**PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Treprostinil Tillomed 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml solution for infusion**

treprostinil

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Treprostinil Tillomed is and what it is used for

### What Treprostinil Tillomed is

The active ingredient of Treprostinil Tillomed is treprostinil.
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. Prostacyclins can also have an influence in preventing blood from clotting.

What Treprostinil Tillomed is used to treat
Treprostinil Tillomed is used to treat idiopathic or heritable pulmonary arterial hypertension (PAH) in patients with moderate severity of the symptoms. Pulmonary arterial hypertension is a condition where your blood pressure is too high in the blood vessels between the heart and the lungs, causing shortness of breath, dizziness, tiredness, fainting, palpitations or abnormal heartbeat, dry cough, chest pain and swollen ankles or legs.

Treprostinil Tillomed is initially administered as a continuous subcutaneous (under the skin) infusion. Some patients may become unable to tolerate this because of local site pain and swelling. Your physician will decide whether Treprostinil Tillomed can be administered by continuous intravenous (directly into a vein) infusion instead. This will require the insertion of a central venous tube (catheter) that is usually located in your neck, chest or groin.

How Treprostinil Tillomed works
Treprostinil Tillomed lowers blood pressure within the pulmonary artery, 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. Treprostinil improves the symptoms associated with PAH and the ability to exercise in patients who are limited in terms of activity.

## 2. What you need to know before you use Treprostinil Tillomed

### Do not use Treprostinil Tillomed

- if you are allergic (hypersensitive) to treprostinil or any of the other ingredients of this medicine (listed in section 6)
- if you have been diagnosed with a disease called "pulmonary veno-occlusive disease". This is a disease in which the blood vessels that carry blood through your lungs become swollen and clogged, resulting in a higher pressure in the blood vessels between the heart and the lungs.
- if you have severe liver disease
- if you have a heart problem, for example:
  - a myocardial infarction (heart attack) within the last six months
  - severe changes in heart rate
  - severe coronary heart disease or unstable angina
  - a heart defect has been diagnosed such as a faulty heart valve that causes the heart to work poorly
  - any disease of the heart which is not being treated or not under close medical observation
- if you are at a specific high risk of bleeding – for example, active stomach ulcers, injuries or other bleeding conditions
- if you have had a stroke within the last 3 months or any other interruption of blood supply to the brain.

### Warnings and precautions

Talk to your doctor or pharmacist before using Treprostinil Tillomed

- if you suffer from any liver disease
- if you suffer from kidney disease
- if you have been advised that you are medically obese (BMI greater than 30 $kg/m^2$)
- if you have Human Immunodeficiency Virus (HIV) infection,
- if you have high blood pressure in your liver veins (portal hypertension).
- if you have a birth defect in your heart which affects the way your blood flows through it.
- if you are on a low sodium diet.

During your treatment with Treprostinil Tillomed, tell your doctor:

- if your blood pressure decreases (hypotension)
- if you experience a rapid increase in breathing difficulties or persistent cough (this can be related to congestion in the lungs or asthma or other condition), **consult your doctor immediately.**
- if you have excessive bleeding as treprostinil may increase the risk, by preventing your blood from clotting

- if you develop a fever whilst receiving intravenous treprostinil or the intravenous infusion site becomes red, swollen and / or painful to touch, as this could be a sign of infection.

**Other medicines and Treprostinil Tillomed**

Tell your doctor if you are taking, have recently taken, or might take any other medicines.

Please tell your doctor if you are taking:
- medicines used to treat **high blood pressure** (antihypertensive drugs or other vasodilators)
- drugs used to increase the rate of **urination** (diuretics) including furosemide

- medicines that stop **blood clotting** (anticoagulants) such as warfarin, heparin or nitric oxide based products

- any non-steroidal anti-inflammatory (**NSAID)** drugs (e.g. acetylsalicylic acid, ibuprofen)

- medicines that may increase or decrease the effect of treprostinil (e.g. gemfibrozil, rifampicin, trimethoprim, deferasirox, phenytoin, carbamazepine, phenobarbital, St. John's Wort) as your doctor may need to adjust your dose of treprostinil.

