

PACKAGE LEAFLET

Package leaflet: Information for the user

Pentamidine Tillomed 300 mg powder for solution for injection/infusion or powder for nebuliser solution

pentamidine diisetionate

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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Pentamidine Tillomed is and what it is used for
2. What you need to know before you use Pentamidine Tillomed
3. How to use Pentamidine Tillomed
4. Possible side effects
5. How to store Pentamidine Tillomed
6. Contents of the pack and other information

1. What Pentamidine Tillomed is and what it is used for

Pentamidine Tillomed contains the active substance pentamidine diisetionate. It is an antiparasitic medicine used in adults and children:

- for the prevention and treatment of pneumonia caused by the pathogen *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*),
- for the treatment of Kala-Azar (visceral leishmaniasis) and cutaneous leishmaniasis,
- for the treatment of the early stage of sleeping sickness (human African trypanosomiasis with *Trypanosoma brucei gambiense* as pathogen).

2. What you need to know before you use Pentamidine Tillomed

Do not use Pentamidine Tillomed

- if you are allergic to pentamidine diisetionate

Warnings and precautions

Talk to your doctor or nurse before using this medicine if:

- you have a high or low blood pressure
- you have a high or low blood sugar level
- you have a low white blood cell or platelet count
- you have anaemia
- you have liver or kidney problems
- you have low levels of calcium (hypocalcaemia)

- you have a slow heartbeat (bradycardia), an uneven heartbeat or any other heart problem
- you have unusual salt levels in your blood, especially if you have low levels of potassium (hypokalaemia) or magnesium (hypomagnesaemia)
- you have asthma or other breathing problems or had a collapsed lung (pneumothorax) in the past
- you smoke

Monitoring of QTc interval is necessary in patients with known or suspected heart disease or taking medications that prolong the QT interval.

Since there may be a sudden and severe fall in blood pressure after an injection of pentamidine, the blood pressure should be continuously monitored.

Other medicines and Pentamidine Tillomed

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

Please tell your doctor if you are taking medicines such as didanosine (used for treatment of HIV-1 infection) due to increased risk of inflammation of pancreas.

Foscarnet, used for treatment of viral infections, may cause severe kidney problems and decreased calcium levels.

Treatment with pentamidine and amphotericin B is associated with severe kidney impairment.

In particular, caution should be exercised when co-administering medicinal products that prolong the QT interval. These include the following medicines:

- medicines for mood or thought problems called “phenothiazines”
- anti-histamines called terfenadine and astemizole (used for treatment of allergies)
- antibiotics such as erythromycin or quinolones (used for treatment of bacterial infections)
- halofantrine (used for treatment of malaria)
- certain antidepressants such as amitriptyline

Pregnancy and breast-feeding

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 using this medicine.

Pregnancy

Due to the lack of data, Pentamidine Tillomed should not be used during pregnancy unless the clinical condition of the woman requires treatment with pentamidine.

Miscarriage was reported after inhalation of pentamidine in the first trimester of pregnancy.

Breast-feeding

If usage of pentamidine is necessary during breastfeeding, breastfeeding must be stopped before starting treatment with pentamidine.

Driving and using machines

Pentamidine has no or negligible influence on the ability to drive and use machines.

Because of possible side effects, such as dizziness or sudden, brief unconsciousness, caution is required.

3. How Pentamidine Tillomed is given

- This medicine will usually be given to you by a doctor or nurse at a clinic or in a hospital.
- After reconstitution/dilution, it will be given either by injection, infusion or by inhalation using a nebuliser.
- If you feel the effect of your medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.
- Your doctor will decide how much to give you. The dose depends on your weight.

To stop further attacks of Lung infection by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia (PCP):

Adults:

300 mg pentamidine diisetonate as a single inhalation every 4 weeks or 150 mg every 2 weeks.

For Treatment of lung infection by *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia (PCP):

- 4 mg per kg body weight once a day.
- The dose is given by a slow infusion (drip) into a vein

The total duration of treatment should not exceed 21 days.

Kala-Azar (visceral leishmaniasis):

- 3 to 4 mg per kg body weight every other day by intramuscular injection.

The number of doses should not exceed 10.

However, it is also possible to administer a second treatment cycle, if necessary.

Skin leishmaniasis:

- 3 to 4 mg per kg body weight every other day for 3-4 doses by intramuscular injection or intravenous infusion.

Sleeping sickness (human African trypanosomiasis):

- 4 mg per kg body weight once a day or every other day by intramuscular injection or intravenous infusion (up to a total of 7 to 10 doses).

Patients with kidney dysfunction

If your kidneys do not function properly your dose will be adjusted, as appropriate.

Patients with liver dysfunction

In patients with a decrease in hepatic function, the benefits of continuation of therapy should outweigh the potential risk.

Elderly patients

There are no specific dosage recommendations.

Method of administration

For intramuscular, intravenous or inhalation use after reconstitution/dilution.

Depending on the indication, the medicinal product is administered by intramuscular injection, intravenous infusion or by inhalation (nasal masks are not suitable).

Instructions for preparation of the solution for injection/infusion and nebuliser solution are provided at the end of the package leaflet.

If given into a vein, they will dilute it further in another liquid.

- You must lie down when you are given Pentamidine Tillomed .
- Your doctor will decide how much to give you. The dose depends on your weight.

If you have been given more Pentamidine Tillomed than you should

Cardiac arrhythmias, including Torsade de pointes (a special form of cardiac arrhythmia), have been reported following an overdose of pentamidine.

In case of severe overdose / poisoning you may need medical help.

If you have any further questions on the use of the medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will closely check for any possible side effects.

Stop taking the medicine and seek urgent medical advice if you notice any of the following side effects:

- If you have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue. (not known)
- If you have severe skin reactions. Signs include blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flulike symptoms and fever. This may be something called 'Stevens-Johnson syndrome' or 'toxic epidermal necrolysis'. (not known)
- Kidney failure - changes in the way your kidneys are working. These would show up in the results of some blood or urine tests. You may also notice signs such as swollen ankles, passing less water (urine) than usual, low back pain. (very common)
- Inflammation of the pancreas (pancreatitis). Signs include severe stomach pain - which may reach through to the back. (rare)
- abnormal or irregular heart beat. (rare)

- You bruise or bleed more easily than usual. This could be because of a blood disorder (thrombocytopenia).
- If you have low levels of calcium in your blood ('hypocalcaemia')
- Low blood pressure (hypotension). Signs include feeling dizzy, lightheaded or fainting.

Possible side-effects after injection

Very common: (may affect more than 1 in 10 people)

- A condition wherein the waste product levels in the blood are too high (azotemia)
- blood in the urine;
- reactions at the injection site: swelling, pain when the soft tissue of different parts of the body, especially the skin, becomes thicker and harder due to an inflammatory process, collection of pus in any part of the body (abscess formation) and death of muscle tissue (muscle necrosis).

Common: (may affect up to 1 in 10 people)

- reduction in the number of red blood cells (anaemia)
- Low numbers of white cells in your blood (leucopenia) - signs include an unexplained infection or fever.
- sudden, short-term unconsciousness, dizziness,
- Low blood sugar level (hypoglycaemia). Signs include feeling nervous, shaky or sweaty.
- too high blood pressure, circulatory problems, feeling hot,
- nausea, vomiting, taste disorders,
- changes in liver function / liver function tests,
- rash
- reduction in serum magnesium levels
- increase in serum potassium levels
- blood sugar increase, diabetes mellitus (persistent)

Rare: (may affect up to 1 in 1000 people)

- abnormal electrical activity of the heart that affects its rhythm

Not known: frequency cannot be estimated from the available data

- atypical heart rhythm (Torsades de pointes)
- slowed heartbeat,
- discomfort such as tingling and / or prickling (paraesthesia) in the arms and legs, reduced sensitivity around the mouth and in other areas of the face (hypoesthesia). These occurred during or shortly after the infusion and resolved after stopping the infusion.
- breakdown of muscle tissue that leads to the release of muscle fiber contents into the blood (rhabdomyolysis)

Possible side effects of inhalation therapy:

Common: (may affect up to 1 in 10 people)

- coughing, shortness of breath, rales, spasms of the bronchial musculature,
- taste disorders, nausea.

Rare: (may affect up to 1 in 1,000 people)

- inflammation of the lung due to allergic reactions (eosinophilic pneumonia).

Not known: frequency cannot be estimated from the available data

- very low blood sugar,
- dizziness,
- slowed heartbeat,
- pink eye (after accidental aerosol contact with the eyes),
- too low blood pressure,
- air accumulation in the chest (after previous *Pneumocystis jirovecii* pneumonia),
- coughing blood (hemoptysis),
- salivation, heartburn, vomiting
- rash, hives, blotchy rash with nodule formation (maculopapular rash),
- kidney problems,
- fever, weakness (fatigue), decreased appetite.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor straight away.

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 national reporting system listed in HPRRA pharmacovigilance Website: www.hpra.ie.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Pentamidine 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 outer carton and the vial after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

After first opening:

The medicinal product must be used immediately.

After reconstitution:

Chemical and physical in-use stability with water for injections has been demonstrated for 36 hours when stored at 2 to 8°C. The solution is also stable for 60 hours at 20-25°C in original container.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

After dilution:

Chemical and physical in-use stability with sodium chloride 9 mg/ml (0.9 %) solution for injection in PVC bag or glucose 50 mg/ml (5 %) solution for injection in PVC bag has been demonstrated for 36 hours at 20-25°C. Do not refrigerate.

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.

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 protect the environment.

6. Contents of the pack and other information

What Pentamidine Tillomed contains

The active substance is pentamidine diisetonate
1 vial contains 300 mg pentamidine diisetonate.

There are no other ingredients.

