
  - Type of IV prostanoid (epoprostenol or treprostinil)
  - Type of bacterial infection (gram-positive/negative)
  - Specific pathogens
  - Number of CRBI/catheter days
  - Use of the closed hub system (yes or no)

CRBI = catheter-related bloodstream infection;
IV = intravenous

Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Children's Hospital Denver
incidence of bloodstream infections before and after hub protection

Closed-Hub Systems with Protected Connections and the Reduction of Risk of Catheter related Bloodstream Infection in Pediatric Patients Receiving Intravenous Prostanoid Therapy for Pulmonary Hypertension (Ivy et al., 2009)

Fifty patients received intravenous prostanoid therapy for a total of 41,840 catheter days.

The rate of CRBI during the study period was 0.51 infections per 1,000 catheter-days for epoprostenol and 1.38 infections per 1,000 catheter-days for treprostinil, which differed significantly ($P < 0.01$).

CRBI caused by gram-negative pathogens occurred more frequently with treprostinil than with epoprostenol (0.91 infections per 1,000 catheter-days vs 0.08 infections per 1,000 catheter-days; $P < 0.01$).

Patients treated with treprostinil after the implemented changes had a significant decrease in CRBI rate (1.95 infections per 1,000 catheter-days vs 0.19 infections per 1,000 catheter-days; $P < 0.01$).

Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Application through intravenous continuous infusion

- IV treprostinil is administered via intravenous continuous infusion through a central venous catheter using an infusion pump for an outpatient setting.
  - It can also be administered temporarily via a peripheral venous cannula, which is ideally inserted into a major vein.
  - The administration of the infusion via a peripheral vein over several hours can be accompanied by an elevated risk of thrombophlebitis.
- Pumps for subcutaneous administration should be avoided in favour of dedicated IV pumps.
  - Subcutaneous pumps generally have output of 0.1 to 0.2 ml/hour and deliver undiluted medication, which is transferred from the bottle directly to the injection container.
  - Concentrated medications are associated with an increased risk of an overdose if an unintentional bolus is given.
  - These pumps run at relatively slow infusion rates, which may be associated with an elevated risk of a catheter blockage.

Application through intravenous continuous infusion

- To avoid potential interruptions in the supply of medication, the patient must have access to a backup infusion pump and a backup infusion set in the event that the device malfunctions
- If problems arise, the patient must be informed of the following:
  - That they must check their pumps and infusion connections at the first signs of inexplicable shortness of breath or other deteriorations in their condition.
  - How to recognise signs of an overdose (hot flushes, headache, jaw pain, nausea, diarrhoea, weakness).
  - That they should urgently seek advice, which may require not using their infusion system temporarily until it can be inspected.
- All suspected dosage errors, overdoses, catheter blockages etc. should be monitored closely and reported using the standard “post marketing safety report” form for side effects, which can be obtained from AOP Orphan Pharmaceuticals GmbH or your local retailer of Treprostinil.

Selection of a suitable infusion pump

- A pump should be selected which has been specifically developed for use with intravenous infusions. In general, the infusion pump for an outpatient setting should have the following features:
  - Small and lightweight,
  - capable of adjusting infusion rates in increments of approximately 0.002 ml/h. Typical flow rates would be between 0.4 ml and 2 ml per hour,
  - fitted with occlusion (no delivery), low battery, programming error and motor malfunction alarms,
  - Accurate to within ±6% of the programmed delivery rate,
  - be positive pressure driven (continuous or pulsated).

The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Example for an infusion pump

	CADD-Legacy™[1,2]
Use	suitable for IV use
Container	50–100 ml Cartridge
Dimensions	41 x 97 x 112 mm
Weight (empty)	391 g

The treprostinil container must be replaced at least every 24 hours.

