CBG MEB

Public Assessment Report

Scientific discussion

Acetylcysteïne Birchwood 600 mg, effervescent tablets

(acetylcysteine)

NL/H/3971/001/MR

Date: 30 October 2018

This module reflects the scientific discussion for the approval of Acetylcysteine Birchwood 600 mg, effervescent tablets. The procedure was finalised on 4 February 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acetylcysteïne Birchwood 600 mg, effervescent tablets from Birchwood Healthcare B.V.

The product is indicated for pulmonary conditions, requiring viscosity reduction of the bronchial secretion to facilitate productive coughing, such as in bronchitis, emphysema, mucoviscidose, and bronchiectasis.

The product is indicated in adults only

A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Fluimucil 600 mg effervescent tablets (NL License RVG 12151) which has been registered in the Netherlands by Zambon Nederland B.V. since 7 July 1987.

The concerned member states (CMS) involved in this procedure were Ireland and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Acetylcysteïne Birchwood 600 mg is a white, round, flat-faced tablet.
The effervescent tablets are packed in polypropylene (PP) tablet containers with silica gel containing PP cap.

The excipients are: anhydrous citric acid (E330), sodium hydrogen carbonate (E500 ii), aspartame (E951), povidone K-30 (E1201), sodium chloride, PEG 6000, lemon flavour (contains corn maltodextrin, flavouring preparations, flavouring substances, natural flavouring substances and alpha-tocopherol (E307)).

II.2 Drug Substance

The active substance is acetylcysteine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white crystalline powder which is freely soluble in water and in ethanol, and practically insoluble in methylene chloride.
Acetylcysteine contains a chiral centre in its structure and shows a specific optical rotation between +21° and + 27°. Infrared spectra indicate a single crystalline form.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the optimization of the composition with respect to disintegration time and taste acceptability. The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference product. Qualitatively the test product contains the same excipients as the reference product. Although the quantitative composition with regard to the excipients is not similar to that of the reference product, it is considered to be largely comparable. Therefore, the absence of a bioequivalence study is considered justified. Disintegration time (not more than 5 minutes) is controlled at release and during stability testing of the drug product. The data included in the dossier is sufficient to support a biowaiver in accordance with the 'Guideline on the Investigation of Bioequivalence'. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The process mainly consists of wet granulation, drying, mixing, compression and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients
The excipients comply with the Ph.Eur. and – for Lemon flavour – with in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, odour, average mass, uniformity of mass, uniformity of dosage units, dimensions, resistance to crushing, friability, disintegration, identity, assay, loss of drying, related substances and microbial quality. The release and shelf-life specification limits are identical. The specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided on three full-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque PP tablet containers with a PP silica gel containing cap. All stability results remain well within the specified limits. The proposed shelf-life of 24 months has been granted, with storage condition 'Store in the original package in order to protect from moisture and light. Keep the container tightly closed.'
In-use stability data have been provided demonstrating that the product, being stored for 2 years at 25°C/60% RH, remains stable for 8 weeks following first opening of the tube, when stored at 25°C/60% RH.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acetylcysteïne Birchwood has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Acetylcysteïne Birchwood 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.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Fluimucil, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Acetylcysteine is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

This is a generic application for Acetylcysteïne Birchwood effervescent tablets referring to Fluimucil effervescent tablets as reference medicinal product. The N-acetylcysteïne effervescent tablets are dissolved in water before administration. Therefore, the test product is administered as an aqueous solution, at the same concentration of active substance as the innovator product. The excipients used for production of Acetylcysteïne Birchwood 600 mg do not affect gastrointestinal transit, absorption, *in-vivo* solubility and stability of the active substance. Therefore, an exemption from *in-vivo* bioequivalence study is acceptable, in accordance with the guideline on the investigation of bioequivalence CPMP/EWP/ QWP/1401/98/Rev1.

IV.3 Risk Management Plan

The MAH 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 Acetylcysteïne Birchwood.

- Summary table of safety concerns as approved in RMP

Important identified risks	Increased bronchial secretions, especially in children aged < 2 years Severe hypersensitivity reactions including anaphylactic shock
Important potential risks	Severe skin reactions (incl. 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

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Fluimucil. No new clinical studies were conducted. Acetylcysteïne Birchwood 600 mg, effervescent tablets are considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. This generic medicinal product can be used instead of the reference product. Risk management is adequately addressed.

Based on the provided literature in the clinical overview, the efficacy and safety in adults is sufficiently justified. The removal of asthma from the indication is considered acceptable as per GINA (Global Initiative for Asthma) the use in the treatment of asthma is not supported.

The risk of suffocation in children <2 years of age because of the risk of abundant mucus is addressed as a contra-indication in line with the innovator. The efficacy and safety of acetylcysteine 600 mg is not established in the remaining age group of the paediatric population, i.e. children from 2 years of age and adolescents. This is adequately addressed in section 4.2.

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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Acetylcysteïne Birchwood 600 mg, effervescent tablets has a proven chemical-pharmaceutical quality and is a generic form of Fluimucil 600 mg effervescent tablets. Fluimucil is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are administered as an aqueous oral solution, at the same concentration of active substance, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

The Board followed the advice of the assessors. Acetylcysteïne Birchwood 600 mg was authorised in the Netherlands on 26 April 2012.

There was no discussion in the CMD(h) during the mutual recognition procedure. Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, mutually recognised the MEB's evaluation for marketing authorisation. The MRP was finalised with a positive outcome on 4 February 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse