

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Fluimucil 600 mg tablets
Zambon Nederland B.V., the Netherlands**

acetylcysteine

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.

It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 109369

20 January 2014

Pharmacotherapeutic group:	expectorants, excl. combinations with cough suppressants, mucolytics
ATC code:	R05CB01
Route of administration:	oral
Therapeutic indication:	pulmonary conditions requiring viscosity reduction of the bronchial secretion to facilitate productive coughing, such as bronchitis, asthma, emphysema, cystic fibrosis and bronchiectasis
Prescription status:	non prescription (OTC)
Date of authorisation in NL:	30 January 2013
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Fluimucil 600 mg tablets from Zambon Nederland B.V. The date of authorisation was on 30 January 2013 in the Netherlands.

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

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

Acetylcysteine is a mucolytic. The mucolytic action is mediated by a reduction in the viscosity of bronchial mucus. This is explained by depolymerisation with the disulphide bridges between the macromolecules in the mucus being opened. In addition, acetylcysteine is a precursor of glutathione. Acetylcysteine is a derivative of the natural amino acid cysteine, which serves as a substrate for the synthesis of glutathione in the body. Acetylcysteine could be capable of normalising a state of glutathione depletion.

This national procedure concerns a line extension to Fluimucil 600 mg FTABS film-coated tablets (NL License RVG 29806), which has been registered in the Netherlands since 10 February 2005. With this application a new composition and pharmaceutical form were introduced. Because of complaints of sulphurous smell, the MAH decided to reformulate the tablets using a dry granulation process instead of a wet granulation process, which was used for the Fluimucil 600 mg film-coated tablets. The new tablet formulation does not have a film coating.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This national procedure concerns a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data. The active substance of Fluimucil 600 mg tablets is considered to be well-known. Reference is made to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Fluimucil authorisations. This information is not fully available in the public domain. Authorisations for line extensions are therefore linked to the 'original' authorised medicinal product. Reference is made to the non-clinical and clinical studies performed with Fluimucil film-coated tablets.

In this case a bioequivalence study between the 'old' and 'new' formulation is not required, as acetylcysteine can be considered a BCS Class I product exhibiting almost complete absorption and high solubility at the doses used. Sufficient comparative dissolution tests have been performed. Assessment of the biowaiver applied for is discussed in section II.3 'Clinical aspects'

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance

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

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 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 several batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No trends or changes are seen at both storage conditions. The proposed retest period of 5 years without any special storage requirements is justified.

** Ph.Eur. is an official handbooks (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Fluimucil 600 mg are white, round tablets containing 600 mg of acetylcysteine.

The tablets are packed in Al-Al blisters.

The excipients are: crospovidone, microcrystalline cellulose, hydroxypropyl cellulose, colloidal anhydrous silica and magnesium stearate.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the optimization of the manufacturing process and quantitative composition of the drug product in order to make a drug product with comparable disintegration and dissolution characteristics as Fluimucil 600 mg film-coated tablets on which this line extension is based. No bioequivalence studies were performed. The change in composition of the excipients is not expected to affect the bioavailability of the drug product. Comparative dissolution studies

were performed with the reference product to justify a biowaiver. Comparative dissolution studies at pH 1.0, 4.5 and 6.8 show similar dissolution profiles in all three media (>85% dissolved in 10 minutes), demonstrating that the dissolution kinetic of the test product is independent of the pH of the solution. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of dry granulation of the active substance, blending with the excipients, 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 pilot-scale and two full-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, uniformity of dosage units, disintegration time, loss on drying, identification, assay, related substances, dissolution and microbiological contamination. Except for related substances the release and shelf-life limits are identical. 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 pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% RH (36 months), 30°C/65% 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 Al-Al blisters. Except for a slight increase in impurities, no changes are seen at each of the storage conditions. Photostability has been demonstrated. The proposed shelf-life of 36 months without any special storage requirements is justified.

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.2 Non-clinical aspects

This product is a line extension to Fluimucil 600 mg film-coated tablets, which is available on the European market. No new preclinical data have been submitted. Therefore the application has not undergone additional preclinical assessment, which is acceptable for this type of application.

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of acetylcysteine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Acetylcysteine is a well-known active substance with established efficacy and tolerability.

Because of complaints of sulphurous smell, the MAH reformulated the tablets using a dry granulation process instead of a wet granulation process, which is currently being used for the Fluimucil 600 mg film-coated tablets. The film-coated tablet presentation is replaced with a tablet presentation without a film coating.

To support this reformulation, the MAH submitted dissolution tests, but no bioequivalence study was conducted. A biowaiver was applied for.

