Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 300 mg pentamidine diisetionate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion or powder for nebuliser solution
white to off-white lyophilized powder/cake.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pentamidine Tillomed is indicated in adults and children for
- Prophylaxis and treatment of *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia.
- Treatment of visceral and cutaneous leishmaniasis.
- Treatment of first-stage of human African trypanosomiasis due to *Trypanosoma brucei gambiense*.

Consideration should be given to official guidance on the appropriate use of antiprotozoal agents.

4.2 Posology and method of administration

Posology
The following dosage recommendations apply to adults, adolescents, children and infants:

Pneumocystis jirovecii (formerly known as*Pneumocystis carinii*) pneumonia
Prophylaxis
Inhalation of pentamidine is recommended for the prophylaxis of *Pneumocystis jirovecii* pneumonia (see "Method of administration").
The adult dosage for inhalation is 150 mg pentamidine diisetionate every two weeks or one dose of 300 mg once a month.
Treatment
For the treatment of *Pneumocystis jirovecii* pneumonia, slow intravenous infusion of the medicinal product is recommended (see below "Method of administration").
4 mg of pentamidine diisetionate per kg body weight once daily preferably administered by slow intravenous infusion over 60 minutes. The recommended duration of therapy for PCP is 21 days.

Leishmaniasis
Visceral: 3-4 mg pentamidine diisetionate per kg body weight every other day administered by intramuscular injection. The number of doses should not exceed 10. However, it is possible to administer a second treatment cycle if necessary.
Cutaneous: 3-4 mg of pentamidine diisetionate per kg of body weight every other day for 3-4 doses by intramuscular injection or intravenous infusion.

Human African Trypanosomiasis
4 mg of pentamidine diisetionate per kg of body weight once a day or every other day. Pentamidine is injected intramuscularly or infused intravenously up to a total of 7-10 doses (see "Method of administration").

Special populations
Renal impairment:
In case of severely impaired renal function (creatinine clearance <10 ml / min) a dose adjustment is required:
- For life-threatening *Pneumocystis jirovecii* pneumonia, 4 mg pentamidine diisetionate per kg of body weight should be given once daily for 7-10 days. Thereafter, the dose is given every 2 days to a total of at least 14 doses.

- In less severe cases of *Pneumocystis jirovecii* pneumonia, 4 mg pentamidine diisetionate per kg body weight should be given every 2 days.
- For trypanosomiasis and leishmaniasis, the dosing interval should not be less than 48 hours.
In milder cases of renal impairment, at least 36 hours should have elapsed between doses of the product.
Hepatic impairment:
No specific dosage recommendations. In patients with a decrease in hepatic function, the benefits of continuation of therapy should outweigh the potential risk.

Elderly:
No specific dosage recommendations.
Paediatric population:
For infants, children and adolescents, the dosage recommendations given above apply.

Method of administration
For intramuscular, intravenous or inhalation use after reconstitution/dilution.
Depending on the indication, the medicinal product is administered by intramuscularly injection, intravenous infusion or by inhalation (nasal masks are not suitable).
The infusion/injection should be done with extra caution and with the patient in a reclining position (see section 4.4)
For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Notes 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 diisetionate contains 2.3 mg pentamidine base; 1 mg of pentamidine base is equivalent to 1.74 mg pentamidine diisetionate.
Displacement value: 300 mg of pentamidine diisetionate 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.**

4.3 Contraindications

- Hypersensitivity to the active substance.

4.4 Special warnings and precautions for use

Pentamidine should be used with caution in patients with hypertension, hypotension, hyper-glycaemia, hypoglycaemia, hypocalcaemia, leukopenia, thrombocytopenia or anaemia, and hepatic or renal impairment. In these patients, a particularly close monitoring of the corresponding laboratory parameters is indicated.
Fatal cases of severe hypotension, hypoglycaemia, acute pancreatitis and cardiac arrhythmias have been reported with pentamidine therapy following intravenous and intramuscular administration. Before administration, blood pressure should be checked with the patient in a supine position. Since there may be a sudden and severe fall in blood pressure after an injection of pentamidine, the patient should be in a reclining position when administered the medicinal product. Blood pressure should be continously monitored during administration of pentamidine and regularly until the end of treatment.

Inhalation therapy should also be performed with caution and under medical supervision. Patients should be monitored for the development of symptoms of a severe adverse reaction.
Bronchospasm has been reported when inhaled with a nebuliser (see section 4.8), especially in patients with a history of asthma or smoking. Pre-administration of an inhaled bronchodilator reduces coughing and bronchospasm and improves aerosol deposition.
Pentamidine diisetionate may prolong the QT interval. Cardiac arrhythmias, such as Torsades de pointes, which indicate a QT prolongation, have been reported occasionally during treatment with pentamidine diisetionate. Therefore, pentamidine diisetionate should be used with caution in patients at an increased risk of developing cardiac arrhythmias such as those with prolonged QT syndrome, cardiac disease (e.g., coronary heart disease, cardiac failure), known ventricular arrhythmias, bradycardia (<50 bpm), uncorrected hypokalaemia and/or hypomagnaesemia or during concomitant administration of pentamidine diisethionate with QT prolonging agents (see section 4.5). Monitoring of QTc interval is necessary in patients with known or suspect cardiac disease or taking concomitant QT-prolonging medications.
Special care should be taken when QTc interval exceeds 500 ms during treatment. Continuous monitoring of cardiac function should be considered in these cases. If the QTc interval exceeds 550 ms, alternative treatment should be considered.

Other precautions
The following examinations should be carried out regularly:
- Blood Urea nitrogen and serum creatinine daily during therapy.
- Complete blood count on each day of therapy.
- Fasting blood sugar on each day of therapy and at regular intervals after the end of the therapy. In some cases, hyperglycaemia and diabetes mellitus have occurred several months after the end of therapy.
- Liver function tests, in particular bilirubin, alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). If baseline values are normal and if there are only minor changes during therapy, a weekly determination is sufficient. If the baseline values or values during therapy are elevated, the tests should be performed once a week, unless the patient is treated with other hepatotoxic agents, 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 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 an occurrence.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of didanosin is associated with an increased risk of pancreatitis.
Coadministration of foscarnet may cause severe renal impairment and hypocalcaemia.
Systemic therapy with pentamidine and amphotericin B is associated with severe renal impairment. Nephrotoxic interaction has not been described with inhalation therapy of pentamidine.
Caution is advised with the simultaneous administration of preparations that prolong the QT interval, such as phenothiazine, tricyclic antidepressants, terfenadine, astemizole, intravenous erythromycin, halofantrine and quinolones (see also section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or very limited experience with the use of pentamidine in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). A miscarriage was reported after inhalation of pentamidine for prophylaxis in the first trimester of pregnancy. Pentamidine Tillomed should not be used during pregnancy unless the clinical condition of the woman requires treatment with pentamidine.
Breast-feeding
It is not known if pentamidine / metabolites are excreted in breast milk. Breastfeeding should be discontinued during treatment with pentamidine.
Fertility
There are no clinical or animal data on the effects of pentamidine on fertility.

4.7 Effects on ability to drive and use machines

Pentamidine has no or negligible influence on the ability to drive and use machines.
Considering the possible undesirable effects (e.g. dizziness, syncope and others), caution is advised.

4.8 Undesirable effects

The frequency of adverse reactions is based on the following categories:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); Not known (cannot be estimated from the available data)

Adverse reactions in parenteral administration

MedDRA system organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	*Common*	Anaemia, leukopenia and thrombocytopenia*
Immune system disorders	*Not known*	Hypersensitivity reactions including anaphylactic reaction, angioedema and anaphylactic shock*
Metabolism and nutrition disorders	*Very common*	Azotemia
	Common	Hypoglycaemia, hyperglycaemia, diabetes mellitus (also persistent), hypomagnesaemia, hyperkalaemia and hypocalcaemia*
Nervous system disorders	*Common*	Syncope and dizziness
	Not known	Paraesthesia of the extremities, hypoaesthesia (perioral hypoaestheia, facial hypoaesthesia).[#]
Cardiac disorders	*Rare*	QT interval prolongation, arrhythmia*
	Not known	Torsades de Pointes, bradycardia
Vascular disorders	*Common*	Hypertension or hypotension*, circulatory collapse, flushing
Gastrointestinal disorders	*Common*	Nausea, vomiting, taste disorders
	Rare	Pancreatitis*
Hepatobiliary disorders	*Common*	Hepatic changes, abnormal liver function tests
Skin and subcutaneous tissue disorders	*Common*	Rash
	Not known	Stevens-Johnson syndrome, toxic epidermal necrolysis
Renal and urinary disorders	*Very common*	Acute renal failure* macroscopic haematuria
General disorders and administration site conditions	*Very common*	Local reactions: ranging in severity from swelling, inflammation and pain to induration, abscess formation and muscle necrosis
	Not known	Rhabdomyolysis after intramuscular administration