IV = intravenous; CADD-MS is a trademark and CADD-Legacy is a registered trademark of Smiths Medical System

1. http://www.smiths-medical.com/
2. http://www.firstbiomed.com/

Calculation of IV solutions

Step 1: calculate required concentration in the syringe mg/ml

$$\frac{\text{(dose) ng/kg/min x (weight) kg x 0.00006*}}{\text{(infusion rate) ml/hour **}} = \text{mg/ml}$$

Step 2: calculate the volume of medication to be taken from the vial

$$\frac{\text{(diluted concentration) mg/ml x (container \& filling volume) ml}}{\text{(vial strength) mg/ml}} = \text{ml}$$

* The factor 0.00006 is used to convert ng/min into mg/hour

- ** using a 20 ml/day pump

Calculation of IV solutions

Example calculation: A patient weighing 70 kg at a dose of 30 ng/kg/min using a 20-ml syringe container, a tube with a 2 ml filling volume, and with 2.5 mg/ml vials

- Initially, the concentration required in the syringe is calculated:

$$\frac{\text{(dose) 30 ng/kg/min x (weight) 70 kg x 0.00006*}}{\text{(infusion rate) 0.83 ml/hour **}} = 0.15 \text{ mg/ml}$$

- The volume of medication to be taken from the vial is then calculated:

$$\frac{\text{(diluted concentration) 0.15 mg/ml x (container \& filling volume) 22 ml}}{\text{(vial strength) 2.5 mg/ml}} = 1.3 \text{ ml}$$

- Saline solution is then added until the total volume is reached (1.3 ml treprostinil + 20.7 ml of saline) = 22 ml

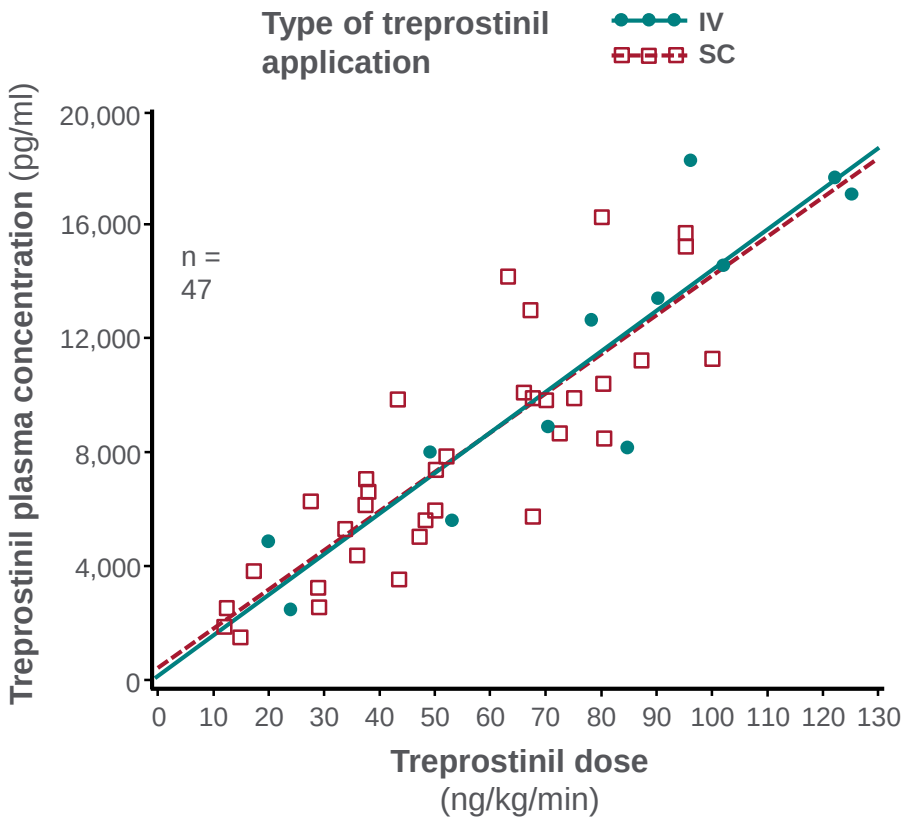
* The factor 0.00006 is used to convert ng/min into mg/hour

- ** using a 20 ml/day pump

The transition from SC to IV treprostinil

Bioequivalence of SC/IV treprostinil

- In patients with PAH, the increase in the dose of SC or IV treprostinil leads to a linear increase in plasma concentrations
- **Conclusion:** Treprostinil plasma concentrations follow a predictable relationship with the dose of treprostinil

