TADIM[1] POWDER FOR NEBULISER SOLUTION

(COLISTIMETHATE SODIUM)

1 NAME OF THE MEDICINE

Colistimethate sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Colistimethate sodium is a polypeptide antibiotic. It is prepared from colistin base by the action of formaldehyde and sodium hydrogen sulphite.

Colistimethate sodium (the active pharmaceutical ingredient) is very soluble in water, slightly soluble in alcohol, and practically insoluble in acetone, chloroform and ether.

3 PHARMACEUTICAL FORM

Tadim is a sterile powder for use, after reconstitution, as a nebuliser solution. The powder is white to off-white.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Tadim powder for nebuliser solution is indicated for the treatment of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF).

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Sputum cultures should be obtained to confirm colonisation with *Pseudomonas aeruginosa* sensitive to colistimethate sodium prior to initiating treatment with Tadim.

The following information provides guidance on recommended doses and the dose should be adjusted according to clinical response.

[1] Tadim is a registered trademark licensed to Zambon S.p.A.

Recommended doses using a conventional nebuliser
Children >2 years, adolescents and adults: 1-2 million IU two or three times daily.

The dosage is determined by the severity and type of infection and renal function of the patient.
The dose may be varied across this range depending on the condition being treated.
The dose placed into the nebuliser may be reduced if the patient is using an I-neb AAD nebuliser system as per the instructions for mixing Tadim for nebulisation table below.

Initial colonisation with *Pseudomonas aeruginosa* sensitive to colistimethate sodium may be treated with a 3-week course of 2 million IU twice daily in conjunction with other parenteral or oral antibiotics.

For frequent, recurrent infections. (Less than three positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period.) The dose may be increased up to a maximum of 2 million IU three times daily for up to 3 months, in conjunction with other parenteral or oral antibiotics.

Chronic colonisation. (Three or more positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a six month period.) May require long-term therapy with 1 to 2 million IU twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection**.**

Nebulised Tadim should be administered after physiotherapy and other inhaled treatments, where used. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators. See Section 4.4 – Special warnings and precautions for use.

Colistimethate sodium is renally excreted and is nephrotoxic if high serum concentrations are achieved. The use of inhaled colistimethate sodium in patients with renal impairment has not been studied but systemic exposure is known to be low following inhalation.

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

Tadim may be reconstituted with Water for Injections (WFI) to produce a clear colourless to pale yellow hypotonic solution or a 50:50 mixture of WFI and 0.9% Sodium Chloride Injection to produce a clear colourless to pale yellow isotonic solution. When reconstituted, Tadim may be used with any conventional nebuliser suitable for delivery of antibiotic solutions. For more information on how to dilute Tadim, please refer to the table below.

Solutions should be used immediately after reconstitution. If this is not possible, reconstituted solutions may be stored for no longer than 24 hours at 2^{o}C to 8^{o}C. The potential for lung toxicity increases the longer Tadim is left in solution; therefore, the recommended maximum 24 hour time

period must not be exceeded. **Any unused solution must be discarded immediately and not used for subsequent dosing. Tadim contains no anti-microbial preservative.**

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.

Instructions for mixing Tadim for nebulisation

Tadim can be administered through any suitable nebuliser. Conventional nebulisers and the I-neb AAD system differ in efficiency (see the data provided in the Clinical Trials section). For this reason it is important that reference is made to the instructions that come with the nebuliser with regard to the use of the nebuliser and the volume of drug to be placed in the nebuliser. The I-neb AAD system is more efficient than conventional nebulisers and the amount of drug placed in the I-neb AAD system needs to be reduced compared to conventional jet nebulisers to avoid overdosing the patient. The I-neb can vary the dose given to the lungs, by changing the size of the medication chamber. Two sizes of chamber are available, a 0.3 mL gray, and a 0.5 mL mauve medication chamber.

The table below provides information on equivalent doses between conventional jet nebulisers and the I-neb AAD nebuliser. Always follow the manufacturer's instructions for using a nebuliser system.