*potentially life-threatening
[#]These occurred during or shortly after i.v. infusion and resolved after completion or discontinuation of the infusion

Adverse reactions of inhalation administration

MedDRA system organ class	Frequency	Adverse reaction
Immune system disorders	*Not known*	Hypersensitivity reactions including anaphylactic reaction, angioedema and anaphylactic shock (potentially life-threatening)
Metabolism and nutrition disorders	*Not known*	Hypoglycaemia
Nervous system disorders	*Not known*	Dizziness
Eye disorders	*Not known*	Conjunctivitis (after accidental contact of the aerosol with the eyes)
Cardiac disorders	*Not known*	Bradycardia
Vascular disorders	*Not known*	Hypotension
Respiratory, thoracic and mediastinal disorders	*Common*	Local reactions of varying degrees of severity: cough, dyspnoea, wheezing, bronchospasm, especially in smokers or asthmatics, which can usually be avoided by prior administration of a bronchodilator
	Rare	Eosinophilic pneumonia
	Not known	Pneumothorax (after previous *Pneumocystis jirovecii* pneumonia (PCP)), hemoptysis
Gastrointestinal disorders	*Common*	Dysgeusia, nausea
	Not known	Salivation, retrosternal burning, vomiting, acute pancreatitis
Skin and subcutaneous tissue disorders	*Not known*	Rash, urticarial and maculopapular rashes, epidermal necrolysis

Renal and urinary disorders	*Not known*	Renal failure
General disorders and administration site conditions	*Not known*	Fever, decreased appetite, fatigue

Note:
As severe, occasionally life-threatening adverse reactions (see above) cannot be excluded with inhalation treatment of pentamidine, patients should be closely monitored for the development of severe adverse reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRAPharmacovigilance Website: www.hpra.ie

4.9 Overdose

Cardiac arrhythmias, including Torsades de Pointes, have been reported after overdose with pentamidine diisetionate.

Treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, Agents against Leishmaniasis and Trypanosomiasis, Other agents against leishmaniasis and trypanosomiasis
ATC code: P01CX01.

Mechanism of action
The antiprotozoonotic pentamidine is an aromatic diamidine which exerts its effects through interactions with DNA, interfering with folic acid metabolism and inhibiting RNA and protein synthesis.

Mechanism of resistance
Pentamidine resistance in *Leishmania* spp. is multifactorial, mediated by several energy-dependent molecular pumps that alter transport of pentamidine into and out of the parasite. Modification of three different transporter proteins responsible for trafficking of pentamidine can mediate resistance, including an ATP-binding cassette (ABC) transporter, pentamidine resistance protein 1 (PRP1), and a P-glycoprotein homolog that causes efflux of pentamidine from the parasite. Pentamidine-susceptible *L. infantum* amastigotes can be rendered pentamidine-resistant by transfecting them with PRP1 genes. The calcium channel blocker verapamil (at therapeutic concentrations) can reverse the effect of the PRP1 gene, restoring *in vitro* pentamidine susceptibility. In *T. brucei gambiense*, mutations in an aquaporin gene (aquaglyceroporin TbAQP2) have been identified that confer cross-resistance to both pentamidine and melaminophenyl arsenic drugs (melarsoprol/cymelarsan). Pentamidine binds to wild-type aquaglyceroporin in nanomolar concentrations and inactivates the porin channel activity that helps maintain osmotic balance and bidirectional flux of solutes. The mutations inhibit binding of pentamidine to this channel protein.