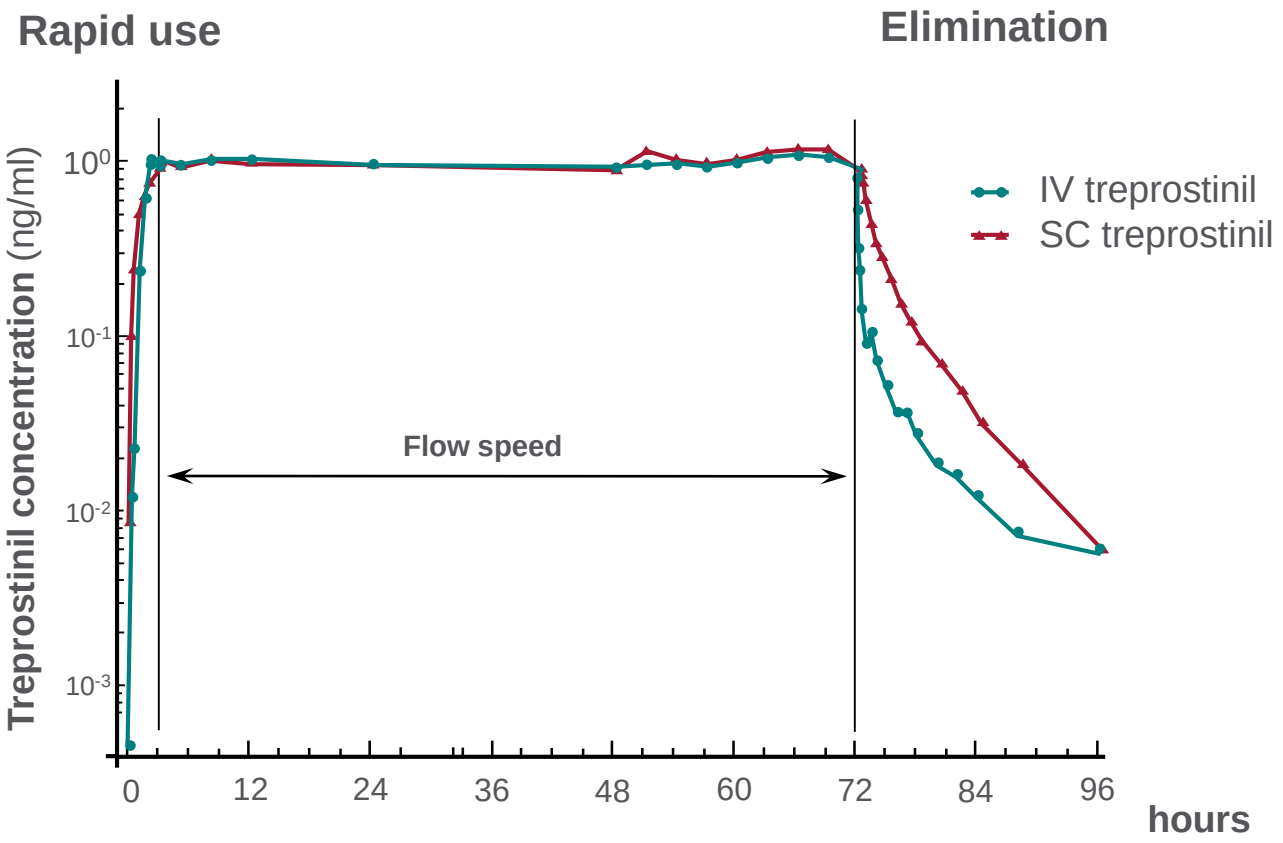


IV = intravenous; PAH = pulmonary arterial hypertension; PK = pharmacokinetics; SC = subcutaneous

McSwain et al. J Clin Pharmacol. 2008;48:19-25

Bioequivalence of SC/IV treprostinil

- Treprostinil plasma concentrations over 72 hours after SC or IV dose [1]



IV = intravenous; SC = subcutaneous

Laliberte et al. J Cardiovasc Pharmacol. 2004;44:209-214

The transition from SC to IV treprostinil

- If you are planning a transition from SC to IV infusion:
  - Select an ambulatory pump with a higher flow rate than the SC micro infusion pumps for undiluted medication.
  - Be careful when recalculating concentrations and infusion rates for the diluted application system.
  - Make sure that the patient is well trained and knows how to use the new pump, the connection tubes and risk management strategies to prevent CRBI.
  - Always perform the transition under clinical observation.
  - Watch for signs of temporary overdose (headache, hot flushes etc.) and be prepared to stop the IV infusion for a short time if necessary, since there may be a short depot effect if the SC injection site continues to deliver any remaining medicine.