	Device	**Number of 1 Million IU Vials**	**Volume of diluent (per vial)**	**Volume added to nebuliser**
Tadim dose of 1 million IU (conventional nebuliser)	**Conventional nebuliser**	1	2-4 mL	2-4 mL
Equivalent dose through an I-neb	**I-neb - 0.3 mL Grey Medication Chamber**	1	1 mL	1 mL
Tadim dose of 2 million IU (conventional nebuliser)	**Conventional nebuliser**	2	1-2 mL	2-4 mL
Equivalent dose through an I-neb	**I-neb - 0.5 mL Mauve Medication Chamber**	1	1 mL	1 mL

The I-neb AAD system has a fill volume of only 1 mL, a very low residual volume (<0.1 mL) and only pulses aerosol into the first 50-80% of inspiration minimising the amount of aerosol wasted during exhalation and maximising efficiency.

Please note that any solution remaining in the nebuliser following dosing should be discarded appropriately.

Clarification statement on the expression of colistimethate units of activity
Colistimethate sodium is chemically synthesised from colistin base (also referred to as colistin or polymyxin E).

As colistimethate sodium is not the same as colistin (or colistin base), care must be taken not to use these terms interchangeably. In addition it should be noted that the term used to express potency in colistimethate sodium drug products varies between Europe and the United States which can lead to confusion.

We recommend that Tadim (colistimethate sodium) is prescribed in International Units (IU) of activity to avoid confusion.

Each vial of Tadim contains 1 million IU which is approximately equal to a weight of 80 mg colistimethate sodium.

The table below may be a useful guide.

Colistin Potency		**Equivalent weights of powder providing stated potency**
Million IU	**mg (base)**	**mg of Colistimethate sodium**
1	33.33	80
2	66.66	160
4.5	150	360

4.3 CONTRAINDICATIONS

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

Colistimethate sodium is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore should not be used in patients with myasthenia gravis.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The dose of Tadim delivered to the lungs may vary according to the nebuliser system used for administration (see Section 4.2 – Dose and method of administration).

Bronchospasm

Nebulisation of colistimethate sodium may induce coughing or bronchospasm. 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 hyper-reactivity in a patient not receiving pre-treatment bronchodilators the test should be repeated on a separate occasion using a bronchodilator. Evidence of bronchial hyper-reactivity in the presence of a bronchodilator may indicate an allergic response and Tadim should be discontinued. Bronchospasm that occurs should be treated as medically indicated.

Bronchial hyper-reactivity in response to colistimethate sodium may develop with continued use over time and it is recommended that pre- and post-treatment FEV_1 is evaluated at regular clinic visits.

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 – Interactions with other medicines and other forms of interactions).

Porphyria

Use with extreme caution in patients with porphyria.

Use in renal impairment

Use with caution in renal impairment as colistimethate sodium is renally excreted.
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 antibiotics. The effect is usually reversible on discontinuation of therapy.

Use in the elderly

The use of Tadim in the elderly should be undertaken with careful consideration of the benefits to the patient in light of the potential risks of the inhaled drug.

Paediatric use

The efficacy of Tadim in children 2 years and under age group has not been studied.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Due to the effects of colistimethate sodium on the release of acetylcholine, non-depolarising muscle relaxants (such as vecuronium) should be used with extreme caution in patients receiving Tadim as their effects could be prolonged. Colistimethate sodium may prolong the effects of depolarising muscle relaxants.

Patients taking colistimethate sodium should be advised to tell anaesthetists they are on colistimethate sodium prior to a general anaesthetic.

Concomitant use of inhaled colistimethate sodium with other medications that are nephrotoxic or neurotoxic, including those which are administered by the intravenous or intramuscular routes, should only be undertaken with the greatest caution.

Co-administration of colistimethate sodium with other antibiotics that are both neurotoxic and nephrotoxic, such as aminoglycosides, should be undertaken with caution and with careful monitoring of renal function.

Co-administration of sodium cephalothin and colistimethate sodium may enhance the development of nephrotoxicity so this combination of antimicrobial medication should be avoided.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no adequate studies with colistimethate sodium to establish the potential for toxic effects on fertility.