5.2 Pharmacokinetic properties

After intravenous infusion of 4 mg pentamidine diisetionate per kg body weight over 2 hours, maximum plasma levels of approximately 0.5 µg/ml are achieved; after intramuscular injection of the same dose, the maximum concentration in plasma is approximately 0.2 µg/ml.

Time period	**intravenous administration (ng/ml)***	**intramuscular administration (ng/ml)***
20 min/15 min	277 ± 184	96.2 ± 94.1
40 min/30 min	330 ± 153	199 ± 59.0
1 hour	404 ± 251	170 ± 51.2
2 hours	484 ± 474	92.5 ± 25.1
4 hours	33.7 ± 20.8	40.1 ± 7.1
8 hours	19.3 ± 16.9	22.9 ± 8.0
12 hours.	9.6 ± 8.2	13.9 ± 5.5
24 hours	2.9 ± 1.4	6.6 ± 3.5

* The mean with standard deviation is indicated.

In addition, the following pharmacokinetic parameters were determined:

Parameter	intravenous administration*	intramuscular administration *
Plasma clearance (l/h)	248 ± 91	305 ± 81
Elimination half life (h)	6.4 ± 1.3	9.4 ± 2.0
Apparent volume of distribution (l)	140 ± 93	924 ± 404
Apparent volume of distribution in Steady State (l)	821 ± 535	2724 ± 1066
Renal Elimination of the unchanged substance in 24 hrs. (%)	2.5	4.1
Renal Clearance (l/h)	6.2 ± 3.6	15.4 ± 14.9

* The mean with standard deviation is indicated.
When administered using a nebuliser, human kinetic studies revealed significant differences when compared to parenteral administration. Aerosol administration resulted in a 10-fold increase in bronchial alveolar lavage (BAL) supernatant fluid and an 80-fold increase in BAL sediment concentrations in comparison with those seen with equivalent intravenous doses.
Limited data suggests that the half-life of pentamidine in BAL fluid is greater than 10 to 14 days. Peak plasma concentrations after inhalation therapy were found to be approximately 10% of those observed with equivalent intramuscular doses and less than 5% of those observed following intravenous administration. This suggests that systemic effects by the inhalation route are less likely.
Long term pulmonary parenchymal effects of aerosolised pentamidine are not known. Lung volume and alveolar capillary diffusion, however, have not been shown to be affected by high doses of pentamidine administered by inhalation to AIDS patients.

5.3 Preclinical safety data

In various toxicological tests, symptoms of hypotension and CNS depression were observed in all species. Hypotension was most pronounced with intravenous bolus injection. With longer administration times, an adaptation occurs. The symptoms become less severe during the course of administration and occur less frequently.
Nephrotoxic effects were mainly observed in toxicity studies in dogs and rats, but no effect on the morphological structure and weight of the kidneys was detected.
There was also evidence in the rat studies that the liver was damaged. Again, the morphology of the liver was not changed; the liver weight was increased, as well as in dogs. After 3 weeks of recovery, the pathological LFTs of the rats returned to normal.
The local tolerance in these two species was very poor. However, in the case of rabbits, there were no indications of relevant local reactions during intravenous and intraarterial administration.
Rabbit teratology revealed a low fetal toxicity, which could be partly explained by the maternal toxic effect.
Studies on embryotoxicity in a second animal species as well as animal studies on fertility and potential harm during use during the gestation period and lactation were not performed.
Pentamidine diisetionate can in principle interact with the DNA. However, the substance was unremarkable in several in vitro and in vivo mutagenicity tests.
Long-term carcinogenicity studies were not performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

3 years
<u>After first opening:</u>
The medicinal product must be used immediately.
<u>After reconstitution:</u>
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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening, after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml Type-I, clear glass vial stoppered with bromobutyl dark grey rubber stopper and sealed with flip-off seal.
Pack sizes: 1 or 5 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of the solution for injection/infusion and nebuliser solution

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 medicinal product is for single use only. Any unused solution left in the vial should be discarded.
For inhalation, if necessary, the required dose may be diluted further with water for injections prior to administration with the nebuliser.

Disposal instructions
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Pharma GmbH
Mittelstrasse 5/5a
Schonefeld
12529
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8 MARKETING AUTHORISATION NUMBER

PA22720/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Authorisation: 21st February 2025

10 DATE OF REVISION OF THE TEXT

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