Swiss Summary of the Risk Management Plan
for
Bronchitol® (mannitol)

Version 1.0 corresponding to the EU-RMP Version 9.1

Disclaimer: The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Bronchitol® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelin-formation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of "Bezeichnung des Arzneimittels" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

EffRx Pharmaceuticals S.A is fully responsible for the accuracy and correctness of the content of the published summary RMP of Bronchitol®.

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Summary of the Risk Management Plan (RMP) for Bronchitol® (Mannitol)

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

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

This summary of the RMP for Bronchitol® 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 Bronchitol® RMP.

I. The medicine and what it is used for

Bronchitol® is authorised for the treatment of cystic fibrosis (CF) in adults and in children aged 6 years and above as add-on therapy to best standard of care.
The efficacy of Bronchitol as an add-on to background therapy with CFTR potentiators has not been studied.

Bronchitol® contains inhaled mannitol as the active substance and it is given by inhalation powder (40 mg) in hard capsules to be used in an inhaler.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Bronchitol, together with measures to minimise such risks and the proposed studies for learning more about Bronchitol'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 Bronchitol, 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 Bronchitol is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Bronchitol are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Bronchitol. 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).

List of important risks and missing information	
Important identified risks	· Haemoptysis · Bronchospasm · Cough
Important potential risks	· Increased risk of respiratory or systemic infection
Missing information	· Patients who have had significant haemoptysis in last 3 months · Patients with <30% predicted FEV_1

II.B Summary of important risks

Important identified risk: Haemoptysis	
Evidence for linking the risk to the medicine	In clinical trials, haemoptysis was noted to be a common adverse reaction. New or increased haemoptysis (all-causality AEs or as a symptom of pulmonary exacerbation) was reported in 10.6% of patients receiving Bronchitol compared with 10.2% of patients receiving control (50 mg mannitol) in 3 phase 3 studies combined. Haemoptysis is considered an important identified risk as massive haemoptysis may be life threatening.
Risk factors and risk groups	The greatest risk factors for haemoptysis are a previous history of haemoptysis, pulmonary exacerbation and cough. Pancreatic insufficiency, diabetes and *Staphylococcus aureus* (*S. aureus*) infections are also major factors associated with massive haemoptysis in the CF population.
Risk minimisation measures	*Routine risk minimisation measures* SmPC section »*Undesirable effects*» SmPC section »*Special warnings and precautions for use*" where advice is given on carefully monitoring patients with a history of significant episodes of haemoptysis (>60 mL) in the previous 3 months PL sections "*When is caution required*" and "*What are possible side effects"* *Additional risk minimisation measures* Educational Material for Health Care Professionals

Important identified risk: Bronchospasm	
Evidence for linking the risk to the medicine	In clinical trials, bronchospasm was noted to be an uncommon adverse reaction. All-causality AEs of bronchospasm were reported in 0.4% of patients receiving Bronchitol compared with 0.4% of patients receiving control (50 mg mannitol) in 3 phase 3 studies combined. Bronchospasm is considered an important identified risk as, together with life-threatening upper airway obstruction and/or hypotension, it can be fatal.
Risk factors and risk groups	The changes in airway dimensions in CF patients, such as a significant increase in airway smooth muscle and wall area and a decrease in cartilage area are thought to contribute to the severe airflow obstruction and increased bronchial responsiveness to bronchodilators and bronchoconstrictors. Severe airflow obstruction develops in most CF patients with increasing age. Inhaled mannitol is a known bronchoconstrictive agent in patients with active asthma. Bronchospasm following the inhalation of an aerosol is common, irrespective of the agent inhaled, with the risk of bronchospasm greater in patients with inherent airway liability due to conditions such as asthma.
Risk minimisation measures	*Routine risk minimisation measures* SmPC "*Posology and method of administration*" and "*Undesirable effects*" SmPC "*Special warnings and precautions for use*" where advice is given on careful monitoring of patients for bronchial hyperresponsiveness to inhaled mannitol during administration of their initiation dose. "*Special warnings and precautions for use*" also provides advice on conducting a formal review after approximately 6 weeks of Bronchitol treatment to assess for signs and symptoms of active substance induced bronchospasm. PL sections "*When is caution required*", "*How to use*" and "*What are possible side effects"* *Additional risk minimisation measures* Educational Material for Health Care Professionals