**Pregnancy, breast-feeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Treprostinil is not recommended if you are pregnant, planning to become pregnant, or think you might be pregnant, unless considered essential by your doctor. The safety of this medicine for use during pregnancy has not been established.

Treprostinil is not recommended for use in breastfeeding, unless considered essential by your doctor. You are advised to stop breastfeeding if treprostinil is prescribed for you, because it is not known whether this medicine passes into breast milk.

The effect of treprostinil on fertility in humans is unknown currently, hence contraception is strongly recommended during treatment with treprostinil.

**Driving and using machines**

Treprostinil may induce low blood pressure with dizziness or fainting. In such a case do not drive or operate machinery and ask your doctor for advice.

**Treprostinil Tillomed contains sodium**

Please tell your doctor if you are on a controlled sodium diet. He will take into account that one vial of Treprostinil Tillomed contains below mentioned amounts of sodium.

**Treprostinil Tillomed 1 mg/ml solution for infusion**

This medicine contains 74.16 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.71% of the recommended maximum daily dietary intake of sodium for an adult.

**Treprostinil Tillomed 2.5 mg/ml solution for infusion**

This medicine contains 75.08 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.75% of the recommended maximum daily dietary intake of sodium for an adult.

**Treprostinil Tillomed 5 mg/ml solution for infusion**

This medicine contains 78.16 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.91% of the recommended maximum daily dietary intake of sodium for an adult.

**Treprostinil Tillomed 10 mg/ml solution for infusion**

This medicine contains 75 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3.75% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to use Treprostinil Tillomed

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor if you are not sure.

Treprostinil Tillomed is administered as a continuous infusion, either:
- subcutaneously (under the skin) via a small tube (cannula) which is located in your abdomen or thigh; or,
- intravenously via a tube (catheter) that is usually located in your neck, chest or groin.

In both cases, treprostinil is pushed through the tubing by a portable pump.

Before you leave the hospital or clinic, the doctor will tell you how to prepare treprostinil and at what rate the pump should deliver your treprostinil. Information on how to use the pump correctly and what to do if it stops working should also be given to you. The information should also tell you whom to contact in an emergency.

Flushing of the infusion line whilst connected may cause accidental overdose.

Treprostinil is diluted only when administered intravenously:

**For Intravenous Infusion Only:** You must only dilute your treprostinil solution with either Sterile Water for Injection or 0.9% Sodium Chloride Injection (as provided by your doctor) if it is being administered as a continuous intravenous infusion.

<u>Adult patients</u>

Treprostinil Tillomed is available as 1 mg/ml, 2.5 mg/ml, 5 mg/ml or 10 mg/ml solution for infusion. Your doctor will determine the infusion rate and dose appropriate for your condition.

Overweight Patients

If you are overweight (weigh 30% or more than your ideal body weight) your doctor will determine the initial and subsequent doses based on your ideal body weight. Please also refer to Section 2 "Warnings and Precautions".

Older people

Your doctor will determine the infusion rate and dose appropriate for your condition.

Children and adolescents

Limited data are available for children and adolescents.

Dosage adjustment

The infusion rate can be reduced or increased on an individual basis under **medical supervision only**.

The aim of adjusting the infusion rate is to establish an effective maintenance rate which improves symptoms of PAH while minimizing any undesirable effects.

If your symptoms increase or if you need complete rest, or are confined to your bed or chair, or if any physical activity brings on discomfort and your symptoms occur at rest, do not increase your dose without medical advice. Treprostinil may no longer be sufficient to treat your disease and another treatment may be required.

The maximum dose to be administered depends on the patient's clinical condition and various co-morbidities.

**How can blood stream infections during treatment with intravenous treprostinil be prevented?**

As with any long-term intravenous treatment, there is a risk of getting blood stream infections. Your doctor will train you on how to avoid this.

**If you use more Treprostinil Tillomed than you should**

If you accidentally overdose on treprostinil, you may experience nausea, vomiting, diarrhea, low blood pressure (dizziness, light-headedness or fainting), skin flushes and/or headaches.

If any of these effects become severe then you should contact your doctor or hospital immediately. Your doctor may reduce or discontinue the infusion until your symptoms have disappeared. The Treprostinil Tillomed solution for infusion will then be reintroduced at a dose level recommended by your doctor.

**If you stop using Treprostinil Tillomed**

Always use Treprostinil Tillomed as directed by your doctor or hospital specialist. Do not stop using treprostinil unless your doctor has advised you to.

Abrupt withdrawal or sudden reductions in the dose of treprostinil may cause the pulmonary arterial hypertension to return with the potential for rapid and severe deterioration in your condition.

If you have any further questions on the use of this product, ask your doctor.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people)
- widening of blood vessels with flushing of the skin.
- pain or tenderness around the infusion site
- skin discoloration or bruising around the infusion site
- headaches
- skin rashes
- nausea
- diarrhoea
- jaw pain

Common side effects (may affect up to 1 in 10 people)
- dizziness
- being sick (vomiting)
- light-headedness or fainting due to low blood pressure
- itching or redness of the skin
- swelling of feet, ankles, legs or fluid retention
- bleeding episodes such as nose bleeds, coughing up blood, blood in the urine, bleeding from the gums, blood in the faeces
- joint pain (arthralgia)
- muscle pain (myalgia)
- pain in the legs and/or arms

Other possible side-effects (Frequency not known (cannot be estimated from the available data))
- infection at the infusion site
- abscess at the infusion site
- a decrease of blood clotting cells (platelets) in the blood (thrombocytopenia)
- bleeding at the infusion site
- bone pain
- skin rashes with discoloration or raised bumps (maculopapular rashes)
- tissue infection under the skin (cellulitis)
- too much pumping of blood from the heart leading to shortness of breath, fatigue, swelling of the legs and abdomen due to fluid build-up, persistent cough

Additional side-effects associated with the intravenous route of administration
- inflammation of the vein (thrombophlebitis)
- bloodstream bacterial infection (bacteremia)* (refer to Section 3)
- septicemia (severe blood bacterial infection)

* life-threatening or fatal cases of blood stream bacterial infection have been reported

**Reporting of side effects**

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Treprostinil Tillomed

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the pack carton after'EXP'. The expiry date refers to the last day of that month.

Do not use Treprostinil Tillomed if you notice any damage to the vial, discoloration or other signs of deterioration.

This medicinal product does not require any special temperature storage conditions. Store in the original outer packaging in order to protect from light. Shelf-life of treprostinil after initial opening: 30 days

During continuous subcutaneous infusion, a single reservoir (syringe) of undiluted treprostinil must be used within 72 hours.

*Shelf life during continuous subcutaneous administration*

Chemical and physical in-use stability has been demonstrated for 72 hours at 37°C. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

During continuous intravenous infusion, to minimise the risk of blood stream infections the maximum duration of use of a single reservoir (syringe) of the diluted Treprostinil should be no more than 24 hours.

*Shelf life during continuous IV administration*

After dilution:

Chemical and physical in-use stability for diluted treprostinil has been demonstrated for 48 hours at 2-8°C, 20-25°C and 40°C. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Any remaining dilute solution should be discarded.

For Instructions on use please refer to Section 3 "How to use Treprostinil Tillomed?".

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use.These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What Treprostinil Tillomed contains

The active substance is treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml.
The other ingredients in Treprostinil Tillomed are: sodium chloride, metacresol, sodium citrate, sodium hydroxide, hydrochloric acid; concentrated, water for injection.

### What Treprostinil Tillomed looks like and contents of the pack

**Treprostinil Tillomed 1 mg/ml solution for infusion**

Clear colorless to slightly yellow solution, practically free from visible particles filled in 20 mL clear glass vial stoppered with 20 mm dark grey bromobutyl rubber stopper with four marks equally spaced 90° apart and with ring at the centre and sealed with 20 mm yellow matte finish flip-off seal.

**Treprostinil Tillomed 2.5 mg/ml solution for infusion**

Clear colorless to slightly yellow solution, practically free from visible particles filled in 20 mL clear glass vial stoppered with 20 mm dark grey bromobutyl rubber stopper with four marks equally spaced 90° apart and with ring at the centre and sealed with 20 mm blue matte finish flip-off seal.

**Treprostinil Tillomed 5 mg/ml solution for infusion**

Clear colorless to slightly yellow solution, practically free from visible particles filled in 20 mL clear glass vial stoppered with 20 mm dark grey bromobutyl rubber stopper with four marks equally spaced 90° apart and with ring at the centre and sealed with 20 mm green matte finish flip-off seal.

**Treprostinil Tillomed 10 mg/ml solution for infusion**

Clear colorless to slightly yellow solution, practically free from visible particles filled in 20 mL clear glass vial stoppered with 20 mm dark grey bromobutyl rubber stopper with four marks equally spaced 90° apart and with ring at the centre and sealed with 20 mm red matte finish flip-off seal.

The vials are packaged in an outer carton.

Pack size: 1 vial/pack

### Marketing Authorisation Holder and Manufacturer

**Marketing Authorisation Holder**

Tillomed Laboratories Limited
220 Butterfield, Great Marlings,
Luton, LU2 8DL
United Kingdom

**Manufacturer**[1]

**Emcure Pharma UK Limited**
Basepoint Business Centre
110 Butterfield
Great Marlings
Luton
LU2 8DL
United Kingdom

**Tillomed Pharma GmbH**
Mittelstrasse 5/5a
12529 Schönefeld
Germany

[1]Only actual manufacturer stated on printed leaflet.

**This medicinal product is authorised in the Member States of the EEA under the following names:**

| | |
|---|---|
| Austria | Treprostinil Tillomed 1 mg / ml, 2,5 mg / ml, 5 mg / ml und 10 mg / ml Infusionslösung |
| Croatia | Treprostinil Tillomed 1 mg / ml otopine za infuziju<br>Treprostinil Tillomed 2,5 mg / ml otopine za infuziju<br>Treprostinil Tillomed 5 mg / ml otopine za infuziju<br>Treprostinil Tillomed 10 mg / ml otopine za infuziju |
| Czech | Treprostinil Tillomed |
| Finland | Treprostinil Tillomed 1 mg / ml, 2,5 mg / ml, 5 mg / ml ja 10 mg / ml infuusioneste |
| France | TREPROSTINIL TILLOMED 1 mg/ml, solution pour perfusion<br>TREPROSTINIL TILLOMED 2,5 mg/ml, solution pour perfusion<br>TREPROSTINIL TILLOMED 5 mg/ml, solution pour perfusion<br>TREPROSTINIL TILLOMED 10 mg/ml, solution pour perfusion |
| Germany | Treprostinil Tillomed 1 mg / ml, 2,5 mg / ml, 5 mg / ml und 10 mg / ml Infusionslösung |
| Hungary | Treprostinil Tillomed 1 mg / ml, 2,5 mg / ml, 5 mg / ml és 10 mg / ml infúziós oldat |
| Italy | Treprostinil Tillomed |
| Lithuania | Treprostinil Tillomed 1mg / ml, 2,5mg / ml, 5mg / ml ir 10mg / ml infuzinis tirpalas |
| Norway | Treprostinil Tillomed |
| Poland | Treprostinil Tillomed |
| Portugal | Treprostinil Tillomed |
| Slovakia | Treprostinil Tillomed 1 mg / ml, 2,5 mg / ml, 5 mg / ml a 10 mg / ml infúzny roztok |
| Slovenia | Treprostinil Tillomed Pharma 1mg / ml, 2,5 mg / ml, 5 mg / ml in 10 mg / ml raztopina za infundiranje |
| Sweden | Treprostinil Tillomed 1mg / ml, 2,5mg / ml, 5mg / ml och 10mg / ml infusionsvätska, lösning |
| United Kingdom | Treprostinil Tillomed 1mg/ml, 2.5mg/ml, 5mg/ml & 10mg/ml solution for infusion |

**This leaflet was last revised in 06/2020**