PACKAGE LEAFLET

Package leaflet: Information for the user

Pentamidine isetionate Tillomed 300 mg powder for solution for injection/infusion

pentamidine isetionate

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 isetionate is and what it is used for

Pentamidine isetionate Tillomed contains the active substance pentamidine isetionate and 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).

The name of your medicine is Pentamidine isetionate Tillomed Powder for Solution for Injection or Infusion, but will be referred to as Pentamidine isetionate throughout this leaflet.

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

Do not use Pentamidine isetionate

- if you are allergic to pentamidine isetionate

Warnings and precautions

Talk to your doctor or nurse before having 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 anemia
- you have liver or kidney problems
- 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
- you smoke

Monitoring of QTc interval is necessary in patients with known or suspect cardiac disease or taking concomitant QT-prolonging medications.

Other medicines and Pentamidine isetionate

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

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
- foscarnet (used for treatment of viral infections)

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 sufficient experience, the medicine should be administered to pregnant women only if strictly necessary because of the woman’s clinical condition.

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

Breast-feeding

If usage of pentamidine is warranted during lactation, one should ablactate before starting therapy.

Driving and using machines

There is no experience of impaired ability to drive and use machines. Because of possible side effects, such as dizziness or sudden, brief unconsciousness, caution is required.

3. How to use Pentamidine isetionate

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

Unless otherwise prescribed by the doctor, the following information applies to adults, adolescents, children and infants.

Pneumocystis jirovecii pneumonia:

Prophylaxis

Inhalation (see also "Method of administration"): For prophylactic administration,

The dosage in adults is 300 mg pentamidine isetionate administered as a single inhalation every 4 weeks or 150 mg every 2 weeks.

Therapy

Infusion (see also "Method of administration"): 4 mg pentamidine per kg body weight once daily, are preferably administered by slow intravenous infusion over 60 minutes. The

duration of the treatment of 14 days is generally sufficient. In some severe cases, prolonging the treatment may be necessary. The total duration of treatment should not exceed 21 days.

Kala-Azar (visceral leishmaniasis):

Every 2 days, 3 to 4 mg of pentamidine isetionate per kg of body weight by intramuscular injection. The number of applications should not exceed 10. However, it is also possible to administer a second therapy cycle, if necessary.

Skin leishmaniasis:

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

Sleeping sickness (human African trypanosomiasis):

Once daily or every other day (up to a total of 7 to 10 applications) 4 mg pentamidine isetionate per kg body weight by intramuscular injection or intravenous infusion (see also " Method of administration").

Patients with impaired kidney function

In case of severely impaired kidney function (creatinine clearance <10 ml/min) a dose adjustment is required:

- For life-threatening *Pneumocystis jirovecii* pneumonia, 4 mg pentamidine isetionate per kg body weight should be given once daily for 7 to 10 days. Thereafter, the dose is given every 2 days to a total of 14 doses.
- In less severe cases of *Pneumocystis jirovecii* pneumonia, 4 mg pentamidine isetionate per kg body weight should be given every 2 days.
- For sleeping sickness and leishmaniasis, the dosing interval should not be less than 48 hours.

In mild cases of kidney impairment, at least 36 hours should have elapsed between doses of the product.

Patients with impaired liver function

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.

Use in children and adolescents:

The dosage recommendations given above are also applicable for infants, children and adolescents.

Method of administration

Administration by intramuscular or intravenous or inhalation use.

1) Having this medicine as an injection
- A doctor or nurse will mix pentamidine isetionate with water for injections. If given into a vein, they will dilute it further in another liquid.
- You must lie down when you are given pentamidine isetionate injection.

2) Having this medicine by inhalation
- It is dangerous for other people to be exposed to this medicine.
- This means that other people should not be in the same room when you are using the nebuliser.
- The medicine is put in the nebuliser.

- Air or oxygen is piped into the nebuliser.
- This turns the medicine into a fine mist or spray.
- This spray is then inhaled into your lungs.

For instructions concerning the preparation of the solution for injection/infusion or nebuliser solution, see end of this leaflet.

If you have been given more Pentamidine isetionate 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.

Possible side-effects after intravenous or intramuscular administration

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

- increase of nitrogenous metabolic products of protein in the blood
- reversible renal diseases: primarily acute renal failure, potentially life-threatening; blood in the urine;
- reactions at the injection site: swelling, inflammation and pain until hardening, abscess formation and death of muscle tissue.

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

- diseases of the blood (sometimes life-threatening): reduction in the number of white blood cells and platelets; reduction in the number of red blood cells (anaemia)
- metabolic disorders (potentially life-threatening): reduction in blood sugar, blood sugar increase, diabetes mellitus (persistent), reduction in serum magnesium levels, increase in serum potassium levels and reduction in serum calcium levels,
- sudden, short-term unconsciousness, dizziness,
- circulatory disorders (potentially life-threatening): too high or too low blood pressure, circulatory problems, feeling hot,
- nausea, vomiting, taste disorders,
- changes in liver function / liver function tests,
- rashes.

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

- QT interval prolongation, cardiac arrhythmia, potentially life-threatening
- pancreatitis, potentially life threatening

Not known: frequency cannot be estimated from the available data

- hypersensitivity reactions including anaphylactic reaction, angioedema and anaphylactic shock, potentially life threatening,
- Torsades de pointes (a special form of cardiac arrhythmia),
- slowed heartbeat,
- severe inflammation of the skin and mucous membrane (Stevens-Johnson syndrome),

- rhabdomyolysis (disintegration of muscle fibers) after intramuscular administration,
- discomfort such as tingling and / or prickling (paresthesia) in the arms and legs, reduced sensitivity around the mouth and in other areas of the face (hypesthesia). These occurred during or shortly after the infusion and
- regressed after cessation or discontinuation of the infusion.

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
- hypersensitivity reactions, including anaphylactic reaction, angioedema and anaphylactic shock, potentially life threatening,
- very low blood sugar,
- dizziness,
- slowed heartbeat,
- conjunctivitis (after accidental aerosol contact with the eyes),
- too low blood pressure,
- air accumulation in the chest (after previous *Pneumocystis jirovecii* pneumonia), hemoptysis,
- salivation, retrosternal burning sensationum, vomiting, pancreatitis, potentially life-threatening,
- rash, hives, blotchy rash with nodule formation (maculopapular rash),
- impaired renal function,
- fever, fatigue, decreased appetite.

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

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 Yellow Card Scheme at: 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 Pentamidine isetionate

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/dilution:

The chemical and physical in-use stability of the solution diluted in glucose 50mg/ml (5%) solution or sodium chloride 9 mg/ml (0.9%) solution has been demonstrated for 24 hours at a temperature (20-25°C).

From a microbiological point of view, the medicinal 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 longer than 24 hours at (2 to 8°C) unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

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 isetionate Tillomed contains

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

What Pentamidine isetionate Tillomed looks like and contents of the pack

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

Pentamidine isetionate Tillomed is supplied in cartons containing 1 or 5 glass vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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

Manufacturer

Emcure Pharma UK Ltd
Basepoint Business Centre
110 Butterfield,
Great Marlings,
Luton, LU2 8DL,
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The following information is intended for medical or healthcare professionals only.

Practical information on preparation and administration of Pentamidine isetionate Tillomed 300mg powder for solution for injection/ infusion (see also Section 3).

<u>Preparation of the solution for injection/infusion and nebuliser solution:</u>

The powder should be reconstituted in a fume cupboard. For reconstitution, 5 ml of sterile water for injections should be added aseptically. After reconstitution, 1 ml solution contains 60 mg of pentamidine isetionate.

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. Discard the vial if visible particles are observed.

For intravenous infusion, withdraw the required volume up to 5 ml (300 mg) of pentamidine isetionate and transfer 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 infusion should not be used.

It is for single use only. Discard any unused portion left in the vial.

In order to reduce the incidence of sudden, severe hypotension, pentamidine isetionate should be administered parenterally only by slow intravenous infusion with the patient lying down. Bolus intravenous injections should be avoided if possible and should never be given rapidly.

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

Note for inhalation:

The optimal particle size for alveolar deposition is between 1 and 5 microns.

