Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Tadim, 1 million International Units (IU) Powder for Nebuliser Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1 million International Units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.

3. PHARMACEUTICAL FORM

Powder for nebuliser solution. The powder is white to off-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Tadim is indicated for the management in adult and paediatric of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis (see section 5.1).

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

4.2 Posology and method of administration

It is recommended that colistimethate sodium (CMS) should be administered under the supervision of physicians with appropriate experience in its use.

Posology

The dosage can be adjusted depending on the severity of the condition and clinical response.

Recommended dose range:

Administration via inhalation

Adults, adolescents and children ≥ 2 years
1-2 MIU two to three times per day (max 6 MIU/day)

Children < 2 years
0.5-1 MIU twice daily (max 2 MIU/ day)

Relevant clinical guidance on treatment regimens, including duration of treatment, periodicity and co-administration of other antibacterial agents should be adhered to.

Older people
Dose adjustment is not considered necessary

Renal impairment
Dose adjustment is not considered necessary; however, caution is advised in patients with renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
Dose adjustment is not considered necessary

Method of administration

Tadim for nebulisation is reconstituted with a diluent solution and administered by nebulisation using a suitable nebuliser.

Drug delivery characteristics from *in vitro* studies with different nebuliser systems are detailed below;

Characteristic		Nebuliser system		
		Respironics I-neb AAD with 0.3mL (grey) medication chamber	Pari eflow rapid	Pari LC Sprint with Pari Boy SX compressor
		Tadim dose placed in nebuliser system		
		1 million IU in 1mL	1 million IU in 3mL	1 million IU in 3mL
(a)	Droplet Size Distribution; Median Particle Size: d_{50} (µm)	4.34	4.56	4.37
(b)	Total Drug Delivered from Nebuliser mouthpiece # (Million IU)	0.333	0.277	0.385
(c)	Fine Particle Fraction (% < 5µm)	59.55	58.19	57.73
(d)	Fine Particle Dose Delivered from Nebuliser mouthpiece # (Million IU < 5 µm)	0.198	0.161	0.222
(e)	Delivery Time #	3 minutes, 36 seconds	5 minutes, 0 seconds	6 minutes, 40 seconds
(f)	Drug Delivery Rate from Nebuliser mouthpiece # (Million IU/minute)	0.055	0.032	0.033

 # Measured using a simulated inhalation: exhalation (I:E) ratio of 1:1, a tidal volume of 500mL and 15 breathes per minute.

- *All Tadim reconstituted with a 50:50 mixture of WFI and 0.9% saline to the recommended volume for each nebuliser system.*
- *Pari Boy SX operated at 1.6 bar pressure, 5.1L/min flow rate.*
- *(d) is calculated from (b) / 100 x (c)*
- *(f) = (d) / (e)*

Characteristic		Nebuliser system		
		Respironics I-neb AAD with 0.5mL (lilac) medication chamber	Pari eflow rapid	Pari LC Sprint with Pari Boy SX compressor
		Tadim dose placed in nebuliser system		
		1 million IU in 1mL	2 million IU in 4mL	2 million IU in 4mL
(a)	Droplet Size Distribution; Median Particle Size: d_{50} (µm)	4.81	4.31	4.35
(b)	Total Drug Delivered from Nebuliser mouthpiece # (Million IU)	0.579	0.601	0.861
(c)	Fine Particle Fraction (% < 5µm)	53.01	63.11	57.73
(d)	Fine Particle Dose Delivered from Nebuliser mouthpiece # (Million IU < 5 µm)	0.307	0.379	0.497
(e)	Delivery Time #	8 minutes, 29 seconds	6 minutes, 38 seconds	11 minutes, 32 seconds
(f)	Drug Delivery Rate from Nebuliser mouthpiece # (Million IU/minute)	0.036	0.057	0.043

 # Measured using a simulated inhalation: exhalation (I:E) ratio of 1:1, a tidal volume of 500mL and 15 breathes per minute.

- *All Tadim reconstituted with a 50:50 mixture of WFI and 0.9% saline to the recommended volume for each nebuliser system.*
- *Pari Boy SX operated at 1.6 bar pressure, 5.1L/min flow rate.*
- *(d) is calculated from (b) / 100 x (c)*
- *(f) = (d) / (e)*

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution.

For special precautions for disposal and handling of reconstituted solutions, see Section 6.6.

If other treatments are being taken, they should be taken in the order recommended by the physician.

Dose conversion table:

In the EU, the dose of colistimethate sodium (CMS) must be prescribed and administered only as International Units (IU). The product label states the number of IU per vial.

Confusion and medication errors have occurred because of the different expressions of dose in terms of potency. The dose is expressed in the US, and other parts of the world, as milligrams of colistin base activity (mg CBA).

The following conversion table is prepared for information and the values must be considered nominal and approximate only.

