The following information is intended for medical or healthcare professionals only:

Summary of Product Characteristics for Tadim 1 million International Units (IU) Powder for Solution for Infusion

1 NAME OF THE MEDICINAL PRODUCT

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

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 solution for infusion

The powder is white to off white

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tadim is indicated in adults and children including neonates for the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options (see sections 4.2, 4.4, 4.8 and 5.1).

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

4.2 Posology and method of administration

The dose to be administered and the treatment duration should take into account the severity of the infection as well as the clinical response. Therapeutic guidelines should be adhered to.

The dose is expressed in international units (IU) of colistimethate sodium (CMS). A conversion table from CMS in IU to mg of CMS as well as to mg of colistin base activity (CBA) is included at the end of this section.

Posology

The following dose recommendations are made based on limited population-pharmacokinetic data in critically ill patients (see section 4.4):

Adults and adolescents

Maintenance dose 9 MIU/day in 2-3 divided doses.

In patients who are critically ill, a loading dose of 9 MIU should be administered.

The most appropriate time interval to the first maintenance dose has not been established.

Modelling suggests that loading and maintenance doses of up to 12 MIU may be required in patients with good renal function in some cases. Clinical experience with such doses is however extremely limited and safety has not been established.

The loading dose applies to patients with normal and impaired renal functions including those on renal replacement therapy.

Renal impairment

Dose adjustments in renal impairment are necessary, but pharmacokinetic data available for patients with impaired renal function is very limited.

The following dose adjustments are suggested as guidance.

Dose reductions are recommended for patients with creatinine clearance < 50 mL/min: Twice daily dosing is recommended.

Creatinine clearance (mL/min)	**Daily dose**
< 50 - 30	5.5 - 7.5 MIU
< 30 - 10	4.5 - 5.5 MIU
< 10	3.5 MIU

MIU = million IU

Haemodialysis and continuous haemo(dia)filtration:

Colistin appears to be dialyzable through conventional haemodialysis and continuous venovenous haemo(dia)filtration (CVVHF, CVVHDF). There are extremely limited data from population PK studies from very small numbers of patients on renal replacement therapy. Firm dose recommendations cannot be made. The following regimes could be considered

Haemodialysis:

No-HD days: 2.25 MIU/day (2.2 - 2.3 MIU/day).
HD days: 3 MIU/day on haemodialysis days, to be given after the HD session. Twice daily dosing is recommended.

CVVHF/ CVVHDF:

As in patients with normal renal function. Three times daily dosing is recommended.

Hepatic impairment

There are no data in patients with hepatic impairment. Caution is advised when administering colistimethate sodium in these patients.

Older people

No dose adjustments in older patients with normal renal function are considered necessary.

Paediatric population

The data supporting the dose regimen in paediatric patients are very limited. Renal maturity should be taken into consideration when selecting the dose. The dose should be based on lean body weight.

Children ≤ 40kg: 75,000 – 150,000 IU/kg/day divided into 3 doses.

For children with a body weight above 40 kg, use of the dosing recommendation for adults should be considered.

The use of doses >150,000 IU/kg/day has been reported in children with cystic fibrosis.

There are no data regarding the use or magnitude of a loading dose in critically ill children.

No dose recommendations have been established in children with impaired renal function.

Intrathecal and intraventricular administration

Based on limited data, the following dose is recommended in adults:

Intraventricular route: 125,000 IU/day.

Intrathecally administered doses should not exceed those recommended for intraventricular use.

No specific dosing recommendation can be made in children for intrathecal and intraventricular routes of administration.

Method of administration

Tadim is administered intravenously as a slow infusion over 30 – 60 minutes.

The volume administered in intrathecal or intraventricular use should not exceed 1 mL.

Patients fitted with a totally implantable venous access device (TIVAD) may tolerate an injection of up to 2 MIU in 10 mL given over a minimum of 5 minutes.

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution. For dose preparation, particularly where combination of multiple vials is needed, reconstitution of the required dose must be performed using strict aseptic technique (see section 6.6).

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

Hypersensitivity to the active substance colistimethate sodium or other polymyxins.

4.4 Special warnings and precautions for use

Consideration should be given to co-administering intravenous colistimethate sodium with another antibacterial agent whenever this is possible, taking into account the remaining susceptibilities of the pathogen(s) under treatment. As the development of resistance to intravenous colistin has been reported in particular when it is used as a monotherapy, co- administration with other antibacterial should also be considered in order to prevent the emergence of resistance.

There are limited clinical data on the efficacy and safety of intravenous colistimethate sodium. The recommended doses in all subpopulations are equally based on limited data (clinical and pharmacokinetic/ pharmacodynamics data). In particular there are limited safety data for the use of high doses (> 6 MIU/day) and the use of a loading dose, and for special populations (patients with renal impairment and the paediatric population). Colistimethate sodium should only be used when other, more commonly prescribed antibiotics are not effective or not appropriate.

Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance (see section 4.2). Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8). Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.

Caution is advised when administering colistimethate sodium to infants < 1 year of age as renal function is not fully mature in this age group. Further, the effect of immature renal and metabolic function on the conversion of colistimethate sodium to colistin is not known.

