Australian Public Assessment Report for Colistimethate sodium

Proprietary Product Name: Tadim

Sponsor: Phebra Pty Ltd

February 2011

About the Therapeutic Goods Administration (TGA)

· The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.

· TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

· A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Dose Form and New Route of Administration
Decision:	Approved
Date of Decision:	13 January 2011
Active ingredient(s):	Colistimethate sodium
Product Name(s):	Tadim
Sponsor's Name and Address:	Phebra Pty Ltd 332 Burns Bay Road Lane Cove NSW 2066
Dose form(s):	Powder for nebuliser solution
Strength(s):	1 million international units (IU) approximately equivalent to 80 mg colistimethate sodium
Container(s):	Clear glass vial
Pack size(s):	30 vials
Approved Therapeutic use:	For the treatment of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Route(s) of administration:	Inhalation
Dosage:	1-2 million IU, two to three times daily when using a conventional nebuliser
ARTG Number:	165709

Product Background

Colistimethate sodium (CMS) belongs to polypeptide group of antibiotics. The drug substance consists of multiple polymyxins but polymyxins E1 (colistin A) and E2 (colistin B) are the main components.[1,2,3]

The parenteral form has a history of over 40 years of use although the use declined in 1970s due to concerns about nephrotoxicity and neurotoxicity. The inhaled drug has a history of use over the last 20 years.

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[1] Li J, Coulthard K, Milne R, Nation RL, Conway S, Peckham D et al. Steady-state pharmacokinetics of intravenous Colistin methanesulphonate in patients with cystic fibrosis. Antimicrob Chemother. 2003a; 52: 987–92.

[2] Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, Paterson DL. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis. 2006a; (6): 589-601.

[3] Polymyxin is also called polymixin but is referred to as polymyxin in this AusPAR except in some figures and tables where the spelling cannot be changed.

CMS is a prodrug and is hydrolysed to active colistin (A and B) which binds with cytoplasmic membranes of Gram-negative bacteria displacing divalent cations (Ca^{+2} and Mg^{+2}) from the negatively charged phosphates in membrane lipids. This detergent-like action interferes with osmotic barrier function of the bacterial cell wall leading to disruption, leakage of intracellular contents, and bacterial lysis.[2,4,5]

The potency of CMS may be described in mg or international units (IU) such that 80 mg is approximately equivalent to one million IU. The proposed labelling expresses the dose in IU.

This AusPAR describes a submission to register CMS powder for nebuliser solution containing 1 million IU, in the treatment of *Pseudomonas aeruginosa (PA)* infection of lungs in patients with cystic fibrosis (CF).

A parenteral formulation of CMS containing 4.5 M IU of colistimethate sodium or approximately 360 mg of colistimethate sodium or 150 mg of colistin base is currently registered in Australia to another sponsor.

The proposed indication for the nebuliser solution of CMS is as follow:

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.

The proposed dosing using a conventional nebuliser is as follows:

Children > 2 years 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.

Further usage guidelines proposed in the Product Information (PI) are as follows:

Initial colonisation with *Pseudomonas aeruginosa* sensitive to CMS 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 CMS 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 CMS 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.

The Australian approved therapeutic indication for parenteral CMS is 'treatment of acute or chronic infections due to sensitive strains of certain Gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of *Pseudomonas aeruginosa*. This antibiotic is not indicated for infections due to Proteus and Neisseria. It has proven clinically effective in treatment of infections due to the following gram-negative organisms:

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[4] Bergen PJ, Li J, Rayner CR, Nation RL. Colistin methanesulfonate is an inactive prodrug of colistin against Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2006(6); 50: 1953–8.

[5] Li J, Nation RL, Milne RW, Turnidge JD, Coulthard K. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. Int J Antimicrob Agents. 2005a; 25 (1): 11-25.

Enterobacter aerogenes, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Pending results of appropriate bacteriologic cultures and sensitivity tests, it may be used to initiate therapy in serious infections that are suspected due to Gram-negative organisms.' This was a grand-fathered product.

There is anecdotal evidence that extemporaneous compounding of parenteral formulation for administration by inhalation in patients with cystic fibrosis has been widespread over the years in Australia, and documented evidence for this practice in the USA. However, the sponsor for this application is supplying CMS powder for nebuliser solution (UK registered, GMP manufactured), as an exempt therapeutic good under item 5 of Schedule 5A of the *Therapeutic Goods Regulations 1990*. The product information document can also be accessed online for supply in Australia.

Regulatory Status

The product was designated as an Orphan Drug in Australia for treatment of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis on 31 October 2008 due to low prevalence of the disease.

The CMS nebuliser solution (Promixin, an alternative brand name for Tadim) has been approved in various European Union (EU) countries since 2003-2004 including the UK. The second round of recognition via the Mutual Recognition (MR) procedure in other EU countries has been completed with new registrations in the following countries: Portugal, Sweden, Austria, Norway, Netherlands, Poland and France (approval is pending in France following this MR procedure).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II.   *Quality Findings*

Introduction

CMS is currently registered in Australia by Link Pharmaceuticals as a powder for intravenous (IV) or intramuscular (IM) injection ("Colistin Link Parenteral"), containing CMS (approximately 360 mg) equivalent to 150 mg Colistin USP activity (4.5 million IU).

The present application seeks to register Tadim, the first CMS product proposed for use by the inhalational route. It comprises one million IU of sterile CMS powder (approximately 80 mg) in a glass vial, with no added excipients. It is reconstituted with Water for Injections or 0.45% sodium chloride injection then administered by nebulisation using a suitable nebuliser. No diluent is provided with the product.

Drug Substance (active ingredient)

Colistin is a mixture of cyclic decapeptides, or polymyxins, produced by fermentation. It is usually isolated as a sulfate salt, with the structure shown below. Colistin is composed primarily of colistin A (polymyxin E1) and colistin B (polymyxin E2).

In the published literature, the drug has been variously called colymycin, colistin, colistin methate sulphonate and colistin sulphomethate.[6] Its current international non-proprietary name (INN) and Australian Approved Name (AAN) is colistimethate sodium.

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[6] Goodwin NJ. Colistin and sodium colistimethate. Med Clin North Am. 1970; 54: 1267-76.

The European Pharmacopoeial monograph describes it as a semi-synthetic substance derived chemically from a fermentation product. In a pre-submission meeting, the TGA stated that it considers this a semi-synthetic product.

polymyxin	X	R1	R2	R3	Mol. Formula	M_r
E1	D-Leu	CH_3	CH_3	H	$C_{53}H_{100}N_{16}O_{13}$	1170
E2	D-Leu	CH_3	H	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E3	D-Leu	H	CH_3	H	$C_{52}H_{98}N_{16}O_{13}$	1155
E1-I	D-Ile	CH_3	CH_3	H	$C_{53}H_{100}N_{16}O_{13}$	1170
E1-7MOA	D-Leu	H	CH_3	CH_3	$C_{53}H_{100}N_{16}O_{13}$	1170
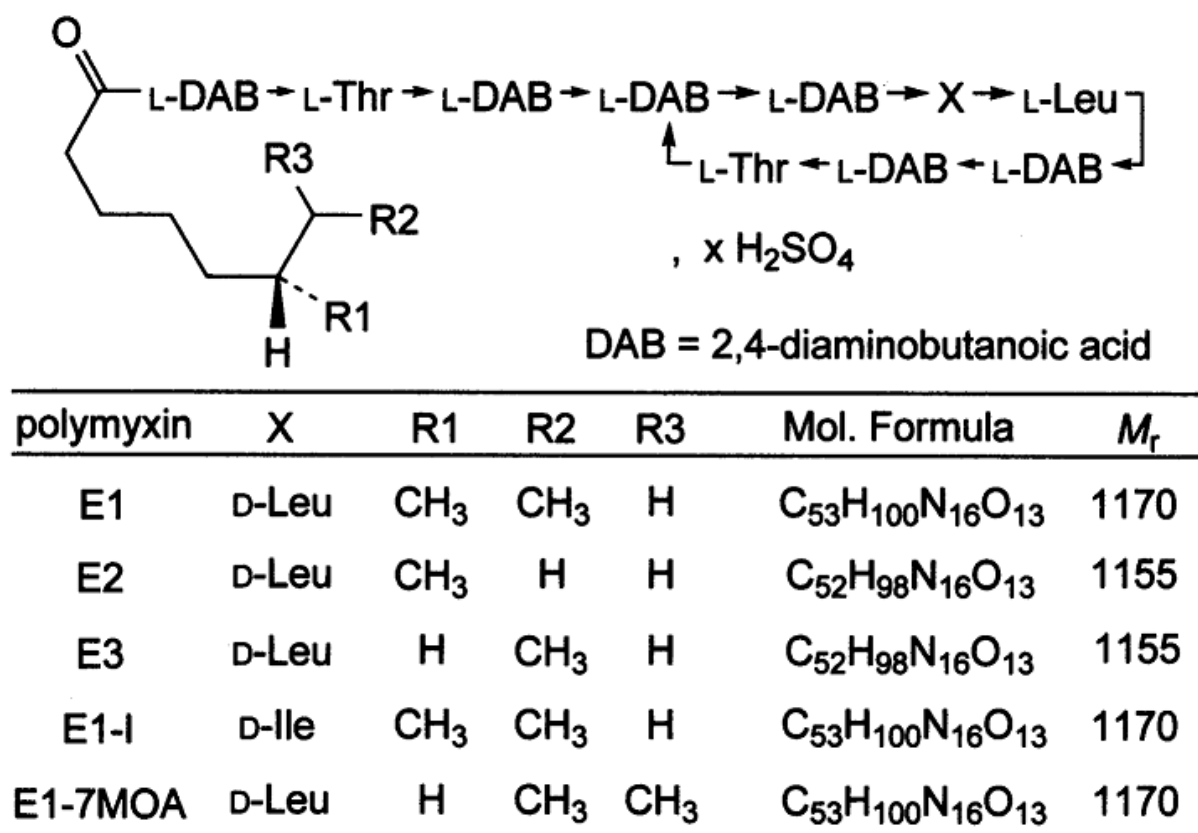
Sterile CMS is manufactured by Axellia Pharmaceuticals ApS, Denmark. The drug substance is the subject of a British Pharmacopoeia (BP)/European Pharmacopoeia (Ph. Eur.) monograph. A European Certificate of Suitability has been issued for the drug substance manufactured by Axellia.

Drug Product

Tadim consists of 1 million international units (IU) approximately equivalent to 80 mg colistimethate sodium in a glass vial.

Reconstitution with 0.45% sodium chloride injection is claimed to give an isotonic solution.

Tadim is intended for the treatment of colonisation and infections of the lung due to susceptible *Pseudomonas aeruginosa* in patients with cystic fibrosis. The proposed dose is 1-2 million IU two or three times daily.

Analytical methods were developed on the basis of the BP and Ph Eur and were considered acceptable.

The proposed shelf life for the unopened product is 3 years below 25°C. The proposed shelf life for the reconstituted solution is 8 hours with storage at 2-8°C. Satisfactory data have been submitted to support these shelf lives.

Dosage and Administration

The recommended dose of Tadim, according to the originally submitted PI, is 1-2 million IU (1-2 vials) two or three times daily. The 'recommended dose' is not the dose delivered to the patient, but is the dose charged into a conventional nebuliser. According to the sponsor, the patient actually inhales less than half of this dose as there is a significant residual volume of solution that remains in the nebuliser after administration and there is significant loss of drug to the atmosphere during use of the nebuliser.

The instructions for use in the proposed PI were subsequently amended to also include instructions for dosing with an "I-neb AAD" system. This system is claimed to be much more efficient than a conventional nebuliser as it has very little residual volume and reacts to the patient's breathing patterns so that it only releases the nebulised drug while the patient is inhaling. Hence, with this system, for a 'recommended dose' of 1 million IU, the nebuliser is charged with only 0.5 million IU and for a 'dose' of 2 million IU it is charged with only 1 million IU. This is potentially confusing for the user, and the sponsor has agreed to amend the PI further to include appropriate explanation. In addition, it was recommended that the TGA Delegate should consider whether the PI should be amended to clearly indicate that the recommended doses differ for the two types of device. For example, under *Recommended doses*, the statement '1-2 million IU two or three times daily' could be amended to '1-2 million IU two or three times daily using a conventional nebuliser or 0.5-1 million IU two or three times daily using an "I-neb AAD" nebuliser system'. Similar amendments would be necessary each time a dose is mentioned.

No data have been provided in the quality submission to demonstrate that the doses delivered from a conventional nebuliser and the "I-neb AAD" system are equivalent when used in accordance with the instructions in the PI. The TGA Delegate was requested to confirm that clinical data have been provided to demonstrate equivalence of the two types of device when used as recommended.

Quality Summary and Conclusions

There were no objections to registration of this product in respect of chemistry, manufacturing and controls.

The TGA Delegate was requested to consider whether adequate data were provided to demonstrate clinical equivalence of a conventional nebuliser and the "I-neb AAD" system when used in accordance with the instructions in the PI.

The sponsor noted the nonclinical evaluator's comments on the submitted sponsor-initiated study (discussed later in this document):

"The study also demonstrated pharmacokinetic equivalence, based on systemic exposures of polymyxin E1 (peak and total), between 2 million IU administered by a conventional jet nebuliser with 0.5 million IU administered using the AAD delivery system.

Based on the comparison between 2 million IU administered by a conventional jet nebulisation and 0.3 million IU units delivered by the AAD system, it can also be inferred that 1 million IU delivered by jet nebulisation will result in equal systemic exposures as 0.3 million IU using AAD."

III.   *Nonclinical Findings*

Introduction

Phebra Pty Ltd has applied to register the polymyxin antibiotic CMS (powder) for inhalation following reconstitution in the treatment of *Pseudomonas aeruginosa* infections in adults and paediatric patients 2 years of age and older with cystic fibrosis. The proposed maximum

clinical dose is 2 million IU (equivalent to 160 mg) administered up to 3 times daily, for up to 3 months, for frequent, recurrent infections. Proposed long-term use for chronic colonisation is two times daily. Currently, CMS (up to 5 mg/kg/day) is available for IV or IM use in the treatment of chronic Gram negative infections. Tobramycin (Tobi), an aminoglycoside antibiotic, and aztreonam (Cayston), a synthetic monobactam antibiotic, are registered for the same indication. Both are indicated for use in both adults and paediatric patients 6 years of age and older with alternating periods of 28 days on/ 28 days off.

The nonclinical package consisted entirely of published literature. The search strategy was validated by the TGA Library. The Good Laboratory Practice (GLP) status was unknown. None of the submitted studies in animals were conducted via the intended route (inhalation) but one such study (a conference poster) was sourced by the nonclinical evaluator. The assessment was mainly based on data obtained after IV or intraperitoneal (IP) administration of CMS or its metabolite colistin, as well as this study. There was limited data due to 50 years of clinical use. Overall, the nonclinical package was not adequate for determining the toxicity profile of the product in order for a sufficient assessment of risk to be determined. The absence of carcinogenesis studies and other deficiencies in the nonclinical package preclude a recommendation for registration on nonclinical grounds. Therefore any decision to register the product will need to be made on clinical grounds.

Pharmacology
Primary pharmacodynamics

Antibacterial activity

CMS is a pro-drug, of which colistin is considered to be both a product of degradation, metabolism and the active moiety. Colistin is presumed to have an identical mechanism of action to that of polymyxin B, interacting with the outer membrane of Gram-negative bacteria and competitively displacing divalent cations (calcium and magnesium) from negatively charged phosphate groups of membrane lipids. The resultant disruption of the outer membrane leads to release of lipopolysaccharide (LPS) and bacterial death.

At the time of compiling this report, the British Society for Antimicrobial Chemotherapy (BSAC) website indicated that the breakpoints for susceptibility and resistance for colistin were ≤ 2 µg/mL and >2 µg/mL, respectively, and EUCAST values (as of April 2010) were ≤ 4 µg/mL and >4 µg/mL, respectively; neither BSAC nor EUCAST included breakpoints for intermediate susceptibility.[7] Many of the submitted reviews (which were quoted in the sponsor's *Nonclinical Overview*) as well as the draft PI stated that the breakpoints for susceptibility and resistance were≤ 4 µg/mL and ≥ 8 µg/mL, respectively, indicating that these breakpoints were revised by these organisations in the intervening period.

In a recent study, Etest and broth dilution methods were considered more accurate in predicting activity of CMS against bacteria species, due to the poor agar diffusion characteristics of polymyxins, as well as the fact that the *in vitro* activity of polymyxins appears to be affected by cation concentrations in agar (Kwa et al, 2008).[8,9] The submitted

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[7] EUCAST (European Committee on Antimicrobial Susceptibility Testing) is convened and financed by ESCMID (European Society for Clinical Microbiology and Infectious Diseases) and is a standing committee of ESCMID. It consists of a body of experts appointed by national societies of clinical microbiology and/or infectious diseases and national breakpoint committees. EUCAST will act with the support of national breakpoint committees to harmonize breakpoints for existing antimicrobials and set breakpoints for new antimicrobials.

[8] The Epsilometer test (usually abbreviated Etest) is a laboratory test used by microbiologists to determine whether or not a specific strain of bacterium or fungus is susceptible to the action of a specific antibiotic.

susceptibility studies from the published literature employed the Etest, broth dilution or agar dilution methodology, but in each case in accordance with prevailing standards.

The main focus of the susceptibility studies submitted with the nonclinical data was to show anti-bacterial activity against *P. aeruginosa*, which is a major pathogenic organism in cystic fibrosis. *P. aeruginosa* was shown to be susceptible according to the latest breakpoint criteria to CMS and/or colistin in *in vitro* studies both in published literature data from various sources. These conclusions were also supported by collated data published on the EUCAST and BSAC websites, although methodological details and sources of the data were not shown. In time-kill experiments, bactericidal activity of colistin (3-log reduction in colony counts at or before 3 hours of exposure) was shown against two strains when the maximal plasma concentration (C_{max}) was at least 3 µg/mL. In another study, there was a delay in the onset of the antibacterial effect after administration of CMS, which was abolished by spiking with 6 µg/mL colistin, indicating that CMS was an inactive pro-drug of colistin. Other studies have indicated that CMS also has antibacterial activity. The extent to which the observed activity of CMS reflects the activity of its breakdown products remains unresolved. Further time-kill studies showed that regrowth occurred despite the presence of colistin, particularly with dosage regimens where there was ≥ 12 hours between doses. Therefore, despite exhibiting concentration-dependent killing, colistin possesses little or no post-antibiotic effect (PAE) at clinically relevant concentrations.

In vitro activity of CMS was also investigated in combination with other antibiotics. Evidence of synergism was seen against at least some *P. aeruginosa* strains when colistin was combined with doxycycline, ceftazidime or rifampin; the synergy with combinations of ceftazidime or rifampin was also shown in time-kill experiments. Combinations of colistin with meropenem or azithromycin resulted in additive or indifferent effects against *P. aeruginosa* strains. Where tested; clear evidence of antagonism between colistin or CMS and other antibiotics was not seen.

In vivo investigation of the efficacy of colistin was limited to one study using a rat IV model of sepsis due to *P. aeruginosa*. Plasma endotoxin and tumour necrosis factor (TNF)-α levels were reduced as a result of treatment with colistin. Lethality over 72 hours and blood culture were also significantly reduced in the presence of colistin and were further reduced when administered in combination with an ineffective dose of rifampicin which suggests a synergistic interaction consistent with the findings from the *in vitro* and time-kill experiments referred to above.

The draft PI lists a number of other bacteria (*Acinetobacter* spp., *Haemophilus influenzae* and *Klebsiella* spp.) as susceptible to CMS. Activity was also shown against *Acinetobacter* and *Klebsiella* species *in vitro*. However, there was no time-kill or *in vivo* evidence for activity, and therefore an assessment on the extent to which the *in vitro* activity translates to clinical efficacy will need to be based on clinical data. There was no compelling evidence from nonclinical studies for activity against *H. influenzae*, but activity appeared to be 'assumed' in some review articles (for example Kwa et al, 2008). While there is evidence to indicate that CMS also has antibacterial activity against a range of other Gram-negative bacteria, only data relating to those were evaluated which were considered directly relevant to the indication, that is, those known to produce concomitant infections in the lungs of cystic fibrosis patients.

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9 Kwa AL, Tam VH, Falagas ME. Polymyxins: A review of the current status including recent developments. Ann Acad Med Singapore 2008; 37: 870-83.

Resistance

Resistance to colistin (as for other polymyxins) appears to arise as a result of changes to the structure of the lipids of the outer membrane. These changes were lost when the cells were grown in the absence of polymyxin. A genetically stable mechanism involves increased production of the outer membrane protein OprH (or H1), by functionally replacing divalent cations in the cell membrane. Other specific mechanisms of resistance found in metabolically active subpopulations of *P. aeruginosa* grown on biofilms included pmr operon-mediated modifications to the LPS, resulting in reduced interaction with colistin, and mexAB-oprM – mediated export of colistin. It was shown that in a non-indicated species (*K. pneumoniae*), colistin resistance occurred independently and not by clonal spreading.

The "Antibiotic Resistance Data" in the submission noted that a product containing polymyxin B (along with neomycin and bacitracin) had been refused rescheduling from S4 to S3 by the National Drug and Poisons Scheduling Committee in 2004, but the decision was based mainly on documented evidence of neomycin resistance. The committee had also taken into account previous Expert Advisory Group on Antibiotic Resistance (EAGAR) advice concerning potential neomycin and bacitracin resistance. It was also noted that polymyxin B and polymyxin B sulfate were registered by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in various products for topical veterinary use, as well as in some animal vaccines. In the submitted literature references, there was considerable variability in the proportions of resistant strains relative to susceptible strains, ranging from 3% to 33% of the total at different locations. In one study, non-mucoid strains were more resistant than mucoid strains. To some extent the variation may be explained by the differences in breakpoints, which recently have been revised. The clinical data reported on a SENTRY surveillance program conducted between 2001 and 2004 with polymyxin B showed no increase in the frequency of polymyxin resistant *P. aeruginosa* (or *Acinetobacter* spp.).[10]

The risk of resistance has been mitigated by the following measures: (1) A dosage regimen which has been shown to minimise the probability of the development of resistance by maintaining consistently high levels of drug at the site of action; (2) the PI advocates that only patients with *P. aeruginosa* infection which is susceptible to CMS will receive this treatment and susceptibility testing be conducted in patients who take this product on a long-term basis and; (3) it is considered that use of the product will mainly be outside the hospital.

