CBG MEB

Public Assessment Report

Scientific discussion

Acetylcysteïne Alpex 600 mg granules for oral solution

(N-acetylcysteine)

NL/H/2843/003/DC

Date: 1 February 2018

This module reflects the scientific discussion for the approval of Acetylcysteïne Alpex 600 mg granules for oral solution. The procedure was finalised on 14 May 2017. 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
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 Acetylcysteïne Alpex 600 mg granules for oral solution, from Alpex Pharma (UK) Limited.

The product is indicated in adults for the treatment of airway secretion in which a reduction in the viscosity of the bronchial secretions is required to facilitate expectoration, especially during periods of acute bronchitis.

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

This decentralised procedure concerns a line extension to the existing marketing authorisation of Acetylcysteïne Alpex 600 mg effervescent tablets (NL/H/2843/001/MR), which was approved for marketing in the Netherlands on 7 February 2011. Both formulations are prepared as oral solution for administration given the same concentration of acetylcysteine. The new application is different from the registered drug in terms of formulation (granules) and composition (excipients).

Acetylcysteïne Alpex 600 mg granules for oral solution is a hybrid 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. Difference compared to this reference medicinal product is a change in pharmaceutical form.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The product consists of white to yellowish granules for oral solution.

Acetylcysteïne Alpex granules for oral solution is packed in sachets (PET/PE/Alu/PE/LLDPE). Each sachet contains as active substance 600 mg of acetylcysteine.

The excipients are maltodextrin (E1542), sucralose (E955), silica colloidal anhydrous (E551) and orange flavour (contains gum Arabic (E414), butylated hydroxyanisole (E320), citric acid monohydrate (E330) and maltodextrin).

II.2 Drug Substance

The active substance is N-acetylcysteine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). N-acetylcysteine is the N acetyl derivative of the amino acid L-cysteine. The active substance is freely soluble in water. The polymorphic form of the drug substance is consistent and identical to the United States Pharmacopoeia (USP) Reference Standard. Furthermore, the MAH has demonstrated that differences in particle size of the drug substance do not affect the dissolution behaviour.

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 Ph.Eur.

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

Quality control of drug substance
The MAH has adopted the Ph.Eur. specifications. These are acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided. All three batches from both drug substance sources comply with the specifications.

Stability of drug substance
Stability data on the active substance have been provided for 13 production scale batches stored at 25°C/60% RH (36 or 72 months) and nine production scale batches stored at 40°C/75% RH (six months). All parameters remain within specifications at both conditions when stored in the current packaging. Based on the provided stability data a retest period of five years and the storage condition "Store in original package to protect from light" can be granted.

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 choice of the excipients and manufacturing process is justified. Sufficient information with respect to the composition and the safety of the orange flavour has been provided. The packaging material chosen is common for this type of product.

A biowaiver was granted based on the Guideline on the investigation of bio-equivalence regarding oral solutions, stating: "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." Sufficient information was provided regarding the differences in excipients between the test and reference product. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process is a wet granulation, followed by blending. The granular mix is subsequently packed in sachets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches at pilot scale and are acceptable.

Control of excipients
The proposed set of specifications for the compendial as well as the non-compendial excipient (orange flavour) is acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance (of sachets, granules and solution), pH, average weight, weight uniformity, loss on drying, identification, assay, related substances, uniformity of dosage units, seal test and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three commercial scale batches stored at 25°C/60% RH and 40°C/75% RH for six months (both according to ICH stability guideline). The batches were stored in the packaging proposed for marketing. Based on extrapolation of the available stability data a shelf-life of two years if stored in the proposed sachet packaging without specific storage temperature condition can be accepted. The labelled storage conditions are: Keep in the original package in order to protect from moisture. The product is photostable.

Specific measures concerning 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 Alpex granules for oral solution 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 Alpex granules for oral solution 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 hybrid 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

N-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.

The application is a line extension to Acetylcysteïne Alpex 600 mg effervescent tablets. A biowaiver for a bioequivalence study is discussed below.

IV.2 Pharmacokinetics

Biowaiver
Acetylcysteïne Alpex granules for oral solution is an aqueous solution at time of administration, containing the same active substance as the registered Acetylcysteïne Alpex effervescent tablets and originator product (Fluimucil). Therefore a clinical bioequivalence study is not required by Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr** provided that there are no excipients that could affect the absorption of N-acetylcysteine.

The composition of concerned Acetylcysteïne Alpex granules is different from that of the registered Acetylcysteïne Alpex effervescent tablets. Compared with the effervescent tablets, the granules do not contain sodium bicarbonate (alkalising agent), citric acid (acidifying agent), but contains maltodextrin as filler and silica colloidal anhydrous as glidant. The differences in the excipients are minor and not

considered to have any impact on either gastro-intestinal transit or absorption of the product. A biowaiver is justified.

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 Alpex granules for oral solution.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Severe hypersensitivity reactions • Increased bronchial secretions, especially in children under two years
Important potential risks	• Clinical effects resulting from anticoagulant and platelet inhibiting properties of acetylcysteine • Severe skin reactions
Missing information	• Limited information on use in pregnancy

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 MAH demonstrated through a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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 Acetylcysteïne Alpex 600 mg effervescent tablets (NL/H/2843/001/MR). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Acetylcysteïne Alpex 600 mg granules for oral solution has a proven chemical-pharmaceutical quality and is a hybrid form of Fluimucil 600 mg effervescent tablets. Fluimucil is a well-known medicinal product with an established favourable efficacy and safety profile.

Since the current product is an aqueous solution at time of administration, containing the same active substance as the registered Acetylcysteïne Alpex effervescent tablets and originator product (Fluimucil), no bioequivalence study is deemed necessary. The differences in the excipients do not have an impact on either gastro-intestinal transit or absorption of the product.

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 Acetylcysteïne Alpex 600 mg granules for oral solution with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 May 2017.

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