In case of an allergic reaction, treatment with colistimethate sodium must be discontinued and appropriate measures implemented.

High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. Monitoring should be performed for perioral paraesthesia and paraesthesia in the extremities, which are signs of overdose (see section 4.9).

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.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnoea and neuromuscular blockade following administration of colistimethate sodium.

Colistimethate sodium should be used with extreme caution in patients with porphyria.

Antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all anti-bacterial agents and may occur with colistimethate sodium. They may range from mild to life-threatening in severity. It is important to consider this diagnosis in patients who develop diarrhoea during or after the use of colistimethate sodium (see section 4.8). Discontinuation of therapy and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Intravenous colistimethate sodium does not cross the blood brain barrier to a clinically relevant extent. The use of intrathecal or intraventricular administration of colistimethate sodium in the treatment of meningitis was not systematically investigated in clinical trials and is supported by case reports only. Data supporting the posology are very limited. The most commonly observed adverse effect of CMS administration was aseptic meningitis (see section 4.8).

Few cases of pseudo-Bartter syndrome have been reported in children and adults with the intravenous use of colistimethate sodium. Monitoring of serum electrolytes should be started in suspected cases and appropriate management should be implemented, however, normalisation of electrolyte imbalance might not be achieved without discontinuation of colistimethate sodium.

Sodium

This medicinal product contains up to 6.4 mg sodium per vial, which correspond to less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of intravenous colistimethate sodium with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with the greatest caution.

Caution should be taken with concomitant use with other formulations of colistimethate sodium as there is little experience and there is a possibility of summative toxicity.

No *in vivo* interaction studies have been performed. The mechanism of conversion of colistimethate sodium to the active substance, colistin, is not characterised. The mechanism of colistin clearance, including renal handling, is equally unknown. Colistimethate sodium or colistin did not induce the activity of any P 450 (CYP) enzyme tested (CYP1A2, 2B6, 2C8, 2C9, 2C19 and 3A4/5) in *in vitro* studies in human hepatocytes.

The potential for drug-drug interactions should be borne in mind when Tadim is co-administered with drugs known to inhibit or induce drug metabolising enzymes or drugs known to be substrates for renal carrier mechanisms.

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

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).

Pregnancy

There are no or limited amount of data from the use of colistimethate sodium in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). However, there is evidence that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if administered during

pregnancy. Hence, Tadim should only be given during pregnancy if the benefits to the mother outweigh any potential risk to foetus.

Lactation

Colistimethate sodium/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Tadim therapy taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the woman.

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 most commonly reported adverse reaction is renal function impairment, and more rarely renal failure, usually following use of higher than recommended doses in patients with normal renal function, or failure to reduce the dosage in patients with renal impairment or when used concomitantly with other nephrotoxic antibiotics. The effect is usually reversible on discontinuation of therapy, but rarely intervention (renal replacement therapy) may be required.

High serum concentrations of colistimethate sodium, which may be associated with overdosage or failure to reduce the dosage in patients with renal impairment, have been reported to lead to neurotoxic effects such as facial paraesthesia, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion, psychosis and apnoea. 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.

Hypersensitivity reactions such as skin rash and angioedema have been known to occur. In the event such reactions occur, treatment with colistimethate sodium should be withdrawn.

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 and angioedema
Nervous system disorders	Very Common	Neurotoxicity such as, facial, mouth and peri-oral paraesthesia, headache, and muscle weakness
	Not known	Dizziness Ataxia
Skin and subcutaneous tissue disorders	Very Common	Pruritus

Body System	Frequency	Reported adverse reaction
Renal and urinary disorders	Very Common	Renal impairment demonstrated by increased blood creatinine and / or urea and / or decreased creatinine renal clearance
	Rare	Renal failure
Metabolism and nutrition disorders	Not known	Pseudo-Bartter syndrome*
General disorders and administration site conditions	Not known	Injection site reaction

*See section 4.4.

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 renal insufficiency, renal failure, apnoea, muscle weakness, vertigo, slurred speech, vasomotor instability, visual disturbances, confusion and psychosis.

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: antibacterials for systemic use, other antibacterials, polymyxins

ATC code: J01XB01

General properties

Mechanism of action

Colistin is a cyclic polypeptide antibacterial agent belonging to the polymyxin group. Polymyxins work by damaging the cell membrane and the resulting physiological effects are lethal to the bacterium. Polymyxins are selective for aerobic Gram-negative bacteria that have a hydrophobic outer membrane.

Resistance

Resistant bacteria are characterised by modification of the phosphate groups of lipopolysaccharide, which become substituted with ethanolamine or aminoarabinose. Naturally resistant Gram-negative bacteria, such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of their lipid phosphate by ethanolamine or aminoarabinose.

Cross resistance between colistin (polymyxin E) and polymyxin B is expected. Since the mechanism of action of the polymyxins is different from that of other antibacterial agents, resistance to colistin and polymyxin by the above mechanism alone would not be expected to result in resistance to other drug classes.

PK/PD relationship

Polymyxins have been reported to have a concentration-dependent bactericidal effect on susceptible bacteria. fAUC/ MIC is considered to be correlated with clinical efficacy.

