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Public Assessment Report

Scientific discussion

Acetylcysteine Abex 600 mg effervescent tablets

Acetylcysteine

ES/H/0902/01/DC

Date: 22/08/2024

This module reflects the scientific discussion for the approval of Acetylcysteine Abex 600 mg effervescent tablets. The procedure was finalised on 25/06/2024.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Acetilcisteína Abex 600 mg comprimidos efervescentes, from Kern Pharma S.L.
The product is indicated for: Reduction of the viscosity of mucous secretions, facilitating their expulsion, in cold and flu processes for adults.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application which has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The originator product is Fluimucil Hustenlöser akut 600 mg Effervescents Tablets by Zambon GmbH registered since 14/08/1995 in Germany. In Spain the originator product is Fluimucil Forte 600 mg effervescent tablets from Zambon, S.A.U, registered since 01/07/1999.

In this procedure a concerned member state has been included: PT.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as effervescent tablet containing 600 mg of acetylcysteine as active substance. The maximum daily dose is 600 mg.
The product is available in polypropylene tubes with polyethylene caps with silica gel or in four-layer laminated paper sachet (paper / polyethylene / aluminum / ionomer) in a hermetically-sealed strip.

II.2 Drug Substance

The CEP procedure is used to support the quality of the drug substance acetylcysteine.

General Information

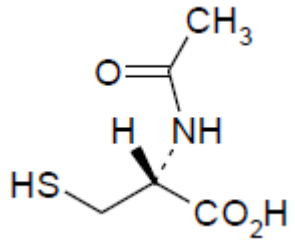
Nomenclature:

INN: Acetylcysteine

Chemical name: (R)-2-acetamido-3-mercaptopropanoic acid

CAS-No: 616-91-1

Structure:



Molecular formula: $C_5H_9NO_3S$

MW: 163.19

General Properties:

Acetylcysteine is a white or almost white, crystalline powder or colourless crystals. Acetylcysteine is freely soluble in water and in ethanol (96 per cent), practically insoluble in methylene chloride.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. Monograph.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Re-test period is included in the CEP. Stability studies have been assessed by EDQM.

II.3 Medicinal Product

Description of the product

The finished product is presented as effervescent tablet, a white round, flat tablet with diameter of approximately 25 mm. The tablet is flat-faced with bevelled edges and with an average weight of 3500 mg. Acetylcysteine 600 mg, effervescent tablet contains drug substance acetylcysteine and the following excipients: ascorbic acid, sodium carbonate, sodium hydrogen carbonate, citric acid, sorbitol, macrogol, sodium citrate, sodium saccharine, and lemon flavour.

The product is packaged in polypropylene tubes with polyethylene caps with silica gel or in four-layer laminated paper sachet (paper / polyethylene / aluminum / ionomer) in a hermetically-sealed strip.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in polypropylene tubes with polyethylene caps with silica gel or four-layer laminated paper sachet (paper / polyethylene / aluminum / ionomer) in a hermetically-sealed strip. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life:

- Sachet: 1 year.

- Tube: 6 months.

Storage conditions:

- Sachet: This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

- Tube: Do not store above 30 ºC. Store in the original package in order to protect from light.

In-use shelf life: Not applicable.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of acetylcysteine are well known. As acetylcysteine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Environmental Risk Assessment (ERA)

Since Acetylcysteine Abex 600 mg effervescent tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Acetylcysteine is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

The applicant has not submitted a bioequivalence study and a waiver is claimed because at time of administration the tablet will be an aqueous solution, which is discussed below. The originator product is Fluimucil Hustenlöser akut 600 mg Effervescents Tablets by Zambon GmbH registered since 14/08/1995 in Germany. In Spain the originator product is Fluimucil Forte 600 mg effervescent tablets from Zambon, S.A.U, registered since 01/07/1999.

IV.2 Pharmacokinetics

Biowaiver

A waiver is claimed as at time of administration the tablet will be an aqueous solution and in accordance with CHMP/EWP/QWP/1401/98 "Guideline on the investigation of Bioequivalence" a waiver is possible if there are not excipients that may alter the bioavailability. In this application the test product contains sorbitol (and macrogol 600, although the relevance of this excipient is not clearly defined as critical), that is not present in the reference, and as this excipient is considered critical for absorption, the biowaiver approach in principle could not be acceptable.

However, the applicant has provided the results from a bioequivalence study between the same product concerned by this application and the reference product Fluimucil® 600 mg effervescent tablets purchased from the Russian market (manufactured by Zambon Switzerland Ltd.) with the same composition as other Fluimucil® 600 mg effervescent tablets marketed in Europe, where both products were bioequivalent in terms of Cmax and AUC parameters as the 90% confidence intervals were within the bioequivalence acceptance criteria (see table below), therefore, concluding that the presence of sorbitol and macrogol 600 has no effect on the absorption of acetylcysteine.

Parameter	Point estimate	90% confidence intervals
AUC_{0-t}	104.39%	94.11-115.79%
C_{max}	100.91%	85.37-119.28%

Although the submission of this study has no regulatory relevance as pivotal evidence for the requested submission because the reference product originated from a non-EU market, it can be accepted as supportive, and the results clearly demonstrate that the existence of sorbitol and macrogol 600 in the requested product does not affect the rate and extent of absorption of acetylcysteine compared to the reference product.

Therefore, the justification the biowaiver can be accepted.

IV.3 Pharmacodynamics

Bibliography submitted by the applicant cover most pharmacodynamics aspects. Based on the long-term and widespread therapeutic use of acetylcysteine, the available pharmacodynamics data are adequate.

IV.4 Clinical efficacy

Not applicable

IV.5 Clinical safety

Not applicable

IV.6 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 Acetylcysteine Abex 600 mg effervescent tablets.
There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Acetylcysteine Abex 600 mg effervescent tablets.

IV.7 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Fluimucil Forte 600 mg effervescent tablets (NAP, Registration number in Spain:62663). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Acetylcysteine Abex 600 mg effervescent tablets is found adequate. There are no objections to the approval of Acetylcysteine Abex 600 mg effervescent tablets from a non-clinical and clinical point of view. The justification for a biowaiver as an oral solution at the time of administration can be accepted. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.