Bisolaclar™ 600 mg effervescent tablets

Risk Management Plan Public Summary

VI.2. Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Respiratory tract infections are the most common, and potentially most severe, of infections treated by health care practitioners (File, 2000). Acute respiratory tract infection (ARI) is considered as one of the major public health problems and it is recognised as the leading cause of mortality and morbidity in many developing countries. In developing countries 30% of all patients' consultation are of ARI (Yousif, 2006). According to estimates taken by the National Centre for Health Statistics in 2006, approximately 9.5 million people (4% of the population), were diagnosed with chronic bronchitis. These statistics may underestimate the prevalence of chronic obstructive pulmonary disease by as much as 50%, because many patients underreport their symptoms, and their conditions remain undiagnosed (Fayyaz, 2013). The exact prevalence of chronic obstructive pulmonary disease worldwide is largely unknown, but estimates have varied from 7-19%. A study found a global prevalence of 10.1% (Mosenifar, 2013).

VI.2.2 Summary of treatment benefits

Acetylcysteine is approved as an over the counter mucolytic (agent that dissolves thick mucus) for children and adults to reduce viscosity of secretions and facilitate coughing in many countries worldwide. It has also been shown to reduce the exacerbation rate or hospitalisation days in patients with chronic bronchitis or chronic obstructive pulmonary disease (COPD) in long-term studies. A number of acute and chronic lung conditions may benefit from acetylcysteine supplementation. Acetylcysteine can reduce lung flare-ups in people suffering from chronic obstructive pulmonary disease. Acetylcysteine can also improve lung function in people with pulmonary fibrosis or chronic bronchitis.

Oral acetylcysteine is generally well-tolerated and safe, even at high doses, and adverse events are usually mild and resolve without intervention (Appelboam, 2002; Ambra, 2005; Dodd, 2008). Serious adverse events to oral acetylcysteine are rare (Algren, 2008).

In most clinical trials in patients with acute or chronic respiratory disease, acetylcysteine provided some benefit compared to placebo and/or provided faster symptom relief. Although some controversy still exists, the use of acetylcysteine is considered justified in patients with respiratory tract disorders.

VI.2.3 Unknowns relating to treatment benefits

Most trials on the efficacy of acetylcysteine have been performed in patients with chronic bronchitis or COPD. Limited clinical data are available for other respiratory diseases that are commonly associated with disturbances of bronchial secretion or impaired mucociliary clearance such as acute bronchitis or cystic fibrosis.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Allergic reactions (Hypersensitivity)	Oral acetylcysteine only resulted in minimal anaphylactic reactions and serious anaphylactic reactions, asthma, and status epilepticus have been only reported after intravenous acetylcysteine (Kanter, 2004). The type of reaction depends on the person's immune system response, which is sometimes unpredictable. In rare cases, an allergic reaction can be life-threatening (known as anaphylaxis).	Perform a thorough history and physical examination for risk factors including previous allergic reaction to acetyl-cysteine, or to any other medicine. The risk of serious adverse reactions can be mitigated by monitoring for early symptoms.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Severe skin reactions (including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) [Stevens-Johnson Syndrome: Serious illness with blistering of the skin, mouth, eyes and genitals] [Toxic epidermal necrolysis: Serious illness with blistering of the skin]	Very rarely, serious skin reactions such as Stevens-Johnson syndrome and Lyell syndrome have been reported in temporal association with the use of acetylcysteine. Mostly these could be explained by the patient’s underlying disease and/or concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with acetylcysteine discontinued as a precaution.
Clinical effects resulting from anticoagulant and platelet-inhibiting properties of acetylcysteine	A decrease in platelet aggregation in the presence of acetylcysteine has been confirmed in various studies. The clinical significance of this has not yet been established.

Missing information	
Risk	**What is known**
Use in pregnant and lactating women	There is a limited amount of data from the use of acetylcysteine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Acetylcysteine

	crosses the placenta. Available data do not indicate a risk to the baby. As a precautionary measure, it is preferable to avoid the use of Acetylcysteine PharOS during pregnancy. It is unknown whether acetylcysteine/metabolites are excreted in human milk. At therapeutic doses no effects of acetylcysteine on the baby are expected. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Acetylcysteine PharOS therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Not applicable. No additional risk minimisation measures are proposed for Acetylcysteine PharOS.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 3: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	02/04/2014	Identified Risks: - Hypersensitivity Potential risks: - None Missing information: - None	None
2.0	16/12/2014	Important identified risks: – Severe hypersensitivity reactions (including anaphylactic shock) Important potential risks: – Severe skin reactions (including Stevens-Johnson syndrome and Toxic Epidermal Necrolysis) – Clinical effects resulting from anticoagulant and platelet-inhibiting properties of acetylcysteine Missing information: – Use in pregnant and lactating women	None