According to the sponsor's *Clinical Overview*, it is assumed that the concentration of antibiotics in bronchial secretions needs to be as high as 10 times the minimum inhibitory concentration (MIC) to allow penetration of antibiotics into biofilms, suppress inhibitory factors and promote bactericidal effectiveness.[11] One published clinical study indicated a maximum sputum concentration of ~40 mg/L which apparently remained at > 4 µg/mL for up to 12 hours. The proposed 2-3 dose regimen is therefore likely to sustain colistin levels at >MIC in sputum. Overall, based on the nonclinical data, the nonclinical evaluator considers, on mechanistic grounds, the risk of development of resistance when the product is used according to the proposed product information is mitigated by the measures proposed in the draft PI.

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[10] The SENTRY Antimicrobial Surveillance Program, initiated in January 1997, was designed to monitor the predominant pathogens and antimicrobial resistance for both nosocomial and community-acquired infections globally.

[11] Sermet-Gaudelus I, Le-Cocguic Y, Ferroni A, Clairicia M, Barthe J, Delaunay J P et al. Nebulized antibiotics in cystic fibrosis. Paediatr Drugs 2002; 4: 455-67.

Cross resistance

Based on the submitted literature references, cross-resistance of colistin with antimicrobials other than other polymyxins (or 'polypeptide compounds' which were not defined) so far has not been described, at least with any of the indicated organisms.[12] This is because the polymyxins have a different mechanism of action compared to the other antibiotics, and colistin is not likely to be a substrate for multi-drug efflux systems given that it interacts preferentially with the outer membrane and cytoplasmic membrane (Li *et al*, 2005).[5]

Secondary pharmacodynamics and safety pharmacology

Colistin bound endotoxin *in vitro*, reduced plasma or serum endotoxin (and TNF-α) levels in rats (1 mg/kg IV colistin following IP LPS) and dogs with endotoxic shock (given 1 mg/kg colistin), and resulted in reduced mortality in the dogs. Mice in which lung inflammation had been induced by pulmonary administration of supernatants of *P. aeruginosa* followed by up to 5 mg/kg colistin intra-nasally had significantly and dose-dependently reduced lung inflammatory cytokines (IL-6, IL-1β and TNF-α) and lung LPS activity. However, it was noted by Falagas *et al* (2005) that the significance of prevention of the endotoxin's ability to induce shock through the release of cytokines for *in vivo* antimicrobial action is not clear because plasma endotoxin is immediately bound by LPS-binding protein and the complex is quickly bound to cell-surface CD14.[13]

Colistin was shown to significantly increase the activity of human neutrophil elastase (NE) in human sputum and *P. aeruginosa* elastase (PE; purified preparation) *in vitro* at ≥ 32 µM and 500 µM, respectively (Jones et al, 2002).[14] Concentrations in sputum samples were not reported. These two proteases are present in increased amounts in the lungs of patients with cystic fibrosis and are associated with pulmonary damage, and therefore they potentially contribute to the pathogenesis of cystic fibrosis airway disease. The extent to which this effect might detract from, or even outweigh, the antimicrobial effects of colistin remains to be determined. However, it was noted in the sponsor's *Nonclinical Overview* that while this was not a desirable effect, the clinical consequences have not been determined and, in clinical practice, no untoward consequences have been observed. The mechanism of action for stimulating NE and PE was not established.

According to the *Nonclinical Overview*, no safety pharmacology studies with CMS or colistin have been identified in the literature. The justification provided for this absence was that appreciable clinical experience has been gained with the use of colistin and CMS. Two single dose toxicity studies in dogs investigated renal parameters induced no significant findings. On the other hand, in view of the known toxicities associated with the use of colistimethate in humans (particularly effects on the renal system) and the considerable local dose intended for the respiratory system, it would have been warranted to undertake a standard battery of GLP compliant safety pharmacology studies addressing effects on these systems as well as the cardiovascular system.

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[12] Savini V, Catavitello C, Talia M, Balbinot A et al. Isolation of colistin-resistant Hafnia alvei. J Med Microbiol 2009; 58: 278-280.

[13] Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005; 40: 1333-1341.

[14] Jones A, Elphick H, Pettitt E, Everard ML, Evans GS. Colistin stimulates the activity of neutrophil elastase and Pseudomonas aeruginosa elastase. Eur Respir J 2002; 19: 1136-1141.

Pharmacodynamic drug interactions

Colistimethate is recommended for use with other oral or parenteral antibiotics. As discussed under *Primary Pharmacology* (above), there is some microbiology data on antimicrobial synergy.

Colistin (the active metabolite of CMS) partially blocked transmission at the neuromuscular junction *in vitro* in rat diaphragm and phrenic nerve preparations (at ≥ 0.1 µg/mL) and frog sciatic nerve and *musculus sartorius* preparations (after 5 minutes at 0.5 µg/mL), as well as *in vivo* in rabbit *musculus tibialis* anterior preparations (at ≥ 0.1 mg/kg) (Yamada et al, 1986).[15] Where tested, these effects were not competitive with eserine (physostigmine) or calcium chloride. It was therefore concluded that colistin sulphate acted as a non-competitive antagonist on the neuromuscular junction. CMS was less effective or non-effective in the same experiments.

In another study colistin reduced the amount of acetylcholine readily available for release at the beginning of a train of stimuli. Therefore, as suggested in the *Nonclinical Overview*, caution should be used if patients receiving CMS undergo anaesthesia requiring muscle relaxation as the effects of non-depolarising muscle relaxants on the neuromuscular junction will be increased. It was noted that, due to the effect of CMS on acetylcholine release, a warning on the concomitant use of non-depolarising muscle relaxants is included in the draft PI, as well as being contraindicated in patients with myasthenia gravis. A similar statement has been included in the UK Summary of Product Characteristics (SmPC) (UK SmPC for Promixin, 2009).

Pharmacokinetics

Elucidation of the pharmacokinetics of CMS and colistin has been hampered by a lack of specific and sensitive methods of analysis. Early pharmacokinetic data were obtained using bioassays and were considered to have been less reliable than those conducted more recently using high pressure liquid chromatography (HPLC). Hence, pharmacokinetic data from animals were very limited. No published papers have been identified relating to the pharmacokinetics of CMS in animals dosed by the inhalation route with the exception of a single congress report (identified by the nonclinical evaluator) in which limited plasma concentration data were presented in rats and dogs. The sponsor noted (in its *Nonclinical Overview*) that in the decades that CMS has been on the market the pharmacokinetics in humans have been well established and are detailed in the clinical expert report. A recent study investigated the comparative pharmacokinetics and absolute bioavailability of CMS (in Promixin an alternative brand name to Tadim) following IV and nebulised dosing in healthy human volunteers (see under *Relative Exposure* below). The maximum absolute bioavailability following an inhaled dose was stated in the study report to be 18%.

Following IV administration in rats, CMS had a shorter terminal half-life ($t_{\frac{1}{2}}$) than did colistin. Half-lives were longer in patients with cystic fibrosis but showed a similar relativity for CMS and colistin to that seen in rats. Clearance of CMS was lower in humans than in rats but volumes of distribution were comparable.

None of the submitted nonclinical studies addressed the distribution of CMS or colistin, including binding to protein or blood cells.

Following IV dosing in rats, CMS underwent partial hydrolysis to colistin but was also extensively cleared unchanged via renal filtration and net renal tubular secretion. In contrast,

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[15] Yamada S, Kuno Y, Iwanaga H. Effects of several antibiotics on the neuromuscular junction: Part II. Int J Clin Pharmacol Ther Toxicol 1986; 24: 171-9.

IV colistin in rats was almost entirely cleared by non-renal mechanisms and the very minor component of elimination that occurred via the kidneys involved very extensive tubular reabsorption.

Although the submitted studies demonstrated that CMS is partially converted to colistin, no specific information was contained in these studies relating to metabolism beyond colistin. However the pharmacokinetics were considered to be complex involving further hydrolysis to various derivatives.

Relative exposure

The proposed dose of CMS is up to 2 million IU, up to 3 times daily, resulting in a daily dose of up to (3 x 160 =) 480 mg (9.6 mg/kg/day for a 50 kg person, and 48 mg/kg/day for a 2 year-old infant [assuming 10 kg body weight]) for up to 3 months. Long term use is also proposed with up to 2 million IU twice daily, resulting in a daily dose of 320 mg (6.4 mg/kg/day for a 50 kg person, and 32 mg/kg/day for a 2 year-old infant). CMS is currently registered for IV use. The maximum IV dose of CMS (according to the PI for Colistin Link Parenteral) is 5 mg/kg (over 2-4 divided doses) which would be expected to result in many fold greater systemic exposures than seen following inhalational exposure in Clinical Study PPCTP/002. It was shown in this clinical study that following an IV dose of 0.58 mg/kg, the systemic exposure (the area under the plasma concentration time curve from time zero to infinity [$AUC_{0-\infty}$]) was 5-fold that after the same dose via the inhalational route, and more than 15 –fold based on C_{max}. The study also showed that a 4-fold increase in the inhaled dose (from 0.58 mg/kg to 2.33 mg/kg) resulted in no increase in AUC or C_{max} (or any of the other pharmacokinetic parameters). This can be explained by differences in efficiency of delivery by the nebulisers used in the study. It is therefore likely that the proposed inhaled doses of CMS (Tadim) would result in considerably lower systemic exposure to colistin or CMS than with the currently registered parenteral product (maximum dose 5 mg/kg/day, compared with 9.6 mg/kg/day for the proposed inhalational product).

Although the product is intended to be administered by inhalation both the local (pulmonary) and systemic exposure were considered.

Systemic exposure

Regarding systemic exposure, in one study (VanDevanter et al, 2001; congress presentation), polymyxin E_1 (a major active component of CMS) was administered by inhalation to rats at doses up to 32.3 mg/kg/day and in dogs at up to 8.6 mg/kg/day for 28 days.[16] The only toxicokinetic data from this study were plasma levels 15 minutes and 1 hour after exposure in rats and dogs, respectively. The results indicated that plasma levels in rats on Day 1 were ~ 6 to 32 –fold, and in dogs ~ 1 to 6 –fold the maximum plasma concentration seen in humans after a single inhaled dose of 160 mg. These data indicated that at these times, on the first day of dosing, the plasma concentrations of polymyxin E_1 in these animal models were greater than that of colistin in humans given a single inhaled dose of CMS. No AUC data were provided in the animal study.

Other toxicokinetic data were limited to data from one IV study in rats. In this study, the AUC for colistin following a single IV dose of 15 mg/kg CMS to rats was 2.6 µg.h/mL.

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[16] VanDevanter DR, Rose LM, Sprugel KH (2001). 28-day inhalation toxicology of polymyxin E1, the major active component of colistin, in rats and dogs. Presented at the European Cystic Fibrosis Congress, June 6-9, Vienna, Austria. Chiron Corporation, Seattle, WA, USA.

Inhalational exposures

Inhalational exposure data were only available from a single congress presentation sourced by the nonclinical evaluator (VanDevanter et al, 2001), and these data were limited to plasma concentrations in rats and dogs (at 15 minutes and 1 hour after dosing, respectively).[16] In order to estimate local exposure, the data from the animal:human comparisons would need to be based on dose per lung surface area and/or on the daily dose per body weight (which would assume a similar relative lung weight:body weight ratio in the animal model as in humans). The dose and dose ratio calculations would need to be based on estimates of total alveolar surface area in adult humans (143 m^2: Derelanko and Hollinger, 1995), and 14.2 m^2 in an infant 22 months of age (Dunnill, 1962), as well as in rats and dogs, (0.387 and 40.7 m^2, respectively: Derelanko and Hollinger, 1995).[17,18] Neither the applicable mass median aerodynamic diameter (MMAD) in the animal toxicity studies nor the anticipated MMAD in clinical use were stated in the submitted studies. Moreover, it is not known to what extent exposure via mouth breathing in dogs (as in this study) might differ from exposure via nose breathing

The sponsor did not provide any exposure ratios due to a lack of toxicokinetic data. Overall, too many assumptions had to be made and therefore meaningful systemic or local animal:human exposure comparisons were not possible.

Toxicology

General toxicity

While no studies by the inhalational route were submitted, it was noted by Jones et al (2002) that a recent, non-peer-reviewed poster of a study has provided *in vivo* evidence that prolonged administration of polymyxin E$_1$ is associated with airway damage in rats and dogs (VanDevanter, Chiron Corporation, Seattle, WA, USA, personal communication).[14,16] This study was sourced by the nonclinical evaluator. It consisted of a poster presented at the European Cystic Fibrosis Congress in 2001 and, although these data do not appear to have been subsequently published as a peer reviewed article, these data are considered in detail below.[16]

Few animal studies were submitted in which the systemic toxicity of CMS had been investigated by the IV route. In studies in rats and pigs the kidney and the nervous system were the main target organs for toxicity following IV treatment with CMS or colistin. While the paucity of toxicology studies prevented meaningful conclusions being made concerning the significance of these findings to humans concerns regarding systemic exposure were mitigated by the anticipated lower systemic exposure with the product proposed for registration relative to the currently registered (IV) product containing CMS.

Toxicity to the respiratory system

CMS is proposed for long-term therapy without dosing holidays. The most common adverse clinical effect arising from treatment with CMS was bronchospasm. Other inhalationally administered antibiotics for the same indication (aztreonam and tobramycin) are recommended for 28-day on-off treatment, and for children 6+ years old.

The only nonclinical study found that was conducted via the inhalation route, while appearing extensive, was minimally documented as a congress poster presentation, reporting evidence of inflammatory changes in the nasal passages and lung of rats and in the airway epithelia of both rats and dogs following 28 days of dosing with polymyxin E$_1$. These changes were

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[17] Derelanko MJ, Hollinger MA. Handbook of Toxicology, CRC Press, 2002
[18] Dunnill MS. Postnatal Growth of the Lung. Thorax 1962; 17: 329-333.

accompanied by nose/muzzle/head swelling and respiratory difficulties in rats. Histologically, mucous cell hyperplasia in the nasal turbinates was seen in rats as well as dose dependent increases in local eosinophil infiltration, eosinophilic inclusions and globule leucocyte infiltration. Rats also showed local inflammation in the trachea and pulmonary parenchyma but the extent to which this was distinguishable from controls was not clear. The inflammatory response was also reflected in increases in systemically circulating eosinophils in both rats and dogs. This appeared to abate later in the treatment in dogs. While some of these changes may be adaptive due to inhalation of droplets/particulates, there was histological evidence that the local effects of polymyxin E_1 in nasal turbinates in rats were distinguishable from those arising from the vehicle.

This nonclinical study showed that inhalational treatment with CMS can potentially result in respiratory inflammation. The extent to which these findings reflect the potential for exacerbation of any underlying inflammation in cystic fibrosis patients is not known. Clinical comment would be needed on the potential impact of drug-induced chronic inflammation in airway epithelia in cystic fibrosis. Bronchial hyper-reactivity has been noted as a Precaution in the draft PI.

No studies were conducted with juvenile animals and the pulmonary doses arising from treatment with the proposed product are considerably greater than those in adults (particularly when expressed in terms of alveolar surface area. According to Dunnill (1962), the mature human lung contains approximately 300 million alveoli, and that number is reached at about 8 years of age.[18] The total alveolar surface area for both lungs in an infant 22 months of age was 14.2 m^2, that is ~ 10% of that in the adult). Thus, compared with the adult and older child, the reserve of alveolar surface area for gas exchange in neonates is smaller. The implications of any respiratory toxicity are potentially greater but this may be mitigated by the lower tidal volume seen in children. There is no paediatric dose adjustment for colistimethate (or with aztreonam or tobramycin).

Considering that it is intended that the main exposure to CMS is to be on a disease affected respiratory system, comment on the potential for respiratory toxicity is warranted. Moreover, the FDA is currently investigating a report of a death of a patient with CF following treatment with inhaled premixed ready to use colistimethate[19] (noted in the sponsor's letter of application for registration). The FDA website suggests that death was caused by breakdown to polymyxin E1 due to the prolonged storage of reconstituted CMS of approximately 5 weeks which is toxic to the lungs. Lung damage could result in increased systemic absorption. The sponsor indicated in the application letter (with reference to McCoy, 2007), that in this case it was not known "whether the product was reconstituted under aseptic conditions, how it was stored, whether it contained a preservative or whether it had been used in other patients".[20] The FDA website also noted that "in animal studies, polymyxin E1 has been shown to cause localized inflammation of the airway epithelia and eosinophilic infiltration". These animal studies are presumably those evaluated above (VanDevanter et al, 2001 conference poster, not submitted: sourced by the nonclinical evaluator).[16] It was recommended that to avoid this toxicity this product should be administered promptly after it is mixed. The draft PI indicates that the product should be stored at between 2 and 8 ˚C and that it should be used within 8 hours of reconstitution. It is noted on the FDA website that this information would be updated when more is known. The FDA appears not to have investigated anything further regarding this single death since 2007. However the issue has

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[19] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124896.htm, last updated on 23 October 2009.

[20] McCoy KS. Compounded colistimethate as possible cause of fatal acute respiratory distress syndrome. N Engl J Med 2007; 357: 2510-11.

apparently not been brought to a final conclusion. In addition, the product used in the USA, Coly-Mycin M is distributed as a vial of 150 mg of colistin base activity which is equivalent to 4.5 million IU. These findings were referred to the attention of the clinical evaluator.

Renal- and neurotoxicity

Nephrotoxicity has been shown in rats and neurotoxicity (reduced neuromuscular transmission) has been shown in mice and rats with repeat IV doses of CMS. Animal toxicokinetic data were lacking, but these effects may be less likely at the lower systemic exposures by the inhalation route. Both of these effects have been documented in patients given high IV doses of colistimethate. The draft PI notes them under Precautions.

Genotoxicity and carcinogenicity

Assays with colistin covering a range of genotoxic end-points have been published. However, not all the genotoxicity studies with colistin had been submitted to the TGA, presumably because the sponsor did not have access to these studies.

A concentration-related increase in chromosomal damage was observed in cultured human lymphocytes which was associated with decreases in the mitotic index and in the rate of cell division. However, methodological issues with this study precluded any firm conclusions. For example, bromodeoxyuridine was added at the initiation of cultures in order to visualise sister chromatid exchanges and no positive controls were included.

An equivocal result was noted in an SOS chromotest for DNA damage in *E. coli* strains. Colistin was tested as one of a range of compounds in a series of screening assays. However, no primary data were provided, therefore the validity of this finding could not be independently assessed.

In a review by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), it was noted that additional unpublished assays, accessed by the committee which included assays for reverse mutation in *Salmonella typhimurium* and *E. coli*, DNA repair in *Bacillus subtilis*, forward mutation in cultured Chinese hamster cells, sister chromatid exchange formation in cultured human lymphocytes and micronucleus formation in bone marrow of treated mice, were negative. The JECFA concluded that, on the weight of evidence, colistin is unlikely to pose a genotoxic hazard.

No carcinogenicity studies were submitted even though colistimethate is proposed for long-term use.

Reproductive toxicity

All reproductive toxicity data were based on literature references that were originally published in Japanese. Sufficient information could be gleaned from the summary and tables contained therein to establish basic methodological details and results. The adequacy of the studies could have been better gauged if the full text had been translated into English.

No adverse effects were seen on fertility at doses up to 25 mg/kg/day in rats. Delayed ossification was seen in a number of studies in the absence of evidence of maternal toxicity. In mice, delayed ossification of cervical and sacral vertebrae was observed following IV treatment over gestation day (GD) 6-15 at ≥ 250 mg/kg/day but not at 125 mg/kg/day. Similarly, in rats given IV CMS at 25 mg/kg/day IV but not at 12.5 mg/kg/day, delayed ossification affecting the cervical and caudal vertebrae and hind paw was seen in a fertility study where males were treated for ~ 63 days prior to mating and females from 2 weeks prior to mating to GD 7. Delayed ossification affected the odontoid process and proximal diaphysis of hind paw was seen in another study when 25 mg/kg/day was given IV to rats over GD 7-

17. In rabbits, delayed ossification of cervical vertebrae and abnormal ossification of lumbar rib (but no other findings) were seen following IV treatment over GD 6-18 at 63 mg/kg/day but not at 80 mg/kg/day. Since the doses were similar in both these treated groups, the finding was considered to be of equivocal toxicological significance.

In developmental studies in mice, resorption rate was increased and fetal survival rate was slightly reduced following IP administration of CMS at 150 mg/kg/day from GD 7 to GD 14. The findings were not statistically significant. In rats, fetal survival, the delivery rate and nursing rate were also reduced following IV treatment at 25 mg/kg/day on GD 7 to GD 17. The resorption rate in F_1 dams was also slightly increased at this dose. While none of these findings were statistically significant, collectively they pointed to potential reproductive toxicity. In another study in rats, fetal body weight decreased (and maternal body weight increased) with a dose in one study at ≥ 5 mg/kg/day CMS administered IP from GD 8 to 15. It is noted that, since the treatment was begun on GD 8, it was unlikely that there was any exposure at the time of implantation (normally GD 6-7 in rats).

Postnatal growth, development and behaviour were investigated following treatment with IV CMS at up to 500 mg/kg/day over GD 6-15 in mice and 25 mg/kg/day IV over GD 7 to 17 in rats. Spontaneous activity (by the rotating drum method) was reduced at ≥ 250 mg/kg in mice and, at the highest dose, increased urination (both species) and rearing on hind legs (rats only) were seen.

Overall, collectively the data provided a potential signal for developmental toxicity. However, the extent could not be determined from the summarised data provided but the risk would be lower with the currently registered IV product due to the lower systemic exposure with the proposed inhalational product.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2. However, in the submitted studies, evidence of embryofetal toxicity included delayed ossification in three species without evidence of maternal toxicity as well as small effects on fetal survival, body weight and/or resorption-rate. In the submitted studies some evidence of embryofetal toxicity was seen (delayed ossification, increased resorptions) following IV administration. However, the systemic exposure with the proposed (inhaled) product is lower, therefore the risk of adverse effects is also likely to be lower. On this basis the proposed pregnancy category is considered acceptable. This is consistent with the Pregnancy Category for parenteral CMS.

Nonclinical Summary and Conclusions

The nonclinical package consisted entirely of published literature so the GLP status was generally unknown. None of the submitted studies in animals were conducted via the intended route of administration (inhalation), therefore the assessment of pharmacodynamics and toxicology was mainly based on data obtained after IV administration of CMS or its metabolite colistin. In the submitted literature references, CMS was used in some studies and colistin in others. The toxicity of the individual polymyxin E components of the product was not assessed separately but this was not considered to significantly impact on the assessment of the risk of the product.

Despite 50 years of clinical use there was limited nonclinical data. Overall, the nonclinical data were not adequate for determining the toxicity profile of the product and assessment of potential risk.

