Patient Brochure

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 patient brochure 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 healthcare professional guide, a patient questionnaire and an event of special interest form (a reporting form for central venous catheter-related blood stream infections and sepsis associated with the intravenous route). 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.

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

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DETAILS OF THE CLINICAL TEAM FOR PATIENT REFERENCE:

Responsible Consultant: _____

Hospital/Clinic name: _____

Contact method to reach clinical team in case patient has issues or queries with treatment:

_____

_____

_____

In case of issues or queries regarding treatment, please contact the responsible clinical team with the details above

_____

Essential Points:

- Prostanoids such as treprostinil are powerful vasodilators (open up blood vessels) which allow more blood to flow through the narrowed blood vessels in the lungs in patients with Pulmonary Arterial Hypertension (PAH).

- Treprostinil is administered with a pump as a continuous infusion which can be delivered subcutaneously (under the skin) or intravenously (via a vein).

- Prostanoids such as treprostinil need to be infused continuously 24 hours a day with an infusion system because the body quickly breaks them down. Your clinical team will train you so you are familiar with all the necessary equipment.

- Intravenous (IV) prostanoids are infused directly and continuously into a large blood vessel via a permanent catheter (a thin, flexible tube that is inserted into a vein). This catheter is called a Hickman line or a Groshong line.

- Due to the risk of blood stream infections via intravenous catheters, the subcutaneous route is the preferred route of delivery for treprostinil infusion therapy. Continuous intravenous infusion is 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.

- Prior to starting this treatment, you will receive appropriate education and support from the clinical team who look after you to ensure you can independently prepare and manage the administration of this medicine. This training will include steps you should take to reduce the risk of infection whilst administering treprostinil via your intravenous catheter.

- If you notice **any signs or symptoms of infection** whilst taking this medicine then you should **contact a doctor/the clinical team responsible for your care urgently.**

- You will be asked to complete a short questionnaire after initial education and after you have been on treatment for at least 3 months. The questionnaire will assess your knowledge of the measures to use your treatment safely as well as identify any particular difficulties that you experience taking your treatment that the clinical team responsible for your care can help address.

- This brochure is intended to support you during your training. Please take it home with you so that you can always refer back to the essential points. Keep it in a safe place. If necessary, your family members and/or carers should also read it.

- In case of issues or queries regarding your treatment, please contact the clinical team responsible for your care with the contact details they have provided you.

INFORMATION ABOUT THE MEDICINE AND THE INFUSION SYSTEM, INCLUDING SPECIFIC MEASURES TO PREVENT BLOOD STREAM INFECTIONS:

YOUR MEDICINE

- Your medicine is called Treprostinil Tillomed Solution for Infusion hereinafter referred to as Treprostinil. The active ingredient is treprostinil.

- Treprostinil is used to treat pulmonary arterial hypertension (PAH) in patients with symptoms of moderate severity. This treatment should be initiated and monitored only by clinicians experienced in the treatment of pulmonary hypertension.

- PAH is a condition where the blood pressure is too high in the blood vessels that supply the lungs (pulmonary arteries) because the walls of these vessels have become thick and stiff, therefore they cannot expand well to allow blood through. The reduced blood flow makes it harder for the right side of the heart to pump blood through these arteries. If the right side of your heart has to continually work harder, it can gradually become weaker. This can lead to heart failure. Symptoms of PAH include shortness of breath, dizziness, tiredness, fainting, palpitations or abnormal heartbeat, dry cough, chest pain and swollen ankles or legs.

- Treprostinil belongs to a group of medicines which work in a similar way to the naturally occurring prostacyclins. Prostacyclins are hormone-like substances which reduce blood pressure by relaxing blood vessels, causing them to widen, which allows the blood to flow more easily.

- Treprostinil lowers blood pressure within the pulmonary arteries by improving blood flow and reducing the amount of work for the heart. Improved blood flow leads to an improved supply of oxygen to the body and reduced strain on the heart, causing it to function more effectively. This in turn can improve the symptoms associated with PAH and the ability to exercise in patients who are limited in terms of activity.

HOW IS IT ADMINISTERED?

- Treprostinil is administered via an infusion system as a 24 hour/day continuous infusion which can be delivered
    - subcutaneously (under the skin) via a small tube (cannula) which is located in your abdomen or thigh. This route involves the use of **undiluted** treprostinil solution.
    - intravenously via a tube (catheter) that is placed into a large vein located in your neck, chest or groin (central venous). This route involves the preparation and use of **diluted** treprostinil solution
- Intravenous administration requires the insertion and use of a cuffed and tunnelled central venous catheter (CVC) with a minimum number of ports. Insertion of the CVC is done by the clinical team using sterile barrier techniques.
- The subcutaneous route is the preferred mode of delivery for treprostinil infusion therapy due to the risks associated with chronic indwelling central venous catheters, including serious blood stream infections.
- Patients using the subcutaneous route may develop intolerance due to pain or swelling at the subcutaneous infusion site.
- Continuous intravenous infusion is reserved for patients who have been stabilised on a subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable.
- To help reduce the risk of infection both the clinical team and patient should use 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.
- Your clinical team will help you choose an infusion system that is best for you. An infusion system will usually include a pump, a drug reservoir, infusion tubing and a closed hub device. The infusion system will be connected to the central venous catheter when it is being used for intravenous infusion.
- Your infusion system should be equipped with a closed hub device and an in-line 0.2 filter to help prevent bloodstream infections.
    - A closed hub device functions like a trap door which helps to reduce how often your infusion system is open to the air. This helps to limit the exposure to bacteria present in the air. 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.
    - An in-line 0.2-micron filter is supplied for eliminating bacteria that may enter the infusion system. If your infusion system is not already equipped with a filter then an in-line 0.2-micron filter should be placed between the infusion tubing and the catheter hub, and replaced every 24 hours at the time of changing the infusion reservoir.

Please consult your clinical team in case of any doubts.

PREPARING YOUR MEDICINE

- Please follow the instructions from the clinical team very carefully on how to take Treprostinil, mix it and fill the drug container of your pump. Please consult with the clinical team in case of any doubts. For reference, always keep the written instructions from the clinical team responsible for your care regarding the amounts to be used and the type of diluent handy.

- Delivery of treprostinil solution via the intravenous route requires a dilution step to prepare the medicine. The clinical team responsible for your care will carefully explain to you how to prepare your medication before use. They will also check that you have understood the necessary steps to prepare your medication correctly. Consult your clinical team in case of any doubts.

- The maximum duration of use of the diluted product should be no more than 24 hours

- At the back of this patient brochure is a notes section where your clinical team can legibly write down the amount of Treprostinil that you need to take from the vial with the strength indicated on the vial label. They should also write down the amount of the specified diluent that you need to mix with the amount of Treprostinil taken from the vial in order to achieve the necessary dilution.

- When filling the pump that you are using, please adhere to the instructions for use for that respective pump and the corresponding drug container.

- Always adhere to the following general points when preparing your medication:

  - Clean the work surface and your hands prior to preparing the medicine.

  - Check the expiry date of all products you use. Also check that all liquids are clear and free of particles. The Treprostinil vial can be used for up to 30 days after the first use.

  - Use an alcohol swab to clean the rubber stopper on the vial.

  - Lightly prick the needle into the rubber stopper on the vial at a 45-degree angle. Ensure that the bevelled edge of the needle is facing upwards.

  - Place the needle at a 90-degree angle before fully inserting it into the rubber stopper. This will prevent holes from forming in the rubber stopper over time. (These holes can let bacteria from the air into the vial).

  - Do not touch the connections with your fingers while preparing the medication.

INFORMATION ON THE INFUSION SYSTEM

- Please follow the instructions from the clinical team very carefully on how to take Treprostinil, mix it and fill the drug container of your pump. Please consult with the clinical team in case of any doubts. For reference, always keep the written instructions from the clinical team responsible for your care regarding the amounts to be used and the type of diluent handy.

- Your clinical team will inform what infusion rate is necessary for you. They will also explain how to set the infusion rate on the pump. This information can be noted down in the notes section at the back of this patient brochure. You can use this for future reference when preparing your treatment at home.