Use in pregnancy

Tadim is Pregnancy Category B2- *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.*

Safety in human pregnancy has not been established. There is evidence that colistimethate sodium crosses the placenta and consequently there is potential for fetal toxicity if administered during pregnancy. Tadim should only be given during pregnancy if the benefits outweigh any potential risk.

Use in lactation.

Colistimethate sodium is excreted in breast milk. Given that safe use in lactation has not been established, breast feeding is not recommended during therapy unless the benefits to the mother outweigh the risks to the breastfeeding infant.

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 ADVERSE EFFECTS (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 (also see Section 4.4 – Special warnings and precautions for use).

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)
- very rare (<1/10,000)
- not known (cannot be estimated from the available data).

Body System	Frequency	Reported adverse effect
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

Cases of sore throat or sore mouth may be due to hypersensitivity or superinfection with *Candida* species.

Should hypersensitivity reactions such as skin rash occur, treatment with colistimethate sodium should be withdrawn.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

General properties

Colistimethate sodium is a polymyxin antibiotic and is derived from *Bacillus polymyxa var. colistinus.* It is a polypeptide and is active against a number of aerobic, Gram-negative bacteria.

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 an outer membrane.

Breakpoints

Susceptible (S) ≤4 mg/L, Resistant (R) ≥4 mg/L.

Susceptibility

The table below lists the bacterial species which are regarded as susceptible to colistimethate sodium. Bacterial resistance may vary according to region and information on resistant species in a specific area is desirable, particularly when treating severe infections. Only bacteria likely to be relevant to the clinical indication are listed.

SUSCEPTIBLE BACTERIA	RESISTANT BACTERIA
Acinetobacter species *Klebsiella* species *Pseudomonas aeruginosa*	*Brucella* species *Burkholderia cepacia* and related species *Serratia* species *Proteus mirabilis*

Resistance

Colistimethate sodium acquired resistance in mucoid *Pseudomonas aeruginosa* has been reported to be approximately 3%. Susceptibility testing should be performed on patients who are treated on a long term basis.

Cross resistance

Polymyxins including colistimethate sodium differ in their mechanism of action compared with other antibiotics and there is evidence to show that Gram-negative bacteria resistant to other antibiotics may be susceptible to colistimethate sodium. The resistance to polymyxins is not known to be crossed with other antibiotic families.

Clinical trials

An open 5-way cross-over pharmacokinetic study was conducted in healthy volunteers that compared plasma concentrations of polymixin E1 following delivery of colistimethate sodium by intravenous injection and using two different nebulisers, a Side Stream (a conventional jet nebuliser) and an I-neb AAD. The following doses of colistimethate were administered: 0.03 million IU and 0.5 million IU, by intravenous injection; 2 million IU by Side Stream nebuliser; and 0.3 million IU and 0.5 million IU by I-neb AAD nebuliser system. The study demonstrated that the Area Under the Curve (AUC) and maximum concentration (C_{max}) with the I-neb AAD was approximately the same with 0.5 million IU of colistimethate sodium when compared to a dose of 2 million IU of colistimethate sodium administered by a Side Stream nebuliser, and was approximately 50% with 0.3 million IU of colistimethate sodium delivered with I-neb AAD when compared to a dose of 2 million IU of colistimethate sodium administered by a Side Stream nebuliser.

Variable	Statistic	I-neb AAD nebuliser 0.3 mL Medication Chamber (1 million IU/mL)	I-neb AAD nebuliser 0.5 mL Medication Chamber (1 million IU/mL)	Side Stream Jet nebuliser (2 million IU in 4 mL)	IV (30,000 IU)	IV (500,000 IU)
$AUC_{0-\infty}$ (ng/mL/h)	N	17	19	17	18	18
	Geometric Mean	350.3	644	668	279	3352
C_{max} (ng/mL)	N	19	19	18	18	18
	Geometric Mean	40	69.3	69.9	83.6	1232

Following inhalation the T_{max} was approximately 2 to 2.5 hours and the half-life was approximately 5 hours for all nebuliser systems.

