CBG MEB

Public Assessment Report

Scientific discussion

Acetylcysteine PharOS 600 mg effervescent tablets

(acetylcysteine)

NL/H/3166/001/DC

Date: 14 April 2016

This module reflects the scientific discussion for the approval of Acetylcysteine PharOS 600 mg effervescent tablets. The procedure was finalised on 18 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
EDMF	European Drug Master File
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 Acetylcysteine PharOS 600 mg effervescent tablets, from Boehringer Ingelheim International GmbH.
Acetylcysteine is indicated in adults for the treatment of airway diseases in which a reduction in the viscosity of the bronchial secretions is required to facilitate expectoration, especially during periods of acute bronchitis. The product is contraindicated for use in children aged under 2 years and unsuitable for use in children and adolescents.

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) by Zambon Nederland B.V., which has been registered in the Netherlands since 7 July 1987.

The concerned member states (CMS) involved in this procedure were Finland, France and Norway.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, a generic application.
In France, Fluimucil 200 mg, effervescent tablets (Zambon France) is used as reference product and therefore the legal basis in France is art 10(3), a hybrid application.

II. QUALITY ASPECTS

II.1 Introduction

Acetylcysteine PharOS 600 mg is an effervescent tablet and contains 600 mg acetylcysteine. The product is a round, white tablet with faultless surface, a score line on one side and diameter of 20 mm. The score line is only to facilitate breaking for ease of dissolving and not to divide into equal doses.

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

The excipients are:
- citric acid (anhydrous)
- ascorbic acid
- sodium citrate
- sodium cyclamate
- saccharin sodium
- mannitol
- sodium hydrogen carbonate
- sodium carbonate (anhydrous)
- lactose (anhydrous)
- magnesium stearate
- 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 acetylcysteine is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is freely soluble in water and in ethanol (96%) and practically insoluble in methylene chloride. Parameters such as polymorphism and particle size have not been included in the drug substance specification. This is accepted, as the product will be dissolved and taken in as a solution.

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

Quality control of drug substance
Two drug substance specifications have been provided by the MAH, covering the test parameters of the respective manufacturers. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur. as well as the additional requirements indicated on the CEPs. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer.

Stability of drug substance
The active substance from both suppliers 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. 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 test for disintegration is in accordance with the Ph.Eur.
The MAH applied for a biowaiver as Acetylcysteine PharOS 600 mg effervescent tablets can be regarded an aqueous oral solution at time of administration and contains acetylcysteine in the same concentration as Fluimucil 600 mg effervescent tablets. The formulation of Acetylcysteine PharOS effervescent tablets and Fluimucil effervescent tablets differs in some excipients. Instead of aspartame, sodium cyclamate and saccharin sodium are used. In addition to sodium hydrogen carbonate, sodium carbonate is used additionally. The other excipients ascorbic acid, sodium citrate dehydrate, anhydrous lactose and mannitol are classical excipients used in typical amounts. The formulation differences are adequately described. Test and reference formulation demonstrate similar acetylcysteine solubility. The general biowaiver criteria are thereby met and the requested biowaiver can be granted. The efficacy of the break mark was demonstrated (according to the Ph.Eur) during development of the product, however it is not intended to divide the effervescent tablets into equal doses.

Manufacturing process
The tablets are manufactured by wet granulation. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production scaled batches, with a slightly different composition (Flavour Blackberry instead of Flavour Lemon). Since this difference is not expected to influence the manufacturing process itself, this is deemed acceptable. No additional validation data are required.

Control of excipients
All excipients comply with the Ph.Eur., except for the Flavour Lemon for which acceptable specifications have been provided.

Quality control of drug product
The product specification includes tests for appearance, odour, diameter, mean of mass, uniformity of mass, resistance to crushing, disintegration, odour of solution, appearance of solution, pH of solution, short term stability test, loss on drying (only at shelf-life), identification, assay, related substances and microbiological quality. Shelf life limits above the qualification threshold (according to the Note for Guidance on Impurities in New Medicinal Products) are proposed for the impurities and certain toxicological data are provided; the shelf life limits for impurities are considered to be acceptable. The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three production scaled batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three production scaled 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 amount of impurities increases, but stays within the proposed specification. The proposed shelf-life of 36 months with storage conditions “Store in the original package in order to protect from moisture” and “This medicinal product does not require any special temperature storage condition” is justified. Results of a formal photostability study showed that the drug product is not sensitive to light exposure.

In-use stability data have been provided for two batches stored at 25°C/60% RH for 36 months. Samples of two batches packaged into PP-tubes with PE-stoppers were used (20 and 25 tablets/tube respectively). The containers were opened on 10 consecutive days and one tablet was taken out each time. The remaining tablets were stored in the closed PP-tubes at 25°C/60% RH. Samples were analysed at the initial time point during ten days and after 3, 6, 12, 18, 24 and 36 months of storage during ten days. Results were comparable to those of the long-term studies. No separate in-use shelf-life has been proposed. This is justified based on the presented data.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The CEP holders have declared the use of material of human or animal origin in the manufacture of the substance. Statements from the respective manufacturers have been provided, confirming that neither source materials nor production processes as defined in the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products are used in the manufacture of the substance. Therefore, the risk of transmitting agents of animal spongiform can be excluded.
Lactose is the only excipient in the drug product which originates from ruminant material. It is prepared using calf rennet. The lactose is not manufactured from animal material susceptible to TSE. The risk of transmitting agents of animal spongiform can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Acetylcysteine PharOS 600 mg effervescent tablets have 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 PharOS 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 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.

For this generic application, the MAH has requested a biowaiver, which is discussed below.

IV.2 Pharmacokinetics

Biowaiver
The MAH requested for a biowaiver, as Acetylcysteine PharOS 600 mg effervescent tablets can be regarded an aqueous oral solution at time of administration containing acetylcysteine in the same concentration as Fluimucil 600 mg effervescent tablets. None of the excipient differences in test and reference product showed to act on absorption, *in vivo* stability or metabolism. The MAH adequately discussed aspects regarding acetylcysteine (e.g. solubility/permeability) and composition/formulation differences. The justification given by the MAH for a biowaiver is accepted, especially since acetylcysteine demonstrates almost complete absorption for test and reference product.

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 PharOS.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	• Severe hypersensitivity reactions (including anaphylactic shock) • Safety in children aged <2 years
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

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 600 mg. No new clinical studies were conducted. The MAH applied for a biowaiver for a bioequivalence study, which was found acceptable. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

The originally requested indication included adolescents aged 14 years and older and adults. This was not considered acceptable as the innovator Fluimucil 600 mg is not indicated for paediatric patients or adolescents. During the procedure the MAH restricted that indication to adults, and adapted the wording as requested by the RMS and CMS. The agreed indication is in line with the outcome of the CMD(h) referral for procedure NL/H/2843/001/MR.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the leaflet of Acetylcysteine YES 600 mg, agreed during procedure number NL/H/2975/001/DC. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Acetylcysteine PharOS 600 mg effervescent tablets have a proven chemical-pharmaceutical quality and are a generic form of Fluimucil 600 mg effervescent tablets. Fluimucil is a well-known medicinal product with an established favourable efficacy and safety profile.

No pharmacokinetic bioequivalence studies were performed. This is accepted as a biowaiver was granted.

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 PharOS with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 June 2015.

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
Change in the name of the medicinal product due to Marketing Authorization Transfers in NL, FI, FR and NO. Introduction of the summary of PSMF of the new MAH Boehringer Ingelheim International GmbH.	NL/H/3166/IB/001/G	IB	17-09-2015	18-12-2015	Approval	No