Activity was shown against *P. aeruginosa in vitro* (as well as *Acinetobacter* and *Klebsiella* species) with colistin using standardised methods as well as in a single study *in vivo*. There

was mainly *in vitro* evidence to suggest a synergistic interaction with doxycycline, ceftazidime or rifampicin. There was also limited time-kill and *in vivo* evidence for activity with *P. aeruginosa* but the extent to which the *in vitro* activity translates to clinical efficacy will need to be based on clinical data. There was no clear evidence from submitted nonclinical studies for activity against *H. influenzae*.

No safety pharmacology studies were submitted. The clinical significance of Colistin bound endotoxin *in vitro*, reduced plasma or serum endotoxin (and TNF-α) levels in rats and dogs with endotoxic shock, reduced LPS-induced lung inflammatory cytokine levels (IL-6, IL-1β and TNF-α) and lung LPS activity following intra-nasal administration is not clear. It was also noted that Colistin sulphate acted as a non-competitive antagonist of acetylcholine activity in animal models of neuromuscular conduction.

Limited pharmacokinetic data were submitted. Systemic exposure to CMS is considerably greater via the currently registered IV route than via the proposed inhalational route in humans (absolute bioavailability was up to 18% in healthy humans). Therefore the risks associated with systemic exposure to CMS, because limited toxicokinetic data were submitted, will largely depend on clinical experience with the currently registered parenteral product. None of the nonclinical studies were of adequate duration to take into account the proposed long-term clinical treatment.

Only one published nonclinical paper (conference poster) by the inhalation route was located. Inhalational treatment with polymyxin E$_1$, a major component of colistin, was shown to potentially result in respiratory inflammation in rats and dogs following 28 days treatment. Local drug exposures could not be reliably estimated. Clinical comment would be needed on the potential for drug-induced chronic inflammation in airway epithelia in cystic fibrosis. Any impact is likely to be greater in children and, due to the absence of relevant juvenile animal studies, an assessment of the safety of this product on the respiratory system, particularly in children, will need to rely on clinical data.

Nephrotoxicity was seen in rats given repeated IV CMS doses for 7 days at 60 mg/kg/day, with severe nephrotoxicity resulting from a single dose at 150 mg/kg. At 60 mg/kg/day, there was only evidence of neurotoxic potential (inhibition of the neuromuscular junction) and evidence of neurotoxicity that ranged from mild (decreased locomotor activity) at low doses to severe (muscular weakness, ataxia, laboured respiration), seen after a single dose of 150 mg/kg. The nephrotoxic and neurotoxic potential of CMS has been noted in the draft PI.

No carcinogenicity studies have been conducted with the product even though this product is proposed for long-term use. Limited genotoxicity studies have not indicated genotoxic potential but a full battery of GLP tests was not submitted for evaluation by the TGA.

No effects were seen on mouse or rat fertility at IV doses up to 25 mg/kg/day. Reproductive toxicity studies indicated delayed ossification in mice, rats and rabbits at doses where there was no evidence of maternal toxicity. Embryofetal development studies indicated increased resorptions and reduced fetal survival in rats (at 25 mg/kg/day) and mice. Spontaneous activity was reduced in offspring mice.

There were sufficient nonclinical data to establish the *in vitro* susceptibility of the target organism *P. aeruginosa* to the active ingredient CMS or its primary metabolite and hydrolysis product, colistin. There were, however, no *in vivo* animal efficacy studies conducted using the inhalation route. Data on drug concentrations in human sputum and alveolar fluid were very limited.

The nonclinical data had a number of major deficiencies. Other than a single published inhalation toxicity study (conference poster) identified by the evaluator, no toxicity studies

were submitted that related to the intended route of administration (inhalation). Animal pharmacokinetic data were very limited, generally precluding comparison of animal to human drug exposures. The toxicity study treatment durations and exposures were inadequate with respect to the proposed clinical treatment regimen. No safety pharmacology studies were submitted. No battery of adequate genotoxicity studies was submitted. No carcinogenicity studies were submitted even though the product is proposed for long-term use. No data from juvenile animals were submitted to support paediatric use.

The single inhalation toxicity paper suggested some potential for airway inflammation in rats and dogs after 28 days of treatment with polymyxin E_1. Limited nonclinical data also indicated potential for renal and neuromuscular toxicity at high levels of systemic exposure, however systemic exposure is likely to be lower when the product is administered by the inhalation route. Evidence for embryofetal toxicity in multiple animal models following IV dosing is mitigated by the lower anticipated systemic exposures after inhalational dosing.

In conclusion, the absence of carcinogenesis studies and other deficiencies in the nonclinical package preclude a recommendation for registration on nonclinical grounds. Therefore any decision to register the product will need to be made on clinical grounds.

IV. Clinical Findings

Introduction

This was a literature-based submission but also included one sponsor commissioned pharmacokinetic study. The literature search was current to 13 October 2008. The search strategy was later validated by the TGA Library.

Pharmacokinetics

Administration by inhalation

Le Brun et al (2002) compared (single dose) pharmacokinetics of inhaled colistin sulphate dry powder (25 mg) in 6 healthy volunteers, inhaled colistin sulphate dry powder (25 mg) in 4 CF patients and inhaled CMS in 5 CF patients.[21]

The results, expressed as colistin serum concentrations, were as follows:

Parameter	Volunteers (DPI 25 mg, $n = 6$)	CF patients (DPI 25 mg, $n = 4$)	CF patients (Neb 160 mg, $n = 5$)	P value Vol-CF_{idh}	P value CF_{idh}-CF_{ieh}
AUC_{0-4} (h mg/l)	106.1 (41.9)	283.5 (87.2)	165.9 (76.5)	0.017	NS
C_{max} (µg/l)	33.6 (14.4)	115.0 (45.8)	51.0 (24.4)	0.003	0.028
T_{max} (h)	0.8 (0.4)	0.4 (0.3)	1.9 (1.2)	NS	0.047
K_a (h^{-1})	9.6 (12.9)	14.8 (10.3)	3.0 (1.8)	NS	NS
$T_{1/2}$ (h)	8.1 (5.1)	2.7 (0.3)	10.4 (3.6)	NS	0.006
Cl/F	0.3 (0.36)	0.06 (0.02)	0.27 (0.15)	NS	0.028

^{a} AUC, area under the curve (trapezium, $t = 0-4$ h); $T_{1/2}$, terminal elimination half-life; C_{max}, maximum serum concentration; T_{max}, time to maximum serum concentration; K_a, absorption rate constant; SD, standard deviation; Vol-CF_{idh}, statistical analysis of the DPI inhalation of 25 mg colistin by the volunteers and by the patients; CF_{idh}-CF_{ieh}, statistical analysis of the DPI inhalation of 25 mg colistin and the nebulization of 160 mg colistin by the patients; NS, not significant ($P > 0.05$); DPI, dry powder inhaler; Neb, nebulization; Cl/F, quotient of clearance and bioavailability.

The colistin sulphate inhalation is not relevant to this application. However, the study showed that the pharmacokinetics were different between colistin sulphate (25 mg) given by dry powder inhalation and CMS (160 mg) given by nebulisation as well as between healthy

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[21] Le Brun PPH, de Boer AH, Mannes GP, de Fraîture DMI, Brimicombe RW, Touw DJ et al. Dry powder inhalation of antibiotics in cystic fibrosis therapy: part 2. Inhalation of a novel colistin dry powder formulation: a feasibility study in healthy volunteers and patients. Eur J Pharm Biopharm 2002; 54: 25-32.

volunteers and CF patients. The colistin sulphate in this study was also less well tolerated than CMS.

This study suggested a time to maximal plasma concentration (T_{max}) of approximately 2 hours with a half-life of 10 hours. The paper did not explain what was being reported as Cl/F (quotient of clearance and bioavailability?). The sponsor's *Clinical Review* reports this figure as clearance of 0.27 L/h/kg.

Ratjen et al (2006) examined single dose pharmacokinetics of CMS in 30 CF patients (mean age 25 ± 9 years; range 12-48 years) following inhalation of 158 mg (2 million IU) dose (comment by **Li & Nation (2006b)**) using 2 different delivery systems as below:[22,23]

	PARI LC Star	eFlow pilot series 03
Percentage of droplets <5 μm	80.8	79.2
MMD (μm)	3.0	3.4
GSD	2.1	1.6
Total output rate (mg/min)	428	150

MMD, mass median diameter; GSD, geometric standard deviation.

The serum levels of polymyxin E1 were measured. The C_{max} was reached approximately at 1.5 hours (T_{max}) after inhalation with both delivery systems. The two delivery systems also showed similar half-lives (4-4.5 hours) and systemic clearances (787-813 mL/min) as shown below:

	PARI LC Star	eFlow pilot series 03
AUC_{0-t} (mg·h/L)	0.913 ± 0.095	0.865 ± 0.187
AUC (mg·h/L)	1.190 ± 0.095	1.167 ± 0.186
T_{max} (h)	1.47 ± 0.16	1.5 ± 0.3
C_{max} (mg/L)	0.178 ± 0.018	0.170 ± 0.036
$t_{1/2}$ (h)	4.09 ± 0.31	4.51 ± 0.57
MRT (h)	6.44 ± 0.43	7.02 ± 0.9
CL/f (mL/min)	787 ± 65.9	813 ± 175.5

AUC, area under the concentration–time curve; T_{max}, time to attain maximum concentration; C_{max}, maximum observed concentration; $t_{1/2}$, half-life; MRT, mean residence time; CL/f, total clearance of the drug. Data are shown as means ± SEM.

The serum concentrations were noted to be well below those which have been previously reported for systemic administration. A mean 4.3% (± 1.3%) of the inhaled dose was detected in urine.

A subgroup of 8 patients received repeat doses after 3 days. The maximum sputum concentrations of drug were at least 10 fold higher than MIC breakpoint for *PA* proposed by the British Society for Antimicrobial Chemotherapy. The mean sputum colistin concentrations begin to decline after 1 hour but were still above 4 mg/L at 12 hours.

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[22] Ratjen F, Rietschel E, Kasel D, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. J Antimicrob Chemother 2006; 57: 306-11.

[23] Li J, Nation RL. Comment on: pharmacokinetics of inhaled colistin in patients with cystic fibrosis. J Antimicrob Chemother 2006; 58: 222-3; author reply 223.

Westerman et al (2007a) was a study in 8 healthy volunteers (mean age 25.4 ± 5.3 years). The pharmacokinetics of polymyxins E1 and E2 were examined following dry powder inhalation of a single 25 mg dose of CMS using a "Twincer" inhaler.[24]

The study indicated a T_{max} of 1.1 hours, $t_{\frac{1}{2}}$ of 2.75 hours and clearance of 0.7 L/h/kg as shown below:

Colistin sulphomethate dry powder inhalation in volunteers: pharmacokinetic results

	Mean	95% CI
Actual dose (mg)	21.5	18.6–24.4
AUC_{0-4} (h µg/l)	275	185–364
C_{max} (µg/l)	89.9	59.4–120.4
t_{max} (h)	1.1	0.9–1.2
$t_{1/2,el}$ (h)	2.75	2.68–2.82
Cl/F (l/h/kg))	0.7	0.5–0.9

Actual dose: nominal dose minus remainder of colistin sulphomethate in inhaler after inhalation. AUC_{0-4}: area under the curve from 0 to 4 h. C_{max}: maximum plasma concentration. t_{max}: time to maximum plasma concentration. $t_{1/2,el}$: terminal half-life. Cl/F: clearance following pulmonary administration; F: bioavailability (unknown). CI: confidence interval.

In addition, on Day 2 serum polymyxins E1 and E2 were measured after oral ingestion of 80 mg CMS solution (dissolved in 3 mL of normal saline) taken on empty stomach. The E1 and E2 values remained undetectable suggesting that only negligible amounts of CMS are absorbed from the gastrointestinal tract (GIT) after inhalation.

In contrast to previous studies with inhaled colistin sulphate salt, such as Le Brun et al (2002) noted above, in this study with CMS the drug was well tolerated and no clinically relevant adverse effects were reported on pulmonary function.

Westerman et al (2007b) examined pharmacokinetics of a dry powder and a liquid formulation of CMS administered by inhalation route to 10 patients with CF.[25] This study also reported results in terms of polymyxins E1 and E2.

It was a randomised, single dose, cross-over comparison. The dry powder dose of CMS by inhalation was 25 mg dose using a "Twincer" inhaler compared to nebulised CMS 158 mg using a "Ventstream" nebuliser. The PK results were as follows:

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[24] Westerman EM, de Boer AH, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HG. Dry powder inhalation of colistin sulphomethate in healthy volunteers: A pilot study. Int J Pharm 2007; 335: 41-5.

[25] Westerman EM, De Boer AH, Le Brun PPH, Touw DJ, Roldaan AC, Frijlink HW, Heijerman HG. Dry powder inhalation of colistin in cystic fibrosis patients: a single dose pilot study. J Cyst Fibros. 2007; 6: 284-92.

Parameters	Mean DPI	95% C.I.	Mean Neb	95% C.I.	p-value
Actual dose (mg)	23.2	22.0-24.3	72.5	60.8-84.3	
AUC_{0-4} (h µg/L)	200.7	129.0-272.4	459.5	259.0-660.0	0.02*
C_{max} (µg/L)	66.3	41.4-91.1	144.3	83.7-205.0	0.02*
t_{max} (h)	0.86	0.80-0.93	1.34	1.23-1.46	<0.001*
$t_{1/2,el}$ (h)	3.2	3.1-3.3	3.0	2.7-3.4	0.23
Cl/F (L/h/kg)	1.2	0.8-1.6	1.6	1.1-2.1	0.17
F_{DPI}/F_{neb}	1.4	-0.2-3.0			

Actual dose: nominal dose minus remainder of colistin in inhalation device after inhalation.
AUC_{0-4}: area under the curve from 0 to 4 h.
C_{max}: maximum plasma concentration.
t_{max}: time to maximum concentration.
$t_{1/2,el}$: terminal half-life.
Cl/F: clearance following pulmonary administration.
F_{DPI}/F_{neb}: relative bioavailability.
C.I.: confidence interval.
* statistically significant.

The study reported T_{max} of 1.34 hours, $t_{1/2}$ of 3 hours and systemic clearance of 1.6 L/h/kg following nebulised CMS in CF patients using both polymyxin E1 and E2 levels. The reported figures also indicate that following conventional administration by jet nebuliser in this study, more than half of the dose remained in the device after the administration.

The results of the foregoing 4 pharmacokinetic studies are captured in the table below:

Parameter	Healthy volunteers, Westerman 2007a	Patients with CF, Le Brun 2002		Patients with CF, Ratjen 2006		Patients with CF, Westerman 2007b	
	Colistimethate sodium	Colistimethate sodium	Colistin sulfate	Colistimethate sodium	Colistimethate sodium	Colistimethate sodium	Colistimethate sodium
Administered dose	25 mg dry powder inhalation	160 mg nebulised	25 mg dry powder inhalation	158 mg PARI LC Star nebuliser	158 mg e-flow nebuliser	25 mg dry powder inhalation	158 mg nebulised
Age, years	mean 25.4, SD=5.3	mean 33.8, SD=6.3		mean 25, SD=9, range 12-48		mean 31, range 20-46	
Gender	2M/6F	NS		18M/12F		3M/7F	
	mean (95% CI)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (95% CI)	mean (95% CI)
Actual dose* (mg)	21.5 (18.6, 24.4)					23.2 (22.0, 24.3)	72.5 (60.8, 84.3)
AUC_{0-4} (h/mg/L)	0.275 (0.185, 0.364)	165.9 (76.5)	283.5 (87.2)			0.201 (0.129, 0.272)	0.460 (0.259, 0.660)
AUC_{0-4} (h/mg/L)				0.913 (0.095)	0.865 (0.187)		
AUC (h/mg/L)				1.190 (0.095)	1.167 (0.186)		
C_{max} (mg/L)	0.090 (0.059, 0.012)	0.051 (0.024)	0.115 (0.046)	0.178 (0.018)	0.170 (0.036)	0.066 (0.041, 0.091)	0.144 (0.084, 0.205)
Ka (h^{-1})		3.0 (1.8)	14.8 (10.3)				
T_{max} (h)	1.1 (0.9, 1.2)	1.9 (1.2)	0.4 (0.3)	1.47 (0.16)	1.5 (0.3)	0.86 (0.80, 0.93)	1.34 (1.23, 1.46)
$t_{1/2,el}$ (h)	2.75 (2.68, 2.82)	10.4 (3.6)	2.7 (0.3)	4.09 (0.31)	4.51 (0.57)	3.2 (3.1, 3.3)	3.0 (2.7, 3.4)
CI/F	0.7 (0.5, 0.9)[b]	0.27 (0.15)[b]	0.06 (0.02)[b]	787 (65.9)[c]	813 (175.5)[c]	1.2 (0.8, 1.6)[b]	1.6 (1.1, 2.1)[b]

CI = confidence interval; NS = not stated; SD = standard deviation

* Actual dose was calculated as nominal dose minus remainder in inhaler after inhalation
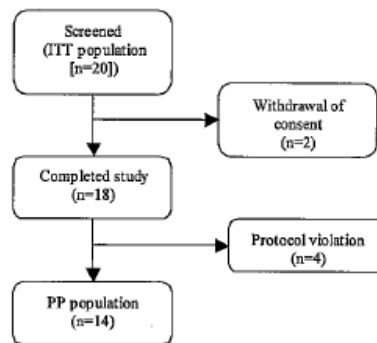
[b] L/h/kg

[c] mL/min

Study PPCTP/002

This was sponsor commissioned study and was undertaken in Europe following first round of mutual recognition procedures. The objective of the study was to determine 'relative bioavailability' of inhaled CMS compared to its intravenous administration based on plasma concentration of polymyxin E1.

It was an open-label, single centre, single dose, five-way crossover trial in adult healthy volunteers. The inhaled CMS was administered using "I-neb AAD"[26] (two metering chambers 0.3 mL and 0.5 mL) and "SideStream"[27] nebulisers to be compared with intravenous administration.

A total of 20 volunteers participated in the study. The patient disposition is shown below:

Flow of subjects through the study

```
          Screened
       (ITT population         Withdrawal of
          [n=20])       ───▶     consent
             │                    (n=2)
             ▼
       Completed study
          (n=18)              Protocol violation
             │          ───▶      (n=4)
             ▼
       PP population
          (n=14)
```

The mean age of the participants was 27 years (± 7.6 years). The five treatment groups and the accompanying treatments thus formed were as follows:

  (1) Treatment 1 = CMS 1 million IU/mL (AAD 0.3 mL), that is 0.3 million IU (24 mg) per inhalation
  (2) Treatment 2 = CMS 1 million IU/mL (AAD 0.5 mL), that is 0.5 million IU (40 mg) per inhalation
  (3) Treatment 3 = CMS 0.5 million IU/mL ("SideStream" 4 mL), that is 2 Million IU (160 mg) per inhalation
  (4) Treatment 4 = CMS 2.4 mg (30,000 IU) IV
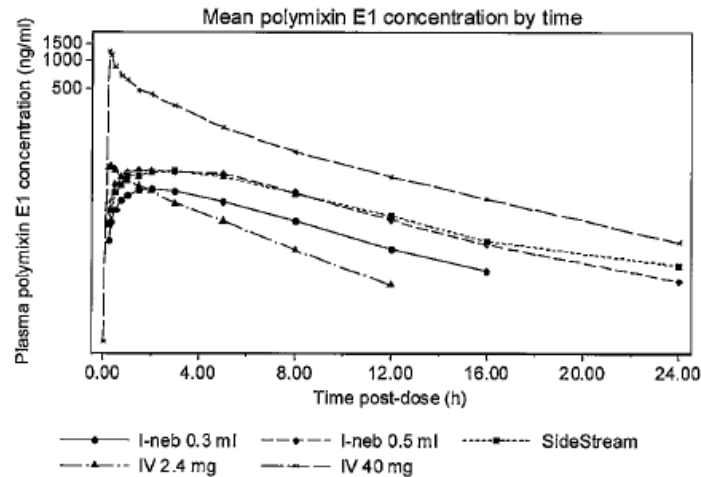 (5) Treatment 5 = CMS 40 mg (0.5 million IU) IV

The mean plasma polymyxin E1 profiles for the five groups are shown below in the figure:

Pharmacokinetic results

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[26] Adaptive Aerosol Delivery system
[27] Conventional continuous jet nebuliser

Mean polymixin E1 concentration by time

With respect to the primary objective of the trial, the results showed that (relative) bioavailability of inhaled CMS in healthy adults, using polymyxin plasma concentration, was a fraction of the intravenous dose as shown by the pharmacokinetic results below:

Variable	Statistic	I-neb 0.3 mL	I-neb 0.5 mL	SideStream	IV 2.4 mg	IV 40 mg
AUC_{0-t} (ng/ml/h)	N	19	19	18	18	18
	GM	309.8	602.2	655.7	259.5	3289
	CV%	51	46	39.2	23.5	16
$AUC_{0-\infty}$ (ng/ml/h)	N	17	19	17	18	18
	GM	350.3	644	668	279	3352
	CV%	49.02	45	32	22.6	16.4
C_{max} (ng/ml)	N	19	19	18	18	18
	GM	40	69.3	69.9	83.6	1232
	CV%	47.5	38.2	26.4	23.3	18.4
$t_{1/2}$ (h)	N	17	19	17	18	18
	Mean ± SD	5.16 ± 0.8	5.02 ± 0.8	5.27 ± 0.8	2.89 ± 0.6	3.66 ± 0.3
T_{max} (h)	N	19	19	18	18	18
	Median	2	2	2.5	0.33	0.25
	Range (min–max)	0.5–5	0.75–5	0.5–5	0.25–3	0.25–2
k_{el} (/h)	N	17	19	17	18	18
	Mean ± SD	0.14 ± 0.02	0.14 ± 0.02	0.13 ± 0.02	0.25 ± 0.04	0.2 ± 0.01

The polymyxin E1 C_{max} following 160 mg nebulised inhalation using a jet nebuliser and 40 mg inhaled administration using the AAD system were approximately 5-6% of the C_{max} after administration of a 40 mg IV dose (a quarter of a standard IV dose).

The polymyxin E1 AUC_∞ following 160 mg nebulised inhalation using a jet nebuliser and 40 mg inhaled administration using the AAD system were approximately 20% of the AUC_∞ after administration of a 40 mg IV dose.

The results further indicated that following inhalation CMS, the $t_{1/2}$ of polymyxin E1 was prolonged by a factor of approximately 1.4 (approximately 5 hours with inhalation compared to 3-3.5 hours with intravenous administration). The half-lives were similar among various nebuliser systems. The median T_{max} was 2-2.5 hours.

