Redunix

Treprostinil Sodium

50mg per 20ml (2.5mg/ml) / 100mg per 20ml (5mg/ml)

Guidelines for healthcare professionals (HCPs)

on the safe administration of Treprostinil Solution For Infusion by continuous intravenous infusion via an external infusion pump and central venous catheter (CVC) to prevent catheter-related blood stream infections (CR-BSI)

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

These guidelines for healthcare professionals are a mandatory part of the approval of Treprostinil Solution For Infusion. It has been assessed as an additional risk-minimisation measure to reduce the risk of occurence of catheter-related blood stream infections upon administration by intravenous continuous infusion via an external infusion pump and a central venous catheter (CVC) and to increase the benefit-risk ratio.

Version: 1.0
Date: December.2022

Important communication [1/3]

- Due to the risk of central venous catheter-related blood stream infection (CR-BSI) 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 a subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable.
- 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.

Abbreviations:
CR-BSI = cathether-related blood stream infection;

Important communication [2/3]

- Carefully instruct your patient on the safe handling of the intravenous usage of Treprostinil Solution For Infusion (Treprostinil).
- After instruction, verify that your patient is able to perform their intravenous treatment independently and understands the risk management techniques to prevent catheter-related blood stream infections (CR-BSI). Use the Patient Questionnaire to verify the patient's knowledge.
- Give your patient the accompanying Patient Brochure to take home. It is recommended to record in writing the quantity and type of diluent used to prepare the diluted solution of Treprostinil for intravenous use and the infusion rate to be set. Use the form sheets in the Patient Brochure for this purpose.

Abbreviations:
CR-BSI = cathether-related blood stream infection;

Important communication [3/3]

- After 3-6 months of therapy start, patients are followed up with a patient questionnaire to confirm that they are correctly using their intravenous treatment with Treprostinil and are following the risk management techniques.
- Furthermore, the patient questionnaire should also be completed in case of CRBSI.
- Report any suspected blood stream infections by e-mail to ***pharmacovigilance@sudairpharma.com***

Abbreviations:
CR-BSI = cathether-related blood stream infection;

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Abbreviations: CR-BSI = catheter-related blood stream infections
CVC = central venous catheter

Background on risks attributable to catheter-related blood stream infections (CR-BSI)

CR-BSI and i.v. prostanoids: Retrospective study on CR-BSI by Centers for Disease Control

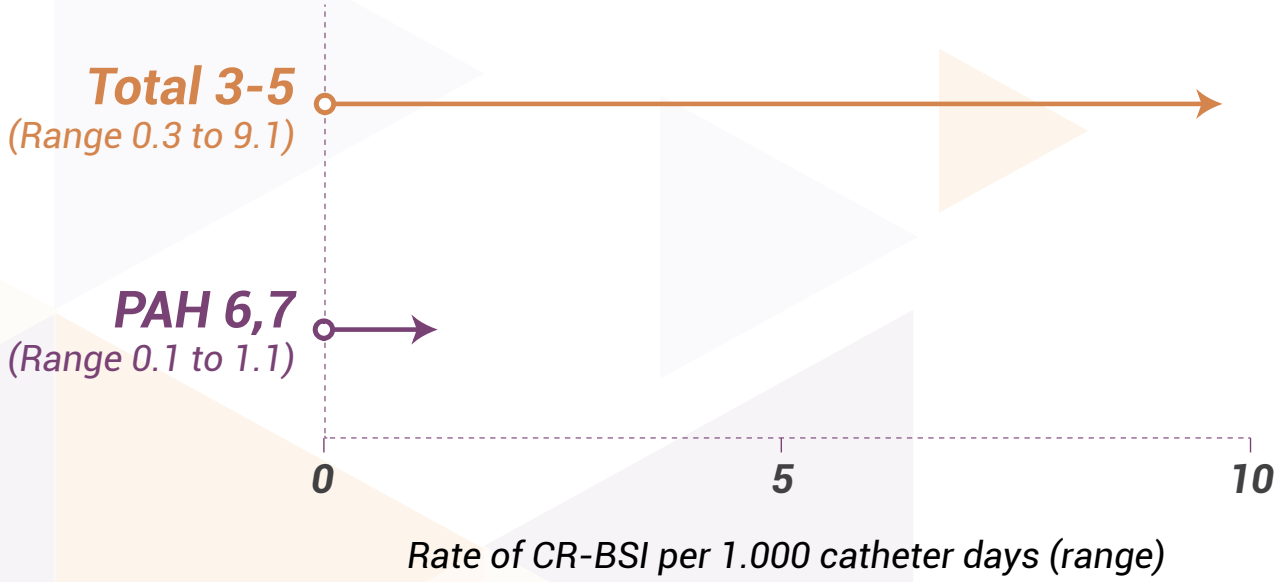
	Medicine days (total)	BSI incidence rate per 1,000 medicine days
i.v. Epoprostenol	201,158	0.43
i.v. Treprostinil	51,183	1.11
Total1	252,341	0.57