CMS conversion table

Potency		**≈ mass of CMS (mg)***
IU	**≈ mg CBA**	
12,500	0.4	1
150,000	5	12
1,000,000	34	80
4,500,000	150	360
9,000,000	300	720

***** Nominal potency of the drug substance = 12.500 IU/mg

4.3 Contraindications

Tadim is contraindicated in patients with known hypersensitivity to colistimethate sodium or other polymyxins.

4.4 Special warnings and precautions for use

Bronchospasm
Nebulisation of colistimethate sodium may induce coughing or bronchospasm. A choking sensation has been reported in some cases. It is advisable to administer the first dose under medical supervision. Pre-dosing with a bronchodilator is recommended and should be routine, especially if this is part of the patient's current therapeutic regimen. FEV_1 should be evaluated pre and post dosing. If there is evidence of colistimethate sodium induced bronchial hyperreactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of bronchial hyperreactivity in the presence of a bronchodilator may indicate an allergic response and colistimethate sodium should be discontinued. Bronchospasm that occurs should be treated as medically indicated.
Bronchial hyperreactivity in response to colistimethate sodium may develop with continued use over time and it is recommended that pre and post treatment FEV_1s are evaluated at regular clinic visits.

Renal impairment
Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. Whilst this is unlikely during inhalation therapy, serum concentration estimations are recommended especially in patients with renal impairment.

Nephrotoxicity
Impairment of renal function has been reported, usually following use of higher than recommended intravenous or intramuscular doses in patients with normal renal function, or failure to reduce the intravenous or intramuscular dosage in patients with renal impairment or when used concomitantly with other nephrotoxic drugs. The effect is usually reversible on discontinuation of therapy.

Neurotoxicity
High serum concentrations of colistimethate sodium after intravenous or intramuscular administration may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, and this may lead to neurotoxicity. Concomitant use with either non-depolarising muscle relaxants or antibiotics with similar neurotoxic effects can also lead to neurotoxicity. Dose reduction of colistimethate sodium may relieve symptoms. Neurotoxic effects that have been reported include: vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. (see also Section 4.5)

Porphyria
Use with extreme caution in patients with porphyria.

Microbial Resistance
Colistimethate sodium acquired resistance in mucoid Pseudomonas aeruginosa during clinical use has been reported. Susceptibility testing should be performed on patients who are treated on a long term basis, at regular clinic visits, and whenever a patient experiences an exacerbation (see Section 5.1).

Other
Colistimethate sodium is known to reduce the presynaptic release of acetylcholine at the neuromuscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants should be used with extreme caution in patients receiving colistimethate sodium as their effects could be prolonged (see Section 4.4).

Concomitant use of inhaled colistimethate sodium with other medications that are nephrotoxic or neurotoxic (e.g. cephalothin sodium, aminoglycosides and non-depolarising muscle relaxants) including those which are administered by the i.v. or i.m. routes should only be undertaken with the greatest caution (see Section 4.4).

Co-treatment with colistimethate sodium and macrolides such as azithromycin and clarithromycin, or fluoroquinolones such as norfloxacin and ciprofloxacin should be undertaken with caution in patients with myasthenia gravis (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety in human pregnancy has not been established. Animal studies do not indicate a teratogenic potential. However, there is evidence that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if administered during pregnancy. Tadim should only be given during pregnancy if the benefits outweigh any potential risk.

Breast-feeding

Colistimethate sodium is excreted in breast milk; breast feeding is not recommended during therapy.

Fertility
There are no data on the effects of colistimethate sodium on human fertility. Animal studies with colistimethate do not indicate adverse effects on fertility (see section 5.3)

4.7 Effects on ability to drive and use machines

Neurotoxicity, characterised by dizziness, confusion or visual disturbances have been reported following parenteral administration of colistimethate sodium. If these effects occur patients should be warned against driving or operating machinery.

4.8 Undesirable effects

The commonest undesirable effects following nebulisation of colistimethate sodium are coughing and bronchospasm (indicated by chest tightness which may be detected by a decrease in FEV_1) in approximately 10% of patients. (See also Section 4.4)
Adverse reactions are tabulated below by system organ class and frequency. Frequencies are defined as 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) and very rare (<1/10,000), not known (cannot be estimated from the available data)

Body System	**Frequency**	**Reported adverse reaction**
Immune system disorders	Not known	Hypersensitivity reactions such as skin rash
Respiratory, thoracic and mediastinal disorders	Very common	Cough, chest tightness, bronchoconstriction or bronchospasm
General disorders and administration site conditions	Not known	Sore throat and sore mouth.

Should hypersensitivity reactions such as skin rash occur treatment with colistimethate sodium should be withdrawn.
Cases of sore throat or sore mouth may be due to hypersensitivity or superinfection with *Candida* species.

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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdosage may cause apnoea, muscle weakness, vertigo, transient facial paraesthesia, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and renal insufficiency.

