EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Polymyxin-based products

INN/active substance: colistin, colistimethate sodium

Procedure number: EMEA/H/A-31/1383;
Colobreathe EMEA/H/A-31/1383/C/1225/0007

Note
Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 16 September 2013, the European Commission initiated a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on the benefit-risk of polymyxin-based products and on the need for regulatory measures to be taken.

The procedure described in Article 32 of Directive 2001/83/EC was applicable.

2. Scientific discussion

2.1. Introduction

The emergence of multi-drug resistant Gram-negative bacteria that cause nosocomial infections is a growing problem worldwide. Limited therapeutic options have led to an increased clinical use of colistin, a polymyxin antibiotic developed over 50 years ago and which has retained activity against a number of multi-drug resistant pathogens. This is possibly due to its limited clinical use as the parenteral formulation quickly decreased in utilisation following authorisation in the 1960s, due to the existence of safer, less neurotoxic and nephrotoxic therapeutic options. As a consequence, the existing preclinical and clinical pharmacokinetic (PK) and pharmacodynamic (PD) information is limited, the product information has not been significantly updated over the years and the dosage regimens in use today are not based upon robust PK/PD data. Indeed, recent clinical experience and the medical literature point to the urgent need to update the product information, in particular the indications, the dosage recommendations and the PK/PD information, as highlighted by recent reports of suboptimal efficacy and the emergence of colistin resistance, in particular when used as monotherapy. In addition, differences across the world in the expression of the strength and dose of colistin products may result in medication errors and put patients at risk.

Polymyxins are currently listed among the critically important antimicrobials and in view of the importance of ensuring the availability of efficacious and safe antibiotics in order to efficiently respond to the threat posed by the spread of antimicrobial resistance, the European Commission initiated a procedure under Article 31 of Directive 2001/83/EC on 16 September 2013, requesting the CHMP to give its opinion on the benefit-risk of polymyxin-based products and on the need for regulatory measures.

The CHMP noted the variations and divergences of the various authorised products in terms of indications and dosage recommendations across the EU, in particular for the parenteral route of administration. The CHMP noted that colistimethate sodium (CMS) is widely approved for use in adults and children without explicit age restriction. One SmPC lists intramuscular use rather than intravenous use as well as the use of intrapleural and intraperitoneal administration, while another includes recommendations for intrathecal and intraventricular administration in meningitis. The CHMP considered that these differences reflect uncertainties in the most appropriate use of colistin due to the limited data in the literature. The CHMP decided that the medical need was greatest for high dose (500.000 IU or higher) medicinal products for parenteral and inhalation use and that the scope of the review should be limited to these products. Consequently, products for oral, topical, vaginal or auricular use were not included in the scope of the procedure, nor were polymyxin-containing products authorised as vaccines. The scope of the procedure includes nationally-authorised medicinal products and a centrally-authorised medicinal product, Colobreath (dry powder for inhalation), authorised in February 2012 and indicated for the treatment of lung infections caused by the bacteria *P. aeruginosa* in patients with cystic fibrosis. While the PK and posology for this product differs from other inhalation solution products, the CHMP considered the recently reviewed data included in the product information to be of relevance to the parenteral and solution for inhalation products.

Of note, a review under Article 5(3) of Regulation (EC) No 726/2004 was initiated by the European Medicines Agency on 13 September 2013, requesting the CHMP to give an opinion on whether the

current manufacturing, the quality control methods and the *Ph. Eur*. Monograph for polymyxin-based products need to be revised.

In its assessment, the CHMP reviewed all available data, including data submitted during the procedure by the MAHs, in response to the questions raised by CHMP. This report presents a summary of the relevant data for the procedure. In the context of the procedure, the CHMP consulted the Pharmacokinetics Working Party (PKWP) and the Infectious Disease Working Party (IDWP).

Polymyxins are a group of naturally occurring multi-component polypeptide antibiotics produced by selected strains of the spore-forming soil bacterium *Paenibacillus polymyxa* (formerly known as *Bacillus polymyxa var. colistinus*). Five major, chemically distinct members of the group have been recognised and are designated as polymyxins A, B, C, D and E, of which B and E are available commercially. Only polymyxin E is approved for clinical use in the EU and is therefore the focus of this procedure. Polymyxin E is usually referred to as colistin and its two main components polymyxin E1 and polymyxin E2 are therefore referred to as colistin A and colistin B, respectively. As colistin is an uneven mixture pf colistin A and B, the comparative antimicrobial activity of both subcomponents would potentially be relevant if the proportional yield of colistin A and B is not consistent, however no data was identified in the published literature and only an abbreviated report of a limited investigation by one MAH was submitted, suggesting that there are no differences in antimicrobial activity between colistin, colistin A and colistin B.

Two forms of colistin are used clinically: colistin sulphate and its microbiologically inactive prodrug, CMS. Colistin sulphate has a relatively high level of toxicity associated with parenteral administration and is therefore mainly used for oral and topical administration. Instead, CMS was developed for parenteral and inhalation use, manufactured from colistin base by the action of formaldehyde and sodium bisulphite. CMS for parenteral use is indicated for the treatment of serious infections caused by Gram-negative pathogens and CMS for inhalation use is indicated for the management of chronic pulmonary infections due to *P. aeruginosa* in patients with cystic fibrosis.

2.2. Pharmacokinetics and pharmacodynamics

2.2.1. Strength expression

The CHMP reviewed the available data to determine the optimal way of expressing the strength and dose of polymyxin-containing finished drug products and noted the currently existing differences. The EU reference standard is declared in international units (IU)/mg, while US reference standard is declared in µg activity/mg of colistin base activity (CBA). Accordingly, in clinical practice in the EU and in the European and British Pharmacopoeia, strength and vial contents are expressed as IU of CMS while in other parts of the world, such as North America and Australia, vial contents are expressed in mg of CBA, even though the drug product content is CMS.

The definition of an international unit of the drug is biological, i.e. 1 IU of colistin is defined as the amount of colistin that inhibits the growth of Escherichia coli 95 I.S.M. under standardised conditions. Based on historical information referenced in Martindale Extra Pharmacopoeia, 29th edition, it is generally accepted that 1 mg of pure CBA has a potency of 30.000 IU CMS, while 1 mg of CMS has a potency of 12.500 IU. These conversions are valid whether the potency result is obtained from testing with US or EU reference material and the potency can therefore be converted from IU/mg to µg activity/mg and vice-versa. Confusion arises when mass units (mg) are used incorrectly as measures of activity.

As a result, 1 million IU (MIU) of CMS is approximately equal to 80 mg CMS or 33.3 mg CBA. In the EU, this results in a conversion factor of 2.4 (80 mg CMS divided by 33.3 mg CBA) which means that 2.4 mg of CMS is required to obtain 1 mg of CBA. However, reference is also found in US publications to a conversion factor of 2.67, obtained when considering that 1 MIU CMS is equal to 30 mg CBA (80 mg CMS divided by 30 mg CBA = 2.67). This small difference between the conversion factor results in large differences for large doses: a US vial labelled as containing 150 mg CBA would contain 4.5 or 5 MIU of CMS, depending on the conversion factor, which would explain some of the differences in maximum daily dose frequently observed in the literature (9 versus 10 MIU).

The CHMP was of the opinion that given the established use of international units in the EU, the strength and dosing recommendations in the EU SmPC and PL for CMS should continue to be expressed in international units, as any potential switch in strength expression risks causing confusion and potential administration errors even if accompanied by advice and educational material to stakeholders. However, the CHMP considered that the multiplicity of terms used is likely to lead to dosage and reporting errors and therefore decided to introduce a table indicating dose content conversions between CMS expressed in IU, CMS expressed in mg and CBA expressed in mg. This table will raise awareness of the different ways of expressing dose and will be of relevance to prescribers who obtain additional information from medical literature or publications using different standards or ways of expressing dose or strength. The final agreed wording is presented in Annex III.

2.2.2. Mechanism of conversion of CMS to colistin

The conversion from CMS to colistin requires hydrolysis of the sulfomethyl peptide linkages, with 85% of CMS converted into the two major active components, colistin A and colistin B, while the remaining 15% are converted into a complex mixture of up to 32 partially sulphomethylated colistin derivatives that also seem to possess variable antibacterial activity, although there is little data on this. It appears that all sulfomethyl groups of the inactive prodrug CMS must be cleaved from the peptide structure to form the active colistin compound.

The CHMP noted that this conversion occurs both *in vitro* in aqueous solutions as well as *in vivo* in human plasma after administration. It is not clear if the *in vivo* hydrolysis involves any catalysing enzymes, or if CMS undergoes a non-hydrolytic degradation process. The available data indicates that *in vitro* conversion is temperature and concentration dependent, with higher conversion rates at lower, less clinically relevant, concentrations. In contrast, more concentrated solutions of CMS, such as those in pharmaceutical formulations, have been shown to be stable for extended periods with respect to formation of colistin. Data by Li et al, 2003 suggest slow conversion in human plasma *ex vivo*, in contrast to the rapid appearance of colistin after CMS administration in rats, leading to the assumption that mechanisms other than blood/plasma-mediated hydrolysis may contribute to the rapid *in vivo* formation of colistin. However, human data from critically ill patients suggest a rather slow conversion *in vivo*. Regarding the extent of conversion, Li et al. and Marchand et al, 2010 estimated a fractional systemic conversion of 6% and 13%, respectively, while Yapa et al, 2014 reported even lower estimates of around 3%. Conversion rates of around 30% have been reported in humans. Slow, sustained conversion of CMS to colistin in epithelial lung fluid was described by Yapa, resulting in a higher rate of conversion of 23%.

In summary, the CHMP noted that the extent and rate of conversion of CMS *in vivo* as well as the mechanism of conversion remain incompletely characterised and that a statement indicating the lack of data on the mechanism of conversion and hence the lack of data on the potential for drug-drug interaction should be included in the SmPC. The CHMP also considered that the known conversion of the reconstituted drug product *in vitro* has potential implications for toxicity, as colistin is less safe and less well tolerated than CMS. The reconstituted drug product should therefore not be stored for extended periods of time before administration, whether intravenously or via inhalation and infusion times should be kept reasonably short. On the other hand, the delay in appearance of colistin after CMS administration makes rapid infusion unnecessary. Infusion times of 30-60 minutes seem suitable and reflect the current recommendations across the EU.

2.2.3. Mechanism of action

Regarding the mode of action of colistin, the CHMP noted that no original data was available but that publications by Davis et al, 1971, Newton et al, 1956, and Schindler et al, 1979 suggest that the target of antimicrobial activity of colistin is the bacterial cell membrane. The initial association of colistin with the bacterial membrane occurs through electrostatic interactions between the cationic polypeptide (colistin) and anionic lipopolysaccharide molecules in the outer membrane of Gram-negative bacteria, leading to a loss of membrane integrity and an increase in the permeability of the cell envelope, leakage of cell contents, and subsequently, cell death. However, there are also reports on an alternative mode of action in which colistin acts intracellularly to precipitate ribosomes and other

cytoplasmic component and uncertainties remain as to the exact mode of action. However, synergistic activity to disrupt membrane integrity is plausible, in particular with hydrophilic antibacterial agents such as rifampicin, carbapenems, glycopeptides and tetracyclines. Colistin is mostly active against Gram-negative clinical isolates. Colistin is active against most species of Enterobacteriaceae, excluding Proteae and *Serratia* spp.. The non-fermentative Gram-negative bacteria *P. aeruginosa* and *Acinetobacter* species are naturally susceptible. Colistin is also active against *Haemophilus influenzae*, *E. coli*, *Salmonella* spp., *Shigella* spp., *Klebsiella* spp., *Legionella pneumophila*, *Aeromonas* spp., *Citrobacter* spp. and *Bordetella pertussis*. *Campylobacter* species vary in susceptibility to colistin.

Colistin was evaluated for antibacterial activity against an extensive collection of Gram-negative pathogens collected as part of the SENTRY Antimicrobial Surveillance Program between 2006 and 2009 (Gales et al, 2011). The study showed that colistin maintained high susceptibility rates above or equal to 98.5% for all key target pathogens and MIC_{90} values that were ≤1 mg/l. The study evaluated 9,130 clinical isolates of *P. aeruginosa* and colistin exhibited good activity against all isolates with an MIC_{90} of 1 µg/ml and 99.6% of isolates being reported as susceptible using EUCAST interpretive criteria. Furthermore, colistin susceptibility rates remained relatively constant over the 4 years of the study.

2.2.4. Mechanism of resistance

Several mechanisms of resistance have been identified in the targeted species, the most common appearing to be modifications to lipopolysaccharides, the initial site of action of colistin. Overall resistance levels to colistin appear relatively low at present, which may in part be explained by the low levels of clinical use. There is complete cross-resistance between the polymyxin B and E. The pathogenic *Neisseria* spp., *Moraxella catarrhalis*, *Helicobacter pylori*, *Proteus mirabilis*, *Serratia marcescens*, *Morganella morganii*, *Chromobacterium* and *Brucella* species are naturally resistant to colistin and isolates of *Inquilinus*, *Pandoraea* and *Burkholderia* associated with cystic fibrosis are also intrinsically resistant to colistin. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), acquired resistance to colistin occurs in Enterobacteriaceae, *Acinetobacter* spp. and *P. aeruginosa*. Stable acquired resistance is rare and high frequency of mutational resistance to colistin when used alone was observed in Gram-negative bacteria including *K. pneumoniae*, *P. aeruginosa, A. baumannii* and *E. coli*. A strong association between the use of colistin and the development of resistance in *A. baumannii* has been reported in clinical isolates collected between 2001 and 2004 and outbreaks with colistin-resistant strains have been reported. A report by the Antimicrobial Advice ad hoc Expert group (AMEG) published by the EMA in 2013 found that "*acquired resistance to colistin was characterised by chromosomal mutations and thus in theory is non-transferable by mobile genetic elements. Polymyxin resistance is mediated by mutations in specific regions (pmrA/B and phoP/Q). With the exception of some well-examined clinical strains, many of the above mutation mechanisms are not stable after several passages* in vitro*. This instability of polymyxin resistance, and the absence of horizontal gene transfer of these mutations, reduces the risk of rapid spread of resistance to colistin. Investigations on consecutive samples of* Acinetobacter baumannii *from nosocomial infections have indicated that this* in vitro *instability of colistin resistance is also found* in vivo *during colistin therapy. Out of 37 patients treated with colistin for <1 to 3 months, in 5 patients (13%) mutations in the pmr locus were found. Colistin susceptibilities returned soon after cessation of colisitin therapy. […] Mutations coding for colistin resistance might even downregulate resistance spread by horizontal gene transfer*".

In summary, mechanisms of acquired resistance to colistin are limited to a stepwise process via mutations in target bacteria. However, clinical data indicate that this clonal resistance can develop and can spread rapidly under certain conditions. Resistance transfer via mobile genetic elements (e.g. plasmids) between bacteria has not been reported. Colistin resistance is surveyed as part of the European Antimicrobial Resistance Surveillance Network. Data from the UK and Denmark suggest that resistance to colistin in multi-drug resistant *P. aeruginosa* has not been observed for 15 years. *In vitro* time-kill studies in a limited number of strains indicate that colistin displays very rapid concentration-dependent killing against *P. aeruginosa* and *A. baumanii*, and appears to have a modest post-antibiotic effect which is only seen at high concentrations (and may hence not be relevant clinically). Regrowth is a common feature seen *in vitro* and *in vivo* in A. baumannii and K. pneumoniae in static time-kill studies utilizing colistin concentrations up to 64× MIC and in P. aeruginosa with colistin concentrations

up to 200 mg/l. Colistin hetero-resistance has been observed in those pathogens and may contribute to the emergence of colistin resistance (Bergen et al, 2008) but the CHMP noted that combination therapy may reduce the emergence of such subpopulations. Colistin-resistant subpopulations in colistin hetero-resistant strains of A. baumannii had remarkably greater susceptibility, compared to their parent strains, to other antibiotics including those that normally are not active against Gram-negative bacteria. The CHMP was of the view that the SmPC should include a warning regarding the risk of development of resistance. Development of resistance associated with inhaled use was considered less problematic, although it is acknowledged that this was based on data generated on the use of colistin in combination with ciprofloxacin.

2.2.5. Pharmacokinetics

The CHMP reviewed a number of PK studies in various patient subpopulations and noted that there is limited PK data for colistin and CMS and that most of this data is based on the results of microbiological assays which are unable to quantify colistin and CMS separately. Even a low percentage of CMS degradation after sampling and during the workup procedure can have a pronounced influence on the colistin concentrations, particularly at time points when the CMS concentration is high and the colistin concentration is low. Reliable high performance liquid chromatography (HPLC)-based methods, which enable colistin and CMS to be measured in biologic specimens accurately and separately were only established relatively recently (Li et al, 2001 and Li et al, 2002). This assessment is therefore generally limited to clinical PK studies using HPLC or liquid chromatography–mass spectrometry assays to determine colistin/CMS plasma concentrations. *Ex vivo* conversion of CMS to colistin may however still contribute to inaccurate results, in particular where urine analysis is involved.

