COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kinemucil acetylcysteïne 600 mg effervescent tablets

(acetylcysteine)

NL/H/4410/001/DC

Date: 22 October 2019

This module reflects the scientific discussion for the approval of Kinemucil acetylcysteïne 600 mg effervescent tablets. The procedure was finalised at 29 May 2019. 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
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 Kinemucil acetylcysteïne 600 mg effervescent tablets from Zambon S.p.A.

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 generic application claiming essential similarity with the innovator product Fluimucil 200 mg effervescent tablets (NL Licence RVG 9988) which has been registered in the Netherlands by Zambon Nederland B.V. since 7 April 1983.

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, because of a difference in strength between Fluimucil 200 mg effervescent tablets and Kinemucil acetylcysteïne 600 mg effervescent tablets.

II. QUALITY ASPECTS

II.1 Introduction

Kinemucil acetylcysteïne is a white circular effervescent tablet.

The tablet contains as active substance 600 mg of acetylcysteine.

The effervescent tablets are packed in blisters.

The excipients are sodium hydrogen carbonate, citric acid anhydrous, aspartame (E951), lemon flavour (contains glucose, maltodextrin, Arabic gum (E414), maize starch modified and ascorbic acid (E300)).

II.2 Drug Substance

The active substance is acetylcysteine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder or colourless crystals and it is freely soluble in water and in ethanol (96%), practically insoluble in methylene chloride. It has one stereochemical centre in the molecule.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three 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 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 qualitative and quantitative composition of the current 600 mg effervescent tablets applied for is the same as the composition of Fluimucil 600 mg effervescent tablets. Compared to Fluimucil 200 mg effervescent tablets the only difference is the amount of the active substance. The amounts of excipients are the same in Kinemucil acetylcysteïne 600 mg and Fluimucil 200 mg effervescent tablets. Pharmaceutical development has been adequately performed.

Since the effervescent tablets are dissolved in a small amount of water to obtain a solution prior to use, no bioequivalence studies are required for the 600 mg test product and the 200 mg reference product. A biowaiver is requested.

Manufacturing process
All components are weighed and a powder blend is prepared. The powder blend is tabletted and the tablets are packaged. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. or in-house requirements. These specifications are 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, average mass/tablet, uniformity of mass, appearance of solution, pH of solution, disintegration time, water content, identification, assay, related substances and microbiological contamination. 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 full scale 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 eleven production scaled batches stored at 25°C/60% RH (up to 36 months), 30°C/75% RH (up to 36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies have been performed and it is demonstrated that the drug product is not sensitive to light. All stability parameters remain unchanged or with respect to the impurities show a small increase over time but remain well within the limits. On basis of the data submitted, a shelf life was granted of 36 months.

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 Kinemucil acetylcysteïne 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 Kinemucil acetylcysteïne 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.

No bioequivalence study has been submitted.

IV.2 Pharmacokinetics

Biowaiver

The biowaiver for a bioequivalence study between test and reference product has been justified, as both the reference formulation Fluimucil 200 mg effervescent tablets, as well as the generic formulation Kinemucil acetylcysteïne 600 mg effervescent tablets, has to be administered as an oral solution. Moreover, the reference formulation and the generic formulation have the same qualitative and quantitative composition, except for the amount of acetylcysteine. This is considered not of concern, as a comparable efficacy is shown between a three times daily dose of 200 mg and a once daily dose of 600 mg (see section IV.3).

IV.3 Clinical efficacy

Indication
The following therapeutical indication was initially proposed:

"Treatment of respiratory conditions associated with excessive mucus production, especially acute bronchitis and acute episodes of chronic disorders".

The proposed indication was not accepted. The proposed indication was considered too general. Moreover the pulmonary/respiratory aspect was lacking in the part of 'acute episodes of chronic disorders'.

The MAH acknowledged the comments and proposed the following indication.

"Kinemucil acetylcysteïne is indicated 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 and acute episodes of chronic respiratory disorders."

The claimed indication was again not found acceptable as it differs from the indications already accepted for the originator in the Netherlands and agreed upon during various EU procedures.

The indication was subsequently adequately changed to:
"Kinemucil acetylcysteïne is indicated 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."

Comparison of 200 mg three times daily dose, versus 600 mg once daily dose
The choice of the reference Fluimucil 200 mg has been acceptably justified by clinical trials in which acetylcysteine 200 mg three times daily was compared with acetylcysteine 600 mg once daily.

In the table below by Sadowska[1] et al. endpoints like FEV1, QOL, dyspnoea and exacerbations are presented . This table facilitated a cross sectional comparison of studies of both the Fluimucil 600 mg once daily and Fluimucil 200 mg three times daily showing comparable results.

[1] Sadowska AM, Verbraecken J, Darquennes K, De Backer W. Role of N-acetylcysteine in the management of COPD. Int J Chron Obstruct Pulmon Dis. 2006;1(4):425-34.

Table 1 Effects of NAC on clinical COPD outcomes

	Dose	Number	Study period	FEV_1	QOL	Dyspnea	Exacerbation	Hospitalisation / sick days	Side effects	Ref
400 mg	200 x 2	259	6 months	–	–	–	⇓	⇓	NO	12
600 mg	600 x 1	248	2 months	–	–	⇓	–	–	23%*	93
	600 x 1	523	3 years	NS	NS	–	⇓#	–	NO	29
	600 x 1	169	6 months		Improvement in cough severity	–	⇓	⇓	NS	73
	600 x 1	20	10 weeks	NS	–	–	–	–	NO	97
	300 x 2	116	6 months	–	–	–	⇓ (NS)	⇓	NO	79
	200 x 3	180	5 months	–	–	–	⇓ (NS)		NS	1
	200 x 3	526	6 months	–	–	–	NS	⇓	Well-tolerated	70
	200 x 3	121	3 months	–	–	–	–	–	Well-tolerated	48
1200 mg	600 x 2	153	22 weeks	NS	NS	–	⇓ (NS)	–	NO	43
***1800 mg**	600 x 3	9	4 days	–	–	–	–	–	NO	55

Note: *short duration COPD; #subgroup without ICS; *percentage of patients suffering from side effects.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; NAC, N-acetylcysteine; NO, no reported side effects; NS not significantly different from placebo group–not reported; QOL, quality of life.

Both 200 mg three times daily and 600 mg once daily provide symptomatic relief, while a reduction in exacerbation rate also appeared to be present.

The number of trials of a head-to-head comparison of 3x 200mg vs 1x 600 mg is limited (n=3). Moreover, there are certain methodological limitations because of the period in which they were performed ('80 of 20th century).

Conclusion
From provided literature it is concluded that efficacy of 200 mg three times daily and 600 mg once daily have provided support for the claim of symptomatic relief during acute exacerbations associated with increased sputum production, while a reduction in exacerbation rate also appeared to be present in patients with chronic bronchitis.

IV.4 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 Kinemucil acetylcysteïne.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Increased risk of respiratory obstruction in children aged <2 years • Severs hypersensitivity reactions including anaphylactic shock
Important potential risks	• Severe skin reactions (including Stevens Johnson Syndrome and toxic epidermal necrolysis)

	• Clinical effects resulting from anticoagulants and platelet-inhibiting properties of acetylcysteine • High-dose NAC-induced gastrolesivity
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.5 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 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

The package leaflet (PL) 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 two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kinemucil acetylcysteïne 600 mg effervescent tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Fluimucil 200 mg effervescent tablets. Fluimucil is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been 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 Kinemucil acetylcysteïne with

the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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