No antidote is available. Management of overdose is by means of supportive treatment and measures designed to increase clearance of colistimethate sodium such as inducing an osmotic diuresis with mannitol, peritoneal dialysis or prolonged haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antibacterials, Polymyxins.
ATC code: J01XB01

General properties

Mechanism of action
Colistimethate sodium is a prodrug of colistin, a polymyxin antibiotic (belonging to the polymyxin E group). It is a polypeptide structure and is derived from *Bacillus polymyxa var. colistinus.*
The polymyxin antibiotics are surface active agents and act by binding to and changing the permeability of the bacterial cell membrane causing bacterial cell death. Polymyxins are bactericidal against Gram-negative bacteria with a hydrophobic outer membrane.

Pharmacodynamic effects
Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria.

Mechanisms of resistance
Resistance develops due to modifications of lipopolysaccharide (LPS) or other components in the bacterial cell membrane.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Acinetobacter species
Haemophilus influenzae
Klebsiella species
Pseudomonas aeruginosa

Species for which acquired resistance may be a problem
Stenotrophomonas maltophilia
Achromobacter xylosoxidans (formerly *Alcaligenes xylosoxidans*)

Inherently resistant organisms
Burkholderia cepacia and related species
Proteus spp
Providencia spp
Serratia spp

Resistance
Colistimethate sodium acquired resistance in mucoid *Pseudomonas aeruginosa* has been reported to be approximately 3%. However, local rates of resistance may vary including higher rates (see Section 4.4).

Cross resistance
The resistance to polymyxins is not crossed with other antibiotic families.

5.2 Pharmacokinetic properties
Absorption
Gastrointestinal absorption is negligible hence the swallowing of colistimethate sodium deposited in the nasopharynx is unlikely to add to the systemic exposure.

Absorption following lung administration is influenced by the nebuliser system, aerosol droplet size and disease state of the lungs.

A study in healthy volunteers, who inhaled colistimethate sodium, demonstrated the Cmax of polymyxin E1 (the active moiety) varied between 40.0 and 69.9 ng/mL and the AUC varied between 350 and 668 ng/mL/h depending on the nebuliser and the fill volume and concentration, which varied the dose from 0.3 million IU to 2 million IU. The half-life was approximately 5.2 hours. The absolute bioavailability was calculated to vary between 5% and 18% depending on the nebuliser. The AUC following an intravenous dose of 0.5 million IU was 3,352 ng/mL/h and the Cmax was 1,232 ng/mL.

Distribution
Protein binding is low. Colistimethate sodium antibiotics are known to persist in muscle tissue, liver, kidney, heart and brain.
Volume of distribution has been calculated to be 0.09 L/kg in a single study in patients with cystic fibrosis.

Metabolism
Colistimethate sodium undergoes conversion to its base *in vivo*.

Elimination
There is no information on the elimination of colistimethate sodium following nebulisation.
Following i.v. administration excretion is primarily renal with 62% of a parenteral dose recovered unchanged in the urine within 8 hours and around 80% in 24 hours. There is no biliary excretion.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity and genotoxicity.
Animal studies with colistimethate do not indicate adverse effects on fertility or embryo-foetal development.
Data on potential carcinogenicity for colistimethate sodium are lacking.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

The addition of other antibiotics to solutions of Tadim may lead to precipitation.
This medicinal product should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 3 years.

After reconstitution;
Chemical and physical in-use stability of solution reconstituted in the original vial has been demonstrated for up to 24 hours at 2 to 8ºC.

Patients self-treating with nebulised antibiotic should be advised to use solutions immediately after preparation. If this is not possible, solutions should not be stored for longer than 24 hours in a refrigerator.

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

The product is supplied in a clear type I glass 10R ISO vial (nominal volume 10mL) sealed with a siliconised chlorobutyl type I rubber stopper and protected by a 20 mm aluminium tear-off cap incorporating a red flip-up central plastic top. The product is supplied in packs of 30 vials.

6.6 Special precautions for disposal and other handling

Tadim may be reconstituted to produce a clear colourless to pale yellow solution, with either Water for Injections (WFI) to produce a hypotonic solution, a 50:50 mixture of WFI and 0.9% sodium chloride to produce an isotonic solution, or with 0.9% sodium chloride to produce a hypertonic solution. The volume used for reconstitution should be in accordance with the instructions for use provided with the nebuliser device, and is normally not more than 4ml. During reconstitution swirl gently to avoid frothing. When reconstituted, Tadim may be used with any conventional nebuliser suitable for delivery of antibiotic solutions.

Solutions should be used immediately after reconstitution, however if this is not possible solutions must be used within 24 hours and stored in a refrigerator. Any unused solution remaining in the nebuliser must be discarded following treatment. Any unused solution or waste material should be disposed of in accordance with local requirements.

Conventional nebulisers operate on a continuous flow basis and it is likely that some nebulised drug will be released into the local environment. When used with a conventional nebuliser, Tadim should be administered in a well-ventilated room, particularly in hospitals where several patients may be using nebulisers at the same time. Tubing or filters may be used to prevent waste aerosol from entering the environment.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

10. DATE OF REVISION OF THE TEXT

2026-03-19