After intravenous administration of a single dose of CMS in healthy subjects, colistin appears in plasma with a delay. It is estimated that approximately 30% of CMS is converted to colistin. The volume of distribution of colistin in healthy subjects is low and corresponds approximately to the extracellular fluid volume. The overall disposition of formed colistin is rate-limited by its elimination rather than its formation as indicated by the substantially longer terminal half-life of formed colistin compared with that of the administered CMS. The half-life of colistin in healthy subjects is reported to be around 3h, with a total clearance of around 3L/h. Mohamed et al, 2012 determined the unbound fraction of colistin in plasma from healthy volunteers and showed it to be concentration-dependent (decreasing with higher concentrations). The measured unbound fractions of total colistin in patients were 34% (median) and ranged from 26 to 41%.

CMS is mainly eliminated renally via glomerular filtration (in healthy volunteers, 60-70% of CMS is excreted in the urine during the first 24 hours), but the fate of the remaining proportion is unclear. At least a proportion of the remaining 40% is converted to colistin. Unusually for a prodrug, its clearance is dependent on creatinine clearance (CrCL) and as renal function decreases, a greater portion of the prodrug is converted to colistin. In patients with very poor renal function (CrCL <30 ml/min), the extent of conversion could be as high as 60 to 70%.

Colistin seems to undergo renal reabsorption and is postulated to be eliminated predominantly by the non-renal route by mechanisms that are not characterised. However, Ma et al, 2009, who studied colistin in the isolated perfused rat kidney, found that 90% of colistin was removed by the kidney, but only 10% appeared in urine, suggesting either renal accumulation of colistin or metabolism of colistin in the kidney and the kidney may therefore be the major organ of elimination for colistin, with little elimination by the liver. Given the known nephrotoxicity of colistin, the potential for renal accumulation is of concern. Little data on multiple dosing in patients has been published and renal accumulation of colistin in humans cannot be fully ruled out. The data published by Mohamed et al, 2012 are reassuring in this regard, as concentration data after the 8th dose are observed to be lower than predicted from the population PK model.

In the same study, active transporters were shown to be involved in the extensive reabsorption of colistin and interactions with drugs that inhibit these renal transporters cannot be excluded. Such inhibition would result in increased renal elimination of colistin and reduced efficacy.

Animal data by Li et al, 2003 suggest that colistin clearance may be largely independent of liver blood flow (low extraction ratio) and, as protein binding is not extensive, would be expected to be mainly

dependent on intrinsic hepatic clearance. However, no difference in the PK for colistin and CMS was found in rats with induced liver failure. While these data are considered inconsistent with the purported extensive non-renal clearance of colistin, they would be expected if the kidney is the main organ of colistin elimination. The translation of these findings to colistin disposition in patients is unclear.

As would be expected, simulations performed by Couet et al, 2011 show that impaired (non-renal) colistin clearance is predicted to lead to significantly elevated plasma concentrations. Given that the respective roles of the liver and kidney in colistin clearance are unclear in patients, a cautionary statement regarding patients with impaired hepatic function was included in the SmPC. In addition, the CHMP considered that a comment indicating the lack of data on the elimination of colistin and hence the lack of data on the potential for drug-drug interaction should be included in the SmPC, together with cautionary advice when colistin is co-administered with drugs known to affect drug metabolising enzymes to a relevant degree. The final agreed wording is presented in Annex III.

Further informative PK data stem from studies in critically ill patients, which all suggested that a two-compartment model for CMS and a one-compartment model for colistin best described the observed data. Both CMS and colistin were reported to display linear PK in the dose ranged used.

Plachouras et al, 2009 found a significant delay to reach Cmax for colistin (7h) and noted that the PK of colistin A and B were found to be very similar. The population PK model did not find a correlation between colistin concentration and creatinine clearance, which is likely due to the lack of patients with significant renal impairment in this study. The T½ of CMS was very similar to that in healthy subjects reported by Couet, while T½ for colistin was longer (14h versus 3h). The estimated volume of distribution of formed colistin was much higher than found in healthy subjects (189l) and colistin clearance was found to be higher (9l/h versus 2.9l/h). Both parameters depend on the estimate for conversion of CMS.

Mohamed et al, 2012 added data from 10 critically ill patients who received a loading dose of CMS to this population PK model. The updated population PK model showed similar results to the study by Plachouras. In addition it was found that colistin A, but not colistin B, had a concentration-dependent binding. There was no obvious difference in plasma binding in the critically ill patients and the healthy volunteers over the concentration range studied, which is not necessarily expected as colistin was demonstrated to bind to alpha-1 acid GP, which is known to be elevated in critical illness.

Garonzik et al, 2011 included 105 critically ill patients with renal impairment and patients on renal replacement therapy (RRT) and showed that there was a strong correlation between CrCL and average plasma concentrations and that CrCL was a relevant covariate for both CMS and colistin plasma concentrations. The half-life of CMS (4.6h) and colistin (9h) in patients with CrCL > 70ml/h was longer than in healthy subjects. It could be speculated that this is due to a larger volume of distribution in the critically ill. In patients with renal insufficiency or renal failure, the excretion of CMS is decreased, possibly resulting in a greater conversion to colistin and increased colistin exposure (Bergen et al 2012, Biswas et al 2012, Michalopoulos et al, 2011).

It was also considered that “critically ill” patients are a poorly defined group, whose characteristics will differ significantly between patients. The high variability of plasma concentrations observed by Garonzik et al can partly be explained by the heterogeneity of this population. Nevertheless, the relatively consistent findings of the main studies support the use of PK data, although it must be considered that patients with less systemic involvement than those termed “critically ill” may display different PK. The CHMP considered that colistin is presently (and should remain) a second or third line antibacterial agent and is likely used in patients who have already failed other treatments or have acquired their infection after a prolonged hospital stay. For these reasons, the typical target population can be expected to be broadly similar to the populations in the studies. The PK of patients with pulmonary exacerbations of cystic fibrosis may differ from those of critically ill patients, however intravenous colistin is not presently approved in this group in the vast majority of member states. Li et al presented data from a small group of patients with cystic fibrosis and reported half-lives of 2 h for CMS and 4.2 h for colistin. The reported clearance may be an overestimate as a mono-exponential model was assumed for CMS. The data by Li et al and Reed et al, 2001 seems to suggest that PK data for CMS and colistin in cystic fibrosis patients receiving intravenous CMS for acute pulmonary

exacerbation are more similar to those in healthy adults and could be a reflection of lesser physiological abnormalities compared to critically ill patients.

In summary, the formation of colistin from CMS *in vivo* is incomplete and relatively slow, leading to a significant delay in reaching effective plasma concentrations, at least in critically ill patients. In normal renal function, approximately 20-30% of CMS is converted to colistin, although the rate of conversion may be higher in critically ill patients. The volume of distribution of colistin approximates the extracellular fluid in healthy subjects, but may also be higher in critically ill patients, although the uncertainty regarding the extent of conversion of CMS to colistin affects the estimates. Protein binding is moderate and dose dependent for colistin A (but not B) and hence for total colistin. The unbound fraction increases at higher doses. CMS and colistin appear to have linear kinetics in clinically relevant doses. T ½ appears longer in critically ill patients (14h) compared to healthy subjects and those with cystic fibrosis (3-4h). T1/2 of colistin is longer than T1/2 of CMS in all patient populations. Around 60-70% of CMS is excreted renally in subjects with normal renal function. Colistin appears to undergo extensive tubular reabsorption and is cleared non-renally, however CrCL is a significant predictor of both CMS and of colistin plasma concentrations, the latter possibly due to changes in the proportion converted from CMS. The effect of hepatic disease on colistin clearance in humans is not known. The potential for drug-drug interactions is equally unknown. CMS and colistin are removed during intermittent haemodialysis and continuous RRT. The CHMP agreed on wording to be inserted accordingly in the SmPC. The final agreed wording is presented in Annex III.

2.2.6. Pharmacodynamics

The CHMP also examined the concentration-effect relationship of colistin, noting that simulated regimens have been carried out in an *in vitro* PK/PD model based on the PK of colistin generated from CMS in humans with normal renal function and allowing for an unbound fraction of colistin in human plasma of approximately 0.5. Killing was the same with 8, 12 and 24 h regimens (which resulted in similar areas under the curve (AUCs)) and the data showed that longer dose intervals may increase the likelihood of resistance development as the emergence of resistance appeared less likely with 8 h dosing. This may be related to the finding that colistin, despite its concentration-dependent killing, possesses little or no post-antibiotic effect at clinically relevant concentrations. It should be noted however that the PK parameters simulated used a T1/2 of 4h, shorter than what was observed in the population of the critically ill, which may affect data interpretation.

A study by Dhudani et al, 2010 investigated the relationship between antibacterial effect and measures of exposure to unbound colistin, showing that the PK/PD parameter that correlated best with its efficacy was fAUC/MIC (area under the concentration-time curve). The fAUC/MIC targets required to achieve 1-log and 2-log kill against the three strains were 15.6 to 22.8 and 27.6 to 36.1, respectively, in the thigh infection model, while the corresponding values were 12.2 to 16.7 and 36.9 to 45.9 in the lung infection model. The findings of this *in vivo* study indicate the importance of achieving adequate time-averaged exposure to colistin and the results were taken into consideration for breakpoint setting by EUCAST. A further study by the same authors found the same index to be relevant for *A. baumanii*.

The CHMP noted the current EUCAST clinical breakpoints (version 1.0, 2010) and that there is insufficient evidence to set non-species-related breakpoints for parenteral colistin. Species-related breakpoints were based on PK data, microbiological data and clinical experience. It was also noted that breakpoints for inhaled and topical colistin are not available.

2.3. Clinical efficacy

2.3.1. Efficacy of intravenous CMS

Regarding the efficacy of intravenous CMS, the CHMP reviewed a number of studies, inculding a prospective study by Dalfino et al, 2012 aiming to validate the dosage proposed by Plachouras et al in the treatment of multi-drug resistant Gram-negative infections. The CMS dosing schedule was based on a loading dose of 9 MIU and a 9 MIU twice daily (bid) maintenance dose, titrated on renal function. In patients with moderate to severe renal impairment, the loading dose was 9 MIU with maintenance

doses of 4.5 MIU/24 hours (CrCL 20–50 ml/min) or 4.5 MIU/48 hours (CrCL <20 ml/min). A high clinical cure rate (82.1%) of predominantly bloodstream infections and ventilator-associated pneumonia (VAP) in their cohort of 286 patients was observed. Acute kidney injury developed during 5 treatment courses (17.8%) subsided within 10 days after cessation of treatment. The CHMP considered that the study provided some clinical support for the use of higher than previously recommended doses of colistin, after administration of a loading dose, in the critically ill population. All patients in the study fulfilled the criteria for sepsis or septic shock. Overall cure rates were relative high, and while renal toxicity was observed in a relatively large proportion, the background rate for renal injury in this population is considered high.

Other data on the clinical efficacy of intravenous colistin stem mostly from retrospective studies on colistin in a range of conditions, as expected in view of the clinical use pattern of colistin. The largest of the cohort studies (Falagas et al, 2009) enrolled intensive-care unit patients mostly with pneumonia (60%), with other diagnoses including bacteraemia (13%), abdominal infections (9%), central venous catheter-related infections (6%) and infections of other sites (12%). Overall, a high success rate was found, with best results for patients with pneumonia. Patients with concurrently administered carbapenems had better outcomes than those with other concurrent antibiotics. The study showed acceptable levels of nephrotoxicity (10% of patients) and considerable effectiveness depending on the dose and infection site (in total, 79.1% of patients were cured). The effectiveness of colistin was not found to be dependent on the type of pathogen. The authors commented that higher doses of colistin (above 6 MIU) than currently recommended in the product information are increasingly used in clinical practice.

Levin et al, 1999 used intravenous CMS for nosocomial infections caused by *P. aeruginosa* and *A. baumannii* resistant to aminoglycosides, cephalosporins, quinolones, penicillins, monobactams, and imipenem. Here, the poorest results were observed in pneumonia (n=20), with only 25% cured. Other studies reported moderately high success rates in pneumonia including VAP (Montero et al, 2009, Kallel et al, 2006, Kwa et al, 2008). Garnacho-Montero et al, 2003 performed a preliminary evaluation of 35 cases of VAP caused by *A. baumannii* that were treated with intravenous colistin or imipenem. Clinical cure was reported in 57% of patients.

Overall, the best evidence for the efficacy of intravenous colistin was found in pneumonia, including VAP. Various studies or case series reported acceptable success rates with colistin in other infections with multi-drug resistant Gram-negative pathogens. The more commonly reported infections are urinary tract infections (UTI), and some cases of intra-abdominal infections (IAI) and skin and soft tissue infections (SSTI), particularly in patients with burns, as may be expected. “Bloodstream infections” are also frequently reported, as are bacteraemia and catheter related infections.

There is limited data to suggest that colistin penetrates into the cerebrospinal fluid (CSF) after intravenous administration of CMS, however no recent data on CSF concentrations were identified. Several case reports have suggested the efficacy of intravenous CMS against meningitis caused by multi-drug resistant *A. baumannii*. The evidence is at present considered insufficient to confirm safety and efficacy. Case reports indicate that colistin has been used intrathecally, but there is very limited safety data and unclear dosages (further discussed later in this report). The CHMP considered that the SmPC should include a comment to point out that there is insufficient data to indicate that colistin crosses the blood-brain barrier to a therapeutically relevant extent and that there is very limited evidence on efficacy in meningitis. The final agreed wording is presented in Annex III.

Data from the literature provide some support for efficacy in VAP, UTI, IAI and SSTI in burns patients and cases associated with bacteraemia; however the focus of the studies is on the pathogens rather than the site of infection, while current regulatory requirement require site specific indications. In line with the position of the IDWP, the CHMP therefore reworded the indication according to the wording for use of antimicrobial agents in patients with limited treatment options suggested in the addendum to the *Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 Rev. 2)*, to allow more appropriate clinical use of intravenous colistin. In addition, the CHMP agreed with the IDWP recommendation to qualify the indication as “serious”, in light of the known safety profile of colistin and adopted the following indication: “*For the treatment of serious infections due to selected aerobic Gram-negative pathogens in patients with limited treatment options”.* In addition, the CHMP emphasised that national guidelines should be adhered to and added

the statement "*Consideration should be given to official guidance on the appropriate use of antibacterial agents*", taking into account the need to adapt national prescriptions, especially regarding the local situation. The SmPC should also include a statement in section 4.4 detailing the limitations of the evidence available, while section 5.1 should detail the list of relevant species.

Although the use of colistin monotherapy is considered to be effective in many cases, it is frequently used in combination with other antibiotics. However, studies do not consistently show improved efficacy when colistin is used in combination treatment, in fact most studies show similar outcomes with colistin alone or in combination, despite the theoretical possibility of a synergistic effect with other antimicrobial classes. The CHMP reviewed *in vitro* and *in vivo* studies supporting the use of colistin in combination with a variety of antimicrobial agents including beta-lactams, penems, rifampicin, glycopeptides and tetracyclines. Additive or synergistic effects against the commonly targeted pathogens were reported in a number of these investigations, while others did not identify clear beneficial effects in terms of improved efficacy. A further relevant aspect when considering the co-administration of antibiotics is the prevention of resistance but no clinical studies were identified specifically addressing this question. Some more recent studies using an *in vitro* PK/PD model reported that at least for some drugs co-administered with colistin, a substantial increase in bacterial killing against colistin-susceptible, hetero-resistant, and resistant organisms (e.g. doripenem/colistin in multi-drug resistant *K. pneumonia*) and reduced emergence of colistin resistance was observed. While the overall resistance to colistin is reported to be low, emergence of resistance under treatment is relatively common. This may be explained by the observation that many of the mutation mechanisms are not stable after several passages in *in vitro* tests (Moskowitz et al, 2004), which, together with the lack of horizontal resistance transfer, reduces the risk of spread of resistance. In the treatment of multi-drug resistant pathogens, combination of antibiotics is common in clinical practice and generally recommended. The CHMP noted the IDWP recommendation that use in combination with other antibacterial agents with the aim of reducing the risk of emergence of bacterial resistance is appropriate for the systemic route of administration and therefore introduced a statement in section 4.4 of the SmPC regarding the co-administration of colistin with other antibiotics, *taking into account the remaining susceptibilities of the pathogen(s) under treatment.*" The final agreed wording is presented in Annex III.

2.3.2. Efficacy in children

Regarding use in children, several case series were identified in children with and without cystic fibrosis. The case mix is very similar to the adult population, with pneumonia including VAP the most commonly treated infection. Other infections are "bloodstream infections", UTI and SSTI and central nervous system infections in some cases. Based on this limited data, the CHMP was of the opinion that the indications agreed for the adult population can be extrapolated to the paediatric population and that no age restrictions should be included in the SmPC. The final agreed wording is presented in Annex III.

2.3.3. Dosage recommendations for intravenous CMS

The CHMP noted that PK/PD-based dose finding is becoming increasingly established and accepted for antibacterial agents and is, in the absence of clinical dose finding studies, considered acceptable for colistin. It was also accepted that plasma concentrations persistently below the MIC for the relevant pathogens, as reported for colistin in some publications, cannot produce successful clinical outcomes. The CHMP therefore agreed that the available data on dosage is a cause for concern, as PK findings and the assumption that fAUC/MIC is the relevant predictive PK/PD parameter indicates that plasma concentrations in at least a proportion of patients is not optimised, which would lead to suboptimal efficacy for the treatment of infections caused by pathogens with MICs for colistin in the upper range, as well as the selection of resistant strains. The CHMP reviewed the data to determine whether a loading dose and longer dosing intervals would be more appropriate, including three main studies.

