CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Acetylcysteïne Alpex 200 mg, effervescent tablets
Alpex Pharma (UK) Limited, United Kingdom

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 107031

9 September 2013

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, mucoviscidose and bronchiectasis
Prescription status:	non prescription
Date of authorisation in NL:	7 February 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), 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 Acetylcysteïne Alpex 200 mg, effervescent tablets from Alpex Pharma (UK) Limited. The date of authorisation was on 7 February 2011 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, mucoviscidose and bronchiectasis.

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

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 generic application claiming essential similarity with the innovator product Fluimucil 200 mg (NL License RVG 09988), which has been registered in the Netherlands by Zambon Nederland B.V. since 7 April 1983.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. The current application does not include a comparative bioavailability or bioequivalence study, but reference is made to fulfilling all requirements for a biowaiver. See paragraph II.3 “Clinical Aspects”. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

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 generic application.

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.). The active substance is freely soluble in water. The polymorphic form of the dug substance is consistent and identical to the 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 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. According to the CEP no additional specifications are considered necessary. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for thirteen production-scale batches stored at 25°C/60% RH (36 or 72 months) and nine production-scale batches stored at 40°C/75% RH (6 months).
All parameters remain relatively stable and well within specifications at both conditions when stored in current packaging. Based on the provided stability data, a re-test period of 5 years and the storage condition “Store in original package to protect from light” were granted.

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

Medicinal Product

Composition
Acetylcysteïne Alpex 200 mg is a round, flat white to yellowish tablet.

The effervescent tablets are packed in polypropylene tablet containers with PE cap and desiccant or in aluminium/aluminium strips inside a carton box.

The excipients are: sodium hydrogen carbonate, citric acid, sucralose and orange flavour.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Several compositions and manufacturing methods have been tested. Wet granulation was chosen as the commercial manufacturing method.
Sufficient information with respect to the composition and the safety of the orange flavour has been provided. Comparative dissolution studies were conducted between Acetylcysteïne Alpex and the reference product Fluimucil at pH 1.2, 4.5 and 6.8. These studies provided confirmation that the solubility characteristic of Acetylcysteïne Alpex effervescent tablets is not influenced by the pH of the medium and that the amount of active substance in the solution to be administrated is equivalent to that of reference product. No bioequivalence studies have been preformed since the MAH applied for a biowaiver. The data included in the dossier is sufficient to support a biowaiver in accordance with the 'Guideline on the Investigation of Bioequivalence'.

Manufacturing process
The manufacturing method is a wet granulation process and consists of granulation, sieving, mixing and compression. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scale batches. The manufacturing process has been adequately described and validated. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with either the Ph.Eur., the USP/NF or - for orange flavour - in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, appearance of solution, pH, disintegration time, average weight, uniformity of dosage units, loss on drying, and microbiological quality. The release and end of shelf-life specifications are identical.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three commercial scale batches stored at 25°C/60%RH (12 months), 30°/75%RH (12 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 a polypropylene tube with a polyethylene cap and desiccant with 10 tablets per tube. Post approval the package was changed to aluminium blister strips.
The stability results show that no changes are observed under all storage conditions and for all parameters tested. Also the in-use stability study did not show significant changes in any of the examined parameters.
On the basis of the submitted data a shelf-life of 24 months can be granted, when stored in the original container to protect from moisture. Photostability has been demonstrated, however, as the condition "Store in original package, to protect from moisture" is applicable to effervescent tablets, the tablets will also be protected from light. Post approval the shelf life has been extended to 3 years.
Stability data has been provided demonstrating that the product remains stable for 10 days following first opening of the container.

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 generic formulation of Fluimucil effervescent tablets, which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

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.

Clinical pharmacokinetics
This is a generic application for Acetylcysteïne Alpex effervescent tablets referring to Fluimicil® effervescent tablets as reference medicinal product. The N-acetylcysteïne effervescent tablets are dissolved in water before administration. Therefore, the test product is administered as an aqueous solution, at the same concentration of active substance as the innovator product. The excipients used for production of Acetylcysteïne Alpex 200 mg do not affect gastrointestinal transit, absorption, *in-vivo* solubility and stability of the active substance. 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.

Clinical experience
No clinical studies are necessary for this generic application. The clinical overview on pharmacology, efficacy and safety prepared, referring to 26 articles up to 2009, is considered adequate.

In conclusion, Acetylcysteïne Alpex 200 mg, effervescent tablets are considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of their reference products.

Risk management plan
Acetylcysteine was first approved in 1963, and there is now more than 10 years 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 SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. 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 and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Fluimucil.

Readability test
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. Based on the results of the pilot test the text of the leaflet was changed. The revised mock-up was used during the first test round. During the first test round practically all questions were answered correctly by almost all test participants and there was no reason to further change the text. During the second test round the same mock-up was used. All questions were correctly answered by all test participants and the text was not revised any further. In both test rounds, more than 90% of the questions were answered correctly. The readability test report is acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Acetylcysteïne Alpex 200 mg, effervescent tablets has a proven chemical-pharmaceutical quality and is a generic form of Fluimucil 200 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, 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 essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Acetylcysteïne Alpex 200 mg, effervescent tablets was authorised in the Netherlands on 7 February 2011.

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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	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
Change in product information regarding risks of use in children younger than 2 years.	--	II	4-4-2011	7-6-2011	Approval	N
Change in pack size of the finished product.	--	IA	18-4-2011	24-8-2011	Approval	N
change in the name and/or address of a manufacturer of the finished product, including quality control site.	--	IA	11-7-2011	22-7-2011	Approval	N
Change in pack size of the finished product.	--	IB	11-8-2011	18-8-2011	Approval	N
Change in immediate packaging of the finished product. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	--	IB/G	15-9-2011	28-9-2011	Approval	N
Change in shelf-life or storage conditions of the finished product.	--	IB	8-11-2011	29-11-2011	Approval	N