VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Airway mucus over secretion is a feature of various diseases affecting the lungs, including chronic bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and asthma.

Chronic obstructive pulmonary disease (COPD)

The exact number of cases of COPD worldwide is unknown. However, it is estimated that about 10% of the population are affected by this disease, although this varies by country. Although COPD occurs more commonly in men, the incidence in women is increasing. COPD occurs mainly in people over 40 years of age, and in adults suffering from posttraumatic stress disorder.[1]

Chronic and acute bronchitis

According to estimates, in 2006 about 9.5 million people, or 4% of the population, were diagnosed with chronic bronchitis. Acute bronchitis affects 44 of 1000 adults annually, and occurred most often in autumn or winter. Less wealthy people and people who live in urban and highly industrialized areas are more likely to get bronchitis. Although found in all age groups, acute bronchitis most often affects children younger than 5 years, whereas chronic bronchitis is more common in people older than 50 years.[2]

Cystic fibrosis

Cystic fibrosis is a disease that can affect many organs of the body but mainly results in chronic respiratory infections, problems with digesting food (pancreatic enzyme insufficien-cy), and if left untreated other complications are likely to occur. The symptoms may vary de-pending n the patient's age. The survival age varies around the world but is typically about 36.9 years, this has improved greatly in the last few decades due to improvements in medical and surgical treatment.[3] In the 27 EU countries the average occurrence of CF is 0.737 per 10,000 inhabitants.[4]

Asthma

Asthma is a common chronic disease worldwide and recent studies indicate that the prevalence of asthma in adults in northern Europe may be as high as 5-8%.[5] It is the most common chronic disease in childhood. The pathophysiology of asthma is complex and involves airway inflammation, intermittent airflow obstruction, and bronchial hyperresponsiveness.[6]

VI.2.2 Summary of treatment benefits[7]

Ambroxol is indicated as a therapy to help loosen and clear the mucus from the airways of productive cough in acute or chronic diseases affecting the lungs.

Chronic respiratory diseases

The results of four studies including a total of 653 patients receiving ambroxol or placebo in patients with chronic bronchitis or COPD showed that ambroxol produce symptomatic improvement. The studies also investigated the effect on exacerbations and found this improved after long-term treatment or in patients with more severe symptoms.

Another study performed on 30 patients suffering from chronic obstructive bronchitis comparing bromhexine with ambroxol found that both substances facilitated expectoration and that ambroxol may result in improved respiratory performance.

A study investigated the efficacy of ambroxol in combination with amoxicillin in 23 patients and found that the improvement in cough, expectoration difficulties and phlegm purulence was statistically more evident and occurred earlier in the ambroxol and amoxicillin group than in the amoxicillin only group.

Acute respiratory diseases

A study investigating the effect, safety and tolerability of myrtol standardized, cefuroxime, ambroxol and matched placebo involving 676 patients with acute bronchitis was performed. Effect of the active treatments vs placebo with little difference among the treatments was confirmed for all further criteria of evaluation. There was no evidence of bronchoconstriction or relapse in any treatment group for the patients continuing treatment. The treatments were safe and comparably well tolerated.

A study investigating whether or not treatment with ambroxol in combination with antibiotics in 120 children with acute lower respiratory tract infections were performed. The children were all given antibiotics plus, at random, either ambroxol or placebo. All the patients in both groups were cured clinically. However, reduction of cough, chest and lung symptoms, and improvement of the lung radiographical pictures were significantly more rapid in children treated with ambroxol than in those who received the antibiotic alone. Ambroxol was tolerated perfectly by all the children

Two studies investigated the effect of ambroxol in 84 patients with asthma or spastic bronchitis. Ambroxol was effective in both studies leading to a decrease in bronchial overreactivity, disappearance of cough and clearance of airways.

One study investigated the effect of ambroxol in 28 children with spastic bronchitis compared with acetylcysteine. Both drugs were effective on quantity and quality of phlegm, difficulty in expectorating, cough, difficulty breathing, bronchial bruits and were well tolerated. Ambroxol proved to be more rapid in achieving a satisfactory improvement than acetylcysteine.

One study investigated the effect of ambroxol compared to acetylcysteine in 36 patients with CF. The results of the study demonstrated that, although no clinical differences were observed between the 3 groups, significant impairment in the placebo group was found for expiration when compared to the active groups, suggesting a therapeutic effect of ambroxol in CF.

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Accumulation of ambroxol in the body (produced in the liver) in patients with severely lowered kidney function and in patients with lowered liver function (Accumulation of ambroxol metabolites (produced in the liver) in patients with severe renal impairment and in	Accumulation of ambroxol in the body produced in the liver can be expected in patients with severely lowered kidney function and in patients with lowered liver function. In patients with lowered kidney function or severely liver function, ambroxol should be given only under medical	Yes, by avoiding the use of ambroxol in patients with lowered kidney or liver function.

Risk	What is known	Preventability
patients with hepatic impairment)	supervision since the dose might need to be lowered or the time between doses increased.	
Severe, potentially life threatening allergic reactions (Anaphylactic reactions including anaphylactic shock)	Severe potentially life threatening allergic reactions can occur with the use of ambroxol.	Yes, by avoiding the use of ambroxol if undesired allergic reactions to the drug is known.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Severe skin reactions such as Stevens Johnson's Syndrome (serious illness with blistering of the mouth, eyes and genitals) and toxic epidermal necrosis (serious illness with blistering of the skin) (Allergic reactions including severe skin reactions (SCARS))	Intake of ambroxol may cause severe disorders of the skin: Stevens-Johnson syndrome (serious illness with blistering of the mouth, eyes and genitals) and toxic epidermal necrosis (serious illness with blistering of the skin). Patients should immediately announce their doctors if any of these skin changes occur.

Missing information

Risk	What is known
Use in pregnancy	In animal studies ambroxol have not shown any harmful effects. Extensive clinical experience after the 28th week of pregnancy has shown no evidence of harmful effects on the foetus. Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed. Especially during the first trimester, the use of ambroxol is not recommended.
Use of ambroxol by breastfeeding mothers (Use in lactation)	Ambroxol is transferred into breast milk and the use of ambroxol is not recommended in nursing mothers.
Use in children	The effects of high ambroxol concentrations in children are not known; therefore it is contraindicated in different age categories depending on the product.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for ambroxol.

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.