The results further showed the systemic exposures (AUC_∞) obtained following 160 mg inhaled administration by a conventional jet nebuliser was similar to 40 mg delivered by the AAD system with 0.5 mL (0.5 million IU) chamber (AUC_∞: 668 versus 644 ng/mL/h) – AUC_∞ ratio of means 0.92 (90% Confidence Intervals [CI] 0.75 to 1.13). The ratio of C_{max} for

this comparison was 0.99 (90% CI 0.82 to 1.20) as shown below in the table of various statistical comparisons:

Variable	Test treatment	Reference treatment	Estimate	Lower 90% CI	Upper 90% CI
AUC_{0-t}	I-neb 0.3 ml	SideStream	0.49	0.40	0.6
AUC_{0-t}	I-neb 0.5 ml	SideStream	0.92	0.75	1.13
AUC_{0-t}	I-neb 0.3 ml	IV 2.4 mg	1.23	1	1.51
AUC_{0-t}	I-neb 0.5 ml	IV 2.4 mg	2.34	1.9	2.87
AUC_{0-t}	I-neb 0.3 ml	IV 40 mg	0.096	0.078	0.12
AUC_{0-t}	I-neb 0.5 ml	IV 40 mg	0.18	0.15	0.22
AUC_{0-t}	SideStream	IV 40 mg	0.20	0.16	0.24
C_{max}	I-neb 0.3 ml	SideStream	0.58	0.48	0.71
C_{max}	I-neb 0.5 ml	SideStream	0.99	0.82	1.20
C_{max}	I-neb 0.3 ml	IV 2.4 mg	0.49	0.40	0.59
C_{max}	I-neb 0.5 ml	IV 2.4 mg	0.83	0.69	1.01
C_{max}	I-neb 0.3 ml	IV 40 mg	0.03	0.027	0.04
C_{max}	I-neb 0.5 ml	IV 40 mg	0.056	0.046	0.068
C_{max}	SideStream	IV 40 mg	0.05	0.05	0.068

Similarly, the C_{max} and the AUC_{∞} obtained with 24 mg AAD administration using a 0.3 mL chamber (0.3 million IU) were approximately 50% those obtained with 160 mg nebulised administration using a conventional jet.

Parenteral Administration

Despite the above pharmacokinetic data, the fate of locally deposited drug remains unclear. A summary of known pharmacokinetics of parenteral administered drug is instead is presented for completeness:

Froman et al (1970) measured blood and urine colistin concentrations after administration of intramuscular IM and IV 150 mg doses of CMS to 10 healthy volunteers. Peak mean serum levels of 5-6 µg/mL were achieved 2 hours following IM injection. The highest serum level for IV (18 mcg/mL) was the at first blood specimens taken at 10 minutes injection. Serum levels after IM injections declined with a $t_{1/2}$ of 2.75-3 hours. Serum levels following IV injection declined initially with a $t_{1/2}$ of 1.5 hours. The maximum mean level in urine (about 200 µg/mL) occurred 2-4 hours following IM injection and within the first 2 hours after IV administration.[28]

Reed et al (2001) reported PKs of colistin in 31 CF patients (mean age 29.4 years – range 13.9 to 52.5 years) who were receiving IV infusions for acute pulmonary exacerbation of disease. A dose of 5 to 7 mg/kg/day was administered in three equally divided doses. The PK parameters were reported after the first dose and at steady-state. The results were as follows:

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[28] Froman J, Gross L, Curatola S. Serum and urine levels following parenteral administration of sodium colistimethate to normal individuals. J Urol 1970; 103: 210-14.

Parameter	Colistin Pharmacokinetic Parameter Estimates			
	First Dose (n = 30)		Steady State (n = 27)	
C_{max} (mg/L)	21.4	(5)	23	(6)
C_{min8h} (mg/L)	2.8	(1.8)	4.5	(4)
$t_{1/2}$ (h)	3.4	(1.4)	3.5	(1)
MRT (h)	4.4	(1.7)	4.6	(1.4)
Vd_{ss} (l/kg)	0.09	(0.02)	0.09	(0.03)
Cl (ml/min/kg)	0.35	(0.09)	0.34	(0.09)
Clr (ml/min/kg)	0.24	(0.15)	—	
Clr:Cl	0.62	(0.32)ᵃ	—	

Data presented as the mean (± SD). C_{max}, maximum plasma colistin concentration; C_{min8h}, 8-hour trough colistin plasma concentration; $t_{1/2}$, elimination half-life; MRT, mean residence time; Vd_{ss}, steady-state volume of distribution; Cl, body clearance; Clr, renal clearance.
a. n = 13.

The characteristics of drug disposition were shown to be similar (clearance, $t_{1/2}$) between first dose and steady state. Overall, 62.5% of the dose was excreted unchanged in the urine during the first 8 hours. The majority of renal excretion occurred in the first 4 hours after dosing.[29]

Li et al (2003b and 2003a) developed a sensitive HPLC that could detect both CMS and colistin (base) in plasma. An open label study to characterise steady-state pharmacokinetics of CMS and colistin was conducted in 12 CF patients (mean age 21.7 years – range 13 to 39 years) who received CMS (body weight ≥ 50 kg 2 million IU; < 50 kg 1 million IU) every 8 hours for ≥ 2 days by the IV route.[1,30]

The plasma CMS concentration at 1 hour ranged from 2.6 mg/L to 9.8 mg/L, while at 6 hours the levels were between 0.36 mg/L and 2.5 mg/L. The colistin (base) was also measurable in all samples with concentrations ranging from 1.0 mg/L to 3.1 mg/L at 1 hour and from 0.23 mg/L to 1.7 mg/L at 6 hours.

At steady-state, the total body CMS Clearance, Volume of distribution and $t_{1/2}$ were 2.01 ± 0.46 mL/minute/kg, 340 ± 95 mL/kg and 124 ± 52 minutes respectively. Colistin had significantly longer $t_{1/2}$ of 251 ±79 minutes.

Markou et al (2008) was an uncontrolled study in 14 critically ill patients (mean age 62.0 years – range 18 to 84 years) with multi-drug resistant (MDR) Gram-negative infections. The patients received IV CMS 225 mg every 8 to 12 hours for at least 2 days. At steady-state, the mean (standard deviation [SD]) colistin C_{max} was 2.93 (1.2) mg/L, and the trough plasma concentration (C_{min}) was 1.03 (0.44) mg/L. The apparent clearance, volume of distribution (V_d) and $t_{1/2}$ were 13.6 (5.8) L/h, 139.9 (60.3) L and 7.4 (1.7) hours respectively.[31]

Goodwin and Friedman (1968) studied the effect of renal impairment was studied following a single IM 75 mg CMS dose in 39 patients with varying degrees of renal impairment including 17 patients undergoing dialysis. The authors reported that with creatinine clearance < 20 mL/min, the CMS blood concentration and duration of elevation were inversely

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[29] Reed MD, Stern RC, O'Riordan MA, Blumer JL. The pharmacokinetics of colistin in patients with cystic fibrosis. J Clin Pharmacol 2001; 41: 645-54.

[30] Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K. Stability of colistin and colistin methanesulfonate in aqueous media and plasma as determined by high-performance liquid chromatography. Antimicrob Agents and Chemother 2003; 47:1364-70.

[31] Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, Gram-negative bacilli infections: A prospective, open-label, uncontrolled study. Clin Ther 2008; 30: 143-51.

proportional to the degree of renal impairment. Peritoneal dialysis approximately removed 1 mg CMS per hour and its clearance was about 30% as efficient as that of urea.[32]

Li et al (2005b) reported data in a single critically ill patient receiving renal replacement therapy who received CMS 150 mg (2.46 mg/kg) IV every 24 hours for 14 days, then reduced to every 48 hours for 6 days). The $t_{\frac{1}{2}}$ for CMS and colistin were 6.83 and 7.52 hours respectively. The CMS clearance was 48.7 mL/min and V_d was 10.9 L. From 0 to 8 hours after dosing, 20.3% of the dose was recovered in the diasylate as CMS and 6.88% as colistin. Continuous venovenous haemofiltration Clearances were similar for CMS and colistin.[33]

Evaluator's comment and PK conclusions

The studies reported in published literature show a wide range of variability for pharmacokinetic parameters following administration of CMS by nebulisation.

Over the years, the discrepancy in parameters may be related to the assay sensitivity and specificity as well as the variable measured and reported such as colistin, polymyxin A, and/or polymyxin B.

However, a large part of variation is also attributable to various delivery systems as well as variation intrinsic to the method of inhalation in individuals.

Hence, the relative bioavailability data generated in the sponsored study PPCTP/002 is considered the most relevant and reliable. The proposed Product Information at that time did not include any description of this study. It was recommended that details and results of this study be included in the Australian PI. This was subsequently actioned.

With respect to nebulised CMS, it is quite definitive that only small amounts of the inhaled drug reach systemic circulation and absorption from the gastrointestinal tract is also negligible. This has an important bearing on the expected toxicity of the inhaled drug compared to parenteral administration as well as on the need to alter the dose in case of renal impairment.

Based on the data from the study PPCTP/002, using polymyxin E1 as a proxy for CMS/colistin, the C_{max} was approximately 70 ng/mL after single dose inhalation of 2 million IU (160 mg) dose using a conventional jet nebuliser, compared to a C_{max} of 1232 ng/mL following an IV dose of 40 mg, noting that the clinical dose of IV form is 160 mg.

Based on the same study, the polymyxin E1 AUC_∞ was 668 ng/mL/h after single dose inhalation of 2 million IU (160 mg) dose using a conventional jet nebuliser, compared to AUC_∞ of 3352 ng/mL/h following an IV dose of 40 mg, noting that the clinical dose of IV form is 160 mg.

The study also demonstrated pharmacokinetic equivalence, based on systemic exposures of polymyxin E1 (peak and total), between 2 million IU administered by a conventional jet nebuliser with 0.5 million IU administered using the "I-neb AAD" delivery system.

Based on the comparison between 2 million IU administered by a conventional jet nebulisation and 0.3 million IU units delivered by the "I-neb AAD" system, it can also be

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[32] Goodwin NJ, Friedman EA. The effects of renal impairment, peritoneal dialysis, and hemodialysis on serum sodium colistimethate levels. Ann Intern Med 1968; 68: 984-94.

[33] Li J, Rayner CR, Nation RL, et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. Antimicrob Agents and Chemother 2005; 49: 4814-5.

inferred that 1 million IU delivered by jet nebulisation will result in equal systemic exposures as 0.3 million IU using AAD.

However, it must be emphasised that the amount of drug deposited in the lungs and its pharmacokinetic disposition characteristics are unknown.

The information regarding metabolism and elimination is thus primarily derived from parenteral administration. After IV administration of CMS to CF patients, the plasma concentrations of CMS at steady-state range from 2.6 mg/L to 9.8 mg/L at 1 hour and between 0.36 and 2.5 mg/L at 6 hours. The base colistin is measurable with concentrations ranging from 1.0 mg/L to 3.1 mg/L at 1 hour and from 0.23 mg/L to 1.7 mg/L at 6 hours. The $t_{1/2}$ of CMS (124 minutes) was approximately half of that for colistin formed within the body.

The urinary recovery of CMS is 62.5% during the first 8 hours after mean doses of 63 ± 13 mg administered IV to patients with CF. Systemic clearance was 0.35 ± 0.09 mL/min/kg. The majority of the renal excretion (50%) occurred during the first 4 hours after the dose. The fate of the remaining CMS, not eliminated by the kidney, remains unclear.

The sputum concentrations following inhaled dose are much higher than plasma concentration. Presumably most of the drug in sputum can be expected to be cleared in expectorated sputum. However, the impairment of respiratory mucocilary clearing mechanism in patients with CF is not expected to be efficient.

No specific instructions for dosing in the presence of renal impairment are proposed. The instructions only advise that dose within the range (1-2 million IU 2-3 times daily) should be used based on the clinical condition of the patient. This is considered acceptable, although the most recent Periodic Safety Update Report (PSUR) provided by the sponsor includes first instance of report of an acute renal failure (acute tubular necrosis) in association with nebulised CMS. However, the context in this case was an adult female diabetic patient on inhaled for CMS for 2-3 months.

Pharmacodynamics
Spectrum of Activity

The susceptibility of polymyxin B was determined among clinical isolates Gram-negative bacteria in a worldwide (Asia-Pacific, Europe, Latin America, and USA and Canada) SENTRY surveillance program between 2001 and 2004 (**Gales *et al* 2006**).[34]

A total of 54 731 Gram-negative isolates from diverse sites of infection were tested. The results were interpreted according to CLSI guidelines. CMS demonstrated activity was against many Gram-negative organisms including *PA, Acinetobacter* species, Klebsiella pneumoniae, and Escherichia coli as shown below (from **Zapantis *et al* 2007**).[35]

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[34] Gales AC, Jones RN, Sader HS. Global assessment of the antimicrobial activity of polymyxin B against 54 731 clinical isolates of Gram-negative bacilli: report from the SENTRY antimicrobial surveillance programme (2001-2004). Clin Microbial Infect 2006; 12: 315-21.

[35] Zapantis A, Lopez M, Hoffman E, Lopez A, Hamilton G. The use of colistin in multidrug-resistant infections. Hosp Pharm 2007; 42: 1127–38.

Organism (No. of isolates)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)	Range (mcg/mL)	% Susceptible (MIC_{90} $\leq$ 2 mcg/mL)
Pseudomonas aeruginosa (8,705)	$\leq$ 1	2	$\leq$ 1 to > 8	98.7
Acinetobacter species (2,621)	$\leq$ 1	2	$\leq$ 1 to > 8	97.9
Klebsiella species (8,188)	$\leq$ 1	$\leq$ 1	$\leq$ 1 to > 8	98.2
Escherichia coli (18,325)	$\leq$ 1	$\leq$ 1	$\leq$ 1 to > 8	99.5

MIC = minimum inhibitory concentration.

The *in vitro* resistance has been reported to vary (2001 report) from 1.1% in Europe, North and Latin America to 2.9% in Asia-Pacific for *PA* and similarly for *Acinetobacter* species. Isolates are considered resistant with MIC of > 4 μg/mL. Anaerobic bacteria, members of *Neisseria*, and Gram-positive aerobes have innate resistance to colistin.

The *in vitro* activity of inhaled CMS in aerosol in filters after ultrasonic or jet nebulisation (**Diot et al 1997**) or in "I-neb AAD" delivery system technology (**Potter et al 2004**) has been studied and reported not to result in alteration of properties of CMS.[36,37]

The interactions of CMS at two different concentrations with other antibiotics (ceftazidime, aztreonam, meropenem, gentamycin, piperacillin and ciprofloxacin) were studied using a representative strain of *PA* isolated from a CF patient (**MacGowan *et al* 1999**).[38] No evidence of antagonism was found.

A synergy between ceftazidime and CMS has been reported (**Gunderson *et al* 2003**).[39] This *in vitro* work demonstrated that CMS in combination with ceftazidime was synergistic ($\geq$ 2 $\log_{10}$ drop in number of CFU/mL from the count obtained with the more active agent) at 24 hours.

Resistance to Colistin

Li et al (2005a) discusses mechanisms of resistance to colistin. Studies on *PA* suggest that over-expression of *OprH* (or *H1*), an outer membrane protein, in low Mg^{+2} environments may play a role in resistance to polymyxin B and gentamycin. There is cross-resistance between various polymyxins. At a molecular level, resistance may occur due to different lipid compositions of lipopolysaccharides or substitution of *OprH* for magnesium in the outer membrane. Additional contributors to intrinsic resistance of *PA* are a number of chromosomally encoded multi-drug efflux systems. However, colistin is considered not likely to be a substrate for such efflux systems as it interacts preferentially with the outer membrane and cytoplasmic membrane.[5]

Pamp et al (2008) showed that spatially distinct subpopulation of metabolically active cells in *PA* biofilms was able to develop tolerance to colistin, whereas cells with low metabolic activity were killed. The subpopulation of metabolically active cells could adapt to colistin by

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36 Diot P, Gagnadoux F, Martin C, Ellataoui H, Furet Y, Breteau M et al. Nebulisation and anti-Pseudomonas aeruginosa activity of colistin. Eur Respir J 1997; 10: 1995-8.

37 Potter R, Hatley RHM, Dyche T, Smith NJ. Output characteristics of the new "I-neb AAD" system when delivering colistimethate sodium. Presented at the Drug Delivery to the Lungs Conference 15, Dec 9-10, London, 2004.

38 MacGowan AP, Rynn C, Wootton M, Bowker KE, Holt HA, Reeves DS. In vitro assessment of colistin's anti-pseudomonal antimicrobial interactions with other antibiotics. Clin Microbial Infect 1999; 5: 32-6.

39 Gunderson BW, Ibrahim KH, Hovde LB, Fromm TL, Reed MD, Rotschafer JC. Synergistic activity of colistin and ceftazidime against multiantibiotic resistant Pseudomonas aeruginosa in an in vitro pharmacodynamic model. Antimicrob Agents Chemother 2003; 47: 905-9.

inducing a specific adaptation mechanism mediated by the *pmr* operon, as well as an unspecific adaptation mechanism mediated by the *mexAB-oprM* genes. Mutants defective in either *pmr*-mediated lipopolysaccharide modification or in *mexAB-oprM*-mediated antimicrobial efflux were not able to develop a tolerant subpopulation in biofilms. In contrast, the conventional antimicrobial agents such as ciprofloxacin and tetracycline were found to kill the subpopulation of metabolically active biofilm cells, whereas the subpopulation with low metabolic activity survived these agents.[40]

The incidence of development of clinical resistance is reported to be low. Resistance to colistin was reported in six children attending a CF centre in the UK who became colonised with CMS-resistant *PA* over a period of 5 years. All patients had received inhaled CMS for a mean duration of 3.1 years. Four had also received IV colistin in the year prior to the first isolation of the resistant strain. As reported by **Denton *et al* (2002)**, there was no significant effect on pulmonary function, clinical status or radiological parameters in these patients.[41] All patients remained positive for colistin-resistant *PA* and were switched to alternative aerosolised and IV therapy. The article suggested that transmission was likely due to patient to patient contact.

Pitt et al (2003) reported results of susceptibility testing in *PA* isolates from 417 CF patients to six commonly prescribed antibiotics. Four hundred and twenty eight isolates of *PA* were received from 17 hospitals. The reported rates of resistance were much lower for colistin than for the other antibiotics as shown below:[42]

Antimicrobial	Breakpoint (μg/mL)	Susceptible n (%)	Intermediate n (%)	Resistant n (%)
Gentamicin	(≤1; ≥8)	55 (13.2)	166 (40.0)	196 (47.0)
Tobramycin	(≤1; ≥8)	230 (55.1)	145 (34.6)	42 (10.1)
Ceftazidime	(≤8; ≥16)	252 (60.4)	–	165 (39.6)
Ciprofloxacin	(≤1; ≥8)	182 (43.6)	111 (26.6)	124 (29.7)
Piperacillin	(≤16; ≥32)	284 (68.1)	–	133 (31.9)
Colistin	(≤4; ≥8)	404 (96.9)	–	13 (3.1)

(Pitt *et al* 2003)

Johansen et al (2008) reported a 17-year long prospective study on colistin susceptibility among chronically infected CF patients. Two outbreaks of colistin-resistant *PA* occurred during this observation period.[43]

The first outbreak started in 1995 and involved 27 patients who had taken inhaled colistin twice daily for a median duration of 10 years. The colistin-resistant isolates persisted in individual patients for a median of 75 days after withdrawal of colistin treatment.

The second outbreak started in 2004 and involved 40 patients of which 17 were also involved in the first outbreak.

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[40] Pamp SJ, Gjermansen M, Johansen HK, Tolker-Nielsen T. Tolerance to the antimicrobial peptide colistin in Pseudomonas aeruginosa biofilms is linked to metabolically active cells, and depends on the pmr and mexAB-oprM genes. Mol Microbiol 2008; Apr; 68(1): 223-40.

[41] Denton M, Kerr K, Mooney L, et al. Transmission of colistin-resistant Pseudomonas aeruginosa between patients attending a pediatric cystic fibrosis center. Pediatr Pulmonol 2002; 34: 257-61.

[42] Pitt TL, Sparrow M, Warner M, Stefanidou M. Survey of resistance of Pseudomonas aeruginosa from UK patients with cystic fibrosis to six commonly prescribed antimicrobial agents. Thorax 2003; 58: 794–6.

[43] Johansen HK, Moskowitz SM, Ciofu O, Pressler T, Høiby N. Spread of colistin resistant non-mucoid Pseudomonas aeruginosa among chronically infected Danish cystic fibrosis patients. J Cyst Fibros 2008; 7: 391-7.

Most resistant isolates belonged to two major clones that had similar genotypes in the two outbreaks. The *PA* isolates were all non-mucoid. Patients were individually isolated to avoid cross-infection and colistin inhalations were avoided in outpatient clinic and in the ward after both outbreaks. The article noted that, since 2004, no further spread has been observed.

During the first European mutual recognition procedure for this product, the sponsor was asked by the Regulator to provide additional long-term data on colonisation. Published data from a Copenhagen hospital were supplied and accepted by the Regulator. In this hospital, the CF patients who developed intermittent colonisation with *PA* have been treated with inhaled CMS and oral ciprofloxacin since 1989. A population of CF patients without chronic *PA* infection have been followed for 15 years and a retrospective review of 146 patients (1106 patient-years) has been published (**Hansen et al 2005 & 2008**).[44,45]

The review showed that the median age at time of diagnosis of CF was 0.5 (range 0 – 12) years. The intermittently colonised patients had a median number of 5 sputum samples (range 1 – 46) with growth of *PA*, and resulted in 1052 treatments. The duration of treatment changed during the study period from 3 weeks to 3-month courses in late 1990s. A total of 39 patients developed chronic infection with *PA* over the observation period of the study. The median age at onset of chronic infection was 14.5 (range 3.6 – 28.3) years. All chronically infected patients were treated with inhaled colistin continuously.

Among chronically infected patients, four patients (14 sputum samples) had growth of colistin-resistant strains of *PA* at some time (0.4% of strains from chronically infected patients, 0.3% of all isolated strains during the study period). These patients had been chronically infected for 2, 4, 8 and 9 years respectively. No intermittently colonised patients had growth of colistin-resistant strains.

Other Pharmacodynamic properties

Jones et al (2002) have shown that aminoglycosides slightly inhibit and CMS and erythromycin increase neutrophil elastase in *in vitro* testing. The effect was dose related. The undesirable effect was not expected and the mechanism has not been determined. NE is a protease enzyme present in increased amounts in the lungs of CF patients and is associated with pulmonary damage.[46] No other publications on this subject were identified.

The ability of polymyxins to bind endotoxin has also been investigated *in vitro*. The data indicate that 1 mg of colistin is able to bind about 5 mg of endotoxin (**Dollery 1991**). This has led to the suggestion that polymyxins could act as adsorbents rather than true antibiotics.[47]

Dosing Regimen

Bergen et al (2008) reported results of an *in vitro* study to identify optimal dosing for CMS against *PA* based on data simulation using PK/PD model to predict the PK of colistin formation in humans when administered three dosage regimens (8, 12 and 24-hours intervals

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[44] Hansen CR, Pressler T, Høiby N. Early aggressive eradication therapy for intermittent Pseudomonas aeruginosa airway colonization in cystic fibrosis patients: 15 years experience. J Cyst Fibros 2008; 7: 523-30.

[45] Hansen CR, Pressler T, Høiby N. Experience from 15 years use of inhaled colistin in treatment of P. aeruginosa in a CF-clinic. J Cyst Fibros 2005; 4: S34-S58.

[46] Jones A, Elphick H, Pettitt E, Everard ML, Evans GS. Colistin stimulates the activity of neutrophil elastase and Pseudomonas aeruginosa elastase. Eur Respir J 2002; 19: 1136-41.

[47] Dollery C. Colistin (sulphate and sulphomethate sodium). Therapeutic Drugs, Eds Boobis et al Churchill Livingstone Vol 1, 1991 C345-C349.

that is C_{max} of 3.0, 4.5 or 9.0 mg/L respectively). The antibacterial activity and resistance were tested over 72 hours using two strains of *PA*. No difference in bacterial killing was observed among the two dosing regimens. However, 8-hourly regimen appeared most effective at minimising emergence of resistance.[48]

Evaluator's comment and PD conclusions

CMS has bactericidal properties against a wide range of Gram-negative organisms, including *PA*, but not against Gram-positive organisms.

The development of resistance appears to be low, probably due to its mechanism of action. Cross-resistance occurs with other polymyxins but is not expected with antibiotics in other classes. The anti-bacterial properties are not altered by aerosolisation.

The validity or otherwise of the clinical breakpoints in relation to inhaled use of drug and presumed local mode of action is not clear. However, these are included in the proposed PI and considered acceptable.

Efficacy

Introduction

The evidence from randomised, controlled, double-blind trials is quite limited; however there is a long-standing history of use in clinical practice.

PA infection in CF patients

Early intervention in *PA* infection in patients with CF has been studied by **Littlewood et al (1985)** which was a report of uncontrolled treatment and **Valerius et al (1991)** which was a report of a trial using randomised design.[49,50]

Retrospective reviews of patients at the Danish Cystic Fibrosis Centre in Copenhagen were reported by **Frederiksen et al (1997)** and **Hansen et al (2008)**. Similarly, retrospective review of patients at the Cystic Fibrosis Centre in Florence has been reported by **Taccetti et al (2001)**.[51,44,52]

Treatment of CF patients with colonisation or chronic *PA* infection were reported in two double-blind trials by **Day et al (1988)** and **Jensen et al (1987)**.[53,54]

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[48] Bergen PJ, Li J, Nation RL, Turnidge JD, Coulthard K, Milne RW. Comparison of once-, twice- and thrice-daily dosing of colistin on antibacterial effect and emergence of resistance: studies with Pseudomonas aeruginosa in an in vitro pharmacodynamic model. J Antimicrob Chemother 2008; 61: 636-42.

[49] Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early Pseudomonas colonisation in cystic fibrosis. Lancet 1985; 865.

[50] Valerius NH, Koch C, Høiby N. Prevention of chronic Pseudomonas aeruginosa colonisation in cystic fibrosis by early treatment. Lancet 1991; 338: 725-6.

[51] Frederiksen B, Koch C, Høiby N. Antibiotic treatment of initial colonisation with Pseudomonas aeruginosa postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediat Pulmon 1997; 23: 330-5.

[52] Taccetti G, Sisi B, Procopio E, Farina S, Repetto T, Campana S. Prevention of chronic P. aeruginosa colonization in cystic fibrosis patients: An 8 year follow up study. 24th European Cystic Fibrosis Conference 2001 Abs P228.

[53] Day AJ, Williams J, McKeown C, Bruton A, Weller PH. Evaluation of inhaled colomycin in children with cystic fibrosis. Abstract of presentation to 10th International Cystic Fibrosis Congress, Sydney; 1988; 106 Abs R(c) 3.

One double-blind study compared CMS with colistin sulphate (**Westerman et al 2004**).[55]

Open-label, controlled studies include **Adeboyeku et al (2006)**, **Hodson et al (2002)** and **Johansen et al (2004)**, whereas **Westerman et al (2007b)** is report of a 30 year cohort study at the Danish CF Centre in Copenhagen.[56,57,58,59]

Early Intervention Studies (Intermittent Colonisation or First Infection)

Littlewood et al (1985) was an early report of the use of inhaled CMS attempting to intervene early in *PA* infection in patients with CF. The study was published in a letter to the editor in the Lancet.[49] Seven young patients (age 21 months to 14 years) were treated with inhaled 0.5 million IU CMS twice daily. There was no control group. The results were reported in terms of frequency of positive *PA* cultures before and after the nebulised treatment and were as follows:

Patient	Months of study: Before	Months of study: After	Frequency of positive pseudomonas cultures: Before	Frequency of positive pseudomonas cultures: After
1	6	13	2/6	0/15
2	7	3	6/7	2/3
3	5	10	3/7	0/16
4	5	13	4/7	4/26
5	3	13	4/5	1/18
6	3	14	2/6	1/40
7	13	11	4/21	0/12
Total			25/59 (42%)	8/130 (6%)

The authors noted their impression that such treatment may reduce the number of isolated *PA* as well as the frequency of isolation from cultures taken respiratory tract of these treated patients.

Valerius et al (1991) reported a randomised study in CF patients with the objective of ascertaining strategy for prevention of *PA* colonisation.[50] The study was carried out at the Danish CF Centre between 1987 and 1989. Thirty consecutive patients who had a positive *PA* culture on routine monthly sputum examination were invited to join the study. A total of 26 patients participated and had previously not received anti-pseudomonas chemotherapy.

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[54] Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection. J Antimicrob Chemother 1987; 19: 831-38.

[55] Westerman EM, Le Brun PPH, Touw DJ, Frijlink HW, Heijerman HGM. Effect of nebulized colistin sulphate and colistin sulphomethate on lung function in patients with cystic fibrosis: a pilot study. Cystic Fibros 2004; 3: 23–8.

[56] Adeboyeku D, Scott S, Hodson ME. Open follow-up study of tobramycin nebuliser solution and colistin in patients with cystic fibrosis. J Cyst Fibros 2006; 5: 261-3.

[57] Hodson ME, Gallagher CG, Govan JRW. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. Eur Respir J 2002; 20: 658-64.

[58] Johansen HK, Norregaard L, Gøtzsche PC, Pressler T, Koch C, Høiby N. Antibody response to Pseudomonas aeruginosa in cystic fibrosis patients: a marker of therapeutic success? A 30-year cohort study of survival in Danish CF patients after onset of chronic P. aeruginosa lung infection. Pediat Pulmon 2004; 37: 427-32.

[59] Westerman EM, De Boer AH, Le Brun PPH, et al. Dry powder inhalation of colistin in cystic fibrosis patients: a single dose pilot study. J Cyst Fibros 2007; 6: 284-92.
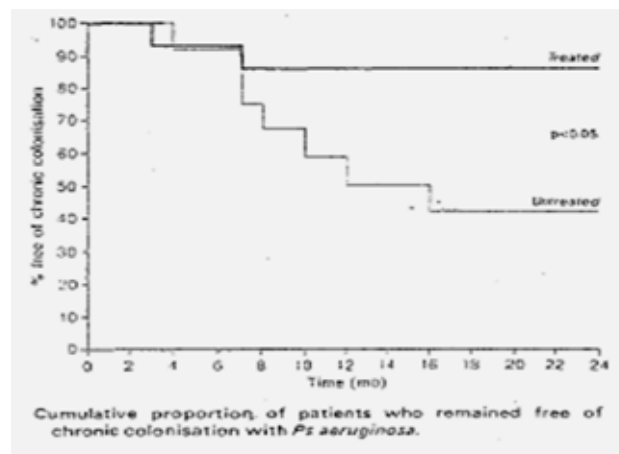
They were randomly allocated to two groups to receive either inhaled CMS (1 million IU twice daily) plus oral ciprofloxacin (250-750 mg twice daily) or no anti-pseudomonas chemotherapy for a treatment duration of 3 weeks. There were 14 and 12 patients in the 2 groups respectively. The baseline features of the patients were as follows:

BASELINE CHARACTERISTICS OF PATIENTS		
—	Treatment (n = 14)	No treatment (n = 12)
Median (range) age in mo	103 (36–228)	129 (23–192)
Male/female	6/8	7/5
Median (range) of previous Ps aeruginosa isolates	1 (0–11)	1 (0–9)
No of patients		
With ≥ 3 Ps aeruginosa isolates	4	5
With Ps aeruginosa isolated within 3 preceding sputum cultures	4	1
With ≥ 2 precipitating Ps aeruginosa antibodies	1	1
Median (range) no of precipitating antibodies against Staphylococcus aureus	3 (1–7)	2 (1–5)

The treatments were to be repeated every time *PA* was isolated from routine sputum cultures over the next 27 months of the trial.

During the 27 months of the trial 7/12 (58%) untreated patients became chronically colonised (positive *PA* in monthly sputum cultures for 6 consecutive months and/or development of precipitating serum antibodies) compared with 2/14 (14%) of the treated patients.

The mean follow-up time for those who did not become chronically colonised was 17·4 (± 8.9) months. The difference between the two groups was significant (p < 0.05).

Cumulative proportion of patients who remained free of chronic colonisation with *Ps aeruginosa*.

There were significantly fewer isolated of *PA* in routine sputum cultures in the treated group (49/214 (23%) vs. 64/158 (41%), p = 0.0004).

Frederiksen et al (1997) reported review of data from the Danish CF Centre comprising 48 CF patients treated with an intensive three-step protocol as follows:[51]

Step 1 *PA* isolated first time

> Inhaled CMS 2 million IU twice daily plus oral ciprofloxacin 25-50 mg/kg/day in 2 divided doses for 3 weeks

Step 2 *PA* isolated more than once

> Inhaled CMS 2 million IU three times daily plus oral ciprofloxacin 25-50 mg/kg/day in 2 divided doses for 3 weeks

Step 3 *PA* isolated for a third time within 6 months

>   Inhaled CMS 2 million IU three times daily plus oral ciprofloxacin 25-50 mg/kg/day in 2 divided doses for 3 months

The Step 1 treatment was given only once. The Step 2 treatment could be given more than once if the duration between the positive cultures of *PA* exceeded the definition in Step 3. If *PA* was cultured shortly after the end of Step 3 treatment, then the patient was by definition chronically infected.

A group of 43 CF patients was used for comparison as historical controls. The baseline characteristics of the patients reproduced below show comparability between the treated group and the historical controls:

The study was carried out over 44 months. The treatment group was observed for a mean of 30 months and the control group for 28 months. There were 218 patient-years of exposure.

Over the course of the study 7/48 (15%) treated patients developed chronic infection compared with 19/43 (44%) historical controls.

Based on a Kaplan-Meier estimate, 16% treated patients developed chronic *PA* infection over 3.5 years compared with 72% historical controls (p<0.005).
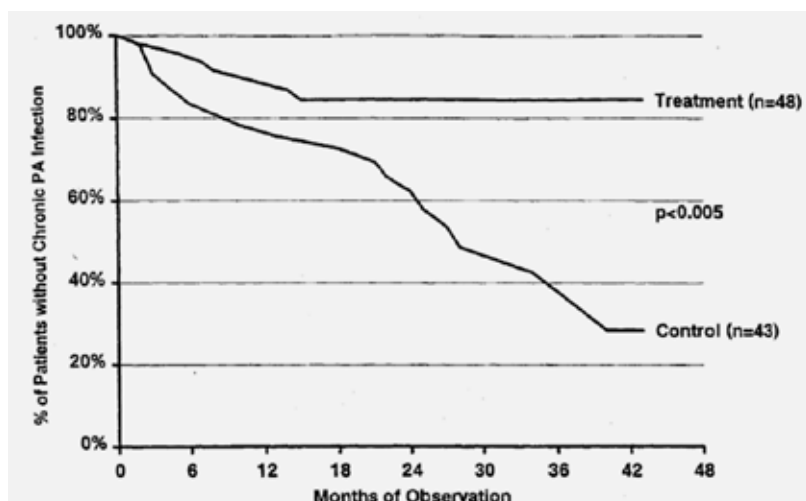
The percentage of sputum samples that were positive for *PA* until onset of chronic *PA* infection or the end of the study was 13.7% in the treated group compared to 24.4% in historical controls (p < 0.00001).

The results of pulmonary function tests (forced vital capacity [FVC] and forced expiratory volume in the first second [FEV_1]) reported for the first and second years of observation, indicate relatively stable function in the treated group compared to historical controls were as shown below:

	1 year after			2 years after		
	Treatment	Control		Treatment	Control	
FVC	12% (-9%- 46%)	-3% (-23%- 41%)	p<0.005	16% (-23%- 41%)	-8% (-31%- 44%)	p<0.05
FEV_1	5% (-20%- 21%)	-5% (-30%- 15%)	p< 0.01	3% (-19%- 24%)	-6% (-25%- 20%)	p<0.05
	Median (range)	Median (range)	M-W	Median (range)	Median (range)	M-W

The hospital admission data are shown below in the time period before and after the treatment:

	Treatment (days) (n = 48)	Control (days) (n = 43)	χ^2 test P-value[1]
In the year before inclusion	164	106	NS (0.18)
In the year after inclusion	182	284	< 0.02
In the 2 years after inclusion	529	743	< 0.00001

[1] By χ^2 test.

The results indicated benefit of treatment with CMS compared to the historical data with respect to days of hospitalisation.

Hansen et al (2008) is more recent publication from the same group reporting a longer observation period as follows: [44]

	Median (range)	
	All (N=146)	First ever isolate in study (N=99)
Age at diagnosis	0.5 years (0-13)	0.5 years (0-13)
Observation time	7.6 years (0.1-15)	7 years (0.1-14.9)
Age at 1st ever isolate	4.2 years (0-28.1)	4.8 years (0.3-28.1)
Number of isolates in the study	5.5 (1-41)	5 (1-29)

All patients who were initially free of chronic infection and developed intermittent colonisation with *PA* between 1989 and 2003 were included. Patients were followed until the end of 2003, or until confirmed as having chronic infection or lost to follow up or progressed to death.

A total of 146 patients developed intermittent *PA* colonisation during the study period, of which 99 had their first ever *PA* isolate.

Out of the 99 patients with first ever isolate in the reporting period, 12 patients developed chronic infection after a median of 3.7 years after first ever isolate (range 0.5 to 10.3 years), and a Kaplan Meyer estimate showed that up to 80% of patients were protected against development of chronic infection for up to 15 years:
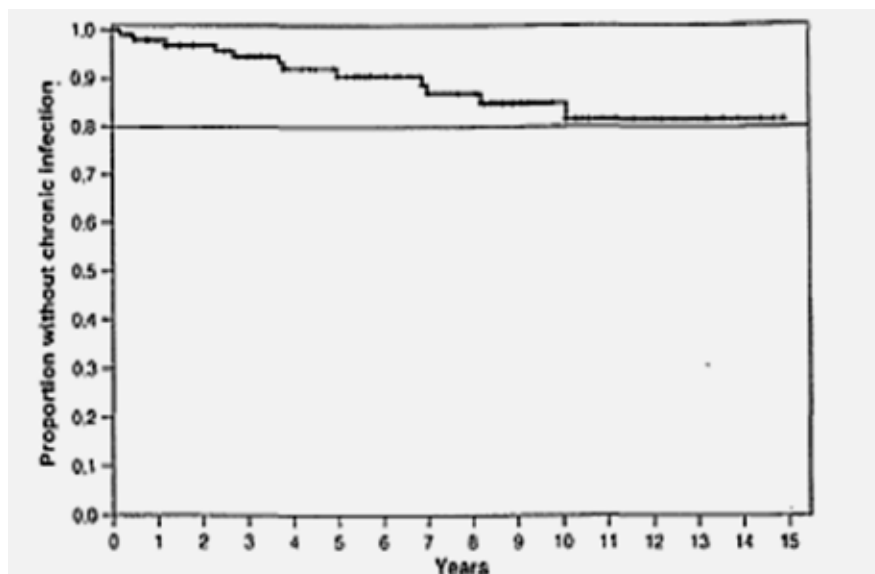
During the period of observation of this study, the standard treatment was changed to 3 months (Step 3 in the Copenhagen model).

In the group of 99 patients with first ever isolate during the study period, 359 colonisation episodes occurred of which 33 (9.2%) colonization were not treated, 87 (24.2%) were treated for 3 weeks and 239 (66.6%) were treated for 3 months.

In the non-treated group, the median time to recurrence of *PA* was 1.9 months (range 0 to 58.3 months).

In the group treated for 3 weeks, the median time to recurrence of *PA* was 5 months (range 0.2 to 112.8 months).

In the group treated for 3 months, the median time to recurrence of *PA* was 10.4 months (range 0 to 98.2).

The difference between no treatment and any treatment (3 weeks or 3 months) was significant at all times ($p<0.02$). The difference between 3 weeks and 3 months of treatment was statistically not significant.

The patients who developed chronic infection (12/99) had significantly shorter *PA*-free interval after treatment of the first ever isolate compared with those who did not develop chronic infection ($p<0.003$).

The treatment failure with CMS/ciprofloxacin after first ever isolate of *PA* was identified as a risk factor for developing chronic infection with an odds ratio of 5.8 (95% CI 1.34 to 25.14).

From the 146 patients in the study, 1093 *PA* isolates were assessed for resistance of which 946 were non-mucoid and 147 mucoid isolates. No isolates resistant to CMS were reported, while 44 ciprofloxacin-resistant isolates were identified from 30 intermittently colonised patients during the study.

Taccetti et al (2001) was report of a retrospective review of inhaled CMS in combination with ciprofloxacin administered with the objective of eradicating *PA* at the time of occurrence of first colonisation.[52]

The paper was presented at the 24th European Cystic Fibrosis conference and was based on data from a CF Centre in Florence. An abstract only was available in the submission reporting 61 episodes of colonisation by *PA* in 43 CF patients over a period of 8 years with a mean of 7.6 colonisations per year. The mean age of patients at time of first colonization was 9 ± 7.6 years (median 8 years). Subsequent colonisations in the same patients recurred 18 times – 2 episodes in 17 patients and 3 episodes in one patient. All episodes were treated with oral ciprofloxacin and inhaled CMS.

In 35 out of 43 patients (81.4%) eradication of *PA* occurred after one cycle of therapy; additional cycles of therapy provided efficacy in a further 9/14 (64%) of patients. In patients who had repeated colonisation the same therapy was effective in 52.9%.

Studies in Chronic Infection or Colonisation

Jensen et al (1987) was a randomised, double-blind, placebo-controlled study in 40 CF patients with chronic bronchopulmonary *PA* infection.[54] The baseline features of the patients indicated comparability of the two groups.

The patients were treated with inhaled CMS 1 million IU or isotonic saline twice daily for a treatment period of 3 months. During the 2 weeks preceding the trial all subjects received parenteral anti-pseudomonal treatment consisting of tobramycin in combination with a beta-lactam antibiotic. The usual supportive therapy such as pancreatic enzymes, vitamins, mucolytic agents and/or and physiotherapy remained unchanged throughout the study in both groups.

Significantly (p < 0.05) more patients had completed the study in the active group (n = 18/20) compared to the placebo group (n = 11/20).

In the active (CMS) group, one patient required elective surgery and received prophylactic anti-pseudomonas therapy for the procedure. Another patient in this group experienced an attack of severe asthma in association with *Aspergillus fumigates* and was withdrawn from the study.

In the placebo group, four patients withdrew due to treatment failure and four claimed no benefit and did not continue. One placebo patient withdrew due to irritating cough after inhalations.

At the end of 3 months of treatment, patients in both groups experienced falls in FVC and FEV_1 although the falls in placebo group were higher. It should be noted that the number for change in the table below represent a decrease (-):

	Treatment day	Colistin $n = 18$ % of normal mean ± s.d.	Placebo $n = 11$ % of normal mean ± s.d.
forced vital capacity (FVC)	0	86 ± 26	89 ± 31
	30	78 ± 20	79 ± 25
	60	76 ± 23	77 ± 27
	90	79 ± 25	71 ± 28
	Change day 0–day 90	7 ± 8	18 ± 14[a]
Forced expiratory volume in the first second (FEV$_1$)	0	71 ± 25	79 ± 29
	30	67 ± 24	68 ± 24
	60	63 ± 24	62 ± 25
	90	60 ± 24	62 ± 29
	Change day 0–day 90	11 ± 6	17 ± 11

[a] $P < 0.05$ when comparing colistin to placebo.

The clinical scores included evaluation of cough, expectoration, dyspnoea, crepitations and rhonchi on auscultation, general state, appetite and subjective assessment and were graded on a semi-quantitative scale. A high score indicated improvement.

The clinical symptom scores at Day 90 were significantly better (p < 0.01) in the CMS group (mean 1.8) compared to placebo (mean 4.7). The progression of the scores over the 3 months was as follows:

Treatment day	Colistin ($n = 18$)	Placebo ($n = 11$)
Day 0	2·8	2·0
Day 30	1·4	2·5
Day 60	1·9	3·2
Day 90	1·8	4·7[a]

[a] $P < 0.01$ when comparing colistin to placebo.

The inflammatory parameters were measured by laboratory tests including erythrocyte sedimentary rate (ESR) and peripheral white blood count. There was a trend towards reduction in the inflammatory response:

	Treatment day	Colistin (mean ± s.d.)	Placebo (mean ± s.d.)
White blood cell count ($\times 10^9$/l)	0	7·4±2·3	6·6± 2·0
	90	6·8±1·2	8·1± 2·1
	Change	−0·6±1·6	+1·5± 1·6
Erythrocyte sedimentation rate (mm/h)	0	12 ±8	21 ±12
	90	11 ±6	27 ±13
	Change	−1 ±7	+6 ±12
Orosomucoid (μmol/l)	0	21 ±5	21 ± 5
	90	25 ±5	35 ±10
	Change	+4 ±5	+14 ± 6[a]

[a] $P < 0.05$ when comparing colistin to placebo.