IV = intravenous; SC = subcutaneous

Summary: CRBI

- CRBI are potentially severe complications in patients who require an IV infusion via a CVC.
- Compared with other chronic diseases, CRBI rates are very low in PAH,[1-5] but sufficient training and awareness are crucial.
- The available data suggest that the rates of CRBI with gram-negative organisms are slightly higher with IV treprostinil (than with IV epoprostenol), although there is a significant overlap.[5]
- The rates of CRBI can be reduced further by
  - CVC systems with a closed hub[4]
  - Avoidance of water contamination[6]
  - Thorough training and preparation of the patient, followed by continuous compliance with good hygiene standards and alertness of nursing staff and patients.

BI = bloodstream infection; CRBI = catheter-related bloodstream infection; CVC = central venous catheter; IV = intravenous; PAH = pulmonary arterial hypertension

1. van Hoff et al. J Clin Oncol. 1990;8:1255–1262; 2. Decker et al. Pediatr Clin North Am. 1988;35:579–612; 3. Moureau et al. J Vasc Interv Radiol. 2002;13:1009–1101; 4. Akagi et al. Circ J. 2007;71:559-564; 5. Barst et al. MMWR Morb Mortal Wkly Rep. 2007;56:170-172; 6. Doran et al. Adv Pulm Hypertens. 2008;7:245-248

Summary:
Essential patient training

- Summary of essential patient training:
  - Hand hygiene
  - Area preparation
  - Maintainance and monitoring of catheter insertion site and dressing
  - The importance and use of inline filters and closed hub systems
  - The importance of maintaining dry connection hubs and the use of waterproof bandages or wrapping when bathing or showering
  - The importance of avoiding swimming or other direct risks of water contact with the infusion connections or dressings
  - Knowledge of the signs of suspected CRBI and system-related medication side effects and prompt reporting of these to healthcare professionals.

Summary of training unit

- Background to the risk of CRBI
  - Retrospective study into CRBI by the Centers for Disease Control
  - Context of the incidence of all treatment-related bloodstream infections
  - Catheter care guidelines from the society for pulmonary hypertension
- Practical techniques to minimise CRBI
  - Important patient training & general principles
  - 0.2 micron inline filter
  - Connection with the closed hub with a split septum and waterproof dressing wrap
- Summary of Product Characteristics for Treprostinil solution for injection
- Patient questionnaire
- Detecting and reporting suspected CRBI, dosage errors and pump/infusion tube malfunctions
  - Risk minimisation, follow-up
  - Administration via intravenous continuous infusion
  - Suitable infusion pumps for the IV administration
  - Calculation of infusion rate and concentration required
- Transition from SC to IV treprostinil
  - SC and IV bioequivalence
- Summary:
  - Summary: CRBI
  - Summary: Important patient training
- Recommended reading

Recommended reading

Doran A. K, Ivy D. D, Barst R.J, et al. “Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension” International Journal of Clinical Practice. 2008 62(s160): 5–9

Akagi S, Matsubara H, Ogawa A, et al. “Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension” Circ J. 2007 71(4):559-64

Ivy DD, Calderbank M, Wagner BD, et al. “Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension” Infect Control Hosp Epidemiol. 2009 30(9):823-9

For reporting side effects that may happen, please contact

Marketing Authorization Holder, headquarters

AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria
Email: Drugsafety@aoporphan.com
Website: https://www.aop-health.com

The National Pharmacovigilance Centre (NPC- Saudi Food and Drug Authority SFDA)

SFDA Call Center: 19999
E-Mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/