Annex III

Amendments to relevant sections of the summary of product characteristics and the package leaflets

Changes agreed by the CHMP to the product information of CMS-containing products for injection or infusion

Summary of Product Characteristics

Section 4.1 Therapeutic indication

Note: The wording of this section should be replaced with the following wording:

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

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

Section 4.2 Posology and method of administration

Note: The wording of this section should be replaced with the following wording:

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

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

Posology

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

Adults and adolescents

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

In patients who are critically ill, a loading dose of 9 MIU should be administered.
The most appropriate time interval to the first maintenance dose has not been established.

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

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

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

The following dose adjustments are suggested as guidance.

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

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

MIU = million IU

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

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

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

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

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

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

Children ≤ 40kg
75.000-150.000 IU/kg/day divided into 3 doses.

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

The use of doses >150.000 IU/kg/day has been reported in children with cystic fibrosis.

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

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

Note: The following intrathecal and intraventricular administration posology recommendations should be included in the SmPC as 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 volume for injection).

Intrathecal and intraventricular administration

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

Intraventricular route

125.000 IU/day
Intrathecally administered doses should not exceed those recommended for intraventricular use.

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

Method of administration

[Product name] is administered intravenously as a slow infusion over 30 – 60 minutes.

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

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

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

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

CMS conversion table

Potency		**≈ mass of CMS (mg)***
IU	**≈ mg CBA**	
12.500	0.4	1
150.000	5	12
1.000.000	34	80
4.500.000	150	360
9.000.000	300	720

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

Section 4.3 Contraindications

Note: If present, any contraindication in myasthenia gravis should be deleted, to be replaced with a warning in section 4.4, as indicated below.

Section 4.4 Special warnings and precautions for use

Note: The wording of this section should be revised for all SmPCs for products for intravenous administration of CMS/colistin to include the following warnings:

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

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

Renal function monitoring should be performed at the start of treatment and regularly during treatment in all patients. The dose of colistimethate sodium should be adjusted according to creatinine clearance (see section 4.2). Patients who are hypovolaemic or those receiving other potentially nephrotoxic drugs are at increased risk of nephrotoxicity from colistin (see sections 4.5 and 4.8).

Nephrotoxicity has been reported to be associated with cumulative dose and treatment duration in some studies. The benefit of prolonged treatment duration should be balanced against the potentially increased risk of renal toxicity.

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

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

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

Colistimethate sodium is known to reduce the presynaptic release of acetyl-choline at the neuro-muscular junction and should be used in patients with myasthenia gravis with the greatest caution and only if clearly needed.

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

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

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

Note: If intrathecal administration is included in the SmPC of your product, the following should also be included:

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

Section 4.5 Interaction with other medicinal products and other forms of interaction

Note: The wording of this section should be revised for all SmPCs for products for intravenous administration of CMS/colistin to include the following statements:

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

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

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

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

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

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

Section 5.1 Pharmacodynamic properties

Note: The wording of this section should be revised for all SmPCs for products for intravenous administration of CMS/colistin to include the following statements:

Pharmacotherapeutic group: antibacterials for systemic use, other antibacterials, polymyxins.

ATC Code: J01XB01

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

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

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

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

EUCAST Breakpoints

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

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

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

Commonly susceptible species
Acinetobacter baumannii
Haemophilus influenzae
Klebsiella spp
Pseudomonas aeruginosa
Species for which acquired resistance may be a problem
Stenotrophomonas maltophilia
*Achromobacter xylosoxidans (*formerly *Alcaligenes xylosoxidans)*
Inherently resistant organisms

Burkholderia cepacia and related species
Proteus spp
Providencia spp
Serratia spp

Section 5.2 Pharmacokinetic properties

Note: The wording of this section should be revised for all SmPCs for products for intravenous administration of CMS/colistin to include the following statements:

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

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

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

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

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

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

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

<u>Package Leaflet</u>

1. What [Product name] is and what it is used for

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below:

[Product name] is given by injection to treat some types of serious infections caused by certain bacteria. [Product name] is used when other antibiotics are not suitable.

2. What you need to know before you <take> <use> [Product name]

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below. If present, any contraindication in myasthenia gravis should be deleted, to be replaced with a warning, as indicated below.

Do not <take><use> [Product name]
- If you are allergic (hypersensitive) to colistimethate sodium, colistin or to other polymyxins.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using [Product name]
- If you have or have had kidney problems.
- If you suffer from myasthenia gravis
- If you suffer from porphyria

In premature and new-born babies, special care should be taken when using [Product name] as the kidneys are not yet fully developed.