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 appears to be variable and clinical work has shown that resultant serum concentrations may range from undetectable to rarely exceeding 4 mg/L (50,000 IU/L) compared to serum concentrations of 10–20 mg/L (approx. 125,000-250,000 IU/L) following intravenous use. Absorption following lung administration is influenced by the nebuliser system, aerosol droplet size and disease state of the lungs. A study in CF patients showed that colistimethate sodium was undetectable in the urine after 1 million IU were inhaled twice daily for 3 months. This is despite the fact that excretion is known to be primarily via the urine.

Distribution

Colistimethate sodium shows a low level of protein binding. Polymyxin antibiotics are known to persist in muscle tissue, liver, kidney, heart and brain.

Serum concentrations and pharmacokinetics in 5 patients receiving inhaled colistimethate sodium

Parameter	160 mg (approximately 2 million IU) nebulised colistimethate sodium
AUC_{0-4} (h.mg/L)	165.9 ± 76.5
C_{max} (mg/L)	0.051 ± 0.0244
T_{max} (h)	1.9 ± 1.2
Ka (h^{-1})	3.0 ± 1.8
$t_{½}$ (h)	10.4 ± 3.6
Cl/F	0.27 ± 0.15

Volume of distribution has been calculated to be 0.09 L/kg in a single study in patients with CF.

Metabolism

Colistimethate sodium undergoes conversion to its base *in vivo*. Approximately 80% of the parenteral dose is recoverable unchanged in the urine. There is no biliary excretion.

Excretion

There is no information on the elimination of colistimethate sodium following nebulisation.

Following intravenous administration, excretion is primarily renal with 40% of a parenteral dose recovered in the urine within 8 hours and around 80% in 24 hours. It follows that consideration of a reduction in dose should be made in the renally impaired in order to prevent accumulation. However, a relatively low amount of systemic absorption takes place via the inhaled route (see **Absorption** above).

The elimination half-life is approximately 1.5 hours following intravenous administration to healthy adults. This compares with an elimination half-life of 3.4 ± 1.4 hours when CF patients were given a single 30 minute intravenous infusion.

Colistimethate sodium kinetics appear to be similar in all patient groups provided renal function is normal.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Data on potential genotoxicity are limited.

Carcinogenicity

No carcinogenicity studies have been conducted with colistimethate sodium.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

The addition of other antibiotics to solutions of Tadim may lead to precipitation.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[2]. The expiry date can be found on the packaging.

Once reconstituted it should be used immediately. If this is not possible, reconstituted solutions may be stored for no longer than 24 hours at 2°C to 8°C. Any unused solution remaining must be discarded immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Tadim is to be stored below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

It is supplied in a clear glass vial with a siliconised chlorobutyl type I rubber stopper and protected by a 20 mm aluminium tear-off cap incorporating a red flip-off central plastic button. Tadim is supplied in packs of 30 vials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

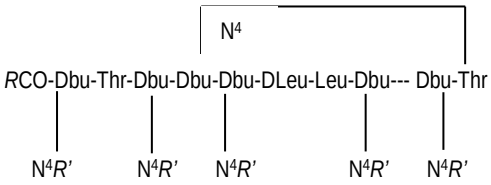
Chemical structure

Structural formula:

[2] AUST R 165709

Dbu = $_{L}$- 2, 4-diaminobutyric acid

R' = CH_2SO_3Na



	R
Colistin A component	-$[CH_2]_4CHMeCH_2CH_3$
Colistin B component	-$[CH_2]_4CHMe_2$

Molecular formula: $C_{58}H_{105}N_{16}O_{28}S_5Na_5$
Colistimethate sodium has a molecular weight of approximately 1,745 g/mol.

CAS number

The CAS number: 8068-28-8
ATC code: J01XB01

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

Phebra[3] Pty Ltd
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Telephone: 1800 720 020

Phebra product code: SOL040

9 DATE OF FIRST APPROVAL

2 February 2011

10 DATE OF REVISION

10 January 2019

SUMMARY TABLE OF CHANGES

[3] Phebra and the Phi symbol are trademarks of Phebra Pty Ltd, 19 Orion Road, Lane Cove West, NSW 2066, Australia.

Section Changed	Summary of new information
NA	PI reformatted to align with new form
NA	Updated Zambon trademark statement