

Public Assessment Report

Scientific discussion

Rivendra Ambroxol hydrochloride

DK/H/2363/001-002/DC

Date: 29-08-2015

This module reflects the scientific discussion for the approval of Rivendra. The procedure was finalised at 8th July 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Rivendra 30mg and 60mg effervescent tablets, from Actavis Group PTC ehf.

The products are indicated for Mucolytic therapy of productive cough in acute or chronic bronchopulmonary diseases associated with pathological mucus secretion and impaired mucus transport. A comprehensive description of the indication and posology is given in the SmPC.

Ambroxol, an active metabolite of bromhexine, is a mucoactive agent that possesses manifested secretolytic effect, regulates the production of mucus and normalizes its viscosity by intracellular activation at formation of serous secretion and reduction of sulfomucine synthesis in cells.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC., a so-called generic application.

The reference products are Mucosolvan 30mg and 60mg effervescent tablets marketed by Boehringer Ingelheim Pharma GmbH & Co. KG. No bioequivalence studies have been conducted to compare the bioavailability of the reference and the Actavis products

Agreement between Member States was reached during a written procedure. There was no discussion in the CMDh.

II. QUALITY ASPECTS

II.1 Introduction

Each effervescent tablet contains 30 mg or 60 mg of ambroxol hydrochloride.

The 30mg effervescent tablet is a white, round tablet, 18 mm in diameter, with a break mark on one side, engraved “3” on each tablet half and with a cherry odour. The tablet can be divided into equal doses.

The 60mg effervescent tablet is a white, round tablets, 18 mm in diameter, with a break mark on one side and a cherry odour. The tablet can be divided into equal doses.

The effervescent tablets are packed into polypropylene tubes which are closed with polyethylene desiccant stoppers. The stoppers are filled with Silica gel dessicant to protect the tablets against moisture.

Approved pack sizes are 10 and 20 effervescent tablets.

The excipients are:

- Citric acid, anhydrous
- Sodium hydrogen carbonate
- Sodium carbonate anhydrous
- Saccharin sodium
- Sodium cyclamate

- Sodium chloride
- Sodium citrate
- Lactose, anhydrous
- Mannitol
- Sorbitol (E 420)
- Simeticone
- *Cherry flavour:*
- Natural/nature identical flavouring substances
- Maltodextrin
- Mannitol (E421)
- Gluconolactone (E575)
- Sorbitol (E420)
- Acacia (E414)
- Silica, colloidal anhydrous (E551)

Compliance with Good Manufacturing Practice (GMP)

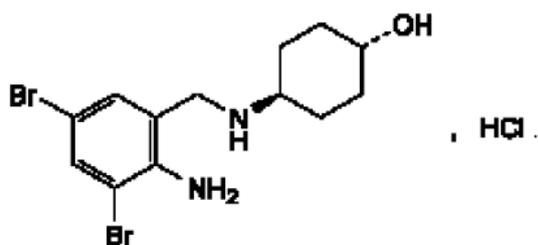
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The product contains the active substance ambroxol hydrochloride which is sourced from two manufacturer. The manufacturers of ambroxol hydrochloride hold a valid Certificate of Suitability (CEP) which verifies that the active substance is suitably controlled by the monograph if supplemented by additional tests for residual solvents as specified in the CEP.

The active substance complies with the Ph. Eur. monograph and additional source specific tests as in the CEPs. The specification for the active substance is adequately drawn up in line with the Ph. Eur. and CEPs.

INN: Ambroxol hydrochloride
 Chemical name: trans-4-[(2-Amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride
 Molecular formula: C₁₃H₁₉Br₂ClN₂O
 Molecular mass: 414.6 g/mol
 Structural formula:



Ambroxol hydrochloride is described in the European pharmacopoeia (Ph. Eur.). It is a white or yellowish crystalline powder. It is soluble in methanol, sparingly soluble in water and practically insoluble in methylene chloride.

