CBG MEB

Public Assessment Report

Scientific discussion

Acetylcysteine YES 600 mg, effervescent tablets

(acetylcysteine)

NL/H/2975/001/DC

Date: 4 March 2015

This module reflects the scientific discussion for the approval of Acetylcysteine YES 600 mg, effervescent tablets. The procedure was finalised on 24 September 2014. 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 a marketing authorisation for Acetylcysteine YES 600 mg, effervescent tablets from Yes Pharmaceutical Development Services GmbH.

The product is indicated in adults in respiratory tract disorders with bronchial hypersecretion to reduce the viscosity of mucus secretion and to facilitate expectoration.

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

This decentralised 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 Belgium, Luxembourg, Portugal and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Acetylcysteine YES 600 mg is a round, white tablet with faultless surface and score line on one side. The tablet can be divided into equal halves.

Each effervescent tablet is either sealed separately into an aluminium paper foil packed in a folding box or the unsealed tablets are packed in a plastic tube with polyethylene desiccant stoppers filled with silicagel or molecular sieve.

The excipients are: citric acid, anhydrous (E330), ascorbic acid (E300), sodium citrate (E331), sodium cyclamate (E952), saccharin sodium (E954), mannitol (E421), sodium hydrogen carbonate (E500), sodium carbonate, anhydrous (E500), lactose anhydrous. Flavour Lemon “AU”, code 132 consisting of: natural lemon oil, natural/nature identical lemon oil, mannitol (E421), maltodextrin, gluconolactone (E575), sorbitol (E420), silica, colloidal anhydrous (E551).

II.2 Drug Substance

The active substance is acetylcysteine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water.

The CEP procedure is used for both suppliers of 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specifications are in line with the Ph.Eur. and the CEPs. One overall specification valid for the active substance from both suppliers has been provided. Batch analytical data

demonstrating compliance with the drug substance specification have been provided for three full-scale batches per manufacturer.

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 CEPs and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The tablet was designed to disintegrate in water within not more than 5 minutes giving an effervescent liquid with a pleasant odour and taste. The manufacture of effervescent tablets is a standard process for the manufacturer. Although the test and reference product differ in used excipients the products are considered to be pharmaceutically similar. The main components of the formulation comply with the components of the reference product. Accordingly, the major physicochemical properties of the two products are almost identical.
Breakability of the tablets has been demonstrated. Since the test product is an aqueous oral solution at the time of administration and it contains active substances in the same concentrations as approved oral solutions, a bioequivalence study may waived. The packages are usual and well known for the proposed product. The efficacy of the desiccant has been demonstrated by the stability studies.
In conclusion, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the manufacturing of the granular effervescent base which is mixed with the active substance. The blend is then compressed and packed. The manufacturing process has been adequately validated according to relevant European guidelines. A process validation on three consecutive production scale batches of finished product has been carried out by the manufacturer.

Control of excipients
All excipients with the exception of the lemon flavour, are in compliance with the Ph.Eur. The specifications are acceptable.
With exception of the natural lemon oils code no 5051 and 5023 the excipients of the lemon flavour are in compliance with the Ph.Eur. The lemon oils comply with Regulation (EC) No 1334/2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods.

Quality control of drug product
The product specification includes tests for appearance of the tablets and of the solution, odour of the tablets and of the solution, diameter, mean of mass, uniformity of mass, resistance to crushing, disintegration, pH, short term stability test, identity, loss on drying, assay, related substances and microbiological quality.
Diameter, mean of mass, uniformity of mass, short term stability and identity are only included in the release specification since these parameters were not considered to be stability indicating. The proposed limits are considered sufficiently justified. The specification is 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 were provided for three full-scale batches stored at 25°C/60% RH (36 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 the proposed packages.
An increase in resistance to crushing was observed at long term and accelerated conditions. Furthermore an increase in certain impurities was observed. This increase was larger in the tablets packed in the PP tube with PE stopper than in the tablets packed in the Al-Paper foil. However, no out-of-specification results were observed. A shelf-life of 36 months was granted for the unopened product.

An in-use study in order to assess the product's stability after opening of the tube was conducted on two batches over a period of 36 months stored at 25°C/60% RH. Based on the results of this study an in-use shelf life of 24 months was granted.
The applicable storage condition is 'Store in the original packaging in order to protect from moisture'.

The stability of the halved tablets has been demonstrated by an in-use stability study leading to the following in-use storage condition in the SmPC: "Halved tablets should be stored in the primary packaging when packed into polypropylene tubes with polyethylene desiccant stoppers. Halved tablets should be used within 24 hours after first opening and replacing them in the primary packaging when packed into aluminium paper foil."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
L-Cysteine is an amino acid obtained by chemical hydrolysis and reduction from keratin extracted from human hair and poultry feathers. Neither of these origins is considered as Specified Risk Material in relation to Transmitting Animal Spongiform Encephalopathies as defined in the EC Decision 2000/418/CE.
Lactose is the only excipient in the drug product which originates from ruminant material. Lactose is prepared using calf rennet. The lactose is not manufactured from animal material susceptible to TSE. Therefore, any risk of transmitting agents of animal spongiform encephalopathies can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acetylcysteine YES 600 mg, effervescent tablets 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 Acetylcysteine YES 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 600 mg effervescent tablets, 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

Biowaiver

The MAH applied for a biowaiver for Acetylcysteine Yes 600 mg effervescent tablets as these can be regarded an aqueous oral solution at time of administration. The product contains acetylcysteine in the same concentration as Fluimucil 600 mg effervescent tablets. The justification given by the MAH is plausible, especially since acetylcysteine demonstrates almost complete absorption. It is agreed that the only difference in excipients that may affect gastrointestinal transit is mannitol. However, due to the low amount of mannitol the influence of this excipient on gastric emptying is considered negligible. 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 Acetylcysteine YES 600 mg, effervescent tablets.

- Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity Anaphylactic reactions and anaphylactic shock
Important potential risks	Use in children younger than 2 years of age Stevens-Johnson syndrome and Lyell syndrome
Missing information	None

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. The pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. A bioequivalence study was not considered necessary. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 a pilot test with 5 participants, followed by two rounds with 10 participants each. Overall, 17 out of 20 respondents (84%) found the answers in the package leaflet at first go and the other three subjects (16%) found the answers after a short search. All readers who found the answers in the leaflet were also able to understand the respective information.
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

Acetylcysteine YES 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 solution, at the same concentration of active substance, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Acetylcysteine YES 600 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 September 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached