Patient Leaflet According to the Pharmacists' Regulations (Preparations) - 1986

This medicine is sold with a doctor's prescription only.

Treprostinil S.K.2.5 mg/ml

Treprostinil S.K.5 mg/ml

Treprostinil S.K.10 mg/ml

Solution for subcutaneous or intravenous injection

Active ingredient:

Treprostinil S.K.2.5 mg/ml: Each ml contains 2.5 mg Treprostinil (as sodium).

Treprostinil S.K.5 mg/ml: Each ml contains 5 mg Treprostinil (as sodium).

Treprostinil S.K.10 mg/ml: Each ml contains 10 mg Treprostinil (as sodium).

For a list of additional ingredients, please see section 6.

See also 'Important information about some of the medicine's ingredients' in section 2.

Read the entire leaflet carefully before using this medicine.
This leaflet contains concise information about the medicine. If you have any further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for treating your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is the medicine intended for?

This medicine is intended:

- For treatment of primary pulmonary arterial hypertension.
- For treatment of pulmonary arterial hypertension associated with connective tissue disorder.
- For treatment of pulmonary hypertension resulting from a congenital heart defect.

Therapeutic group: Synthetic prostacyclin analog, platelet aggregation inhibitor.

2. Before using the medicine

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other additional ingredients this medicine contains (for a list of additional ingredients, please see section 6).
- The solution is not clear, if it is cloudy, if there is a change in the solution color, if the solution contains foreign particles and/or if there is any defect in the vial.

Special warnings regarding the use of this medicine:

- When **Treprostinil S.K.**is administrated by intravenous infusion, there is a risk of blood

infection and sepsis. This condition may be life threatening. Refer to a doctor or a hospital emergency room

immediately if signs develop which may indicate an infection (see section “Side effects”). The medical staff will instruct you on how to reduce this risk.

- The medicine may reduce blood pressure. Refer to a doctor if you experience a decrease in blood pressure.
- The medicine inhibits platelet aggregation thereby raising the risk for bleeding.
- Refer to a doctor immediately if you experience worsening of breathing difficulties or persistent cough.
- If a problem with the pump is suspected, refer to the medical team.
- Inform all your doctors and pharmacists that you are treated with Treprostinil S.K..

Before treatment with Treprostinil S.K.tell your doctor if:

- You suffer or have previously suffered from kidney/urinary system problems or liver problems.
- You suffer or have previously suffered from problems of the circulatory system (such as coagulation problems), heart and/or blood vessels.
- You suffer from low blood pressure.
- You receive or have previously received epoprostenol.

Drug interactions:

If you are taking or have recently taken any other medicines, including non-prescription medicines and nutritional supplements, please tell your doctor or pharmacist. Especially inform your doctor or pharmacist if you are taking the following medicines (it should be noted that the following list mentions the active ingredients of the medicines. If you are unsure whether you are using one of these medicines, please consult with your doctor or pharmacist):

- Medicines used to treat high blood pressure, medicines that dilate blood vessels or diuretics: Combined use increases the risk of a decrease in blood pressure.
- Anticoagulants: Combined use increases the risk of bleeding.
- Gemfibrozil - increases exposure to Treprostinil S.K., therefore, the doctor may adjust the dosage.
- Rifampicin - reduces exposure to Treprostinil S.K., therefore, the doctor may adjust the dosage.

Pregnancy and breastfeeding:

If you are pregnant, planning to become pregnant or breastfeeding, consult with your doctor before using the medicine.

There is no information on the medicine’s effect on milk production, whether the medicine is secreted into breast milk, or its effect on the nursing baby.

Driving and use of machinery: The medicine may cause a decrease in blood pressure including dizziness and/or fainting. If you experience these effects, do not drive or operate machinery.

Children and adolescents:

The safety and efficacy of this medicine in children and adolescents (under the age of 16) was not tested.

Use in special populations:

Consult a doctor regarding dose adjustment in elderly patients, patients with impaired kidney or liver function.

Important information on some of the ingredients of Treprostinil S.K.

Treprostinil S.K. 2.5 mg/ml each bottle contains 55.2 mg sodium
Treprostinil S.K. 5 mg/ml each bottle contains 58.7 mg sodium

Treprostinil S.K. 10 mg/ml each bottle contains 54.8 mg sodium

You should consult your doctor if you are on a low-sodium diet, since the medicine contains sodium. See section 6.