EUCAST Breakpoints

	Susceptible (S)	Resistant (R) [a]
Acinetobacter	S≤2	R>2 mg/L
Enterobacteriaceae	S≤2	R>2 mg/L
Pseudomonas spp	S≤4	R>4 mg/L

[a] *Breakpoints apply to dosage of 2-3 MIU x 3. A loading dose (9 MIU) may be needed.*

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 baumannii

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

5.2 Pharmacokinetic properties

The information on the pharmacokinetics of colistimethate sodium (CMS) and colistin is limited. There are indications that pharmacokinetics in critically ill patients differ from those in patients with less severe physiological derangement and from those in healthy volunteers. The following data are based on studies using HPLC to determine CMS/colistin plasma concentrations.

Absorption

Absorption of colistimethate sodium from the gastrointestinal tract does not occur to any appreciable extent in the normal individual.

Distribution

The volume of distribution of colistin in healthy subjects is low and corresponds approximately to extracellular fluid (ECF). The volume of distribution is relevantly enlarged in critically ill subjects. Protein binding is moderate and decreases at higher concentrations. In the absence of meningeal inflammation, penetration into the cerebrospinal fluid (CSF) is minimal, but increases in the presence of meningeal inflammation.

Both CMS and colistin display linear PK in the clinically relevant dose range.

Biotransformation

After infusion of colistimethate sodium the inactive pro-drug is converted to the active colistin. Peak plasma concentrations of colistin have been shown to occur with a delay of up to 7 hours after administration of colistimethate sodium in critically ill patients.

Elimination

It is estimated that approximately 30% of colistimethate sodium is converted to colistin in healthy subjects, its clearance is dependent on creatinine clearance and as renal function decreases, a greater portion of CMS is converted to colistin. In patients with very poor renal function (creatinine clearance < 30 mL/min), the extent of conversion could be as high as 60% to 70%. CMS is eliminated predominantly by the kidneys via glomerular filtration. In healthy subjects, 60% to 70% of CMS is excreted unchanged in the urine within 24 hours.

The elimination of the active colistin is incompletely characterised. Colistin undergoes extensive renal tubular reabsorption and may either be cleared non-renally or undergo renal metabolism with the potential for renal accumulation. Colistin clearance is decreased in renal impairment, possibly due to increased conversion of CMS.

Half-life of colistin in healthy subjects and those with cystic fibrosis is reported to be around 3h and 4h, respectively, with a total clearance of around 3L/h. In critically ill patients, half-life has been reported to be prolonged to around 9-18h.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of repeated dose toxicity and genotoxicity.

Based on older pre-ICH guideline studies in rats, delayed ossification and reduced postnatal survival has been observed at the high dose of 25 mg/kg colistimethate sodium (10 mg colistin base/kg). No effects were reported in rabbits at IV doses of 80 mg/kg colistimethate sodium (32 mg colistin base/kg").

Data on potential carcinogenicity for colistimethate sodium are lacking.

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

Unopened:

3 years

After reconstitution:

Hydrolysis of colistimethate sodium to the active substance colistin is significantly increased when reconstituted and diluted below its critical micelle concentration of about 80,000 IU per mL.

The chemical and physical in-use stability of reconstituted solution in the original vial, with a concentration of ≥ 80,000 IU/mL, has been demonstrated for 24 hours at 2 to 8ºC or for up to 8 hours at room temperature. Solutions which have been diluted beyond the original vial volume and/or with a concentration of < 80,000 IU/mL should be used immediately.

From a microbiological point of view unless the method of opening/reconstitution/ dilution precludes the risk of microbial contamination, the solution should be used immediately. If not used immediately in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

No special precautions for storage

For storage conditions of the reconstituted/diluted product see section 6.3.

6.5 Nature and contents of container

The product is supplied in a clear type I glass 10R ISO vial (nominal volume 10 mL) 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 pack sizes of 10 vials.

6.6 Special precautions for disposal and other handling

For single use only.

Tadim must be reconstituted under aseptic conditions to produce a clear colourless to pale yellow solution.

The solution should be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Bolus injection

Reconstitute each vial necessary for the required dose with not more than 10mL water for injection or 0.9% sodium chloride solution.

Intrathecal and intraventricular use

Reconstitute the vial with 0.9% sodium chloride solution. The volume taken for administration should not exceed 1 mL and the solution should be used immediately after reconstitution. To achieve the recommended solution concentration of 125,000 IU/mL reconstitute the vial with 8 mL of 0.9% sodium chloride solution.

Infusion

Reconstitute a sufficient number of vials to obtain the required dose by adding an appropriate volume of water for injection or 0.9% sodium chloride solution to each vial, not exceeding 10 mL per vial. Draw up the content from each vial to make up the required dose which may then be further diluted, usually with 50 mL of 0.9% sodium chloride solution, as appropriate for the volume and method infusion. Solutions should be used immediately after reconstitution (see section 4.2).

Discard any unused solution.

Waste material should be disposed of in accordance with local requirements.

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

[To be completed nationally]

<{DD month YYYY}>

10 DATE OF REVISION OF THE TEXT

2025-01-17