All relevant aspects of the manufacturing process have been evaluated by the European Directorate for the Quality of Medicines (EDQM) prior to granting the CEP.

The finished product manufacturer employs the analytical methods described in Ph. Eur.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained. Process validation data obtained with three production scale batches of maximum size of both tablet strengths have been provided.

The drug product specifications cover appropriate parameters for this dosage form. Validation of the analytical methods has been performed. The stability-indicating nature of the HPLC method should be clarified.

Batch analysis has been performed on three production scale batches of each tablet strength. The batch analysis results show that the drug products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline.

The proposed shelf-life of 3 years when stored below 30°C for the drug product is considered acceptable.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of ambroxol are well known. As ambroxol is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The provided non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Rivendra is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

The reference products are Mucosolvan 30mg and 60mg effervescent tablets marketed by Boehringer Ingelheim Pharma GmbH & Co. KG. No bioequivalence studies have been conducted to compare the bioavailability of the reference and the Actavis products

Pharmacokinetics

The active substance is almost completely absorbed following oral administration. Maximum plasma levels are obtained in 1 to 2.5 hours after administration of an immediate-release dosage. The absolute bioavailability is 79% for a 30 mg tablet. There is no food effect on bioavailability of the active substance.

The active substance is rapidly distributed from the blood to the tissue. The highest concentration of the active substance is found in the lungs. The estimated volume of distribution is 552 L following oral administration.

About 30% of the dose is subject to first-pass metabolism following oral administration. The active substance is primarily eliminated by biotransformation to 2 major metabolites of phase I reactions called 6,8-dibromo-3-(trans-4-hydroxycyclohexyl)-1,2,3,4-tetrahydroquinazoline (DHTQ) and 3,5-dibromoanthranilic acid (DBAA). The metabolites and the active substances are also converted to conjugates primarily in the form of glucuronides.

The active substance is almost completely excreted in the urine. For tablet formulations the mean transit time is 6.8 hours.

After 3 days of oral administration, 6% of the active substance is eliminated unchanged and 26% of the active substance is eliminated as conjugates.

The terminal elimination half-life is about 10 hours. The total clearance is about 660 mL/min. The renal clearance accounts for about 8% of the total clearance.

Biowaiver

A waiver for not conducting a bioequivalence study is claimed for both strengths referring to the dosage form i.e. an aqueous oral solution at the time of administration and the concentrations of the active substance being identical to that of the reference products.

According to the EMA Guideline on the investigation of bioequivalence (2010), "If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data.

It is considered unlikely that the applied content of mannitol should have any significant impact on the absorption of the active substance. The biowaiver has been adequately justified

Clinical efficacy

The effect of ambroxol in patients with chronic bronchitis/COPD is supported by randomized controlled trials in 6 publications. In these studies 735 patients were included. In the active treatment groups 15 patients received 45 mg/day, 110 patients received 75 mg/day, 78 patients received 120 mg/day, and 115 patients received 150 mg/day. 15 patients received bromhexine 36 mg. 300 patients received placebo For 70 patients dosing details were not provided.

Various efficacy endpoints were used, among others reduction in number of bronchitis exacerbations, days of antibiotic therapy, improved expectoration, and sputum viscosity. Although the endpoints varied, consistent results in improving respiratory symptoms were shown.

In these studies, the 120 mg dose showed consistent effect, and effects were seen for the 150 mg dose and the 75 mg daily dose of ambroxol.

For additional support, 23 chronic bronchitis patients with exacerbation were all treated with amoxicillin 1500 mg/day, for 10 patients ambroxol was added. Daily sputum volume was greater in the ambroxol treated group and improvement in cough and sputum purulence occurred earlier in the ambroxol +amoxicillin group.

Observational trials in patients with chronic bronchitis:

In a large observational study in patients with chronic bronchitis 5635 patients were dosed with 75 mg/day for 6 months. The number of exacerbations were reduced with 3 or more episodes, and a high percentage of patients did not experience recurrent exacerbations; 81.6% in the 1st month, 58% in the 3rd and 44.9% in the 6th month of therapy.

In two smaller observational studies, 115 patients with bronchitis received ambroxol 90 mg/day. Endpoints were reduction in cough and improvement in expectoration. In 34 patients with silicosis the results were better than in the 28 patients with bronchitis.

Effect in acute bronchitis:

Patients with acute bronchitis were included in a randomized multi center placebo and active controlled trial. 676 patients were dosed for 2 weeks; 163 with ambroxol 3 x 30 mg for days 1-3 and 2x30 mg for days 4-14, 170 with myrtol and 171 with cefuroxime/cephalosporin. 172 patients received placebo. For rates of responders and for patient diary recording of symptoms, the three active treatments were similar, and better than placebo. The responder rates for the active treated groups were around 90 %, and the responder rate 77.3% for placebo. In this population with acute bronchitis ambroxol in the 90 mg/60 mg daily dose showed better effects than placebo and results similar to a myrtol (pine/eucalyptus) product.

To investigate the effect in children with pneumonia, 120 children the age from 1 months to 11 years were treated with relevant antibiotics. Ambroxol was added to the antibiotic in 60 children, placebo was added in 60 children. The doses were similar to the doses proposed in the SmPC for adults and adolescents. For 79% of the children dosed with ambroxol chest x-ray was considered normalised after 7-10 days of dosing. For the placebo group, chest x-ray was considered normalised for 53%.

Supportive studies in asthma is presented;

For effect of ambroxol in patients with asthma 73 patients were dosed for about 2 weeks in an observational study (doses not provided). 47 % of patients had complete disappearance of cough and clearance of airways, and 38.4 % had a significant improvement.

A smaller study evaluated effects of ambroxol on other parameters in patients with asthma; effect on methacholine provocation test (n =11). After 14 days of dosing with ambroxol 90 mg /day, mean methacholine PD20 was more than double that of placebo treated patients. The difference was statistically significant.

Another small study evaluated effect of ambroxol on capsaicin cough threshold (n=14) in a cross over design with carbocysteine. The cough threshold after carbocysteine was significantly greater than for ambroxol (p=0.047) and placebo (p=0.047), respectively.

In a study with 28 children with asthma, 14 children were dosed with ambroxol 30 mg, and 14 children with acetylcysteine. Both drugs had effects on cough, dyspnoea, and difficulty in expectorating. Ambroxol was considered to achieve the improvements faster.

The results in adults and children with asthma are considered to be supportive of the efficacy of ambroxol.

Effects in Cystic fibrosis

The effects of ambroxol in cystic fibrosis patients have been evaluated in two studies with a

total of 62 patients. In total 24 (11/13) patients were dosed with ambroxol (90-100 mg/day), 13 patients with carbocysteine lysine salt, 10 patients with N-acetylcysteine and 11 patients with placebo.

In these trials ambroxol showed effects on paO_2 , and forced expiratory flow.

Overall the effects of ambroxol in patients with cystic fibrosis were considered similar to the effect of the comparator drugs.

Effects of ambroxol have been shown in randomised blinded trials in patients with chronic bronchitis. Results for patients with asthma and with cystic fibrosis provide support to the cough relieving and mucolytics effects of ambroxol.

The publications have different endpoints. Different dosing schedules and treatment durations have been used.

In summary, ambroxol 90 mg has been shown to be effective in acute and chronic bronchitis in reducing cough and loosening phlegm / clearing of airways. The proposed SmPC is in line the SmPC of the reference product and in the EU workshare core safety profile although some revision is needed.

Clinical safety

Ambroxol has been available in the market since 1973 and its safety is based on its use in >15,000 patients in > 100 studies and an estimated total of 4,789,563 patient-years in a Periodic Safety Update Report reviewed in 2008. Skin rashes, nausea and vomiting, abdominal pain, dyspepsia, anaphylactic reactions, and allergic reactions were the most prominent reports. Ambroxol is considered to be generally safe and well tolerated (*Malerba and Ragnoli 2008*).