- Retrospective study of bloodstream infections among patients treated with i.v. prostanoids (Epoprostenol or Treprostinil) at seven sites in USA between 2003 and 2006.
- Observed BSI incidence rate in patients treated with i.v. Treprostinil compared with patients treated with i.v. Epoprostenol.

Abbreviations:
BSI = Blood stream infection; CDC = Centers for Disease Control; CR-BSI = cathether-related blood stream infection; i.v. = intravenous
1. Barst et al. MMWR Morb Mortal Wkly Rep. 2007;56:170-172

The incidence of CR-BSI connected with the use of CVC

- In USA, patients who regularly received i.v. treatments via a CVC resulted in approximately 5 CR-BSI per 1000 catheter days1
  - This amounts to 80,000 CR-BSI/year2



Abbreviations:
CR-BSI = cathether-related blood stream infection; CVC = central venous catheter; i.v. = 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

Entry of pathogens in CVC

Ivy et al.1:

- Pathogens can enter the CVC via the hub connection
- Experiment with the catheter hub connection using pigment-dye:
  - The dye follows the thread track
  - Contamination occurs upon disconnection (opening of catheter hub connection)
- A sealable plastic wrap (e.g. GLAD Press'n Seal®) can be used to protect the catheter hub connection from water-borne contaminations

Abbreviations: CVC = central venous catheter

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

Pulmonary Hypertension Association: Guidelines for catheter care and the prevention of central venous catheter-related blood stream infections [1/2]

Possible blood stream infection entry points

- Cather insertion site on the skin
- Catheter hub and tube connections
- Prostaglandin bottle and container

Pulmonary Hypertension Association: Guidelines for catheter care and the prevention of central venous catheter-related blood stream infections [2/2]

Follow the guidelines of the Pulmonary Hypertension Association1 for preventing CR BSIs

- Protection of the catheter hub is key
- Avoiding contact with water is important
- Paying attention to the type of plaster at the catheter insertion site and regular observation of this site

Abbreviations: CR-BSI = cathether-related blood stream infection

1 Doran AK et al. Int J Clin Pract Suppl. 2008;160: 5–9. doi:10.1111/j.1742-1241.2008.01811.x.

Practical techniques for minimizing the risks of CR-BSI

Important patient education & general principles [1/3]

- Patients must be able to perform their intravenous treatment with Treprostinil infusion solution independently and safely. Careful training of the patients and the verification of their knowledge is therefore very important.
- Patients must understand the risks associated with treatment and be aware of the role they themselves can play in minimising these risks. It is the responsibility of the responsible clinical team to educate and train patients in the following areas:
  - **Hand hygiene** - the importance of thorough cleaning of hands with appropriate solutions and simple and effective techniques for maintaining preparation of their infusion solutions aseptically.
  - **Surface preparation** - the need for careful preparation and maintenance of the working surface each time before changing the solution in the container solution and the tubing must be discussed.
  - **Maintenance and Observation** - the catheter insertion site and its transparent dressing must be regularly monitored and maintained.