- Please consult your clinical team in case of any doubts. Your infusion system should be equipped with a closed lifting device and an in-line 0.2 filter to prevent bloodstream infections

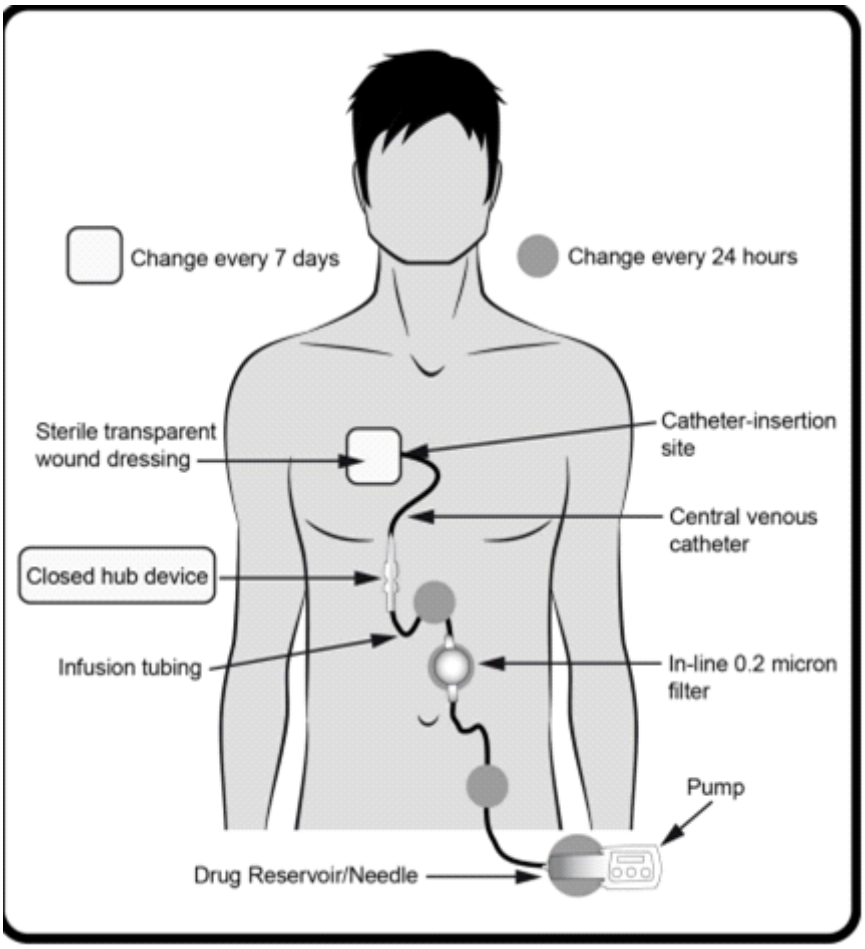
- Closed hub devices function like a trap door. They help in reducing how often your infusion system is opened for bacteria in the air

Illustration of a closed lifting device
(Eg.: BD Q-SyteTM)

- An in-line 0.2 micron filter is supplied for eliminating bacteria that may enter the system. Some infusion systems contain an integrated filter. If your infusion system is not already equipped with a filter, an in-line 0.2 micron filter should be added between the pump and the closed lifting device.

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

An infusion system looks like this



The above picture depicts an example of an infusion system. The central venous catheter that leads into a large, deep vein in the chest is shown. The central venous catheter is connected by a closed hub device to the infusion tube, which contains a 0.2 micron filter, and is connected to a portable pump. This infusion system is equipped with a pump that uses a syringe as the drug container. However, there are other types of pumps that use a bag as a drug container. Your infusion system may look different depending on the pump and other accessories you use

- You must replace the contents of your drug container and the infusion tube daily (every 24 hours). This is because the medication expires after 24 hours.
- The infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement
- Please ensure you prepare your medicine shortly before the end of the 24-hour treatment period and place it in the drug container of your pump, as per the training you received from your clinical team.
- The split-septum closed hub device should be replaced every 7 days. Use an alcohol swab to clean the closed hub device each time you remove the infusion tubing.
- Change directly from the old to the new infusion system so that there is no interruption in medication delivery.
- Do not interrupt treatment unless under the direction of your clinical team. Interruption of treatment can result in a “rebound effect” where you may become unwell and experience symptoms such as shortness of breath and dizziness.

To ensure that your infusion system runs without interruption, you should:

- Check your infusion tubing daily to ensure that there are no kinks or loose connections
- Check that the catheter clamp (if present) is open during administration
- In case of unexpected system failure, you should always have spare accessories available: a reserve pump, drug container, infusion tubing and a closed hub connection.