The microbiological testing showed that *PA* was not eradicated from the sputum of any patient during the trial, and this was not the objective of the study, since patients are chronically colonised. However, the MIC of colistin against *PA* did not change during the study and resistance to colistin was not reported.

No superadded infection with other colistin-resistant microorganisms, notably *P. cepacia, Serratia marcescens, Proteus mirabilis* or Gram-positive organisms was seen.

No change in resistance pattern to other commonly used anti-pseudomonas agents was reported during the treatment period.

Colistin was not detectable in the urine in any patient in this study.

Day et al (1988) was a double blind, crossover study comparing 1 million IU inhaled CMS twice daily with placebo (saline) in 14 CF patients with *PA* colonisation.[53] Each treatment period was of 6 months duration. Patients entered the trial following a course of IV anti-pseudomonas antibiotics and were evaluated every 2 months. The mean age was 11 (range 5-16) years. An abstract only was available in the submission.

The reported results include significantly worsened cough ($p < 0.05$), increased sputum quantity ($p < 0.05$) and decrease in FEV_1 and FVC with placebo compared with the group receiving nebulised CMS. After 6 months of the trial, CMS treatment was associated with a greater ($p < 0.05$) mean FVC (74%) compared with placebo (67.5%).

Westerman et al (2004) reported a double blind, randomised, (single dose), crossover trial comparing nebulised colistin sulphate (100 mg) with CMS (160 mg≈ 2 million IU) in nine CF patients who had chronic *PA* infection.[55] The mean age of the group was 29 (range 20-41) years.

There was a washout interval of 5 days between the two treatments. The patients were instructed not to use any inhaled medication on the day of visit.

On the day of the randomised treatment, the patients received nebulised solution of either colistin sulphate or CMS. Lung function tests were performed immediately before, and 15 and 30 minutes after nebulisation.

The results showed that administration of nebulised colistin sulphate caused significantly greater mean fall in lung function tests compared to nebulised CMS at 30 minutes time point post-nebulisation. The treatment effect started early and was evident at 15 minutes.

At 30 minutes, the mean change in FEV_1 from baseline was -10.2% in colistin sulphate group compared with -2.9% in CMS group (p=0.03).

At 30 minutes, the mean change in FVC from baseline was -10.5% in colistin sulphate group compared with -2.1% in CMS group (p=0.01) for FVC.

	Change in FEV1 (S.D.) (15 min vs. baseline)	Change in FEV1 (S.D.) (30 min vs. baseline)	Change in FVC (S.D.) (15 min vs. baseline)	Change in FVC (S.D.) (30 min vs. baseline)
Colistin sulphate	-11.3% (12.6%)	-10.2% (9.4%)	-10.4% (9.9%)	-10.5% (9.5%)
Colistin sulphomethate	-6.0% (7.0%)	-2.9% (3.3%)	-4.7% (8.1%)	-2.1% (4.9%)
Results (difference)	-5.3% (12.2%)	-7.3% (8.6%)	-5.7% (7.3%)	-8.4% (7.5%)
	P=0.225	P=0.034	P=0.047	P=0.010

Change in ∆FEV1 (S.D.): mean change in FEV1 from baseline after colistin sulphate nebulization minus mean change in FEV1 from baseline after colistin sulphomethate nebulization. SD = standard deviation.

Change in ∆FVC (S.D.): mean change in FVC from baseline after colistin sulphate nebulization minus mean change in FVC from baseline after colistin sulphomethate nebulization. SD = standard deviation.

Seven patients were not able to complete treatment with colistin sulphate due to throat irritation and severe cough and one patient required bronchodilator medication after completion of lung function tests. All patients in CMS group completed the nebulisation.

Hodson et al (2002) was a report of an open-label, randomised, controlled study in 115 CF patients with chronic *PA* pulmonary colonisation.[57]

The patients were randomised to receive tobramycin nebuliser solution 300 mg (n=53) or CMS 1 million IU (n=62) twice daily for 4 weeks.

At the end of 4 weeks of study, the mean change (improvement) in predicted FEV_1 was statistically significantly (p = 0.008) higher in tobramycin group (6.7%) compared to CMS in which it did not change (0.37).

The trial has been included in the Cochrane review conducted by **Ryan et al (2004)** and the reported treatment difference was 6.33% with 95% CI of -0.04% to 12.70%.[60]
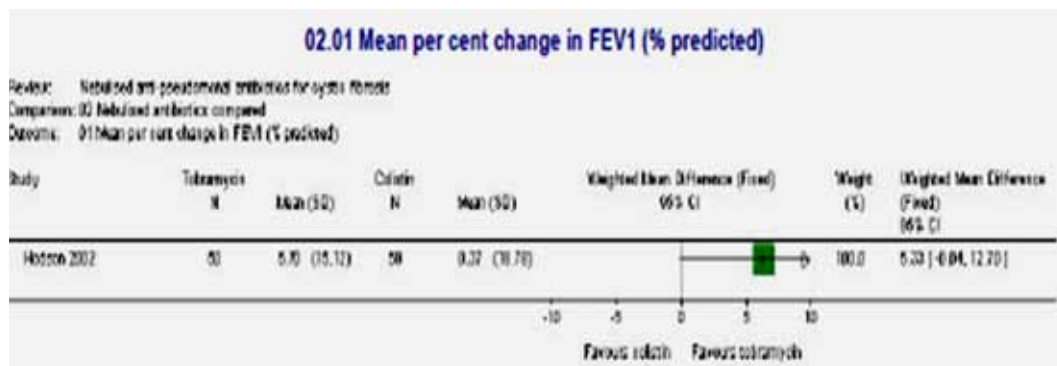
The breakdown of results with various age strata is provided in the table below:

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[60] Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis (Cochrane Review). The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Assessment	FEV₁ % pred % change from baseline		p-value*
	TNS	Colistin	
ITT population			
Patients at week 4 n	50	59	0.008
Mean±SD	6.70±15.12	0.37±18.78	
p-value (within)#	0.006	0.473	
Age group 6–12			
Patients at week 4 n	11	11	
Mean±SD	11.51±24.33	-8.11±18.38	
p-value (within)#	0.148	0.17	
Age group 13–17			
Patients at week 4 n	11	14	
Mean±SD	14.43±7.32	6.01±25.78	
p-value (within)#	<0.001	0.399	
Age group >18			
Patients at week 4 n	28	34	
Mean±SD	1.77±10.80	0.79±14.75	
p-value (within)#	0.393	0.757	

TNS: tobramycin nebuliser solution; ITT: intent-to-treat; FEV₁: forced expiratory volume in one second. #: within-group paired t-testing; *: between-group testing using Wilcoxon rank-sum test.

Treatments by both antibiotics significantly (p = 0.007) decreased sputum *PA* density, although the suppression with tobramycin was greater -0.86 $\log_{10}$ colony forming units (CFU)/mL compared to that with CMS which was -0.6 $\log_{10}$ CFU/mL.

$\log_{10}$ cfu·mL⁻¹	Change from baseline	
	TNS	Colistin
ITT population		
Patients assessed at week 4 n	50	50
Mean±SD	-0.86±1.43	-0.60±1.61
p-value (within)#	<0.001	0.007
Microbiologically-evaluable patients		
Assessed at week 4 n	42	37
Mean±SD	-0.79±1.35	-0.47±1.53
p-value (within)#	<0.001	0.049

TNS: tobramycin nebuliser solution; cfu: colony forming unit; ITT: intent-to-treat. #: between-group testing using the Wilcoxon rank-sum test.

The published report provided useful comparison of adverse effects for the two inhaled drugs (see *Safety*).

Adeboyeku et al (2006) was report of an open-label, randomised, cross-over study in 21 patients recruited from the preceding study (Hodson et al 2002).[56] The patients continued the same treatment for 5 additional months. This was followed by a 2-week washout period after which the patients crossed over to the other treatment (inhaled CMS or tobramycin) for 5 months.

A total of 10 patients received tobramycin 300 mg and 11 patients received CMS 1 million IU in the first treatment period. Overall, 6 patients discontinued the study – 2 had tobramycin-resistant *PA*, one experienced anaphylaxis due to IV ceftazidime given for exacerbation of infection and 3 were not compliant with the treatment.

The authors reported an advantage for tobramycin over CMS with respect to change in predicted FEV₁ over time. Using an ANOVA model, the CMS slope (decrease) was -0.88% per month compared to tobramycin slope (decrease) -0.35% per month (p=0.0002).

There were no statistically significant differences between the treatments for days on IV or oral antibiotics, or quality of life.

Westerman et al (2007b) reported study of CMS dry powder inhaler (25mg) in 10 CF patients in comparison with nebulised CMS (158mg≈ 2 million IU). [59] All patients had chronic *PA* infection and the study design was randomised crossover.

On two separate treatment days, patients inhaled a single dose of CMS in a dry powder formulation or nebulised CMS solution in a randomised order. A period of 3-10 days was allowed between the two treatments. The pulmonary function tests were carried out before, 5 and 30 minutes after inhalation.

The dry powder inhalation was reported by the authors to have been was well tolerated. No clinically relevant reduction in FEV_1 was seen after inhalation of the dry powder at 5 and 10 minutes.

Following CMS nebulisation, 2 patients showed transient reduction in FEV_1 of 11.4% and 12.8% respectively at 5 minutes which improved at 30 minutes. Two patients showed a reduction in FVC of 13.9% and 16.3% at 5 minutes after dry powder inhalation. Two patients had a FVC reduction of 15.1% and 12.7% after CMS nebulisation. The FVC improved for all patients after 30 minutes except for one patient after dry powder inhalation. The FVC of this patient remained at approximately 95% of predicted at 1 and 4 hours post-dose.

This study primarily collected pharmacokinetic data comparing the two methods for drug delivery. These have been reported above.

Johansen et al (2004) reported long-term data from the Danish CF Centre to document the effect of increasingly intensive treatment regimens on anti-pseudomonal antibody response and survival in 5 successive cohorts of CF patients following acquisition of chronic *PA* lung infection.[58]

These study comprised all patients (n = 157) who developed chronic *PA* lung infection and were followed at the Centre since 1971. The time periods of 5 cohorts were 1971-1975 (n=21), 1976-1980 (n=64), 1981-1986 (n=27), 1987-1993 (n=26), and 1994-2000 (n= 19).

During this 30-year period, elective 2-week courses of chemotherapy every third month in all chronically infected patients, early aggressive treatment with inhaled CMS, oral ciprofloxacin for 3 months whenever *PA* was cultured in sputum from non-colonised patients, and inhalation of recombinant human dornase alfa were introduced in the patient management.

There was a significant correlation between the calendar year of chronic *PA* infection acquisition and subsequent increase in the level of precipitins against *PA*. The median number of precipitins increased by 5 per year in the cohort from the oldest calendar year compared with 1 per year in the cohort from the most recent calendar year.

The median age at first appearance of chronic *PA* was 11 years in the oldest calendar cohort and decreased to 9.4 years and 9.3 years in the 1976-1980 and 1981-1986 cohorts respectively. In the most recent time period, it increased to 13.8 years.

The survival after acquisition of chronic *PA* lung infection was higher in more recent cohorts (p = 0.008). There were few deaths in recent time periods, and the positive trend was reported to be caused by a high death rate in the oldest cohort. The median survival was 14.0 years.
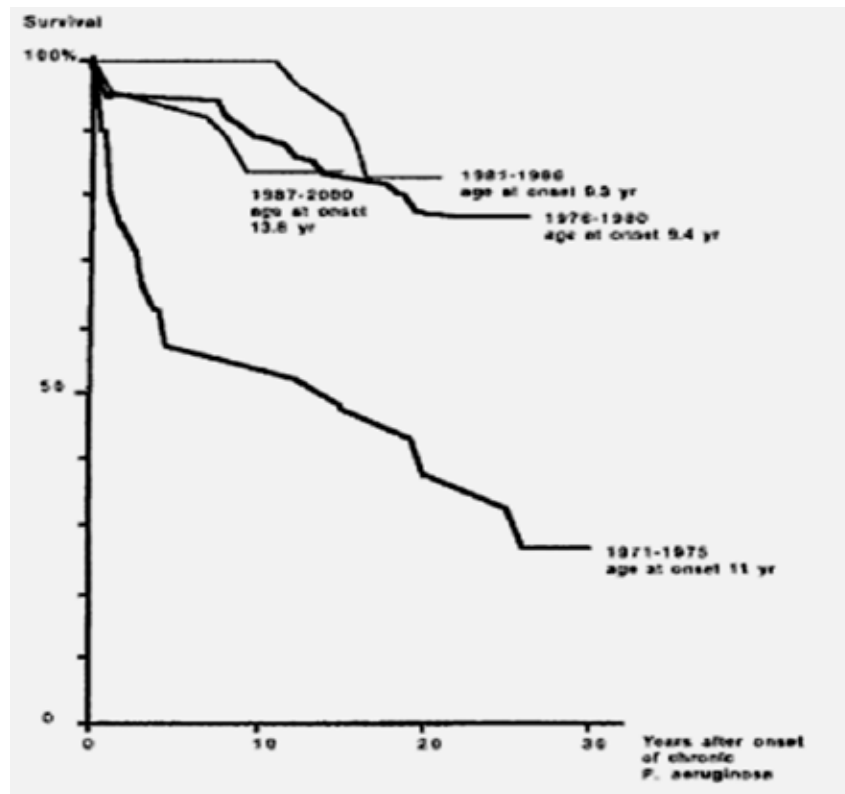
The authors concluded that patients with CF who are treated intensively following acquisition of chronic *PA* lung infection have lower antibody responses and longer survival than those treated less intensively.

Ryan et al (2004) has published a Cochrane review aiming to examine the evidence for treatment effect of nebulised anti-pseudomonal antibiotics in the management of CF patients.[60] The review looked at outcomes such as frequency of exacerbations of infection, lung function, quality of life, survival and adverse effects of nebulised anti-pseudomonal antibiotic treatment.

The selection criteria for trials to be included in this meta-analysis were nebulised anti-pseudomonal antibiotic treatment for at least 4 weeks in patients with CF, randomised or quasi-randomised allocation of treatment, and inclusion of a control group.

A total of 33 trials were identified with 11 meeting the inclusion criteria which resulted in a total of 873 patients. Of these, 10 trials with 758 patients were placebo-controlled or included usual treatment. One trial accounted for 68% of total participants. The duration of follow-up ranged from 1 to 32 months.

However, the pooling of results was not possible for most outcomes because of differences in trial duration, methods of measuring and reporting of outcomes, missing estimates of variance and a high proportion of crossover trials (7 out of 11).

The authors, nevertheless, concluded that nebulised antibiotic therapy in CF patients improved lung function (FEV_1) and reduced acute exacerbations compared to control groups. The resistance to antibiotics increased more in the antibiotic treated group than in placebo group.

The results from Hodson et al (2002) which compared nebulised CMS and tobramycin have been discussed above separately.

Mukhopadhyay et al (1996) was report of an earlier meta-analysis examining risks and benefits of nebulised anti-pseudomonal antibiotics in CF patients.[61] The review included 5 and excluded 8 identified studies concluding that although inferences from individual randomised controlled trials of this form of therapy were conflicting, pooled effect size supported benefit from administration of nebulised anti-pseudomonal antibiotics in CF patients.

Supporting studies

Bauldoff et al (1996) was report of use of inhaled CMS 30 mg three times daily in 19 CF patients awaiting lung transplant.[62] The therapy was initiated at the time of identification of a pan-resistant *PA* strain.

Following the treatment, sensitive strains were reported to have emerged in 17/19 patients. The mean time to emergence of sensitive strains was 49 ±19 (range 20 to 89) days. Attempts were made to discontinue any concomitant parenteral antibiotics.

Five patients received lung transplant and were reported well at 1 to 7 months post-transplant. Four patients died awaiting transplant but had developed sensitive strains. Five active transplant candidates continued to demonstrate sensitive strains.

Three inactive transplant candidates initially developed sensitive strains but with resumption of IV therapy pan-resistant organisms reappeared.

Of the two patients who failed therapy, one was transplanted but succumbed to an early post-operative fungal infection and the other remained inactive.

The authors concluded that aerosolized CMS may be a useful tool to promote emergence of sensitive microbes in lung transplant candidates with pan-resistant strains of *PA*.

Bauldoff et al (1997) report a second study in 32 CF patients with pan-resistant *PA* identified awaiting lung transplant.[63] Of these 20 volunteered to commence inhaled CMS 75 mg twice daily and interrupt IV antibiotics. All were reported to have become colonised with sensitive *PA* (sensitive to at least one parenteral antibiotic used in this condition from 2 different classes). It took an average of 45 days for re-emergence of sensitive strain. Among CF patients who chose not to receive nebulised CMS, 3/10 also redeveloped sensitive *PA*. In this latter group emergence of sensitive strain took an average of 144 days.

Reported use of in other conditions

There were a number of other studies which were not relevant to the current application and were mentioned by the clinical evaluator for completeness.

Evaluator's comment and conclusions on clinical efficacy

The published literature presented in support of this submission consisted of studies for use of inhaled CMS in early treatment of *PA* infection in CF patients in an attempt to prevent or delay the onset of established infection, as well as studies demonstrating its use as

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[61] Mukhopadhyay S, Singh M, Cater JI, Ogston S, Franklin M, Olver RE. Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks. Thorax 1996; 51: 364-8.

[62] Bauldoff GS, Nunley DR, Amaya M, Manzetti JD, Williams PA, Dauber JH et al. Use of aerosolised colistin in patients with cystic fibrosis awaiting lung transplantation. J Heart Lung Transplant 1996; S54 Abstract 63.

[63] Bauldoff GS, Nunley DR, Manzetti JD, Dauber JH, Keenan RJ. Use of aerosolized colistin sodium in cystic fibrosis patients awaiting lung transplantation. Transplantation 1997; 64(s): 748-52.

suppressive therapy in chronic colonisation with the purpose of maintaining or delaying respiratory function.

Although newer studies such as those that would have followed current guidelines for investigation of drugs in CF were not available, the evaluator was of the opinion that sufficient information was available based on existing literature which indicate that inhaled CMS is effective in treating pulmonary infections with *PA* which occur on the background of cystic fibrosis.

The studies provided reasonable evidence of efficacy of the proposed use in both roles as treatment in early infection or suppression in chronic infection by *PA* in CF patients.

Although the studies included some double-blind controlled trials, many of these were crossover trials. The appropriateness of crossover design in clinical studies of CF patients involving treatment with an antibiotic is not established due to persisting effects of the drug and changes in the clinical status of the patient overtime. Presumably this was considered a reasonable design as it is efficient with respect to number of patients required especially in a rare disease.

On the other hand, the most limiting aspect of controlled studies with parallel groups in the data presented was the fewer number of participants in addition to paucity of details available in published papers especially the older studies. Among the controlled studies Hodson et al (2002) was notable because of comparison with inhaled tobramycin and indicated somewhat better efficacy (suppression of *PA* in sputum culture) and tolerance (fall in FEV_1).[57] The sponsor subsequently commented that the mean improvement in FEV_1 reported in the tobramycin group compared to CMS may have been influenced by the 1 million IU dose of CMS studied and confounded by extensive previous exposure to CMS in the 6 months prior to the study for CMS patients (81%) whereas only 6% of patients had received tobramycin within the previous 6 months.

Because of these limitations of the controlled data and the nature of disease, the published literature included datasets using observational designs particularly retrospective reviews. These datasets such as those based on Danish CF Centre data, form important supporting evidence of use of inhaled CMS.

Overall, inhaled CMS therapy was favourably associated with delaying the time to development of chronic colonisation, suppression of *PA* growth in sputum samples, and clinical scores. Treatment failure with CMS/ciprofloxacin combination at the time of first diagnosis of *PA* infection was identified as a risk factor for developing chronic infection with odds ratio of 5.8 (95% CI: 1.34 to 25.14).

Better care of CF patients over last few decades, including vigorous early treatment using inhaled and parenteral antibiotics, has been associated with improved overall survival in patients with CF. The current life expectancy is stated to be 37 years.

The data presented in the submission, in combination with many years of clinical experience, support clinical benefit of inhaled CMS therapy both in early intervention and use in chronic colonisation of *PA* in patients with CF.

Safety

Overview

The parenteral administration of CMS has a well known association with nephrotoxicity and neurotoxicity. These effects are well established although subsequent reviews (**Ledson et al 1998; Conway et al 2000, Falagas and Kasiakou 2006**) suggest that toxicity may be less

than previously reported.[64,65,66] Avoidance of concurrent nephrotoxic or neurotoxic drugs, careful dosing and patient selection, and better management of fluid and electrolyte disturbances have been suggested as some of the factors which may explain the discrepancy between the old and recent literature regarding toxicity of parenteral CMS.

However, the systemic exposure following inhalation is very low. Hence, systemic toxicity relating to target organs such as kidney, nervous system and muscles is also expected to be low.

For inhaled CMS, chest tightness/bronchoconstriction is the most commonly reported adverse effect. It may or may not be associated with fall in FEV_1.

Adverse Effects

Administration by inhalation

Maddison et al (1994) reported a study in 46 CF patients (mean age 21 years; range 15-35) with chronic *PA* infection who were challenged with nebulised CMS (2 million IU).[67]

A total of 35 out of 46 patients reportedly developed bronchoconstriction. The maximum effect was seen immediately after administration in 30 patients.

There was a statistically significant ($p = 0.01$) correlation ($r = 0.42$) between severity of airways disease (percent predicted FEV_1) and the maximum percent change in FEV_1 to CMS challenge. The mean predicted FEV_1 in patients tolerant of CMS (56.8%) was significantly ($p = 0.02$) greater than the mean predicted FEV_1 in intolerant patients (41.4%).

Alothman et al (2005) concluded that history of asthma and/or atopy may indicate a greater propensity for bronchial reactivity to CMS.[68] This was based on a placebo-controlled crossover trial in CF patients using challenge test with 75 mg nebulised CMS compared with placebo solution of same osmolarity. The patients were classified high risk (history of wheezing, family history of asthma and/or atopy, or bronchial lability) or low risk (without these features) for sensitivity to inhalation of CMS.

The mean FEV_1 of the high risk group (n = 12) fell 12.9% after challenge in the placebo group compared with 17.10% after CMS challenge. In low risk group (n = 8), the mean FEV_1 fell 9.4% following placebo compared to 13.8% after CMS challenge. There were more patients in the high risk group who experienced a mean fall in FEV_1 of > 15% compared to the low risk group ($p < 0.01$) after inhalation of CMS. The difference between placebo and CMS in the low risk group was not significant.

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[64] Ledson MJ, Gallagher MJ, Cowperthwaite C, Convery RP, Walshaw MJ. Four years' experience on intravenous colomycin in an adult cystic fibrosis unit. Eur Respir J 1998; 12: 592-4.