The freshly prepared solution should be administered by inhalation using a suitable nebuliser such as a Respirgard II (trademark of Marquest Medical Products Inc.), Modified Acorn system 22 (trademark 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) The powder should be reconstituted in a fume cupboard.

b) 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.

c) 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

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

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

5-10 minutes prior to inhalation therapy, a bronchodilating substance should be used as a spray. 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.

Since the pathogens in the *Pneumocystis jirovecii* pneumonia are in the air sacs (alveoli), it is important that the nebulised pentamidine particles reach there. This is only possible if the particle size is between 1 and 5 microns. Therefore, only suitable nebulisers may be used for the inhalation of pentamidine.

Only clear solutions practically free from particles should be used.

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.

Presentation

A sterile white to off-white lyophilized powder/cake supplied in single dose vials containing 300mg pentamidine isetionate.

Precautions

Pentamidine isetionate should be used with particular caution in patients with hepatic and/or renal dysfunction, hypertension or hypotension, hyperglycaemia or hypoglycaemia, leukopenia, thrombocytopenia or anaemia.

Fatalities due to severe hypotension, hypoglycaemia, acute pancreatitis and cardiac arrhythmias have been reported in patients treated with pentamidine isetionate, by both the intramuscular and intravenous routes. Baseline blood pressure should be established and patients should receive the drug lying down. Blood pressure should be closely monitored during administration and at regular intervals until treatment is concluded.

Therefore patients receiving pentamidine isetionate by inhalation should be closely monitored for the development of severe adverse reactions. Bronchospasm has been reported to occur following the use of the nebuliser. This has been particularly noted in patients who have a history of smoking or asthma. This can be controlled by prior use of bronchodilators.

Pentamidine isetionate may prolong the QT interval. Cardiac arrhythmias indicative of QT prolongation, such as Torsades de Pointes, have been reported in isolated cases with administration of pentamidine isetionate. Therefore, pentamidine isetionate should be

used with care in patients with conditions known to increase the proarrhythmic risk, including patients with long QT syndrome, cardiac disease (e.g. coronary heart disease heart failure), a history of ventricular arrhythmias, uncorrected hypokalaemia and / or hypomagnesaemia, bradycardia (<50 bpm) or during concomitant administration of pentamidine isetionate with QT prolonging agents.

Particular caution is necessary if the QTc exceeds 500 msec whilst receiving pentamidine isetionate therapy, continuous cardiac monitoring should be considered in this case. Should the QTc- interval exceed 550 msec then an alternative regimen should be considered.

Laboratory monitoring: The following tests should be carried out regularly:

- Blood Urea nitrogen and serum creatinine daily throughout the therapy.
- Complete blood count on each day of therapy.
- Fasting blood glucose on each therapy day and at regular intervals after the end of the therapy. In some cases, hyperglycaemia and diabetes mellitus have occurred months after the end of therapy.
- Liver function tests, in particular bilirubin, alkaline phosphatase, aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT). For baseline values and in case of only minor changes, a weekly determination is sufficient. If the pre therapy values or values during therapy are elevated, the tests should also be performed once a week, unless the patient is treated with other hepatotoxic preparations, in which case it should be checked approximately every 3-5 days.
- Serum Calcium once a week, Serum magnesium twice a week.
- Urinalysis and determination of serum electrolytes daily during the period of therapy.
- Electrocardiograms at regular intervals.

The benefit of pentamidine inhalation therapy in patients at high risk for pneumothorax should be weighed against the clinical consequences of such manifestation.

Pharmaceutical precautions

This product should be reconstituted in a fume cupboard.

This medicine does not require any special storage conditions.

<u>After reconstitution/dilution:</u>

The chemical and physical in-use stability of the solution diluted in glucose 50mg/ml (5%) solution or sodium chloride 9 mg/ml (0.9%) solution has been demonstrated for 24 hours at a temperature (20-25°C).

From a microbiological point of view, the medicinal 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 longer than 24 hours at (2 to 8°C) unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

Concentrated solutions for administration by the inhalation route should be used immediately.

After reconstitution with Water for Injections, pentamidine isetionate should not be mixed with any injection solution other than glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection.