Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Colistimethate sodium (COLOBREATHE®)

This is a summary of the risk management plan (RMP) for Colistimethate sodium (Colobreathe®). The RMP details important risks of Colistimethate sodium (Colobreathe®), how these risks can be minimised, and how more information will be obtained about Colistimethate sodium (Colobreathe®)'s risks and uncertainties (missing information).

Colistimethate sodium (Colobreathe®)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Colistimethate sodium (Colobreathe®) should be used.

This summary of the RMP for Colistimethate sodium (Colobreathe®) should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Colistimethate sodium (Colobreathe®)'s RMP.

I. The Medicine and What It is used for

Colistimethate sodium (Colobreathe®) is authorised for control of persistent lung infections caused by bacterium *Pseudomonas aeruginosa* in adult patients and children aged 6 years and older with cystic fibrosis (see SmPC for the full indication). It contains colistimethate as the active substance and it is given as inhalation powder.

Further information about the evaluation of Colistimethate sodium (Colobreathe®)'s benefits can be found in Colistimethate sodium (Colobreathe®)'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001225/human_med_001507.jsp&mid=WC0b01ac058001d124.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Colistimethate sodium (Colobreathe®), together with measures to minimise such risks and the proposed studies for learning more about Colistimethate sodium (Colobreathe®)'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Colistimethate sodium (Colobreathe®), these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Colistimethate sodium (Colobreathe®) is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Colistimethate sodium (Colobreathe®) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Colistimethate sodium (Colobreathe®). Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 1: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Cough / productive cough • Throat irritation • Chest discomfort / pain • Wheezing / bronchospasm • Dyspnoea • Lower respiratory tract infection • Dysgeusia
Important potential risks	• Exacerbation of myasthenia gravis • Oropharyngeal infection with *Candida albicans* or other yeast like organisms • Nephrotoxicity • Neurotoxicity • Hepatotoxicity • Increased sensitisation to colistimethate due to inhaled route of administration • Capsule fragmentation
Missing information	• Pregnancy / foetal harm • Lactating women

II.B Summary of Important Risks

Table 2: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Cough/Productive cough	
Evidence for linking the risk to the medicine	MAA (clinical trials: Cough was one of the most commonly reported adverse reactions of all Colobreathe® treated patients). Coughing may occur on inhalation.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause cough.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Throat irritation	
Evidence for linking the risk to the medicine	MAA (clinical trials: Throat irritation was one of the most commonly reported adverse reactions of all Colobreathe® treated patients). This is a class effect following use of a dry powder inhalation. Sore throat or mouth has been reported with nebulised colistimethate sodium and may occur with Colobreathe®.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled by such patients may cause throat irritation.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Chest discomfort/Chest pain	
Evidence for linking the risk to the medicine	MAA (clinical trials).
Risk factors and risk groups	Chest discomfort occurs as a symptom of cystic fibrosis.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Wheezing/Bronchospasm	
Evidence for linking the risk to the medicine	MAA (clinical trials). Bronchospasm may occur with inhalation.
Risk factors and risk groups	Patients with cystic fibrosis are likely to have sensitive airways and thus any substance inhaled may cause wheezing/bronchospasm.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Dyspnoea	
Evidence for linking the risk to the medicine	MAA (clinical trials: Dyspnoea was one of the most commonly reported adverse reactions of all Colobreathe® treated patients).
Risk factors and risk groups	Persistent dyspnoea may result in complications if untreated. Adult patients with cystic fibrosis presenting with dyspnoea should be investigated for possible coronary artery disease or pulmonary etiology.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Important identified risk: Lower respiratory tract infection	
Evidence for linking the risk to the medicine	MAA (clinical trials).
Risk factors and risk groups	Patients with cystic fibrosis are at risk of lower respiratory tract infections as a normal course of the disease.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important identified risk: Dysgeusia	
Evidence for linking the risk to the medicine	MAA (clinical trials: Unpleasant taste was the most commonly reported adverse reactions of all Colobreathe® treated patients).
Risk factors and risk groups	This is potentially a disadvantage, and could affect correct use of the product. However, medication of these patients is highly supervised and the patients are motivated to take the required medication.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important potential risk: Exacerbation of Myasthenia Gravis	
Evidence for linking the risk to the medicine	MAA (clinical trials).
Risk factors and risk groups	Patients who already have underlying myasthenia gravis comprise the at risk group.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.5. PL section 2. Prescription only medicine. Additional risk minimisation measures: None.

Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> None.
Important potential risk: Oropharyngeal infection with *Candida albicans* or other yeast-like organisms	
Evidence for linking the risk to the medicine	MAA (clinical trials).
Risk factors and risk groups	Patients taking oral antibiotics are at risk of developing oral candidiasis. However, antibiotics used by the inhalation route could also give rise to oral candidiasis (see SmPC section 4.4).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4. PL section 2. Prescription only medicine. <u>Additional risk minimisation measures:</u> None.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> None.
Important potential risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	Nephrotoxicity is the primary adverse effect that limits systemic use of the polymyxin class of antibiotics. There is no evidence of any nephrotoxicity in patients treated with Colobreathe®. The nephrotoxic potential of colistimethate sodium administered systemically seems to be dose related and reversible upon discontinuation, although complete recovery has been reported to take several weeks or longer.
Risk factors and risk groups	It is presumed that those with existing impaired renal function and using other potentially nephrotoxic drugs would be more susceptible to such a risk.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.4 and 4.5. PL section 2. Prescription only medicine. <u>Additional risk minimisation measures:</u> None.
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> None.
Important potential risk: Neurotoxicity	
Evidence for linking the risk to the medicine	There were no reports of neurotoxicity in clinical trials with Colobreathe®. Neurotoxicity has been associated with systemic use of colistimethate, normally at doses much higher than those employed in modern treatment regimens. Care should still be taken in administering Colobreathe® to patients who are known to have a propensity for neurotoxic events.
Risk factors and risk groups	Patients with pre-existing neurotoxic conditions.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.5. PL section 2. Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important potential risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	There were no reports of hepatotoxicity in clinical trials with Colobreathe®. There is no clear evidence of association with this risk.
Risk factors and risk groups	None known, although it is presumed that those with existing impaired liver function would be more susceptible to such a risk.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Important potential risk: Increased sensitisation to colistimethate due to inhaled route of administration	
Evidence for linking the risk to the medicine	There were no reports of increased sensitisation to colistimethate due to inhaled route of administration in clinical trials with Colobreathe®. There is no clear evidence of association with this risk.
Risk factors and risk groups	None known.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3. PL section 2. Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Important potential risk: Capsule fragmentation	
Evidence for linking the risk to the medicine	Capsule fragmentation is a quality issue that may potentially have safety consequences. As of September 2017 hard gelatin capsule has been replaced with PEG capsule, which are standard gelatin capsules containing polyethylene glycol as an additional plasticizer. The addition of PEG renders the capsules less brittle compared to standard gelatin capsules, even at lower moisture content, which is advantageous for formulations that are hygroscopic and are manufactured under lower humidity conditions, as is the case with Colobreathe®.
Risk factors and risk groups	No risk groups and no risk factors have been identified regarding this quality issue and possible safety consequences.
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine. Additional risk minimisation measures: An educational DVD and Colobreathe® patient and healthcare professional guide in leaflet form are distributed.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Pregnancy/Foetal harm	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6. PL section 2 Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.
Missing information: Lactating women	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6. PL section 2 Prescription only medicine. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation of Colistimethate sodium (Colobreathe®).

II.C.2 Other Studies in Post-Authorisation Development Plan

Not applicable.