[65] Conway SP, Etherington C, Munday J, Goldman MH, Strong JJ, Wootton M. Safety and tolerability of bolus intravenous colistin in acute respiratory exacerbations in adults with cystic fibrosis. Ann Pharmacother 2000; 34: 1238-42.

[66] Falagas ME and Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. Critical Care 2006; 10: R27.

[67] Maddison J, Dodd D, Webb AK. Nebulised colistin causes chest tightness in adults with cystic fibrosis. Respir Med 1994; 88: 145-7.

[68] Alothman GA, Ho B, Alsaadi MM, Ho SL, O'Drowsky L, Louca E, Coates AL. Bronchial constriction and inhaled colistin in cystic fibrosis. Chest 2005; 127: 522-9.

Cunningham et al (2001) reported effects of inhaled CMS in 58 children with CF (mean age 12 years; range 5-17 years).[69] Of these 55 were regular users and 3 were naive to CMS. Inhaled CMS was associated with a significant fall in mean FEV_1 at zero (-5.9%) and 15 minutes (-3.3%) post-nebulisation.

Twenty children experienced more than a 10% reduction in FEV_1. This group had a mean decrease in FEV_1 of 17.8% with a maximum fall of 37.5%. The time to maximum fall in FEV_1 was 0 minutes in 13 children, 15 minutes in five, and 30 minutes in two children.

A reduction in oxygen saturation at zero (mean 0.6%) and 15 minutes (mean 0.4%) was also reported. Sixteen children had oxygen desaturation of at least 2% following nebulised CMS with a maximum reduction of 4%.

No significant correlations were reported between baseline FEV_1, age, or serum immunoglobulin E (IgE).

Loukou et al (2001) was an abstract of a study of comparative effects of 3 antibiotics (CMS, gentamycin and tobramycin) on bronchial reactivity in 60 children with CF (mean age 8.7 years; range 1-20 years).[70] The challenge test was considered positive if FEV_1 fell by > 10% and/or the oxygen saturation fell by $\geq$ 3% within 30 minutes of the inhalation.

The patients were divided into 2 subgroups in age groups 1-5 years (n = 25) and 6-20 years (n=35).

The challenge test was conducted 79 times and was positive in 12 cases. Bronchial reactivity was seen in 4/39 (10%), 8/25 (32%) and 0/15 (0%) patients challenged with CMS, gentamycin and tobramycin respectively.

A total of 24/60 patients had initial colonisation with *PA*. All of them received CMS and bronchial reactivity was reported in one patient. In 36 patients with chronic *PA* colonisation, bronchial reactivity was reported in 11 patients.

Dodd et al (1997) examined the relationship between chest tightness and lung function tests in response to inhalation of a range of tonicities of nebulised CMS solution.[71]

Twenty-seven adult patients with inhaled a nebulised solution of hypertonic, isotonic, and hypotonic CMS over 3 consecutive days in random and double-blind manner.

All solutions resulted in a similar fall in FEV_1 and an increase in chest tightness. However, the mean time to the maximum fall in predicted FEV_1 was significantly different between the solutions (hypertonic 7.8 ± 2.1 minutes; isotonic 19.2 ± 5.5 minutes; hypotonic 34.2 ± 5.9 minutes) with a mean difference between hypotonic and hypertonic solutions of 28.04 minutes (95% CI 14.6 to 41.5), between isotonic and hypertonic solutions of 12.0 minutes (95% CI -0.1 to 24.1), and between hypotonic and isotonic solutions of 15.6 minutes (95% CI 1.8 to 29.4).

A significant positive correlation was reported for the maximum fall in FEV_1 between hypertonic and isotonic solutions (r = 0.62, p < 0.001) and between hypotonic and isotonic solutions (r = 0.64, p < 0.001). Most patients preferred isotonic or hypotonic solution.

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[69] Cunningham S, Prasad A, Collyer L, Carr S, Balfour Lynn I, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. Arch Dis Child 2001; 84: 432-3.

[70] Loukou I, Adam G, Doudounakis S. Bronchial reactivity to inhaled antibiotics in children with cystic fibrosis. 24th European Cystic Fibrosis Conference 2001Abs P234.

[71] Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis. Thorax 1997; 52: 656-8.

The authors concluded that isotonic solution was representative of all solutions with respect to the effect on FEV_1. The fall in FEV_1 to the hypotonic solution occurred over a longer period and may be better tolerated by some patients.

Götz et al (2001) recommends administration of isotonic CMS for inhalation based on experience in seven CF patients and four non-CF controls who were challenged with hypotonic, isotonic or hypertonic solutions of 1 million IU.[72] Both hypo (-6.2%) and hypertonic (-6.8%) solutions resulted in a fall in FEV_1.

No direct data exist but indirect comparison between studies are reported to suggest that pre-treatment with inhaled beta-agonists about 10 minutes prior to CMS nebulisation may reduce bronchospasm by a magnitude of 10% **(Adeboyeku et al 2001)** to the decrease in incidence may be from 34% **(Cunningham et al 2001)**.[73,69]

Roberts et al (1992) studied the stability of the compounds after mixing salbutamol and CMS and report that CMS interacted with the benzalkonium chloride preservative in salbutamol (7% decrease after 1 hour and 14% after 24 hours at 24°C) but would not reduce the efficacy of either drug if the solution was used within one hour of mixing or if preservative-free salbutamol was used.[74] However, the safety and efficacy of such a combination has not been studied.

Dominguez-Ortega et al (2007) reported a case of a 63 year old critically ill man with bronchiectasis and bronchopleural fistula who developed severe bronchospasm after using nebulised CMS.[75] A skin prick test with CMS was performed and was negative. The authors then described a successful procedure for desensitisation and induction of tolerance.

Hakeam and Almohaizeie (2006) reported a case of hypotension associated with aerosolised CMS in a critically ill patient but not with systemically administered CMS.[76]

The sponsor also reported that during the first round of mutual recognition in Europe, a Member State requested further information about the incidence of bronchial reactivity in CF patients on chronic CMS therapy.

A retrospective audit of data from Wythenshawe Hospital was undertaken. Adult patients with CF attending Wythenshawe Hospital had at least 3 data points when FEV_1 had been measured. The records covered several years of use with a median duration of 6 years. Data for 78 patients were reviewed and 71 included in the analysis.

The review indicated no evidence of increasing bronchoconstriction in association with chronic/long-term use of CMS. The incidence of bronchoconstriction after 1 year was lower

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[72] Götz M, Schimmelpfennig A, Koller DY. Aerosolised colistin in patients with cystic fibrosis (CF): Effects on pulmonary function and markers of inflammation. Abstract of the Cystic Fibrosis Conference, Orlando, Florida 2001; 265: Abs 230.

[73] Adeboyeku DU, Agent P, Jackson V, Hodson M. A double blind randomised study to compare the safety and tolerance of differing concentrations of nebulised colistin administered using Halolite in cystic fibrosis (CF) patients. 15th Annual Cystic Fibrosis Conference, Orlando Florida, 2001, Poster session abstract No 339.

[74] Roberts GW, Badcock NR, Jarvinen AO. Cystic fibrosis inhalation therapy: Stability of a combined salbutamol/colistin solution. Austr J Hosp Pharm 1992; 22: 378-80.

[75] Domínguez-Ortega J, Manteiga E, Abad-Schilling C, Juretzcke MA, Sánchez-Rubio J, Kindelan C. Induced tolerance to nebulized colistin after severe reaction to the drug. J Investig Allergol Clin Immunol 2007; 17: 59-61.

[76] Hakeam HA, Almohaizeie AM. Hypotension following treatment with aerosolized colistin in a patient with multidrugresistant Pseudomonas aeruginosa. Ann Pharmacother 2006; 40: 1677-80.

than the incidence in patients on initial use who went on to receiving CMS for a median of 6 years. The audit reported an incidence of 14.1% (95% CI 7.8 to 24.0) at the first time point and an incidence of 5.6% (95% CI 2.2 to 13.6) at the later time point.

Hodson et al (2002) reported a useful summary of adverse effects of inhaled CMS in comparison with inhaled tobramycin in this study as follows:[57]

	TOBI	Colistin
Patients n	53	62
Patients with ≥1 treatment-emergent AE[a]	34 (64.2)	31 (50.0)
Respiratory system AE		
Total[#]	26 (49.1)	22 (35.5)
Cough-increased[#]	5 (9.4)	11 (17.7)
Sputum-increased[#]	6 (11.3)	8 (12.9)
Dyspnoea[a]	5 (9.4)	7 (11.3)
Pharyngitis[#]	7 (13.2)	3 (4.8)
Patients with ≥1 serious AE[#]	8 (15.1)	7 (11.3)

The comparison shows that 50% of CMS patients reported a treatment-emergent adverse effect (AE) compared with 64% in tobramycin patients. Overall, respiratory system AEs were reported by 35% of CMS patients and 49% of tobramycin patients. The incidence of dyspnoea was reported by 9-11% of patients in both groups.

Michalopoulos et al (2008) was a report of 60 critically ill adult patients (mean age 59 years) who received aerosolised CMS as adjunctive treatment in the management of ventilator-associated pneumonia due to multi-drug resistant Gram-negative pathogens including *PA*.[77] The authors reported that among 57 patients who received a combination of antibiotics and had a normal renal function prior to admission, 9 developed acute renal failure. However, the paper stated that majority of these were associated with multiple organ failure. The all-cause hospital mortality was 15/60 (25%).

Michalopoulos et al (2005) was a retrospective report in 8 out 152 patients of use of aerosolised CMS as adjunct to IV antimicrobial therapy for treatment of Gram-negative nosocomial pneumonia.[78] The daily dose of aerosolized colistin ranged from 1.5 to 6 million IU (divided into three or four doses), and the mean duration of administration was 10.5 days.

Two patients with history of chronic obstructive pulmonary disease (COPD) required concurrent treatment with an inhaled beta$_2$ agonist. One patient with a history of polycystic kidney disease and chronic renal failure, who died from septic shock and multiple organ failure showed worsening renal function during aerosolised colistin treatment. No deterioration in renal function was observed in the other seven patients during colistin treatment. No deterioration in serum creatinine was reported in one patient who was on haemodialysis at baseline.

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[77] Michalopoulos A, Fotakis D, Virtzili S, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. Respir Med 2008; 102: 407-12.

[78] Michalopoulos A, Kasiakou SK, Mastora Z, Rellos K, Kapaskelis AM, Falagas ME. Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis. Critical Care 2005; 9: R53-R59.

Falagas & Kasiakou (2006) discussed overdose and report that majority of cases with polymyxin overdose result in acute renal failure and various manifestations of neurotoxicity, including neuromuscular blockade and apnoea.**Error! Bookmark not defined.**

Drug Interactions

Based on the pharmacological properties of CMS, interactions are expected on co-administration of CMS with neurotoxic drugs, nephrotoxic drugs, muscle relaxants used in general anaesthesia and beta blockers.

FDA Alert

The US Food & Drug Administration issued an Alert in 2007 following the death of a CF patient after nebulisation with CMS.

The advice contained details of the incident. This patient obtained a premixed CMS solution from a pharmacy for nebulisation at home. Within hours of use, the patient developed respiratory distress. Consequently, the patient was admitted to ICU with acute respiratory distress syndrome and died of multi-organ system failure 19 days later.

The advice informed that premixing of CMS into an aqueous solution and storage for more than 24 hours was considered to have resulted in high (toxic) concentration of polymyxin E1 in the solution which increased the potential for lung toxicity.

The advice recommended that CMS solution should be used immediately after reconstitution and any unused portion remaining in the nebuliser must be discarded.

Post Marketing Safety Data

PSURs generated since first approval of inhaled CMS (Promixin) in Europe, current to 19 June 2010, were provided for evaluation. The reports cover both nebulised and IV use.

The serious ADRs were as follows:

MedDRA System Organ Class	Number of Primary Events			
	Medically Confirmed Spontaneous Sources*	Literature Sources	Profile Sponsored Studies	Total
Eye disorders	1	0	0	1
General disorders and administration site conditions	1	0	0	1
Immune system disorders	1	0	0	1
Renal and urinary disorders	1	0	0	1
Respiratory, thoracic and mediastinal disorders	2	3	0	5
Total	6	3	0	9

* Includes Regulatory authority reports

The serious renal injury reported in this period was the first instance of acute renal failure reported in association with nebulised CMS. The investigation showed it to be acute tubular necrosis. This was in a 63 year old female patient with long-standing (42 years) diabetes, who had been taking inhaled CM for 2-3 months for the treatment of bronchiectasis. The patient was also taking a number of concomitant medications.

The non-serious ADRs were as follows:

System Organ Class	Number of primary events	
	Medically Confirmed Spontaneous Sources	Literature Sources
Cardiac disorders	1	0
Gastrointestinal disorders	1	0
Immune system disorders	1	0
Injury, poisoning and procedural complications	5	0
Nervous system disorders	4	0
Total	12	0

The confirmed non-serious expected ADRs with nebulised CMS (Promixin) in the present reporting period were as follows and are representative of the current adverse drug reactions profile of the nebulised CMS:

System Organ Class	Preferred term	Total
Gastrointestinal disorders	Oral pain	1
		1
Immune system disorders	Hypersensitivity	1
		1
Infections and infestations	Oral candidiasis	1
	Oral fungal infection	1
		2
Respiratory, thoracic and mediastinal disorders	Cough	2
	Dyspnoea	1
	Oropharyngeal pain	2
		5
Skin and subcutaneous tissue disorders	Rash pruritic	1
		1
Grand Total		10

The confirmed serious (all) and non-serious (unexpected) ADRs with nebulised CMS (Promixin) in the reporting period were as follows:

System Organ Class	Preferred term	Total
Cardiac disorders	Palpitations	1
		1
Eye disorders	Eye haemorrhage	1
		1
Gastrointestinal disorders	Abdominal pain upper	1
	Dry mouth	1
	Gingivitis	1
	Lip dry	1
	Nausea	2
	Vomiting	1
		7
General disorders and administration site conditions	Chest discomfort	1
	Chest pain	1
	No adverse event	5
	Oedema peripheral	1
		8
Immune system disorders	Anaphylactic reaction	1
	Hypersensitivity	2
		3
Injury, poisoning and procedural complications	Accidental overdose	1
	Drug administration error	1
	Drug exposure during pregnancy	1
	Medication error	1
	Wrong technique in drug usage process	2
		6
Metabolism and nutrition disorders	Decreased appetite	1
		1
Musculoskeletal and connective tissue disorders	Muscular weakness	1
	Myalgia	1
	Pain in extremeties	3
		5
Nervous system disorders	Aphonia	1
	Burning sensation	1
	Dizziness	1
	Dysgeusia	1
	Paraesthesia	1
		5
Renal and urinary disorders	Renal failure acute	1
		1
Respiratory, thoracic and mediastinal disorders	Bronchospasm	4
	Dyspnoea	2
	Epistaxis	1
	Nasal Septum Perforation	1
	Oropharyngeal pain	1
	Rhinorrhoea	1
		10
Skin and subcutaneous tissue disorders	Pain of skin	1
		1
Grand Total		49

*or colistin sulphomethate where Promixin cannot be excluded

Late-breaking news in the current PSUR also mentioned a report of bronchospasm in a 60 year old man who was nebulised with CMS solution on the weekend which had been reconstituted on Friday. The patient was already on long-term bronchodilator and is reported to have recovered.

Resistance development

In addition to the details discussed in *Pharmacodynamics* above, the sponsor has included an assessment of risk of development of resistance, as required by the TGA business rules.

Some of the additional information included in sponsor's risk assessment is reproduced below. More information may be found in the pre-clinical assessment.

The increasing occurrence of metallo-beta-lactamases (MBLs), in strains of *PA, Acinetobacter baumannii, Klebsiella pneumoniae* and *enterobacteriaceae* has been described. Such strains demonstrate resistance against the majority of available antibiotics. MBL-producing bacteria that exhibit colistin-only susceptibility pattern are being increasingly detected worldwide. In practice this phenotype translates to pan-resistance. *In vitro* studies reveal that tigecycline and colistin are the only agents with consistent activity against multi-drug resistant or pan-resistant MBL-producing strains.

The first isolation of two colistin-resistant emerging pathogens, *Brevundimonas diminuta* and *Ochrobactrum anthropi* in a woman with CF have been described. It was noted that the frequency of infection with these species is relatively low and their significance is unclear.

However, these bacteria do present a challenge to diagnostic laboratories as they are difficult to identify and can be misidentified as belonging to the *Burkholderia cepacia* complex. The patient had received a course of colistin to treat *Alcaligenes xylosoxidans* colonisation 10 months before the onset of this pneumonia. This may have contributed to the selection of these two colistin resistant bacteria in this patient. The paper commented that the use of antibiotics to treat *PA* may enable selection and emergence of new pathogens inherently resistant to anti-pseudomonal antibiotics.

Colistin hetero-resistance has been reported among *Acinetobacter* isolates, including a report of hetero-resistance in isolates from Australia. Its association with prior CMS therapy had not been described. A population analysis profile identified resistant *Acinetobacter* subpopulations in colistin-susceptible clinical isolates. The proportion of cells exhibiting hetero-resistance was significantly higher among isolates recovered from patients treated with colistin. The sample of 19 multi-drug resistant isolates of *Acinetobacter* baumannii-calcoaceticus complex used in this study included 7 samples from patients previously exposed to colistin. The resistant subpopulations isolated during the population analysis profile demonstrated stable colistin MICs exceeding 16 µg/mL, which is above the peak serum levels achievable at standard doses and well above the current definition of colistin resistance in *Acinetobacter*. It is possible that the hetero-resistant proportion of the bacterial population might be selected and become predominant during colistin therapy leading to treatment failure. However, the clinical relevance of colistin hetero-resistance is unknown at this time.

The first isolation of a genetically identical clone of *PA* from 5 CF clinics along the Eastern seaboard of Australia separated by a distance of 1800 km has been described. Previously it had been thought that CF patients were generally infected for prolonged periods by unique lineages of environmentally acquired *PA*. This was the first report of the same strain of *PA* identified in patients from 5 CF clinics in 3 geographically dispersed regions. Further investigations suggested that *PA* cross-infection may be more common than previously believed. The authors recommended more widespread use of molecular surveillance for *PA*.

Clinical Resistance – further comments

Cross-resistance occurs with other polymyxins. However, no other antibiotic in this class are registered for systemic or inhaled use in Australia.

The resistance to polymyxins is not expected to cross with other antibiotic groups. No data have been identified on transfer of resistance genes between bacterial species.

PA is a ubiquitous organism and is generally not pathogenic in healthy individuals. The sponsor considered the potential for the spread of resistant *PA* in non-CF community to be minimal.

The impact of respiratory disease caused resistant *PA* in patients with CF is considered by the sponsor to be high. In practice, CMS is indicated in such patient population because of the low resistance know to this agent.

Colistin was rated as High by the sponsor on EAGAR rating - essential antibiotics for treatment of human infections where there are few or no alternatives for many infections

Evaluator's comment and conclusions on clinical safety

The expected adverse effects associated with nebulised CMS administration include hypersensitivity, oral/throat pain, oral candidiasis or other oral fungal infections, rash and cough/dyspnoea/chest tightness/bronchospasm. The bronchial reactivity may or may not be associated with fall in FEV_1. Routine prior treatment with bronchodilator therapy is advised

for preventing such reaction. This may be critical in patients on beta blocking agents, although this is not likely in the patient population proposed for treatment

Parenteral CMS has been associated with nephrotoxicity and neurotoxicity. The systemic exposure following inhaled administration is only a fraction of levels after intravenous use. Hence, these effects are expected to be of lesser concern with inhaled therapy.

The reported incidence of development of resistance appears to be low with CMS. This is likely related to its mechanism of action.

Overall, the safety profile of nebulised CMS appears reasonable.

Clinical Summary and Conclusions

Risk Benefit Assessment

Chronic pulmonary infection with *PA* is the most common cause of morbidity and mortality in patients with CF. Its presence in respiratory cultures is a predictor of patient survival in this condition. *PA* is a ubiquitous organism in the environment and is capable of assuming a protective mucoid phenotype after establishing in lungs in patients with CF.

The published evidence suggests that inhaled CMS has a role in delaying the onset of chronic colonisation by *PA* in patients with CF and is also able to suppress bacterial burden in chronically infected patients with favourable reported long-term clinical outcomes such as morbidity and mortality based on epidemiological studies. The incidence of development of resistance is reported to be low.

Inhaled administration is most noticeably associated with risk of bronchial reactivity which may manifest itself as chest tightness, dyspnoea, cough, wheezing or intolerance to therapy. In Hodson et al (2002), the respiratory system AEs were reported with an incidence of 35.5% with inhaled CMS. The incidence of dyspnoea in this study was 11%.[57] Prior bronchodilator therapy is therefore recommended to control this risk.

Hypersensitivity to CMS is also well known.

The risks such as nephrotoxicity and neurotoxicity associated with parenteral use are mitigated to a large extent in the case on inhaled administration due to low systemic exposure. Nevertheless, a number of precautions such as coadministration with other medications need to be articulated as prescribing information to further enhance the safety of the proposed use.

A particular risk is pulmonary toxicity associated with reconstituted solution upon ageing. Immediate use after reconstitution is therefore the preferred clinical practice.

Conclusion

Overall, the evaluator considered that the risk-benefit of inhaled CMS therapy for the proposed indication and in the proposed population was favourable with appropriate risk management advice in the prescribing information.

The exclusion of children less than 2 years of age and the proposed dose range of 1-2 million IU two to three times daily were supported based by the data.

It should be noted that the clinical submission does not fully comply with the guidelines in Europe for development of drugs in cystic fibrosis which were finalised on 22 October 2009 (after the submission of this application) and subsequently adopted by the TGA on 17 December 2010 that occurred after the conclusion of this evaluation.[79] However, in view of

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[79] EMEA, Committee for Medicinal products for Human Use (CHMP), 22 October 2009. Guideline on the

the long-standing history of use of this drug in clinical practice a reliance on published data is considered acceptable, although it would have been useful to obtain minimal data to delineate the kinetics of drug deposition in lungs.

Recommendation

The evaluator recommended that this submission be approved based on the provided data. The recommended therapeutic indication and dosing instructions are as follows:

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.

Children > 2 years 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.

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.

V.   *Pharmacovigilance Findings*

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The sponsor identified the following important identified risks and important potential risks and the pharmacovigilance actions proposed for Tadim.