3. How to use the medicine?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are unsure of the dosage or manner of treatment with the medicine.
The dosage and manner of treatment will be determined by the doctor only.
Treprostinil S.K.is administered as continuous infusion using a pump, subcutaneously via a small tube (cannula), or intravenously via a catheter.

Treatment with Treprostinil S.K.is initiated at the hospital under close medical supervision by a doctor or a nurse, who will give you detailed instructions regarding the manner of use, appropriate dosage, medicine administration rate appropriate specifically for you and pump adjustment.
The medical staff will instruct you regarding proper use of the pump, and what to do if you are unsuccessful at operating it appropriately.
Use the pump type recommended to you by the doctor. Read the instructions enclosed with the infusion pump and act accordingly. Ensure availability of another infusion pump and infusion set to avoid the situation of not receiving regular delivery of the medicine in case of device failure.

The standard dosage is usually: The dosage of Treprostinil S.K. (infusion rate and dose) will be determined by the doctor according to your age, weight, health condition and your response to treatment.

- Subcutaneous infusion use: The medicine is delivered without dilution at a rate to be determined by the doctor. The medicine is stable in a syringe without dilution for 72 hours.

- Intravenous infusion: Dilute the medicine solution, according to medical staff instruction, with sterile water for injection or physiological saline (0.9% sodium chloride solution). The infusion rate will be determined by the doctor. The diluted medicine is stable for 48 hours.

Do not exceed the recommended dose.

If you experience a change in your health condition, or are concerned that the medicine is no longer helpful for you – refer to the doctor.

For your attention!
Rinsing the infusion cannula while the cannula is connected to the body may cause an overdose.

<u>Instructions for use:</u>

Treprostinil S.K.is used for either subcutaneous infusion or intravenous infusion by an appropriate infusion pump enabling slow and continuous intravenous infusion.
The treatment is intended for long-term use and therefore, you must ensure that you know how to use the pump and how to place the infusion set according to instructions.
Use an infusion set suitable for the pump. Replace the infusion set according to instructions received from the medical staff.
Treprostinil S.K.solution is dispensed in a multiple use vial (containing more than one dose). Therefore, in order to prevent penetration of contaminants into the vial due to repeated use, wipe the vial stopper with an alcohol sponge before and after piercing the stopper with the needle.
The solution must be visually inspected in order to rule out the presence of foreign particles or color changes. Do not use Treprostinil S.K.if the solution is not clear, if it contains foreign particles and/or if a change in the solution color is observed (see also section 'Do not use the medicine if').
Prior to injection, thoroughly wash your hands and the site intended for needle insertion with soap and water to prevent any contamination at the infusion site.
While refilling the infusion, ensure that no large air bubbles were left in the syringe or catheter.
Replace the infusion set (catheter and needle) according to the doctor's instructions.
Ensure availability of another pump and infusion set in case of pump system failure.

If you have accidentally used a higher dosage than that determined for you, you may experience symptoms of overdose, including: flushing, headache, low blood pressure (which may

be manifested by dizziness, light-headedness and/or fainting), nausea, vomiting, diarrhea, seizures, loss of consciousness.
In case of overdose, refer immediately to a doctor or a hospital.

Continue with treatment as recommended by the doctor.
Even if your health condition improves, do not stop treatment with this medicine without consulting your doctor.

If you stop using Treprostinil S.K.: Do not stop using the medicine without consulting with your doctor. Abrupt withdrawal or extreme reduction in the dosage of Treprostinil S.K.without consulting the doctor may result in recurrence of pulmonary hypertension symptoms and worsening of your condition.

Do not take or use medicines in the dark! Check the label and the dose each time you take or use a medicine. Wear glasses if you need them.

If you have any further questions regarding the use of the medicine, refer to the doctor or pharmacist.

4. Side effects

Like any medicine, the use of Treprostinil S.K.may cause side effects in some users. Do not be alarmed while reading the list of side effects, you may not suffer from any of them.

Refer to your doctor or a hospital emergency room immediately if during intravenous infusion symptoms which may indicate an infection, such as: fever, redness, swelling, pain, bleeding/ hematoma and/or tenderness to touch at the catheter site.

Additional side effects:

Very common side effects (appear in more than one in ten users):
- Headache, diarrhea, nausea, rash, jaw pain, dilated blood vessels.

Common side effects (appear in 1-10 users out of 100):
- Edema, low blood pressure, loss of appetite, vomiting, weakness, abdominal pain.

Side effects whose frequency is unknown (effects whose frequency has not yet been determined)
- Dizziness, itching.
- Joint pain, muscle pain, muscle spasm, limb pain.
- Decrease in platelet count (thrombocytopenia) which may cause bleeding; bone pain, inflammation of subcutaneous tissue (cellulitis).
- Breathing difficulties, tiredness, chest pain, heart failure (of the right ventricle), pallor. These effects may be related to the underlying disease.

Additional side effects related to the route of administration:
Subcutaneous administration:
Very common side effects (appear in more than one user out of ten)
- Pain at the injection site, local reaction at the injection site such as: redness, hardness, rash.

Common side effects (appear in 1-10- users out of 100):
Infection at the injection site.

Intravenous administration:
Side effects whose frequency is unknown (effects whose frequency has not yet been determined)
- Infection related to intravenous administration (these signs may include: fever, redness, swelling, pain and/or tenderness to touch at the catheter site) - see also 'Special warnings regarding the use of this medicine', in section 2.

- Vein inflammation related to thrombus (thrombophlebitis) if a peripheral vein is used for administration.
- Bleeding/hematoma.
- Tingling sensation.
- Pain, swelling of the arm.

Side effects which may be caused by problems in the infusion system:
Very common side effects *(appear in more than one user out of ten):*
Signs of recurrence of pulmonary hypertension, such as breathing difficulties.
Signs of overmedication, such as nausea (see overdose symptoms in section 'If you have accidentally used a higher dosage').

If side effects appear, if one of the side effects worsens or if you suffer from side effects not mentioned in this leaflet, consult with your doctor immediately.

Side effects may be reported to the Ministry of Health by clicking on the link "Reporting side effects following drug treatment" found on the Ministry of Health homepage (www.health.gov.il) which leads to an online form for reporting side effects, or by entering the link:

https://sideeffects.health.gov.il/

5. How to store the medicine?

Avoid poisoning! This medicine and any other medicine must be stored in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by a doctor.

- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.

Storage conditions:

- **Store below 25^{O}C**.
- **After the initial opening, the solution in the vial may be used for up to 30 days and no later than the expiry date appearing on the package.**
- **Undiluted solution in a syringe may be kept for 72 hours at 37°C.**
- Diluted solution in a syringe (dilution up to 0.004 mg/ml) may be kept for 48 hours at 40°C.

However, to minimise the risk of blood stream infections the maximum duration of use of the diluted product should be no more than 24 hours.

- Do not use the medicine if you notice any signs which may indicate a defect in the medicine such as: if the solution is not clear, if it is cloudy, if there is a change in the solution color, if the solution contains foreign particles and/or if there is any defect in the vial.

6. Additional Information

In addition to the active ingredient, the preparation also contains:
Sodium citrate dihydrate, Sodium chloride, Metacresol, Water for injection, Sodium hydroxide, Hydrochloric acid.

What does the medicine look like and what does the package contain?
A clear colorless or yellowish solution in a package containing a transparent glass vial of 20 ml with a rubber stopper and colored cap.

Treprostinil S.K.2.5 mg/ml: blue cap. Treprostinil S.K.5 mg/ml: green cap. Treprostinil S.K.10 mg/ml: red cap.

Manufacturer:
DR REDDY'S LABORATORIES LTD., INDIA
8-2-337, ROAD NO. 3, BANJARA HILLS, HYDERABAD, TELANGANA –□500□034□INDIA.

Registration Holder:
K.S.KIM INTERNATIONAL LTD
94 YIGAL ALON STR., TEL-AVIV-YAFO, 6789139
Drug registration number in the National Drug Registry of the Ministry of Health:

Treprostinil S.K. 2.5 mg/ml:	162-29-35640
Treprostinil S.K.5 mg/ml:	162-28-35641
Treprostinil S.K. 10 mg/ml:	162-27-35642

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