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

Background

- To minimise the risk of central venous catheter-related blood stream infections and sepsis with intravenous infusion of treprostinil, an educational programme for healthcare professionals and patients has been developed by Orpha-Devel Handels und Vertriebs GmbH.
- This educational programme has been approved by the Health Products Regulatory Authority (HPRA).
- The programme consists of a DHPC/Dear Doctor Letter, these training slides and a Patient Brochure.
- A patient questionnaire has also been developed to assess patients' abilities to apply the risk minimisation advice and identify any particular difficulties that they experience.

Summary of key messages

a) Due to the risk of central venous catheter-related blood stream infection (CRBI) the subcutaneous route is the preferred mode of delivery for treprostinil infusion therapy.

b) Continuous intravenous infusion should be reserved for those patients who are stabilised on subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable.

c) 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 these training slides.

d) Patients requiring treatment with a continuous intravenous infusion should be fully trained and competent in using the chosen infusion device and in proper aseptic technique. The Patient Brochure has been developed to support patient training.

Summary of key messages

e) The clinical team responsible for the care of the patient should provide the patient with the short patient questionnaire, after he/she have been on treatment for 3-6 months and if he/she experiences a suspected CRBI.

f) Any suspected cases of catheter-associated infections of the bloodstream, which have occurred in any patient of yours treated with IV treprostinil should be reported to the pharmaceutical safety department immediately. Any suspected cases of dosage errors or pump/infusion tube malfunctions should also be reported. Please refer to slide 27 for reporting instructions.

Main components of this training unit

- Treposuvi: Indications and posology
- The risk of catheter-related bloodstream infections (CRBI)
- Practical techniques to minimise CRBI
- Administration of Treposuvi
- Patient training and monitoring
- Reporting of suspected CRBI, dosage errors and pump/infusion tube malfunctions
- Summary
- Recommended readings

CRBI = catheter-related bloodstream infection

Treposuvi: Indications and posology

Summary of Product Characteristics of Treposuvi

Therapeutic indications

Treatment of idiopathic or heritable pulmonary arterial hypertension (PAH) to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) functional class III.

Posology

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

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

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**

- Retrospective investigation of a sample of patients treated with IV treprostinil and IV epoprostenol in seven PAH centres in the US from 2003 to 2006
- The overall BSI pooled mean rate (per 1,000 medicine days) was significantly higher for patients receiving IV treprostinil compared with those receiving IV epoprostenol (1.11 versus 0.43; pooled incidence rate ratio [IRR] = 2.57; 95% confidence interval [CI] = 1.81--3.64)

BSI = 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; https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5608a5.htm

Incidence rates of CRBI

All IV therapies, for example for cancer treatment, for emergency medical care or nutritional support, carry an infection risk whether delivered as an acute hospital therapy or as long-term community-based therapy, and great care needs to be taken with IV access sites and associated equipment.

- 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]

In comparison with the risks associated IV therapy in general, the risks associated with PAH therapy are shown below:

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

Total IV treatment via CVC (all clinical conditions) : **Range 0.3 to 9.1** [3-5]
The median rate of CRBIs in ICUs of all types **ranged** from **1.8 to 5.2** [1]
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

Pathogenesis of CRBI

Several interrelated factors have been proposed to participate in the pathogenesis of CRBSI.

The catheter itself can be involved in different pathogenic pathways:

- Colonization of the catheter tip and cutaneous tract with skin flora
- Colonization of the catheter lumen caused by contamination
- Hematogenous seeding of the catheter from another infected site
- Contamination of the lumen of the catheter with infusate

Gahlot R et al. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci. 2014;4(2):162–167

Practical techniques to minimise CRBI

Minimising the risk of catheter related blood stream infections – General Principles

- Use of a cuffed and tunneled 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 when the catheter is inserted, replaced, accessed, repaired or when the catheter insertion site is examined and/or dressed.
- A sterile gauze (replaced every two days) or sterile, transparent, semi-permeable dressing (replaced at least every seven days) should be used to cover the catheter insertion site.
- 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 antimicrobial-resistant bacteria.

Description of the risk minimisation advice

- Duration of use of the diluted Treposuvi solution must not exceed 24 hours.
- Use of a split septum closed hub system
  - The catheter hub is the most common source of central venous catheter infections.[1,2]
  - 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.
- 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.
  - Eliminates bacteria, fungi, moulds and foreign particles from the infusion tube

1. Sitges-Serra et al. JPEN J Parenter Enteral Nutr. 1984;8:668-672
2. Sitges-Serra et al. Surgery. 1985;97:355-357

Infusion system luer lock inter-connections

- 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 connection is wet when changing 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.

Administration of Treposuvi

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.
  - **Treposuvi should be diluted with either sterile WFI or 0.9% NaCl for injection**
- The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Application through intravenous continuous infusion

- 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).

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

An example of the calculation of IV solutions

(Please refer to SmPC for full details)

- Example: a 70 kg patient 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
- The concentration formula is:

$$\frac{\text{Dose (ng/kg/min) x Weight (kg) x 0.00006}}{\text{Infusion rate (ml/hour)}}$$

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

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

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

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

- 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

Patient training and monitoring

Patient training and 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.
  - **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.

Patient training and 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.

Patient training and general principles

- The decision to initiate therapy with treprostinil should take into consideration the high probability that a continuous infusion will have to be continued for a prolonged period. The patient's ability to accept and to be responsible for an indwelling catheter and infusion device should be considered carefully.
- The clinical team responsible for treatment must ensure the patient's full training and competent to use the chosen infusion device.
- A period of personal instruction and supervision should continue until the patient is judged competent to change infusions, alter flow rates/doses as instructed, an be able to deal with common device alarms.
- Patients must be trained in proper aseptic technique when preparing the treprostinil infusion reservoir and priming the infusion delivery tubing and connection.

Patient questionnaires

- The primary purpose of the questionnaire is to assess patients' abilities to apply the risk minimisation advice and identify any particular difficulties that they experience.
- Each patient who undergoes treatment with IV treprostinil is offered a questionnaire by his healthcare professional in order to enable Orpha-Devel Handels und Vertriebs GmbH to assess the effects and acceptance of measures for risk minimisation for patients.
  - Patients receive the questionnaire from their healthcare specialist to be completed within three to six months after the start of treatment and if they experience a suspected CRBI
  - Patients should return the completed questionnaire to the HCPs
  - Furthermore, the patients are asked to complete the questionnaire in addition to the "Treposuvi event of special interest – bloodstream infection" form, which is used to report any suspected event of a bloodstream infection.

  Completed questionnaires are collected by the local retail partner from the HCPs and returned to Orpha-Devel Handels und Vertriebs GmbH within an appropriate time frame. The data is analysed and published by the department for medical affairs as well as Orpha-Devel's pharmacovigilance department.

Reporting of suspected CRBI, dosage errors and pump/infusion tube

Reporting suspected CRBI, dosage errors and pump/infusion tube malfunctions

Reporting of suspected adverse reactions after authorisation of a medicinal product is important. Please report any suspected adverse reactions with Treposuvi, particularly any suspected cases of catheter-associated bloodstream infections, bacteraemia and sepsis. Any dosage errors or pump/infusion tube malfunctions should also be reported.
Reports of catheter-associated bloodstream infections should be reported using the form provided ("Treposuvi event of special interest – bloodstream infection").

Please report all adverse reactions 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

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.

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