Important patient education & general principles [2/3]

- Patients must understand the risks associated with treatment and be aware of the role they themselves can play in minimising these risks. It is the responsibility of the responsible clinical team to educate patients in the following areas (continued)
  - The **importance** and **use** of in-line filters & closed hub systems. This includes the point that the infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement.
  - **The importance of maintaining dry connection hubs** and the use of waterproof bandages or wraps when bathing and showering.
  - **The importance of avoiding** swimming or other direct risks related to contact of infusion connections or bandages with water
  - **The knowledge of signs and symptoms** of suspected CR-BSI and their reporting to the treating physician

Abbreviations:
CR-BSI = cathether-related blood stream infection

Important patient education & general principles [3/3]

- A patient brochure has been designed to help you educate patients about key issues. Following your verbal instructions, it is important to check the patient's understanding of the contents of this brochure.
- The patient brochure also contains form sheets in which important information regarding the quantity and the type of diluent used for preparing the diluted solution of Treprostinil as well as the infusion rate to be set can be written down for the patient's reference at home.

In-line 0.2 micron filter

- Eliminates bacteria, yeasts and moulds, and foreign bodies from the infusion line
- In a study conducted by United Therapeutics the catheter tube was contaminated on purpose to assess the efficiency of the filter
- Fluid samples collected from the filter and cultured on media to identify
- pathogens showed no signs of contamination[1].

Image of an in-line 0.2 micron filter (Eg: BD Medical MFX1823)

1. Phares. Protokoll: TTP-LRR-M00329. Daten vorhanden, Ferrer Internacional, S.A.

Split septum closed hub system

- The catheter hub is the most common source of infection of the central catheter.1,2
- Closed hub systems were introduced in the late 1980s.
- A split septum closed hub system is preferred 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.
- A needleless device with split septum is preferred over a mechanical valve device. If a mechanical valve device is used, it should have a flat, smooth surface for disinfection before access.
- Closed hub systems provide direct access to the fluid path for drug delivery and also a self-sealing in case of separation. (Note: Closed hub systems do not prevent backflow; a clamp on the Hickman line is therefore required before removing the infusion line).
- 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*

Split septum closed hub systems reduce the risk of CR-BSI

- Akagi et al. demonstrated the effectiveness of closed hub systems1
- Here, 20 patients with PAH (24 events) were evaluated:
  - closed hub system (n=13)
  - non-closed hub system (n=11)
- CR-BSI:
  - closed hub system : 0.10 per 1.000 catheter days
  - non-closed hub system : 0.89 per 1.000 catheter days

Eg.: BD Q-SyteTM

Abbreviations: CR-BSI = catheter-related blood stream infections; PAH = pulmonary arterial hypertension

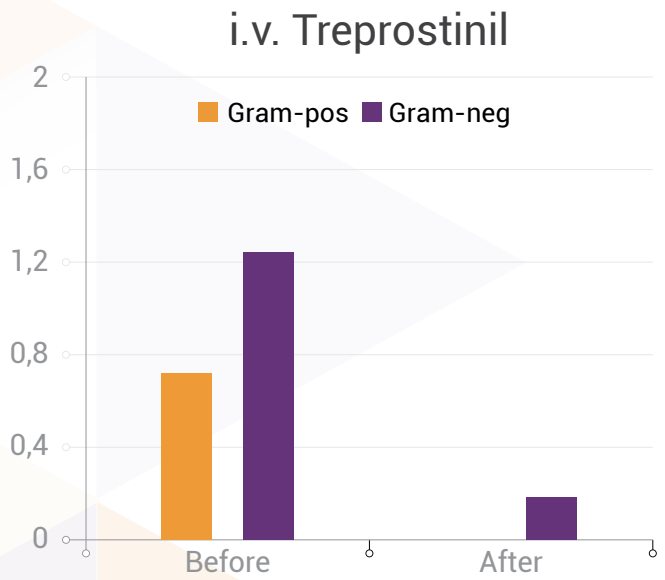
1. Akagi et al. Circ J. 2007;71:559-564

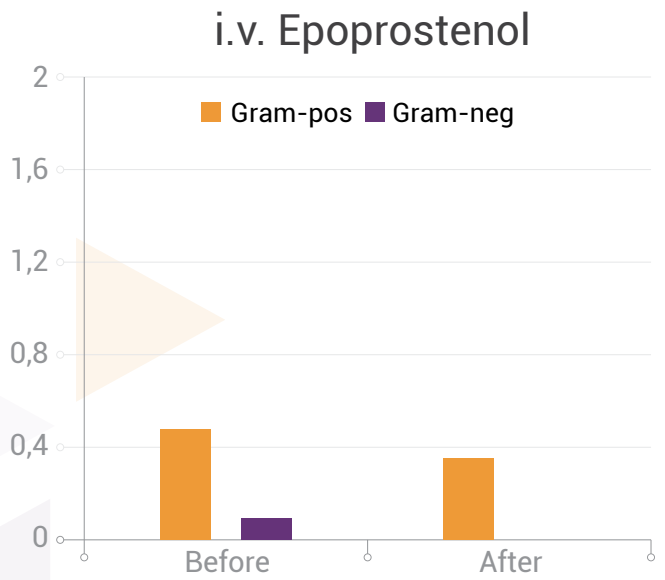
Hub protection in Children's Hospital Denver

- Incidence of CR-BSI in patients treated with i.v. Prostanoids-before and after the introduction of the closed hub system.
- Data was recorded on:
  - Type of i.v. Prostanoid (Epoprostenol or Treprostinil)
  - Type of bacterial infecton (Gram-positiv / -negativ)
  - Specific pathogens
  - Number of CR-BSI events / catheter days
  - Use of a closed hub system (yes or no)

Abbreviations: CR-BSI = catheter-related blood stream infections; i.v. = intravenous
Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Children's Hospital Denver, Incidence of CR-BSI: before and after introduction of protective closed hub





Patients treated with treprostinil showed a significant reduction in CR-BSI incidence rates after introduction of changes (1.95 vs 0.19 pro 1,000 catheter days, $p < 0.01$).
Statistical significance analysed using χ^2 test
CR-BSI = cathether-related blood stream infection; Neg = negativ; Pos = positiv; i.v. = intravenous Adapted from Ivy et al. Infect Control Hosp Epidemiol. 2009;30:823-829

Patient questionnaire for reviewing patient knowledge regarding the safe use of the intravenous treatment with treprostinil and techniques for minimisation of risks of CR-BSI

Patient Questionnaire [1/2]

- Each patient undergoing intravenous treprostinil treatment is provided with a patient questionnaire by their treating physician to verify that the patient can safely use and self-administer their intravenous treatment and knows the risk management techniques regarding CR-BSI.
  - After initial training, patients receive the patient questionnaire from their treating physician.
  - Patients receive the patient questionnaire once again from their treating physician 3 to 6 months after the start of therapy.
  - In addition, patients are asked to complete the patient questionnaire at the same time as reporting any suspected CR-BSI.

Abbreviations:
CR-BSI = catheter-related blood stream infections

Patient Questionnaire [2/2]

- The Patient Questionnaire
  - Patients must be given time to consider their answers carefully - without interference from, for example, an interviewer.
  - Each patient receives the same patient questionnaire. The answers are standardised by the predominantly closed questions, which is helpful for an interpretation of the data.
  - By addressing a number of important topics and questions in a relatively efficient way, it is possible to achieve a high response rate.
  - If one of the questions in the patient questionnaire is not answered correctly by the patient, the patient must be retrained on this question.
  - Completed questionnaires are returned to the clinical team responsible for the patient's care.

Information on dosage and pump usage

Administration by continuous intravenous infusion

- i.v. Treprostinil is administered by continuous intravenous infusion through a central venous catheter using an outpatient infusion pump.
  - It can also be administered temporarily through a peripheral venous cannula, preferably inserted into a large vein.
  - The use of a peripheral infusion over several hours may be associated with an increased risk of thrombophlebitis.
- Pumps for subcutaneous infusion should be avoided in favour of dedicated i.v. pumps.
  - Subcutaneous pumps usually run at 0.1 to 0.2 ml/h and deliver undiluted drug which is transferred from the bottle directly into the syringe container.
  - More concentrated drug is associated with an increased risk of overdose, particularly if an unintended bolus is administered.
  - These pumps run at relatively slow infusion rates, which may be associated with an increased risk of catheter occlusion.

Abbreviations:
i.v. = intravenous

Formulae for preparing a diluted solution of treprostinil for intravenous (i.v.) administration

- The diluted i.v. Treprostinil concentration (mg/ml) can be calculated using the following formula:

  Step 1

  $$\text{Diluted intravenous treprostinil concentration (mg/ml)} = \frac{\text{Dose (ng/kg/min) x weight (kg) x 0.00006*}}{\text{Intravenous Infusion rate (ml/hour)}}$$

  ** conversion factor of 0.00006 = 60 min/hour x 0.000001mg/ng*

- The amount of treprostinil required to make the required diluted intravenous (i.v.) Treprostinil concentration for the given reservoir size can then be calculated using the following formula:

  Step 2

  $$\text{Amount of Treprostinil (ml)} = \frac{\text{Diluted intravenous Treprostinil concentration (mg/ml)}}{\text{Treprostinil vial strength (mg/ml)}} \times \text{Total volume of diluted treprostinil solution in reservoir (ml)}$$

- The calculated amount of treprostinil is then added to the reservoir along with a sufficient volume of diluent (sterile water for injection or 0.9% (w/v) sodium chloride for injection) to achieve the desired total volume in the reservoir.
- The quantity and the type of diluent should be recorded by the physician in writing for the patient‘s reference. The provided Patient Brochure may be used for this purpose.

Summary of Product Characteristics, Treprostinil Solution For Infusion
The conversion factor of 0.00006 is used for recalculation from ng/min to mg/h
i.v. = intravenous

Formulae for preparing a diluted solution of treprostinil for i.v. Administration-Example calculation [1/2]

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 ml/h and a reservoir of 50 ml, the Diluted Intravenous Treprostinil Solution Concentration would be calculated as follows:
The concentration required in the syringe is calculated in step 1:

Step 1

$$\text{Diluted intravenous treprostinil concentration (mg/ml)} = \frac{\text{Dose (ng/kg/min) x weight (kg) x 0.00006*}}{\text{Intravenous Infusion rate (ml/hour)}}$$

$$= \frac{\text{5 ng/kg/min x 60 kg x 0.00006*}}{\text{1 ml/hour}}$$

$$= \text{0.018 mg/ml (18 ng/ml)}$$

**The conversion factor of 0.00006 is used for recalculation from ng/min to mg/h*
i.v. = intravenous

Formulae for preparing a diluted solution of treprostinil for i.v. Administration-Example calculation [2/2]

The Amount of Treprostinil (using 1 mg/ml Vial Strength) needed for a total Diluted Treprostinil Concentration of 0.018 mg/ml and a total volume of 50 ml would be calculated as follows:
The concentration required in the syringe is calculated in step 1:

Step 2

$$\text{Amount of Treprostinil (ml)} = \frac{\text{Diluted intravenous Treprostinil concentration (mg/ml)}}{\text{Treprostinil vial strength (mg/ml)}} \times \text{Total volume of diluted treprostinil solution in reservoir (ml)}$$

$$= \frac{0.018\ (\text{mg/ml})}{1\ \text{mg/ml}} \times 50\text{ml} = 0.9\ \text{ml}$$

The Diluted Intravenous Treprostinil Concentration for the person in this example would thus be prepared by adding 0.9 ml of 1 mg/ml Treprostinil to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 ml in the reservoir. The pump flow rate for this example would be set at 1 ml/h.

The required volume will be achieved by addition of diluent (0.9 ml treprostinil + 49.1 ml diluent) = 50 ml

i.v. = intravenous

Behaviour in the event of a technical fault and reporting of technical faults

- To avoid possible interruptions in drug delivery, the patient must have access to a reserve infusion pump and a reserve infusion set in case of a malfunction of the application device
- In case problem arise, patients must be taught the following:
  - That they check their pump and infusion connections at the first sign of unexplained shortness of breath or other deterioration in their condition.
  - How to recognize signs of overdose (hot flashes, headache, jaw pain, nausea, diarrhea, weakness).
  - That they seek urgent advice, which may require temporary suspension of their infusion system until it can be checked.
- Any suspected dosing errors, overdosing, catheter occlusion, etc. should be closely monitored and reported by e-mail to: pharmacovigilance@sudairpharma.com

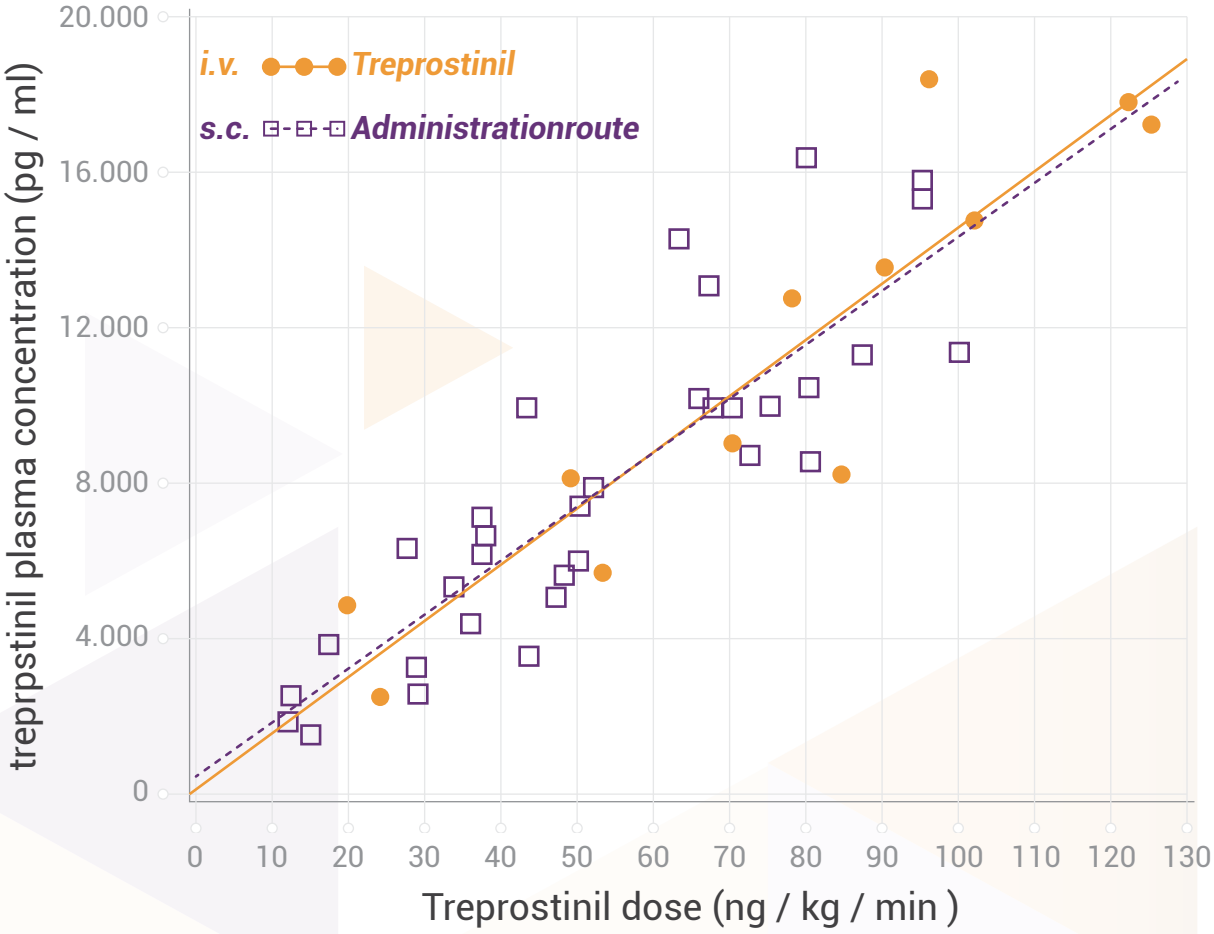
Selection of a suitable pump