Other medicines and [Product name]
- medicines which can affect how your kidneys function. Taking such medicines at the same time as [Product name] can increase the risk of damage to the kidneys
- medicines which can affect your nervous system. Taking such medicines at the same time as [Product name] can increase the risk of side effects in your nervous system
- medicines called muscle relaxants, often used during general anaesthesia. [Product name] can increase the effects of these medicines. If you have a general anaesthetic, let your anaesthetist know that you are having [Product name]

If you suffer from myasthenia gravis and are also taking other antibiotics called macrolides (such as azithromycin, clarithromycin or erythromycin) or antibiotics called fluoroquinolones (such as ofloxacin, norfloxacin and ciprofloxacin), taking [Product name] further increases the risk of muscle weakness and breathing difficulties.

Having [Product name] as an infusion at the same time as receiving [Product name] as an inhalation can increase your risk of side effects.

3. How to <take><use> [Product name]

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below. A tabulated presentation of the posology could be considered acceptable.

[Product name] is given to you by your doctor as an infusion into a vein over 30 – 60 minutes.

The usual daily dose in adults is 9 million units, divided into two or three doses. If you are quite unwell, you will be given a higher dose of 9 million units once at the start of treatment.

In some cases, your doctor may decide to give a higher daily dose of up to 12 million units.

The usual daily dose in children weighing up to 40 kg is 75.000 to 150.000 units per kilogram body weight, divided into three doses.
Higher doses have occasionally been given in cystic fibrosis.

Children and adults with kidney problems, including those on dialysis, are usually given lower doses. Your doctor will monitor your kidney function regularly while you receive [Product name].

Changes agreed by the CHMP to the Product Information of CMS-containing products for solution for inhalation or nebulisation

Summary of Product Characteristics

Note: The wording of this section should be replaced with the following wording:

Section 4.1 Therapeutic indications

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

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

Section 4.2 Posology and method of administration

Note: The wording of this section should be replaced with the following wording:

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

Posology

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

Recommended dose range:

Administration via inhalation

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

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

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

Older people
Dose adjustment is not considered necessary

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

Hepatic impairment
Dose adjustment is not considered necessary

Method of administration

For inhalation use.
[*Information on suitable nebuliser(s) and output characteristics may be included*]

Colistimethate sodium undergoes hydrolysis to the active substance colistin in aqueous solution.
For special precautions for disposal and handling of reconstituted solutions, see section 6.6.

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

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

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

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

CMS conversion table

Potency		**≈ mass of CMS (mg)***
IU	**≈ mg CBA**	
12.500	0.4	1
150.000	5	12
1.000.000	34	80
4.500.000	150	360
9.000.000	300	720

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

Package Leaflet

1. What [Product name] is and what it is used for

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below:

[Product name] is given as an inhalation to treat chronic chest infections in patients with cystic fibrosis. [Product name] is used when these infections are cause by specific bacteria called *Pseudomonas aeruginosa*.

2. What you need to know before you <take> <use> [Product name]

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below. If present, any contraindication in myasthenia gravis should be deleted, to be replaced with a warning, as indicated below.

Do not <take><use> [Product name]

- If you are allergic (hypersensitive) to colistimethate sodium, colistin or to other polymyxins.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using [Product name]
- If you have or have had kidney problems.
- If you suffer from myasthenia gravis
- If you suffer from porphyria
- If you suffer from asthma.

In premature and new-born babies, special care should be taken when using [Product name] as the kidneys are not yet fully developed.

Other medicines and [Product name]

- medicines which can affect how your kidneys function. Taking such medicines at the same time as [Product name] can increase the risk of damage to the kidneys.
- medicines which can affect your nervous system. Taking such medicines at the same time as [Product name] can increase the risk of side effects in your nervous system
- medicines called muscle relaxants, often used during general anaesthesia. [Product name] can increase the effects of these medicines. If you have a general anaesthetic, let your anaesthetist know that you are having [Product name]

If you suffer from myasthenia gravis and are also taking other antibiotics called macrolides (such as azithromycin, clarithromycin or erythromycin) or antibiotics called fluoroquinolones (such as ofloxacin, norfloxacin and ciprofloxacin), taking [Product name] further increases the risk of muscle weakness and breathing difficulties.

Having [Product name] as an infusion at the same time as receiving [Product name] as an inhalation can increase your risk of side effects.

3. How to <take><use> [Product name]

Note: The existing package leaflet shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the wording below. A tabulated presentation of the posology could be considered acceptable.

The usual dose for adults, adolescents and children aged 2 years or older is 1-2 million units two to three times per day (maximum 6 million units per day).

The usual dose for children less than 2 years old is 0.5-1 million units twice daily (maximum 2 million units per day).

Your doctor may decide to adjust the dose depending on your circumstances. If you also take other inhaled medicines, your doctor will tell you which order to taken them in.