What Pentamidine Tillomed looks like and contents of the pack

The medicinal product is a powder for solution for injection/infusion or powder for nebuliser solution. It is a white to off-white lyophilized powder/cake filled in 20 ml Type-I, clear glass vial stoppered with bromobutyl dark grey rubber stopper and sealed with flip off seal.

Pentamidine Tillomed is supplied in cartons containing 1 or 5 glass vials.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Tillomed Pharma GmbH
Mittelstraße 5/5a
12529 Schönefeld
Germany

Manufacturer¹

MIAS Pharma Limited
Suite 1, Stafford House,
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D13 WC83, Co. Dublin,
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Tillomed Malta Limited
Malta Life Sciences Park,
LS2.01.06 Industrial Estate,
San Gwann, SGN 3000,
Malta

¹Only actual manufacturer stated on printed leaflet

This medicine is authorised in the Member States of the European Economic Area under the following names:

Country	Product Name
Germany	Pentamidindiisetionat Tillomed 300 mg Pulver zur Herstellung einer Injektions-/Infusionslösung oder Pulver zur Herstellung einer Lösung für einen Vernebler
Norway	Pentamidine diisetionate Tillomed
Denmark	Pentamidine Tillomed
Finland	Pentamidine Tillomed
Sweden	Pentamidine Tillomed
Ireland	Pentamidine Tillomed 300 mg powder for solution for injection/infusion or powder for nebuliser solution

This leaflet was last revised in 03/2024.

The following information is intended for healthcare professionals only.

Preparation of the solution for injection/infusion and nebuliser solution:

For intramuscular, intravenous or inhalation use after reconstitution/dilution

The powder should be reconstituted in a fume cupboard. Goggles, mouth guard, gloves and protective coat must be used. For reconstitution, 5 mL of sterile water for injections should be added aseptically. After reconstitution, 1 mL solution contains 60 mg of pentamidine diisetionate.

The solution for injection/infusion should be inspected visually for particulate matter and discolouration prior to administration. After reconstitution the medicine is a clear, colourless solution free from visible particles. The vial should be discarded, if visible particles are observed.

For intravenous infusion, the required volume up to 5 mL (300 mg) of pentamidine diisetionate should be withdrawn and transferred into an intravenous bag containing 50-200 ml of Glucose 50 mg/ml (5 %) solution for injection or sodium chloride 9 mg/ml (0.9 %) solution for injection. The diluted solution should be mixed by gentle inversion. Other solutions for infusions should not be used.

The medicine is for single use only. Any unused solution left in the vial should be discarded.

Storage and shelf-life of the medicinal product and diluted solution: see section 5.

For inhalation, if necessary, the required dose may be diluted further with water for injections prior to administration with the nebuliser.

Note for inhalation:

Since the pathogens in the *Pneumocystis jirovecii* pneumonia are located in the air sacs (alveoli), it is important that the nebulised pentamidine particles also reach there. The optimal particle size for alveolar deposition is between 1 and 5 microns. Therefore, only suitable nebulisers may be used for the pentamidine inhalation therapy.

The freshly prepared solution should be administered by inhalation using a suitable nebuliser such as a Respirgard II (trade-mark of Marquest Medical Products Inc.), Modified Acorn system 22 (trade-mark of Medic-Aid) or an equivalent device with either a compressor or piped oxygen at a flow rate of 6 to 10 Litres/Minute.

The nebuliser should be used in a vacated, well-ventilated room. Only staff wearing adequate protective clothing (mask, goggles, gloves) should be in the room when nebulisers are being used.

A suitable well fitted one-way system should be employed such that the nebuliser stores the aerosolised drug during exhalations and disperses exhaled pentamidine into a reservoir. A filter should be fitted to the exhaust line to reduce atmospheric pollution. It is advisable to use a suitable exhaust tube which vents directly through a window to the external atmosphere. Care should be taken to ensure that passers-by will not be exposed to the exhaust.

All bystanders including medical personnel, women of child-bearing potential, pregnant women, children, and people with a history of asthma, should avoid exposure to atmospheric pentamidine resulting from nebuliser usage

In order to minimise the indoor air contamination when using pentamidine as an aerosol, the corresponding functional rooms should be frequently and extensively ventilated and the inhaler systems should be switched off during the inhalation pauses.

Dosage equivalence: 4 mg of pentamidine diisetonate contains 2.3 mg pentamidine base; 1 mg of pentamidine base is equivalent to 1.74 mg pentamidine diisetonate.

Displacement value: 300 mg of pentamidine diisetonate displace approximately 0.15 ml of water.

5-10 minutes prior to inhalation therapy, a bronchodilator should be used as a metered dose inhaler. Bronchospasm has been reported to occur following the use of nebuliser (see section 4.8). This has been particularly noted in patients who have a history of smoking or asthma. This can be controlled by prior use of bronchodilators.

Only clear solutions practically free from particles should be used.

Because inhalation therapy of pentamidine can cause severe, sometimes life-threatening side effects (see above), patients should be closely monitored for the development of severe side effects.