A first study, by Plachouras et al, 2009 investigated plasma CMS and colistin concentrations on the basis of the model developed for the currently used dosage regimen (3 MIU as 15 min infusions tid) and for dosage regimens with a loading dose and a maintenance dose of 4.5 MIU bid (with infusion

lengths of 15 min to 2 h). Based on these data, the authors proposed a loading dose of 9 million IU followed by 3 MIU q8h, commenting that "the results from this study indicate that for a typical patient, colistin concentrations are below the MIC breakpoints (2 mg/l) after the first few doses of the currently used dosing regimen, in effect signifying a delay in appropriate treatment. Even at steady state, the plasma concentrations, as measured in the present study, are, in many cases, below the MIC breakpoints for the *Enterobacteriaceae* and *P. aeruginosa*, frequent multi-drug resistant pathogens in critically ill patients. A second study by Mohammed et al, 2012 modelled the time courses of the PK plasma concentrations and a semi-mechanistic PK/PD model for predictions of bacterial kill. Time courses of total and unbound colistin concentrations and bacterial counts following a maintenance dose of 2 MIU three times per day (tid) or 3 MIU bid and loading doses of 4 MIU, 6 MIU, and 8 MIU were predicted for an individual with the typical population value, with approximately 12.5 h to achieve a 3-log-unit kill of wild-type *P. aeruginosa* following a loading dose of 6 MIU, whereas a dose of 2 MIU did not reach a 3-log-unit kill at all. For loading doses of 9 MIU and 12 MIU, the times to 3-log-unit kill decreased further and were estimated to be 6.5 and 5 h, respectively. The authors concluded that the results showed that a loading dose was beneficial for all concentration-time profiles predicted and a loading dose of 6 to 9 MIU is recommended in critically ill patients. In the third study, Garonzik et al, 2011 developed dose suggestions for CMS in critically ill patients based on the population PK model for patients not on RRT described earlier.

Data suggests that without the administration of a loading dose, it may take 2 to 3 days before the steady-state concentration of colistin is obtained for a typical individual. A loading dose of 9 MIU or even 12 MIU CMS and a maintenance dose of 4.5 MIU CMS bid would result in the same average steady-state concentration of colistin achieved with the current dosing schedule but would achieve the target concentration faster and lead to the need for less frequent administration, although some publications have indicated that extended interval dosing may be associated with increased nephrotoxicity in rats (Wallace *et al*, 2008) and increased resistance (Bergen et al, 2008). A 9 MIU loading dose followed by 4.5 MIU bid was shown to be effective in a series of 28 courses of infections in 25 patients. This regimen was not associated with renal toxicity and colistin resistance was not observed during the follow up period (Dalfino et al, 2012). The CHMP noted that several MAHs already included an option for a loading dose and a maintenance dose of up to 9 MIU/day in the product information of their products.

The CHMP, taking into consideration the available data and the input from the IDWP therefore considered that a loading dose should be used in the critically ill population. While a loading dose of 9 MIU for all patients seems supported, there is little data, including on safety, from clinical studies for doses > 9 MIU and there is almost no clinical data in support of a 12 MIU loading dose. The CHMP therefore proposed a simplified loading dose of 9 MIU for patients above 60kg and 6 MIU for patients below 60kg in critically ill adult patients, together with a statement that doses up to 12 MIU may be required for patients but that the clinical experience with such doses is limited. The loading dose should apply to all patients regardless of renal function. The need for, and size of, a loading dose in other populations is not clear.

Regarding the maintenance dose, the CHMP agreed that data indicates that for patients with normal or at least not significantly impaired renal function, the presently recommended daily doses of up to 6 MIU are not sufficient and are likely to achieve plasma concentrations lower than desirable.

Although there is data indicating that doses of 9 MIU or higher are associated with an acceptable overall clinical success rates in patients with normal renal function, there is concern regarding the increased risk, in particular of nephrotoxicity, associated with higher doses. A suggestion by Li et al, 2006 that Levin et al, 1999 used doses of up to 13 MIU in some patients could not be confirmed in the original article. Studies by Plachouras and Garonzik have indicated that (at least in patients with good renal function) loading and maintenance doses above 9 MIU may be preferable, although the lack of clinical data with such doses is of concern. None of these studies reviewed reported using loading doses above 9 MIU. In the study by Garonzik, maintenance doses of 9 MIU were used, but only in three patients. The CHMP therefore concluded that maintenance doses higher than 9 MIU/day are at present not supported by the available clinical data and that a total daily dose of 9 MIU is appropriate and should be recommended. In line with the position of the IDWP, the CHMP considered that additional wording could be added to the SmPC to indicate that modelling suggests that higher doses

up to 12 MIU may be justified in some cases, but also pointing out the present lack of supporting clinical data. In view of the long half-life at least in critically ill patients, a bid regimen appears sufficient, although other data suggest that a tid regimen may be preferable to reduce the likelihood of resistance development. The CHMP considered it acceptable to allow both bid and tid dose intervals in critically ill patients, however if colistin were to be used in other populations, where shorter T1/2 have been reported (e.g. in cystic fibrosis), tid would be preferable. As weight does not seem to relevantly affect maintenance dose, the dose could be applied to all adults (and paediatric patients above the commonly applied cut-off of 40kg). Even higher doses in excess of 9 MIU/day may be appropriate, however clinical safety data are lacking to support such a recommendation at present.

Regarding time to first maintenance dose, it was suggested that after a loading dose, the first maintenance dose should generally be given according to the maintenance-dose schedule. Modelled data by Mohamed et al suggest that after a 9 MIU loading dose, extended dosing interval of 12h had a limited impact on the bacterial kill for all individual PK profiles predicted, while longer dosing intervals resulted in pronounced regrowth for shorter exposures. Additional simulations based on the available PK data suggested that in patients with normal CrCL, plasma concentrations will fall below the target Css,avg even after a 9 MIU loading dose. However, given the lack of data, the CHMP decided not to include any recommendations on the time interval to the first maintenance dose.

Regarding the maintenance dose in patients with renal impairment or those on renal replacement therapy (RRT), dose recommendations could be based on the relationship identified between CrCL and CL CMS/colistin. According to this model, with an upper limit for the daily dose of 9 MIU as proposed in normal renal function, a daily dose of 9 MIU for all patients with CrCL at or above 50 ml/min would be appropriate. Below this, approximate daily doses of 6 (30-40 ml/min), 5 (20 ml/min) or 4 MIU (10 ml/min) are calculated. It should however be noted that the resulting exposures for patients with renal impairment will be higher than for those with normal renal function, which may have implications for safety and requires further consideration. The CHMP therefore recommended dose reductions for patients with creatinine clearance below 50 ml/min, with bid dosing. For patients with reasonably good renal function (CrCL of 80 ml/min or greater), a daily dose of 9 MIU may not be sufficient to achieve a target Css,avg of 2.5 mg/l. In general, a loading dose of 9 MIU is supported, as is the interval of 24h before administering the next dose, although in patients with reasonably good renal function, it appears that it may be beneficial to administer after 12h.

In patients receiving intermittent haemodialysis or continuous RRT, both CMS and colistin undergo efficient extracorporeal clearance, which is in agreement with previous case reports. Based on a fixed Css,avg of 2.5mg/l, this corresponds to a maintenance dose of 2.25 MIU/day on non-HD days and 3 MIU/d on haemodialysis days, to be given after the HD session (bid dosing is recommended).

For patients on continuous RRT, in line with the recommendations for patients with normal renal functions, it is advised not to exceed a total daily dose of 9 MIU in the absence of safety data and hence apply the same dose as in patients with normal renal function (9 MIU in 3 divided doses). The CHMP noted that the dose recommendations for patients on RRT derived by Garonzik are based on a very small dataset and have to be regarded with caution. Nevertheless, the risk of basing dose recommendation on such limited data must be balanced against the risk of providing no guidance to the prescriber and the CHMP therefore agreed to include dose recommendations in this patient population with a cautionary statement on the limitations of the data.

In most studies, paediatric doses range from 50.000 – 75.000 IU/kg of CMS and it appears that this dose has been applied to children of all ages, including preterm neonates, although Iosifidis et al, 2010, Celebi et al, 2010 and Antachopoulos et al, 2010 describe the safe use of doses over 75.000 IU/kg and up to 225.000 IU/kg in single cases. None of the studies report the use of a loading dose, and clinical or PK data are missing, but evidence from critically ill adult patients makes the need for a loading dose in the paediatric population likely. The CHMP reviewed the currently approved SmPCs and noted that the recommended daily paediatric CMS doses range from 50.000 to 75.000 IU/kg/day in 3 divided doses in most EU member states, although one SmPC recommends doses of 150.000-225.000 IU/kg/day. In the United States, dose recommendations range around 75.000-150.000 IU/kg/day (83.000 to 166.000 IU/kg/day using the alternative conversion factor).

In view of the dose considerations in adults, it was expected that paediatric doses used in the past may also be inadequately low and the CHMP reviewed additional, recently published studies in support of higher doses. One study by Karbuz et al, 2014, enrolled children with a median age of 17 months (range 3–217 months) and although small, provides interesting data as some of the patients received a non-EU colistin product and others an EU product, resulting in administration of a higher dose of colistin in those receiving the non-EU product. The median dosage in the non-EU group was reportedly 150.000 IU/kg (69.000–168.000 IU/kg) compared to 75.000 IU/kg/day (50.000–80.000 IU/kg/day) in the EU group. Treatment success was observed to be higher in the high dose group (85% versus 70%), while the incidence of reported adverse events was low. The study was too small to draw firm conclusions regarding the dose, however given the scarcity of the data overall, the CHMP considered that the efficacy and safety data supports doses superior to 75.000 IU/kg/day in paediatric patients. Another study by Alan et al, 2014, included 21 preterm neonates (mean gestational age 28 weeks). In this population, doses of 75.000-150.000 IU/kg/day were reportedly used. Clinical success rate was around 80%, mortality 20%. Renal impairment was observed in 20% of patients, but was reversible. Efforts were made to assess neurotoxicity, considered particularly relevant in this population, but data are essentially non-interpretable in the absence of a control group.

The CHMP therefore concluded that the dose in paediatric populations is likely too low to achieve effective plasma concentrations in at least a significant proportion of cases and although the paediatric data is limited, the CHMP agreed on an increased dose recommendation of 75.000-150.000 IU/kg/day. It is expected that a loading dose is also required in the paediatric population, however no studies using a loading dose in children have been identified and a loading dose is not included in the US product information so while the magnitude of the loading dose in adults largely corresponds to the daily maintenance dose, and a similar principle may apply in the paediatric population, the CHMP concluded that the SmPC wording should be limited to a statement indicating that there is no data regarding the use or magnitude of a loading dose in critically ill children. Similarly, a statement was included to indicate that no dose recommendations are established in children with impaired renal function.

2.3.4. Efficacy of inhaled CMS

Regarding the efficacy of inhaled CMS, the CHMP reviewed studies conducted on CMS in pneumonia as well as in cystic fibrosis. The CHMP noted that inhaled CMS is not currently approved in the treatment of hospital-acquired pneumonia (HAP) or VAP in the EU, neither as monotherapy nor as an adjunct to intravenous antibiotics. Little data in support of inhaled colistin as monotherapy in these indications was identified and the evidence identified is considered insufficient at present. To justify the use of colistin in addition to systemic antibiotics, improved clinical cure rates over treatment with systemic antibiotics alone should be provided. In a small study, Kofetridis found no benefit in adding inhaled colistin to parenteral colistin when compared to parenteral colistin alone. However, a larger retrospective cohort study by Korbila et al found a significant difference in outcome when inhaled colistin was added to intravenous treatment in VAP. The magnitude of the effect is rather unexpected and suggests that other factors than the addition of inhaled colistin alone may be involved. Among the studies where colistin was used as an adjunct to intravenous treatment with parenteral colistin and or other antibiotics, the only randomised controlled trial investigating the benefit of adding inhaled CMS to systemic antibiotics (Rattanaumpawan et al) did not show improved clinical outcomes in the colistin arm. In another retrospective analysis in patients with VAP, Naessens et al showed higher clinical success rates when inhaled colistin (alone or with parenteral colistin) was compared to parenteral colistin alone. The CHMP concluded that the effect of adding inhaled colistin to various intravenous antibiotic treatment regimens cannot be reliably judged from the available data as results are conflicting, studies were small and had relevant design flaws. In addition, due to the retrospective, non-randomised nature of the trials, treatment groups are not comparable and most studies are thought to have used sub-optimal doses. While a beneficial effect of adding inhaled CMS to intravenous antibiotic agents in the treatment of HAP or VAP cannot be ruled out, the data presented is insufficient to conclude on such an effect with any confidence. A positive aspect is the apparent lack of a relevant increase in adverse events (both pulmonary and renal) with additional inhaled colistin.

In contrast to the limited data in non-cystic fibrosis patients, there is extensive experience with inhaled CMS and colistin in patients with cystic fibrosis. This includes the management of early and chronic colonisation/ infection with *P. aeruginosa*. Aerosolized colistin has been successfully used to prevent pulmonary exacerbation and lung deterioration in patients with cystic fibrosis colonized with *P. aeruginosa* and the efficacy of colistin in these conditions is considered well established. The CHMP did note that comparative data suggests that inhaled tobramycin may be more effective than colistin in the management of cystic fibrosis patients, but considered that prescribers should have a variety of agents available to deal with specific organisms as appropriate and to allow alternating treatments. *P. aeruginosa* is the most prevalent infection in cystic fibrosis, with 37.5% of patients of all ages having a chronic infection in 2010, according to the UK cystic fibrosis trust (2010). The studies presented for colistin include children mostly aged 2 years or older, in line with the prevalence of *P. aeruginosa* colonisation, which increases with age. The CHMP noted that most colistin products approved in the EU did not include a lower age limit for inhalational therapy, which was considered acceptable. The CHMP took into account the IDWP recommendation to align the wording of the indication with that agreed for other recently approved inhalation products for cystic fibrosis and adopted the following indication: "*For the management in adult and paediatric patients of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis.*"

2.3.5. Dosage recommendations for inhaled CMS

There are no breakpoints for inhaled/topical colistin and no PK/PD data that could contribute to dose considerations, instead the dose has to be established based on the available clinical data. The CHMP reviewed the currently authorised SmPCs and based its recommendation on the existing posology and longstanding experience with a combination of nebulised CMS (2 MIU tid) and oral ciprofloxacin (10–20 mg/kg bid) used in a Danish cystic fibrosis centre for aggressive eradication therapy of lower respiratory tract infections by multi-drug resistant P. aeruginosa. The outcome has been very encouraging: chronic P. aeruginosa infection was prevented in 85% of patients treated with the combination compared with only 42% in the non-treated group ($p<0.05$) and despite of use against intermittent P. aeruginosa colonisation for 15 years by this group, there has been no development of antibiotic resistance. Nevertheless, some national guidelines make different recommendations and the CHMP considered that in addition to the recommended posology in adults and children above 2 years of age of 1-2 MIU, bid or tid, a statement that national guidelines should be adhered to should be added to the SmPC, "*Consideration should be given to official guidance on the appropriate use of antibacterial agents"*, in accordance with the European guideline taking into account the need to adapt national prescriptions, especially regarding the local situation.

2.3.6. Non-critically ill patients

Regarding patients who are not considered critically ill, the CHMP assessed whether a loading dose is required in this population. Very little additional data in non-critically ill patients was identified in the published literature but a study in healthy Japanese patients compared the PK after a single and multiple bid doses of CMS and found C_{max} and AUC_{0-12} of colistin increased by 72 % and 63 %, respectively, after the repeated dose. The need for a loading dose was not specifically addressed. Another study by Lee et al, 2013 was performed in patients with burns, a special population characterized by hyper-metabolic patients with physiological changes in e.g. glomerular filtration rate, plasma protein levels and extracellular fluid. These changes may affect drug disposition and PK parameters significantly. Of note, the subpopulation with relevant oedema had lower CMS plasma concentrations and the rate of conversion to colistin was reportedly lower in these patients. This suggests that a loading dose may be required in this population, although the study did not address this question and no firm conclusions can be drawn. The CHMP was therefore unable to conclude on the need of a loading dose in non-critically ill patients and the wording of the SmPC should be limited to a statement on the need of a loading dose in critically-ill patients.

2.3.7. Other routes of administration

Regarding intrathecal and intraventricular administration, the CHMP reviewed the available data together with searches conducted by some MAHs of their pharmacovigilance and clinical trial databases to identify case reports relating to colistin administered via the intrathecal/intraventricular route. The CHMP noted that the available data demonstrates that CMS and colistin penetrate poorly into the cerebrospinal fluid (CSF), even if the meninges are inflamed. *In vitro* data suggest that conversion of CMS into colistin occurs in the CSF. Imberti et al, 2012 reported information on a total of 92 patients (adult and paediatric) who received intrathecal or intraventricular CMS for Gram-negative meningitis, frequently associated with trauma, surgery and indwelling devices. Intravenous antibiotics were usually administered concomitantly and 65.000 or 130.00 IU/day administered intraventricularly continuously resulted in CSF concentrations of colistin above the minimum MIC of 2 mg/l and with AUC0–24/MIC between 74 and 141 and Cmax/MIC between 45 and 72. The overall clinical and/or microbiological cure rate was around 90%. Adverse effects (mostly aseptic meningitis) were reported in 15% of patients. Another study reported that drugs administered intrathecally do not distribute uniformly in the CSF and that ventricular concentrations may be much lower and inadequate, while intraventricular administration results in high concentrations throughout the CSF. This does not explain the higher doses recommended for intraventricular administration. Meningitis is associated with high mortality and morbidity, and where caused by multi-drug resistant Gram-negative pathogens, therapeutic options are very limited. The failure to obtain effective CSF concentrations after intravenous administration of colistin makes intrathecal or intraventricular administration necessary in cases of central nervous system infections with multi-drug resistant pathogens. While data is limited, it appears that the presently approved formulation of CMS can be administered directly into the CSF.