Due to its good safety profile, ambroxol has been administered at doses up to 3 g per day for 53 days or used at oral doses of 1.3 g per day for 33 days (*Weiser 2008*).

In the meta-analysis of randomized clinical trials that compared at least two months of regular oral mucolytic drugs with placebo conducted by Poole and Black (2001), in 23 studies, there were 1890 AEs in 2450 subjects taking mucolytic drugs and 1882 events in 2453 subjects taking placebo (mean of 0.77 events per subject in both groups). There is, therefore, probably no difference between mucolytic and placebo treatments in terms of the total number of AEs (*Poole and Black 2001*).

In the multicentre, randomized, placebo- and actively controlled, double-blind, parallel group study in patients with acute bronchitis conducted by Matthys et al (2000), there was a total of 131 AEs in 104/676 subjects: 15.9, 16.3, 14.0 and 15.3% of the subjects treated with myrtol stand., placebo, cefuroxime and ambroxol, respectively, experienced at least one AE. 17/676 (2.5%) patients were discontinued because of AE: 5, 2, 8 and 2 patients treated with myrtol stand., placebo, cefuroxime and ambroxol, respectively. The treatments scored comparably well upon evaluation of tolerability by patients and physicians: for 88%, 86%, 90% and 90% (ITT) the tolerability was scored as "good" or "very good" by the physicians (85%, 86%, 84% and 87% for the scores by the patients) at visit 2 for the treatment groups with Myrtol stand., placebo, cefuroxime and ambroxol, respectively (*Matthys et al 2000*).

Schulz et al (2006) evaluated the "real life" behaviour of consumers with non-prescription access to an ambroxol cough syrup with special focus on tolerability and the pattern of product usage. 2,707 participants were recruited in 266 pharmacies. 2,664 questionnaires were evaluable. According to the results of the study, at baseline, the respondents reported a complex pattern of symptoms. Productive coughs, congested airways, dry cough, cough irritation in the throat and soreness in the throat were the most common ones. 67 patients (2.5%) reported a

total of 81 AEs which were usually mild in nature and mostly affecting the gastrointestinal tract (n = 53) followed by skin and subcutaneous tissue disorders (n = 9). Only adverse events already in the SmPC were reported. In general, 97% of the participants assessed the safety as "very good" (51%) or "good" (46%). Overall, the respondents complied with the indications for use and the recommended dosages, with only 0.7% of the participants using the maximum daily dose. 92% of the patients assessed the self-perceived effectiveness as "very good" (29%) or "good" (63%) and 89% were willing to purchase this ambroxol cough syrup again. The authors concluded that ambroxol is used according to the advice given in the patients' leaflet and supports the already established safety and efficacy of this product in acute bronchitis (*Schulz et al 2006*).

IV.1 Risk Management Plan

The Marketing authorisation holder has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rivendra.

The following summary list of safety concerns with no additional pharmacovigilance measures or risk minimisation measures has been agreed.

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Accumulation of ambroxol metabolites (produced in the liver) in patients with severe renal impairment and in patients with hepatic impairment • Anaphylactic reactions including anaphylactic shock
Important potential risks	<ul style="list-style-type: none"> • Allergic reactions including severe skin reactions (SCARS)
Missing information	<ul style="list-style-type: none"> • Use during pregnancy • Use during lactation • Use in children

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the areas traceability, comprehensibility and applicability sufficiently.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rivendra 30mg and 60mg effervescent tablets have a proven chemical-pharmaceutical quality and are generic forms of Mucosolvan 30mg and 60mg effervescent tablets. Ambroxol hydrochloride is a well-known active substance with an established favourable efficacy and safety profile.

An adequately justified waiver for not conducting a bioequivalence study has been presented.

The marketing authorisation holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other ambroxol containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rivendra with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 8th July 2015.