Clinical Development of Medicinal Products for the Treatment of Cystic Fibrosis, CHMP/EWP/9147/2008. http://www.tga.gov.au/docs/pdf/euguide/chmp/914708enfin.pdf

Safety Concern	Implemented Action(s)
Important identified risks (observed following inhalation)	
• Induction of coughing or bronchospasm; bronchial hyperreactivity	- Routine pharmacovigilance practices - Labelling
• Sore throat or sore mouth due to hypersensitivity or superinfection with *Candida* species.	- Routine pharmacovigilance practices - Labelling
Important potential risks (observed following parenteral administration)	
• Nephrotoxicity	- Routine pharmacovigilance practices - Labelling
• Neurotoxicity	- Routine pharmacovigilance practices - Labelling
• Use in renal impairment	- Routine pharmacovigilance practices - Labelling
• Co-administration with non-depolarising muscle relaxants such as curare and vecuronium	- Routine pharmacovigilance practices - Labelling
• Co-administration of colistimethate sodium with other antibiotics that are either neurotoxic or nephrotoxic, such as aminoglycosides, or cephalothin sodium	- Routine pharmacovigilance practices - Labelling

The OMSM reviewer noted that the sponsor proposed to use routine pharmacovigilance and risk minimisation activities to address identified and potential safety concerns. [80,81] The described pharmacovigilance activities in the Risk Management Plan are those undertaken by Profile Pharma Limited. It should be confirmed with Phebra that the Australian pharmacovigilance activities proposed in relation to Tadim are identical and these activities should be provided in an updated Risk Management Plan. It was suggested that the proposed Risk Management Plan be revised to:

- include the detailed pharmacovigilance system
- address any nonclinical safety concerns raised by the TGA that have not been adequately addressed by clinical data or which are of unknown significance
- detail any clinical trial exposure to nebulised colistimethate sodium
- provide justification for not proposing as contraindications use of Tadim in the elderly, patients with renal impairment and pregnant or lactating women
- address potential off-label use in children aged under 2 years

It was suggested that the sponsor be requested to provide the most up-to-date Periodic Safety Update Report (PSUR) for review as part of the evaluation of this submission. This was subsequently actioned.

In addition, it was suggested that information on off-label use and any available information on *Pseudomonas aeruginosa* resistance to colistimethate sodium/colistin in cystic fibrosis patients be included in the PSURs.

The OMSM reviewer also made a number of recommendations with regard to the proposed Australian PI for Tadim but these are beyond the scope of this AusPAR.

VI.   Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Colistin is a mixture of cyclic decapeptides, or polymyxins, produced by fermentation and composed primary of colistin A (polymyxin E_1) and colistin B (polymyxin E_2).

There were no objections to registration in respect of chemistry, manufacture and quality control. A sterilisation filter validation report was recommended as a condition of registration. The PI includes instructions for dosing with an "I-neb AAD" system in addition to a conventional nebuliser. No quality data were submitted to support equivalence of doses from a conventional nebuliser and an "I-neb AAD" system when used in accordance with instructions in the PI. The sponsor noted that relevant information was included and reviewed in the clinical part of the submission.

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[80] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[81] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Nonclinical

Nonclinical data were submitted as a literature based submission.

Nonclinical data established *in vitro* susceptibility of the target organism *P. aeruginosa* to colistimethate sodium or its metabolite, colistin. There were no *in vivo* animal efficacy studies by the inhalational route.

No toxicity studies were submitted of colistimethate sodium administered by inhalation. One published nonclinical paper, a conference poster, reported inhalational treatment with polymyxin E1 (colistin A) potentially results in respiratory inflammation in rats and dogs after 28 days treatment. Local drug exposures could not be reliably estimated.

Limited nonclinical data indicate potential for renal and neuromuscular toxicity at high systemic exposures. No safety pharmacology studies were submitted. Genotoxicity studies were not comprehensive and no carcinogenicity studies were submitted, although the product is proposed for long-term use. No studies from juvenile studies were submitted to support paediatric use.

The absence of carcinogenesis studies and other deficiencies in the nonclinical package preclude a recommendation for registration on nonclinical grounds. Therefore any decision to register the product will need to be made on clinical grounds.

Clinical

Clinical data were submitted as a literature based submission, and with one sponsor commissioned pharmacokinetic study. The TGA Library approved the 2008 literature search strategy.

Colistimethate sodium (CMS) is a prodrug hydrolysed to active colistin A (polymyxin E_1) and colistin B (polymyxin E_2), which bind with cytoplasmic membranes of Gram-negative bacteria and interfere with the osmotic function of the bacterial cell wall.

Pharmacology

There is considerable variability in reported pharmacokinetic (PK) parameters. The sponsor commissioned PK study provides the most relevant PK data. Study PPCTP/002 had the objective of determining the relative bioavailability of inhaled CMS compared to CMS administered intravenously based on plasma concentration of polymyxin E1. The study compared five treatments in a single dose crossover design. These treatments were inhaled CMS administered by an "I-neb AAD" at a dose of 0.3 million IU (24 mg) or 0.5 million IU (40 mg), CMS administered by conventional nebuliser at a 160 mg dose, CMS administered intravenously at a dose of 30,000 IU (2.4 mg) and at a dose of 0.5 million IU (40 mg). A total of 20 healthy volunteers were involved in the study. The polymyxin E1 plasma concentration C_{max} following nebulised CMS was approximately 5-6% of the C_{max} following a 0.5 million IU IV dose. The polymyxin E1 plasma concentration AUC_∞ following nebulised CMS was approximately 20% of AUC_∞ following a 0.5 million IU IV dose. The elimination $t_{1/2}$ was approximately 5 hours after inhalation compared to 3-3.5 hours after IV doses.

Based on polymyxin E1 systemic exposures, 2 million IU administered by conventional jet nebuliser showed pharmacokinetic equivalence to 0.5 million IU administered by "I-neb AAD", and it can be inferred that 1 million IU administered by jet nebulizer will result in similar systemic exposure to 0.3 million IU administered by "I-neb AAD".

The submission did not provide any data on distribution of drug in the lungs. Literature supported negligible absorption of CMS from the gastrointestinal tract after inhalation.

CMS has bactericidal properties against a wide range of gram-negative organisms, including *P. aeruginosa*.

The development of resistance appears to be low, probably due to mechanism of action. Cross-resistance is not expected with other classes of antibacterials. Antibacterial properties are not altered by aerosolisation.

Clinical

Despite the history of CMS administered by inhalation for more than 20 years, there are few randomised, controlled, double blind studies.

Studies of inhaled CMS attempting to intervene early in PA infection in patients with CF include one randomised study (Valerius, 1991) conducted at the Danish Cystic Fibrosis Centre and two retrospective reviews (Frederiksen, 1997; Hansen 2008) of patients at the Danish Cystic Fibrosis Centre.[50,51,44]

Valerius et al (1991) reported a randomised clinical study involving cystic fibrosis patients with positive PA culture on routine monthly sputum culture.[50] Groups were allocated to receive inhaled CMS (1 million IU twice daily) and oral ciprofloxacin (250-750 mg twice daily) or no anti-pseudomonal therapy. Treatments were repeated every time PA was isolated from routine sputum cultures. Fourteen patients were enrolled to active treatment and 12 to no treatment. Over the 27 months of the study 7/12 (58%) untreated patients became chronically colonised compared with 2/14 (14%) treated patients. The mean follow-up time for those who did not become chronically colonised was 17.4 months. The differences between groups were statistically significant.

Frederiksen et al (1997) reported inhaled CMS and oral ciprofloxacin regimens compared to historical control patients with positive PA culture on routine monthly sputum culture.[51] The treatment group was 48 patients followed for a mean of 30 months. Rates of chronic infection were reduced in the treatment group, with improvements in pulmonary function tests and days of hospitalisation compared to historical controls. Hansen et al (2008) is a more recent publication from the same group.[44] A total of 146 patients developed intermittent PA colonisation between 1989 and 2003. Of the 99 patients with first isolate of PA in the period, 12 patients developed chronic infection after a median of 3.7 years. Up to 80% of patients were protected against chronic infection.

Studies in chronic infection or colonisation included Jensen et al (1987), a randomised, double-blind study in CF patients with chronic bronchopulmonary PA infection.[54] Following 2 weeks of parenteral anti-pseudomonal treatment patients were randomised to inhaled CMS 1 million IU or isotonic saline twice daily for a period of 3 months. In the active treatment group 18/20 completed the study compared to 11/20 in control group. In the control group four withdrew due to treatment failure and four did not continue because of no benefit. Clinical symptoms scores were better in the CMS group than control group at end of therapy and the fall in FVC and FEV_1 was of lesser magnitude than control group. Microbiological testing did not show PA eradication from sputum in any patient. However, the MIC of colistin against PA did not change and no patient resistance to colistin was reported. No infection with other colistin resistant bacteria was seen.

Hodson et al (2002) was a report of an open-label, randomised study in 115 CF patients with chronic PA pulmonary colonisation.[57] Patients were randomised to receive tobramycin nebuliser solution (3000 mg) or CMS 1 million IU twice daily for 4 weeks. At the end of 4 weeks the mean change in predicted FEV_1 was statistically significant higher in the tobramycin group (6.7%) compared to CMS (0.37%). Both treatments decreased sputum PA

density. The sponsor noted that a large number of patients in the CMS group had received pre-treatment while there was a low number in the tobramycin group.

Adeboyeku et al (2006) was an open-label extension of 21 patients recruited for Hodsen et al, in which patients continued the same treatment for 5 additional months, then after a 2 week washout period crossed over to the other treatment for 5 months.[56] An advantage for tobramycin over CMS was reported for FEV_1 over time. Using an ANOVA model, the decrease in CMS slope was -0.88% per month compared to tobramycin slope decrease of -0.35%. Two patients discontinued for tobramycin resistant PA.

Safety

A number of published studies examined chest tightness/bronchoconstriction, and associated change in FEV_1.

Maddison et al (1994) reported that in CF patients with chronic PA infection (mean age 21 years) challenged with nebulised CMS 2 million IU, a total of 35 of 46 developed bronchoconstriction.[67] In 30 patents the maximum bronchoconstriction was seen immediately after administration.

Cunningham et al (2001) reported effects of inhaled CMS in 58 children with CF (mean age 12 years).[69] Of these 55 were regular users of CMS. Inhaled CMS was associated with a significant fall in mean FEV_1 at zero (-5.9%) and 15 minutes (-3.3%). Twenty children reported more than 10% reduction in FEV_1.Maximum decrease in FEV_1 was -37.5%. Sixteen children had oxygen desaturation $\geq 2\%$ with maximum reduction of 4%.

Loukou et al (2001) was an abstract that of a study of comparative effects of 3 antibiotics on bronchial hyperreactivity in 60 children with CF (mean age 6.7 years).[70] The challenge was considered positive if FEV_1 decreased by >10% and/or oxygen saturation fell by $\geq 3\%$ within 30 minutes of inhalation. A positive challenge test was reported in 4/39 (10%), 8/25 (32%) and 0/15 (0%) who received CMS, gentamicin and tobramycin, respectively.

Alothman (2005) concluded that history of asthma and/or atopy may indicate a greater propensity for bronchial reactivity to CMS, based on a challenge with 75 mg nebulised CMS.[68] Dodd (1997) and Götz (2001) assessed nebulised solutions of CMS which were isotonic, hypertonic or hypotonic.[71,72] Isotonic solution was representative of all solutions for fall in FEV_1.

Westerman et al (2004) compared nebulised CMS and nebulised colistin sulphate in 9 CF patients with chronic PA infection.[55] At 30 minutes after administration FEV_1 and FVC mean change in the CMS group was -2.9% to -2.1%, respectively and in the colistin sulphate group was -10.2% and -10.5% respectively. All patients could complete CMS nebulisation whereas 7/9 did not complete colistin sulfate due to irritation.

Westerman et al (2007b) compared nebulised CMS with CMS dry powder inhaler in 10 CF patients with chronic PA infection.[59] Following nebulised CMS 2 patients showed FEV_1 reduction of 11.4% and 12.8% respectively, and FVC reduction of 15.1% and 12.7% which resolved at 30 minutes. Two patients showed reduction of FVC after dry powder inhaler by 13.9% and 16.3%.

A retrospective audit of adult CF patients from one hospital, submitted in EU mutual recognition procedures, did not report evidence of increasing bronchoconstriction with long/term use of CMS.

Hodson et al (2002) presented a comparison of adverse effects of inhaled CMS and inhaled tobramycin.[57] Fifty percent of CMS patients reported a treatment emergent AE compared

with 64% of tobramycin patients. Overall respiratory system AEs were reported by 35% of CMS patients and 49% of tobramycin patients.

Parenteral administration of CMS has well described nephrotoxicity and neurotoxicity. There are published reports of renal failure in patients who received aerosolised CMS as well as a report of hypotension, but the patients were critically ill and had confounding conditions are present.

A US FDA alert in 2007 discussed the death of a CF patient after nebulisation with CMS. The patients obtained a premixed CMS form a pharmacy. Within hours of use the patient developed acute respiratory distress, and subsequently died of multi-organ system failure. The premixing of CMS into an aqueous solution and storage for more than 24 hours was considered to have resulted in a high concentration of polymyxin E1 in the solution which increased the potential for lung toxicity. The advice recommended CMS solution should be used immediately after reconstitution and unused solution remaining in the nebuliser must be discarded.

The evaluator reviewed PSURs since the first approval of Promixin in Europe through to June 2010. Supply in Australia under S5A was identified as 240,000 vials and 4,700,000 vials worldwide in the period June 2007 to June 2010. Nine serious ADRs were reported in this period which included one report of anaphylaxis and one report of acute renal failure. There were a total of 49 serious and non-serious ADRs identified.

Conclusion of the Clinical Evaluator

The evaluator concluded that the efficacy data submitted, in combination with many years of clinical experience, support clinical benefit of inhaled CMS therapy both in early intervention and use in chronic colonisation of PA in patients with CF. Inhaled CMS is most notably associated with bronchial reactivity which may be manifest as chest tightness, cough, wheezing and intolerance of therapy. An incidence of 35.5% for respiratory system AEs was reported by Hodson (2002).[57] Hypersensitivity to CMS is also well known. Nephrotoxicity and neurotoxicity are risks associated with parenteral use but are mitigated to a large extent due to the low systemic exposure associated with inhaled CMS. The evaluator supported registration for the proposed indication

Resistance Risk Assessment

The sponsor submitted an Antimicrobial Resistance Risk Assessment. There are low rates of development of resistance to CMS in prolonged and continuous use in treating pulmonary PA infections. In Danish experience among chronically infected patients receiving nebulised CMS 0.4% of isolated PA strains have been colistin-resistant. There have, however, been documented episodes of transmission of CMS resistant *P. aeruginosa* between patients within CF units. A genetically identical clone of PA isolated from patients in 5 CF clinics in 3 dispersed locations in Australia has also been described suggesting PA cross-infection may be more common than previously believed. Cross resistance occurs with other polymyxins. There are, however, no other registered agents in this class in Australia. Cross-resistance has not been demonstrated with other classes of antibacterials. The EAGAR importance rating is high.[82]

Risk Management Plan

An evaluation of the RMP has been completed. Routine pharmacovigilance activities are to be undertaken by the sponsor.

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[82] If an antibiotic is classified as "High", it implies that if resistance develops there will be very limited or in some cases no alternatives available to treat serious bacterial infections.

Risk-Benefit Analysis

Delegate Considerations

The nonclinical evaluation concludes that nonclinical data are inadequate to support registration. Despite the inadequate nonclinical data, the Delegate considered that the long history of clinical use of colistimethate sodium by inhalation allows consideration for use in the proposed patient population.

Published experience demonstrates that anti-pseudomonas therapy, including inhaled CMS, has a role in delaying the onset of chronic colonisation by PA in patients with cystic fibrosis and is also able to decrease bacterial burden in chronically infected patients. This is associated with favourable long-term clinical outcomes in epidemiological studies. Inhaled administration is associated with bronchial hyperreactivity is some patients but this did not lead to substantial rates of withdrawal of patients in the few controlled clinical studies in the submission. Post-marketing safety data support low number of serious ADRs. The Delegate concurred with the evaluator that the benefit/risk ratio for CMS is favourable for the proposed indication and population.

The quality evaluator commented on lack of any data to support equivalence of doses with the two systems. Clinical Study PPCTP/002 compared a 2 million IU dose administered by conventional jet nebulizer and 0.3 million IU and 0.5 million IU doses administered by "I-neb AAD" System. Pharmacokinetic equivalence of 2 million IU administered by conventional and 0.5 million IU administered by AAD system was reported based on plasma concentration of polymyxin E1. No information was provided on drug distribution in the lungs or other information to support equivalent dose at the site of action. The study was a conducted in healthy volunteers and did not report any adverse event experience. The current dosage recommendation in proposed Australia PI are still regarded as confusing as 1 million IU/ 1 mL are added to both AAD 0.3 mL medication chamber AAD the 0.5 mL medication chamber, and there is no statement to discard surplus volumes after inhalation. These were subsequently revised and following review a dosing table referring to each nebuliser system is in the 'Dosage and Administration' section of the PI, as is the instruction to discard any excess after use. The study results are now presented in the PI.

The Delegate proposed to register Tadim powder for nebuliser solution for:

the treatment of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis.

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

Response from Sponsor

The sponsor has submitted a response to the clinical evaluation report that comments on the review of efficacy for Hodson et al (2002). The sponsor commented that the mean improvement in FEV_1 reported in the tobramycin group compared to CMS may have been influenced by the 1 million IU dose of CMS studied and confounded by extensive previous exposure to CMS in the 6 months prior to the study for CMS patients (81%) whereas only 6% of patients had received tobramycin within the previous 6 months.

The sponsor proposed inclusion of dosage guidance for administration with an "I-neb AAD" system.

With regard to the FDA Alert the sponsor noted that the US case report which initially raised concerns regarding the reconstitution of CMS and its subsequent storage, involved a solution which was 40 days old (reconstituted on 16th March 2007 and administered on 26th April

2007, four days short of its labelled expiry date of 30th April), and hence, was stored for considerably longer than the 24 hour period alluded to in the Delegate's comments, or indeed the 8 hours currently proposed in the Australian Product Information. The sponsor made a number of other comments in regard to the proposed PI but these are beyond the scope of this AusPAR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal and recommended approval for the following indication:.

For the treatment of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

In making this recommendation, the ACPM considered the data submitted demonstrated sufficient safety and efficacy to provide a positive overall risk benefit profile.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Tadim powder for nebuliser solution vial containing colistimethate sodium 1million IU, with the indication:

For the treatment of colonisation and infections of the lung due to susceptible Pseudomonas aeruginosa in patients with cystic fibrosis.

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

Included among the specific conditions of registration was the full implementation of the Risk Management Plan outlined in the sponsor's letter dated 18 August 2010, as agreed with the Office of Product Review.

Attachment 1.   Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

TADIM (colistimethate sodium)

Powder for Nebuliser Solution

NAME OF THE MEDICINE

(Colistimethate sodium)

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

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

Colistimethate sodium has an approximate molecular weight of approximately 1745g/mol.

Structural formula:

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                              N⁴ ──────────────┐
                               │               │
        RCO-Dbu-Thr-Dbu-Dbu-Dbu-DLeu-Leu-Dbu--- Dbu-Thr
            │       │   │               │   │
            │       │   │               │   │
          N⁴R′    N⁴R′  N⁴R′          N⁴R′ N⁴R′
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Dbu = ∟- 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: $C_{58}H_{105}N_{16}O_{28}S_5Na_5$
The CAS number: 8068-28-8.

ATC code: J01XB01

DESCRIPTION

Tadim is a sterile powder for use, after reconstitution, as a nebuliser solution. The powder is white to off-white. Each vial contains 1 million International Units (IU) which is approximately equivalent to 80 mg of colistimethate sodium.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: other antibacterials, Polymyxins.

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	*Brucella* species
Klebsiella species	*Burkholderia cepacia* and related species
Pseudomonas aeruginosa	*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.

Pharmacokinetics

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

$t_{1/2}$ (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 cystic fibrosis (CF).

Biotransformation

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.

Elimination

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, 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.

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 (Cmax) 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)	SideStream Jet nebuliser (2 million IU in 4 mL)	IV (30,000 IU[1])	IV (500,000 IU[1])
$AUC_{0-\infty}$ (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 Tmax was approximately 2 to 2.5 hours and the half life was approximately 5 hours for all nebuliser systems.

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.

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

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.

PRECAUTIONS

The dose of Tadim delivered to the lungs may vary according to the nebuliser system used for administration (see Dosage and Administration).

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.

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.

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 **Interactions with Other Medicines**).

Use with extreme caution in patients with porphyria.

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

Use in Pregnancy (Category B2)
Safety in human pregnancy has not been established. 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.

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.

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."

Use in Children Aged 2 Years and Under
The efficacy of Tadim in this age group has not been studied

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.

Carcinogenicity
No carcinogenicity studies have been conducted with colistimethate sodium.

Genotoxicity

Data on potential genotoxicity are limited.

Interactions with other Medicines

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.

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

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.

ADVERSE 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 **Precautions**).

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.

DOSAGE AND 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.

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 **Precautions**.

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.

<u>Solutions should be used immediately after reconstitution. If this is not possible, reconstituted solutions may be stored for no longer than 8 hours at 2ºC to 8ºC.</u> The potential for lung toxicity increases the longer Tadim is left in solution; therefore, the recommended maximum 8 hour time period must not be exceeded. <u>Any unused solution must be discarded immediately and not used for subsequent dosing. Tadim contains no anti microbial preservative.</u>

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 0.3mL 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	2-4mL	
Equivalent dose through an I-neb	I-neb - 0.3mL 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 - 0.5mL Mauve Medication Chamber	1	1 mL	1 mL	

The I-neb AAD system has a fill volume of only 1mL, a very low residual volume (<0.1mL) 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 showing dosing should be discarded appropriately.

Clarification statement on the expression of colistimethate units of activity

Colistimethate sodium is chemically synthesised from colistin base (also refered 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 80mg 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

OVERDOSAGE

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.

In Australia, contact the Poisons Information Centre on 13 11 26 for further advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

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

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

Tadim is to be stored below 25ºC. <u>Once reconstituted it should be used immediately. If this is not possible, reconstituted solutions may be stored for no longer than 8 hours at 2 ºC to 8 ºC. Any unused solution remaining must be discarded immediately.</u>

Phebra product code: SOL040

AUST R 165709

POISONS SCHEDULE

Schedule S4- Prescription Only Medicine.

NAME AND ADDRESS OF THE SPONSOR

Phebra Pty Ltd, 332 Burns Bay Road, Lane Cove NSW 2066, Australia.

Telephone: 1800 720 020

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Therapeutic Goods Administration