For oral solid 'immediate-release' dosage forms where the active ingredient is very soluble in water and quickly absorbed, the guideline CPMP/EWP/QWP/1401/98 "Note for guidance on the investigation of bioavailability and bioequivalence" indicates that two dosage forms can be considered equivalent if in the pH 1-6.8 range, 85% of the active ingredient is dissolved within 15 minutes. The MAH provided results of dissolution tests at pH 1, pH 4.5 and pH 6.8. More than 85% of acetylcysteine was dissolved after 10 minutes at all three pHs for both the tablets and film-coated tablets.

Acetylcysteine can be considered a BCS Class I product exhibiting almost complete absorption and high solubility at the doses used. The composition between the film-coated tablets and the new formulation differ qualitatively and quantitatively in excipients including the quantity of magnesium stearate. The latter is considered to affect solubility and not absorption. This means that the composition of the tablets can be considered comparable in the light of a BCS Class I waiver. In conclusion, the requirements for a biowaiver are considered fulfilled and a bioequivalence study is not required.

Risk management plan

Fluimucil has been available on the EU market for many decades, and there is extensive post-authorisation experience with the active substance. The safety profile of acetylcysteine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. A Risk Management Plan was not required at the time of submission of this application.

Product information

SmPC

The content of the SmPC approved during the national procedure is in accordance with that accepted for Fluimucil film-coated tablets. The applicable prescription status is non-prescription, which is in accordance with previously approved oral Fluimucil formulations.

Readability test

National registration procedure

Initially, the package leaflet (PL) was not evaluated via a user consultation study. The text is largely in line with that accepted for Fluimucil effervescent tablets. It is therefore acceptable that the PL was not user tested with regard to the content. However, contrary to other Fluimucil presentations, the proposed package leaflet is printed on a green background. The MAH was therefore requested to provide readability testing results that emphasise on evaluation of the leaflet's layout, and in particular on the background colour. Results of a user test on the PL for Lysomucil Junior, an acetylcysteine syrup authorised in Belgium, were provided. The results indicate that findability and understandability meet the requirements. The green background colour was judged acceptable by most participants, but not by all (approx. 60-70% based on this test). The Board considered readability of the green leaflet insufficiently demonstrated, as there were concerns with regard to the contrast between the text and the background, particularly for people with reduced contrast vision (e.g. colour blindness). Upon closure of the registration procedure, the leaflet was accepted with a white background.

Post-approval readability testing

After closure of the procedure, the MAH submitted the results of a new user test on the leaflet for Fluimucil 600 mg tablets, printed with a green background colour.

The aim of the test was to investigate if the proposed layout is fully readable, particularly for people with reduced contrast vision. The information as presented in the new layout should convey the correct messages to those who read the document and should be acceptable in terms of layout and design.

The test was performed with 20 volunteers. Ten subjects had reduced vision. All of them were colour blind; one subject was also visually impaired due to uveitis. Colour blindness was detected by means of a basic Ishihara test for colour blindness.

The PL of Fluimucil 600 mg tablets used for evaluation had the character's size, type and colours and general layout of the actual PL of the medicinal product. The PLs with green background colour and with white background colour were both tested in 20 participants (10 with reduced contrast vision and 10 with normal vision). Half of the participants of both groups were questioned about the green-background leaflet first, followed by the white-background leaflet. The other half was questioned about the white-background leaflet first, followed by the green leaflet. The leaflet was written in Dutch.

The test results show that all participants, with reduced vision as well as normal vision, could read the leaflet text with either green or white background fluently, according to their opinion. The readability test meets the set requirements. The MEB approved the green package leaflet on 2 January 2014.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Fluimucil 600 mg tablets has a proven chemical-pharmaceutical quality and is a legitimate line extension to Fluimucil 600 mg FTABS film-coated tablets. Fluimucil 600 mg FTABS is a well-known medicinal product with an established favourable efficacy and safety profile.

A bioequivalence study between the 'old' and 'new' formulation was not required, as acetylcysteine can be considered a BCS Class I product exhibiting almost complete absorption and high solubility at the doses used. Similarity of dissolution profiles has been demonstrated.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of other Fluimucil formulations. The SmPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that reformulation of Fluimucil 600 mg tablets is justified and has therefore granted a marketing authorisation. Fluimucil 600 mg tablets was authorised in the Netherlands on 30 January 2013.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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
Introduction of a summary of pharmacovigilance system for medicinal products for human use (Pharmacovigilance System Master File).	--	IA	4-10-2013	14-10-2013	Approval	N
Results of a technical readability test on the PL with green background colour.	--	Post-approval user test	18-9-2013	2-1-2014	Approval	See page 5-6