MINIMISE EXPOSURE TO WATER

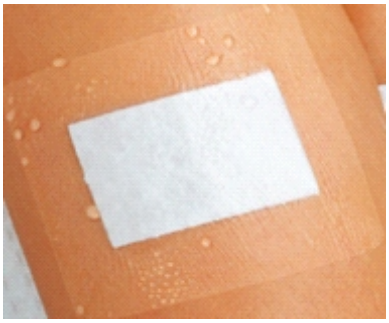
Exposure of the infusion system to water can increase the risk of bacterial infection. It is therefore important to keep water away from the infusion system.

- Do not immerse the infusion system in water. Do not swim with it.
- Do not disconnect the infusion system for bathing, showering or swimming.
- Wrap a waterproof covering around the connections while showering.

  This will prevent the connections from getting wet. Once you have finished showering and have dried yourself, remove the waterproof covering and discard it.
- At the time of replacing the closed-hub device, there should not be any water visible in the luer lock connection threads. Do not disassemble your infusion system if any of the connections are wet.

REGULAR INSPECTION AND CHANGING OF CATHETER INSERTION SITE DRESSINGS

- Keep the skin surrounding the catheter insertion site covered at all times with a wound dressing. This will keep the area clean, dry and free of bacteria.
- Check your dressing daily. If your dressing is damp, loose or dirty, you should change it immediately.
- There are two types of dressings you can use:
  - "Sterile transparent" dressing – change this dressing at least every 7 days
  - "Sterile gauze" dressing – change this dressing at least every 2 days.

Sterile transparent dressing	Sterile gauze dressing
	

- Use of either dressing is acceptable. If you need to pull the edges of the dressing upwards to look underneath, you should change the dressing.
- The "sterile transparent" dressing has the advantage of allowing you to see through it so you can directly inspect the catheter insertion site for any signs of infection without lifting the edges of the dressing.

SIGNS OF INFECTION TO WATCH OUT FOR

You must remain vigilant for signs and symptoms of infection every day.

If you notice any of the following possible signs of infection you must speak to a doctor / the clinical team responsible for your care urgently.

- **Red, warm or tender skin at the catheter insertion site**
- **Oozing, discharge or a bad odour at the catheter insertion site**
- **Fever, chills, generalised aches and pain (similar to flu symptoms)**
- **General malaise (feeling of general discomfort, fatigue, or illness)**

Topical antibiotic ointments or creams should not be applied as they may promote fungal infections and antimicrobial-resistant bacteria.

Washing your hands

You must wash your hands thoroughly before the daily preparation of your infusion system

First of all, you should remove any jewelry from your wrist and hand.

- Use an antibacterial liquid soap. Do not use a solid soap bar since bacteria can grow on its surface.
- Use an alcohol gel if there is no liquid antibacterial soap and clean, running water.

Use the 6-step cleaning procedure shown here

Use running water to rinse your hands from wrist to fingertips (for at least 20 seconds!). Never immerse your hands in standing water, as bacteria can grow in it. Use paper towels to dry your hands and turn off the taps. Then dispose the paper towels.

SUMMARY REMINDER OF TIMING OF CHECKS AND EQUIPMENT CHANGE

Always follow the instructions of the clinical team responsible for your care. Please consult your clinical team in case of any confusion or need for clarification with respect to the timing of checks and equipment changes. The following points are provided as a reference.

- The maximum duration of use of the diluted product should be no more than 24 hours
- The infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement
- A 0.2-micron filter should be placed between the infusion tubing and the catheter hub, and replaced every 24 hours at the time of changing the infusion reservoir
- 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 through the skin
- The split-septum closed hub device should be replaced every 7 days

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

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

PATIENT NOTES:

For the reference of the patient, the clinical team can use the sheet below.

Important information on the dilution of Treprostinil for intravenous use (to be filled out by the clinical team)

I.

Take_____millilitres (ml) from the Treprostinil vial of the following strength_____milligrams per millilitre (mg/ml) as indicated on the vial label.

II.

Diluent (cross out whichever is not applicable):
Sterile water for injection or 0.9 % (w/v) sodium chloride for injection.

III.

Please mix the amount of Treprostinil taken at step **I**. with _____millilitres (ml) of the diluent specified at step **II**.

Important information regarding the infusion rate for intravenous use (to be filled out by the clinical team)

Please set the infusion rate of_____**millilitres per hour (ml/h)** on your pump.

Name of clinical team member: _____
Role: _____
Date: _____