The IDWP agreed that there is a medical need for the intrathecal/intraventricular route of administration of colistin in small numbers of patients and that it should therefore be included in the SmPC.

Regarding dosage, a review by Karaiskos et al, 2013 reports that the most commonly used dose was 125.000 IU/day in adults, ranging from 20.000-500.000 IU/day. In the study by Imberti, doses ranged from 32.500 IU/day to 65.000 IU bid. A dose of 65.000 IU/day achieved CSF concentrations persistently above MIC and an AUC/MIC ratio above 50 (with a MIC of 2mg/l), however the authors also recommend a dose of 120.000 IU/day to compensate for losses via CSF drainage. This appears to be consistent with the dose recommendations of the Infectious Diseases Society of America (IDSA). The IDWP suggested that the dose recommendations of the IDSA could be used for the intraventricular route and that the intrathecal route dose should be stated not to exceed this dose. Based on the available data and the IDWP advice, the CHMP therefore concluded that 125.000 IU/day is the most appropriate dose in adults for intraventricular administration.

Regarding paediatric patients, the study by Karaiskos et al reported doses for nine patients, ranging from 2.000 to 125.000 IU/kg. This included one neonate who received a total daily dose of 20.000 IU and four children below 1 year, of whom three received a weight-based dose. Assuming these three children were of normal weight, their daily dose would also have been around 20.000 IU in total. The fourth child (aged 2 months) received a total daily dose of up to 125.000 IU. The remaining four children aged 3-9 years received 50.000 to 125.000 IU/day. The IDWP considered that the available data does not allow the definition of dose recommendations for children, who have smaller cerebrospinal fluid volumes. The CHMP agreed that the small number of cases and the wide range of doses used prevents the determination of a paediatric dose although based on anatomical and physiological considerations, it could be assumed that the dose at least in adolescents should be the same as in adults.

Because the current pharmaceutical formulation of all products included in this procedure is suitable for these routes of administration (based on the pH, absence of preservatives and antioxidant and administered volume), it was agreed that recommendations for intraventricular and intrathecal administration should be reflected in section 4.2 of the SmPC. Due to the paucity of data to support these recommendations and in line with IDWP advice, the CHMP agreed to include a cross-reference in section 4.2 to a warning in section 4.4.

No data on the use of CMS by injection were made available, as all clinical studies reviewed used CMS administered as an infusion. The CHMP considers that information on the injection route of administration can be retained in the SmPCs where it is already included. Similarly, data on the use of CMS with a TIVAD (totally implantable venous access device) were not made available during the procedure and the use of these devices was therefore not reviewed. The CHMP considers that information on the use of TIVADs can be retained in the SmPCs where it is already included.

2.4. Safety data

As part of the benefit-risk review, the CHMP also reviewed the safety profile of colistin and identified a number of warnings and precautions and a number of statements on interactions to be harmonised and implemented in section 4.4 and 4.5 respectively of the SmPC of all products for intravenous use.

Nephrotoxicity is the major safety concern relating to colistin and almost every clinical study investigating intravenous colistin reports occurrences of renal impairment during treatment. In clinical studies focusing on efficacy, the reported proportion of patients with renal impairment ranges between 0-50%. The differences may reflect different definitions of the interpretation of renal impairment, differences in population enrolled and investigator judgment regarding causality. The Hartzell et al, 2009 study, which was designed to investigate the effect of colistin on kidney function, found that the incidence of acute renal failure, defined by the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney disease), in 66 patients was 45%, and that 21% of patients discontinued therapy because of nephrotoxicity. The authors argue that because of their cohort of patients with few co-morbidities, the results are reflective of the direct nephrotoxic effects of CMS. Sorli et al, 2011 found a similar rate of renal impairment in their study. Two other studies found an incidence of acute kidney injury of 40% in a population of critically ill patients. Falagas et al, 2005 and Hartzell et al found a correlation between cumulative dose, duration of therapy (> 14 day) and nephrotoxicity, an effect first seen by Koch-Weber, 1970. Rocco et al, 2013 did not see such an effect after 8 days of CMS treatment, which suggests that treatment durations of 14 days or more should be avoided where possible.

However, the CHMP noted that not all studies confirm these findings. Dalfino et al, 2012 did not see a correlation between daily dose, duration or cumulative dose in their small patient population. It is not clear if the longer dose interval may have reduced acute kidney injury in this study. The authors comment that this would be in line with the recent hypothesis by Sorli et al which attributes CMS nephrotoxicity to the minimum plasma concentration of colistin, as seen with aminoglycosides. Sorli et al consider Cmin monitoring to be helpful in the management of patients to prevent renal failure although it is not clear what Cmin range should be targeted. There appears to be insufficient data at present to make a recommendation.

Regarding the possible mechanisms for nephrotoxicity, a number of theories are described in the literature. One study suggests that the D-amino acid and fatty acid molecules of the structure of polymyxins have been associated with the development of nephrotoxicity. Another study found evidence that caspase-mediated apoptosis may be involved. The cationic nature of colistin and potential accumulation in proximal tubular cells have also been implicated and several sensitive biomarkers of renal injury and histopathological changes point towards proximal tubular damage. Ma et al, 2009 reported net tubular reabsorption of colistin and suggested that renal accumulation of colistin may occur. Suzuki et al, 2013 reported the endocytosis receptor megalin, expressed in renal proximal tubules, to be involved with the renal accumulation and nephrotoxicity of colistin. Co-administration with other megalin ligands (e.g. aminoglycosides) may hence lead to increased toxicity. Two recent papers by Yousef et al, both 2011, on the protective effects of antioxidants on the kidneys of rats when treated with colistin have hypothesised that the tubular toxicity is caused by oxidative stress induced by colistin. Vaara et al, 2008, postulate that like aminoglycosides, polymyxins are thought to cause damage to the kidneys at the level of the proximal tubules, where both classes of drugs are thought to be extensively reabsorbed via the endocytic receptor protein megalin. Data in rats indicate that colistin may accumulate in the kidneys. An alternative explanation may be renal metabolism. Colistin is thought to cause tubular damage by increasing the membrane permeability of epithelial cells, leading to leakage of contents and cell death. This effect has been related to drug concentration and treatment duration, with a significant relationship between creatinine increase and cumulative dose of CMS (Falagas et al, 2005).

The CHMP agreed that the nephrotoxic effects of colistin are well established, but that the causative mechanism is not clearly established. Due to the differences in study design, population and definition of renal injury/ impairment, the extent and frequency of renal impairment is difficult to assess and most enrolled patients are critically ill from severe infections and have a high risk of renal damage from the presenting condition. Concomitant treatments including nephrotoxic antibiotics further contribute to this risk. The CHMP noted that renal impairment was in most cases found to be reversible and that although discontinuation of treatment is reported in a number of cases, RRT was not required. Nevertheless, colistin therapy is associated with a risk of renal impairment and acute kidney injury and the CHMP therefore considered it appropriate to include a warning regarding the potential for nephrotoxicity of colistin and the need for dose adjustments in renal impairment in the SmPC, together with a caution regarding co-administration with other nephrotoxic drugs. A statement regarding the potential for accumulation in the kidney was also added. The final agreed wording is presented in Annex III.

Another frequently reported adverse event is neurotoxicity, although this was not observed to be a major problem in most studies reviewed. Falagas et al conclude from their review that the neurotoxic effects of polymyxins are usually mild and resolve after prompt discontinuation of the antibiotics. Neurological adverse events were more commonly seen in a study in cystic fibrosis patients, indicating that such events may be masked in the critically ill patients. Cases of apnoea have been reported in the past, and all the reported cases seem to have occurred after intramuscular administration although it is not understood why the route of administration would be of significance.

Other adverse events reported also seem to largely correspond with what is already included in the SmPCs and include hypersensitivity reactions, rash, urticaria, generalized itching, fever, gastro-intestinal disorders, and pseudomembranous colitis. The incidence of allergic reactions due to colistin use has been reported to be about 2%. Bronchoconstriction and chest tightness are reported as rare complications when colistin is used by inhalation route. Nebulized CMS can cause bronchoconstriction even in patients with no history of asthma. Local pulmonary toxicity seems to be associated primarily with colistin rather than CMS, as illustrated by a case report where CMS was prepared about 24 hours before administration by nebulisation. Within hours of administration, the patient developed severe respiratory distress and acute lung injury, thought to be due to the *in vitro* conversion of CMS to colistin, resulting in colistin induced toxicity. There is no data on the effects of inhaled CMS on other organ systems, e.g. on renal function or neurotoxicity. In view of the low plasma concentrations usually seen after inhaled administration, any dose dependent adverse events are expected to occur at considerably lower frequency than those seen after parenteral administration.

In addition, the CHMP noted that CMS is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular junction, which presents a serious risk in patients with myasthenia gravis. However, given the seriousness of the conditions for which CMS is indicated, the CHMP considered that its use in patients with myasthenia gravis should not be contraindicated but that instead a warning should be added to section 4.4, advising the use of CMS with great caution and only if absolutely needed.

In conclusion, the CHMP was of the opinion that colistin has been shown to cause renal impairment and acute renal injuries, and to a lesser extent neurotoxicity and other adverse events, which may be related to cumulative doses. The frequency of adverse events may be underestimated due to small study sizes and the likely masking of such effects in a population consisting mainly of critically ill patients, many of whom will be sedated and/ or ventilated. Nevertheless, the CHMP considered that these risks must be balanced against the risk of the underlying disease and the high mortality from the treated conditions. The risks can be mitigated by appropriate statements in section 4.4 and 4.5 of the SmPC, including warnings advising against the concurrent administration of nephrotoxic and/or neurotoxic drugs as well as recommendations to perform regular renal function monitoring, mentioning the potential correlation with cumulative dose and treatment duration. The final agreed wording is presented in Annex III.

2.5. Consultation of the PKWP and the IDWP

In the context of the procedure, the CHMP consulted the PKWP to provide support to the CHMP assessment. The PKWP reviewed the population PK data on which the dose proposals were based and the additional performed simulations based on data from the published literature. It was noted that the PK data comes from a number of sources and is often limited to PK parameters rather than full profiles. In addition, the assay methodology limits the usefulness of some of the data, since the analytical assays used to determine the drug levels did not distinguish between the active drug and the prodrug and thus could not be used to determine whether *ex vivo* conversion was occurring. The PKWP therefore deemed the simulations performed by the CHMP to be useful for the understanding of the exposure and potential PK differences in different patient populations but considered that the degree to which these simulations can be considered 'qualified' is limited by the data. In addition the simulations do not give any information on the variability in the PK of this drug. The advice of the PKWP was taken into account by the CHMP when revising the SmPC wording.

The CHMP also consulted the IDWP to provide support to the CHMP assessment. Regarding the acceptability of the available PK/PD data as supportive of the dose recommendations proposed by the CHMP, the IDWP recognised the limitations of the PK/PD data but agreed that the data could be taken into account to determine dosage recommendations, including for loading and maintenance doses and in the relevant patient populations. The advice of the IDWP was taken into account by the CHMP when revising the SmPC wording.

2.6. Risk management plan

The CHMP, having considered the available data, is of the opinion that no additional pharmacovigilance activity, nor any risk minimisation activities are required beyond the recommended changes to the product information.

2.7. Changes to the product information

Having reviewed all available data, the CHMP considered that a number of changes are needed to the product information of CMS products for parenteral and inhaled use. In particular, the wording of the indications was revised and aligned with the existing clinical experience and current guidelines. The posology and method of administration section was also significantly revised to provide appropriate and up-to-date guidance on the use of colistin to prescribers. The available data confirms that colistin exhibits nephrotoxic and neurotoxic properties but these risks can be mitigated by appropriate statements in section 4.4 and 4.5 of the SmPC, including warnings against concurrent administration of nephrotoxic and/or neurotoxic drugs and recommendations for regular renal function monitoring. Additional changes were also agreed to sections 4.4 and 4.5 to update the information on warnings and interactions observed with colistin therapy. Finally, extensive revisions were made to sections 5.1 and 5.2 to reflect current pharmacokinetic and pharmacodynamic data. The CHMP also agreed corresponding changes to the package leaflets.

The CHMP was of the view that the product information of the centrally-authorised product Colobreath is up-to-date, with no need for revision.

2.8. Benefit-risk balance

Having reviewed all available data, the CHMP considered that CMS and colistin represent a crucial therapeutic option in the armamentarium available to prescribers in the context of the treatment of

infections caused by multi-drug resistant Gram-negative pathogens. A large number of PK/PD studies were reviewed together with data from clinical experience and the CHMP considered the available data to be sufficient to support revisions of the indication for both parenteral and inhalation use products, in line with clinical experience and current therapeutic guidelines. It was agreed that colistin can be used without age restrictions, but only for the treatment of serious infections. A key concern is to maintain the efficacy of colistin against multi-drug resistant pathogens and to avoid the selection of resistance arising from monotherapy and the CHMP therefore agreed recommendations for the co-administration of parenteral colistin with other antibiotics. The posology and method of administration section was also revised in its entirety, for all patient subpopulations, in order to define the optimal treatment regimens for achieving plasma concentrations above the critical minimal inhibitory concentrations. In particular, the CHMP considered that a loading dose should be administered, to ensure plasma concentrations above the minimum inhibitory concentration from the very first administration. However, data was extremely limited in certain patient populations and as a result, no firm recommendations could be made for patients with renal impairment, on renal replacement therapy or with hepatic impairment. Data was also particularly limited for paediatric patients.

The CHMP reviewed the optimal way of expressing the strength and dose of polymyxin-containing products and was of the opinion that given the established use of international units (IU) in EU clinical practice and in the European and British Pharmacopoeia, the EU product information for CMS should continue to be expressed in IU. However, the CHMP introduced a dose content conversion table between CMS expressed in IU, CMS expressed in mg and CBA expressed in mg, to raise awareness of the different ways of expressing the strength and dose and to help prescribers who obtain additional information from the literature.

The CHMP also reviewed the data on adverse events observed with the use of colistin and agreed that the use of colistin for parenteral use is associated with nephrotoxicity and neurotoxicity but considered that these risks must be balanced against the risk of the underlying disease and the high mortality from the treated conditions and that they can be satisfactorily mitigated by statements in the SmPC. Finally, extensive revisions were made to reflect current pharmacokinetic and pharmacodynamic data, including an update of the EUCAST breakpoints and the list of susceptible species. Corresponding changes were made to the package leaflets.

In conclusion, the CHMP is of the opinion that the benefit-risk of the polymyxin-based products included in the scope of this procedure remains positive, provided that changes, as applicable, are made to their product information as set out in Annex III to the opinion. Regarding the centrally-authorised product Colobreathe, the CHMP considered the product information to be up to date, with no need for revision.

Therefore, for the medicinal products referred to in Annex I, the CHMP recommended the variation to the terms of the marketing authorisation, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion. For Colobreathe, referred to in Annex A, the CHMP recommended the maintenance of the marketing authorisation, without any variations to the term of the marketing authorisation.

3. Conclusion and grounds for opinion

Whereas

- the existing preclinical and clinical data and the product information including the indications, dosage recommendations and pharmacokinetic and pharmacodynamic information for polymyxin-based products in the EU are not up to date or based on robust data, as highlighted by recent reports of suboptimal efficacy and the emergence of colistin resistance,
- the CHMP carried out a benefit-risk evaluation of polymyxin-based products under Article 31 of Directive 2001/83/EC, reviewing all available data, including responses submitted by the marketing authorisation holders during the procedure and recommendations from the Pharmacokinetics and the Infectious Disease working parties,
- the CHMP considered that colistimethate sodium and colistin represent a crucial therapeutic option in the context of the treatment of infections caused by multi-drug resistant Gram-negative pathogens,
- the CHMP considered that the dose and strength of polymyxin-based products should continue to be expressed in international units,
- the CHMP considered the available data to be sufficient to support revisions of the indication for both parenteral use and inhalation use medicinal products, in line with clinical experience and current therapeutic guidelines
- the CHMP considered that the risks of nephrotoxicity and neurotoxicity observed with colistin for parenteral use should be balanced against the risk of the underlying disease and the high mortality from the treated conditions and that it can be satisfactorily mitigated by warnings and recommendations in the SmPC,
- the CHMP made extensive revisions to the SmPC to reflect current pharmacokinetic and pharmacodynamic data, including an update of the EUCAST breakpoints and the list of susceptible species,

The Committee, as a consequence, concluded that the benefit-risk balance of the polymyxin-based products included in the scope of this procedure remains positive under normal conditions of use, taking into account the agreed changes to the product information, as applicable.