- A pump should be selected that has been specially developed for the application of intravenous continuous infusions. In general, the ambulatory infusion pump should have the following features:
  - It should be small and lightweight.
  - It should have adjustable infusion rates in doses of about 0.05 ml/hour. Typical flow rates would vary between 0.4 ml/hour and 2 ml/hour.
  - It should be equipped with warning signals for blockages / no infusion and indicators for empty batteries, programming errors and malfunctions.
  - Accuracy should be within +/- 6% of the pre-programmed infusion rate or a higher accuracy.
  - It should be positive pressure driven. The pump container must be made of polyvinyl chloride, polypropylene or glass.

Transition from subcutaneous to intravenous administration of Treprostinil

Bioequivalence of Treprostinil administered subcutaneous (s.c.) vs intravenous (i.v.) [1/2]

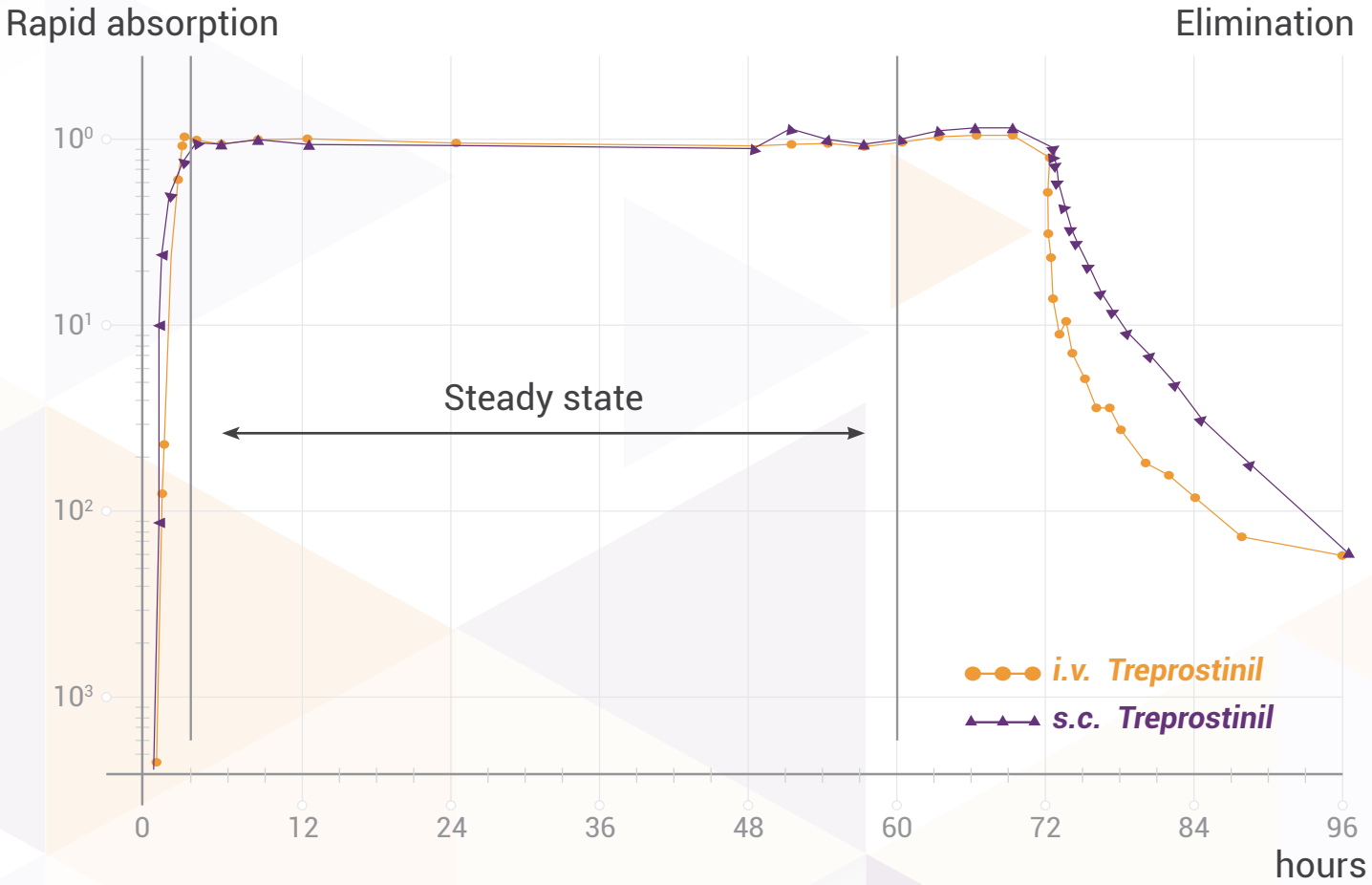
- In patients with PAH, increasing the dose of s.c. or i.v. treprostinil results in a linear increase in plasma concentrations
- Conclusion: Treprostinil plasma concentrations follow a predictable relationship to treprostinil dose.



i.v. = intravenous; PAH = pulmonal arterial hypertension;
s.c. = subkutanenous, i.v. = intravenous
McSwain et al. J Clin Pharmacol. 2008;48:19-25
SmPC Treprostinil Solution For Infusion

Bioequivalence of Treprostinil administered subcutaneous (s.c.) vs intravenous (i.v.) [2/2]

- Plasma concentration of treprostinil monitored over 72 hours after s.c. or i.v. administration [1]



i.v. = intravenous; s.c. = subcutaneous

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

Transition from subcutaneous to intravenous administration of treprostinil

- When you plan to transition from s.c. to i.v. administration
  - Choose an ambulatory pump with a higher flow rate than the s.c. micro infusion pump for undiluted medicine
  - Be careful when recalculating concentrations and infusion rates for the diluted delivery system
  - Ensure that the patient is well trained and familiar with the new pump, connection tubing and risk management strategies to prevent CR-BSI.
  - Always perform the transition under clinical supervision.
  - Watch for signs of transient overdose (headache, hot flush, etc.) and be prepared to stop the i.v. infusion for a short time if necessary, as there may be a short depot effect if the old s.c. site continues to deliver remaining medication.

i.v. = intravenous; s.c. = subcutaneous, CR-BSI = catheter-related blood stream infection

Summary: CR-BSI

- CR-BSI are potentially serious complications in patients requiring an i.v. infusion via a central venous catheter.
- Compared with other chronic diseases, CR-BSI rates in PAH are very low[1-5], but adequate training and vigilance are essential.
- In spite of a significant overlap, the available data suggest that rates of CR-BSI due to Gram-negative bacteria are slightly higher with i.v. Treprostinil (than with i.v. Epoprostenol).[5]
- The rates of CR-BSI may be further reduced using
  - Using closed hub CVC systems [4]
  - Preventing contamination through water[6]
  - Thorough training of the patient, followed by continuous adherence to good hygiene standards and vigilance of clinical staff and patients.

i.v. = intravenous; CR-BSI = catheter-related blood stream infection, CVC = central venous catheter; 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

Recommended Literature Reading

- Doran AK, Ivy DD, Barst RJ, Hill N, Murali S, Benza RL; Scientific Leadership Council of the Pulmonary Hypertension Association. „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. doi: 10.1111/j.1742-1241.2008.01811.x.
- 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

Further information

You can report adverse drug reaction ADR via the below reporting channels:
Sudair Pharma Company;
Email:pharmacovigilance@sudairpharma.com
Online: https://sudairpharma.com/report-a-side-effect/
Tel: 920001432 ext. 107
Mobile: 0546030507

Saudi Food and Drug Authority SFDA;
Email: npc.drug@sfda.gov.sa
online: https://ade.sfda.gov.sa
tel: 19999

Further information:
For full information, please refer to the Summary of Product Characteristics (SmPC) for Solution For Infusion.
You will find the current SmPC and PIL on the Saudi Drug Information System (SDI) https://sdi.sfda.gov.sa/

Additional information may be requested from **Sudair Pharma Medical Team**:
Tel: +44 (0)1748 828873
Email: drreddys@EU.ProPharmaGroup.com