Important identified risk: Cough	
Evidence for linking the risk to the medicine	In clinical trials, cough was noted to be a common adverse reaction. All-causality AEs of cough were reported in 17.3% of patients receiving Bronchitol compared with 13.5% of patients receiving control (50 mg mannitol) in 3 phase 3 studies combined. Cough is considered an important identified risk as episodes of cough may be accompanied by events of haemoptysis or cough-induced neurological deficits, e.g., cough-syncope, associated headache and paralysis.
Risk factors and risk groups	All patients with CF will experience cough as part of their disease. Cough, and its frequency and productivity, may depend on the severity of disease, which may increase with advancing age. Cough is often associated with acute pulmonary exacerbation of CF, and more frequent and productive cough may be indicative of a decline in lung function.
Risk minimisation measures	*Routine risk minimisation measures* SmPC section "*Undesirable effects*" SmPC section "*Special warnings and precautions for use*" where advice is given on providing training to practice correct inhaler technique during treatment PL sections "*When is caution required*", "*How to use*" and "*What are possible side effects"* *Additional risk minimisation measures* Educational Material for Health Care Professionals

Important potential risk: Increased risk of respiratory or systemic infection	
Evidence for linking the risk to the medicine	In clinical trials, certain infections were noted to be uncommon adverse reactions. All-causality AEs of respiratory and systemic infections were reported in 38.9% of patients receiving Bronchitol compared with 37.6% of patients receiving control (50 mg mannitol) in 3 phase 3 studies combined. Increased risk of respiratory and systemic infections is considered an important potential risk as these types of infections are frequent in patients with CF, but it is unclear if administration of Bronchitol increases this risk.
Risk factors and risk groups	Although patient-to-patient transmission generally occurs due to prolonged social contact, the routes of transmission are not fully understood and thought to be due to infected respiratory secretions contaminating the healthcare environment. *B. cepacia* complex bacteria have also been recognised as particularly virulent pathogens in CF, and infection with the organisms is associated with a rapid decline in lung function and markedly shorter median survival. Currently, *B. cepacia* complex has been isolated from 3% to 4% of patients with CF in the US and these bacteria have been found to possess innate and acquired mechanisms of multidrug resistance. All but one

	of the identified bacterial species in the *B. cepacian* complex, have been cultured in CF sputum and *B. cenocepacia* and *B. multivorans* are the two most common species, accounting for approximately 45% and 40% of infections, respectively. *B. cepacia* infections can be transmitted from patient to patient due to close contact between CF patients and sharing of equipment. Strict policies have been adopted worldwide for segregation of CF patients with *B. cepacia* infections, and segregation is considered the most successful prevention strategies. *S. aureus* and *H. influenzae* infections are commonly seen in infants with CF and an increase in *methicillin-resistant S. aureus* (MRSA) has been noted in CF patients in recent years. Patient-to-patient transmission of these organisms has been observed and policies to prevent these modes of transmission will help to control infections among CF patients.
Risk minimisation measures	*Routine risk minimisation measures* SmPC section "*Undesirable effects*" PL section "*Possible side effects"* *Additional risk minimisation measures* None

Missing information: Patients who have had significant haemoptysis in last 3 months	
Risk minimisation measures	*Routine risk minimisation measures* SmPC section "*Undesirable effects*" SmPC section "*Special warnings and precautions for use*" where advice is given on carefully monitoring patients with a history of significant episodes of haemoptysis (>60 mL) in the previous 3 months *Additional risk minimisation measures* Educational Material for Health Care Professionals

Missing information: Patients with <30% predicted FEV1	
Risk minimisation measures	*Routine risk minimisation measures* SmPC section "*Undesirable effects*" SmPC section "*Special warnings and precautions for use*" where it is recommended not to use Bronchitol in patients with a FEV1 of less than 30% of predicted *Additional risk minimisation measures* 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 or specific obligation of Bronchitol.

II.C.2 Other studies in post-authorisation development plan

Not applicable.