IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Carbocisteine 375mg Hard Capsules
Carbocisteine
PA0688/045/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Carbocisteine 375mg Hard Capsules, from Chanelle Medical on 9th December 2016 for a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

This application was submitted as a decentralised procedure application in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application. The RMS is IE.

This is a prescription medicine which may be renewed (B).

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	**Carbocisteine**
Name(s) of the active substance(s) (INN)	Carbocisteine
Pharmacotherapeutic classification (ATC code)	R05CB03
Pharmaceutical form and strength(s)	375 mg Capsules Hard
MRP/DCP No.	IE/H/466/001/DC
Reference Member State	IE
Marketing Authorisation Holder	Chanelle Medical

II. QUALITY ASPECTS

II.1. Introduction

This application is for Carbocisteine 375mg Hard Capsules

II.2 Drug substance

The active substance is Carbocisteine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each capsule contains 375mg carbocisteine.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or USP and are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for capsules, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Carbocisteine 375mg Hard Capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Mucodyne 375 mg Capsules by Aventis Pharma Limited on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

The justification for the absence of an environmental risk assessment is acceptable as the active substance is a dibasic amino acid, the use of which, as indicated the guideline on ERA assessment (EMEA/CHMP/SWP/4447/00 corr 2), is unlikely to result in a significant risk to the environment. Additionally, since Carbocisteine 375mg hard capsules 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.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of Carbocisteine are well known.The active substance is a generic formulation of Mucodyne 375 mg Capsules by Aventis Pharma Limited on the European market. No new preclinical data have been submitted. This is acceptable for generic applications to avoid the need for repetitive tests on animals.

IV. CLINICAL ASPECTS

IV.1 Introduction

Carbocisteine is a well-known mucolytic agent used in the treatment of disorders of the respiratory tract associated with excessive or viscous mucus.

Therapeutic indications:
Carbocisteine 375mg capsules is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

Posology and method of administration:
Adults including the elderly:
Dosage is based upon an initial daily dosage of 2250 mg Carbocisteine (6 capsules) in divided doses, reducing to 1500 (4 capsules) mg daily in divided doses when a satisfactory response is obtained. For example, two capsules three times a day reducing to one capsule four times a day.

Paediatric population:
This formulation is not recommended for children.

Method of administration:
Carbocisteine 375mg capsules are for oral use.

Clinical pharmacology
The clinical pharmacology of carbocisteine is well known. With the exception of the bioequivalence study no new pharmacodynamics or pharmacokinetic studies were conducted. This is acceptable as this application was submitted under Article 10(1) of Directive 2001/83/EC.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Mucodyne 375 mg Capsules by Aventis Pharma Limited on the European market.

For this generic application, the applicant has submitted a single bioequivalence study in which the pharmacokinetic profile of the test product was compared with the pharmacokinetic profile of the reference product Mucodyne

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out.
The bioequivalence study compared Carbocisteine 375mg capsules with the reference product Mucodyne 375 mg capsules.

Subjects were enrolled and given a single oral dose of 375mg carbocisteine or the test or reference product after an overnight fast. Blood samples were taken pre dose and up to 12 hours post dose.

The main pharmacokinetic results for carbocisteine are presented below.

90% confidence intervals of parametric means Pharmacokinetic parameter

CMax
AUC0-t
AUC 0-∞

Point estimate %	Lower limit%	Upper Limit %
101.74	94.39	109.67
100.63	95.63	105.90
100.37	95.37	105.64

CMax maximum plasma concentration
AUC0-t area under the plasma concentration-time curve form time zero to t hours
AUC 0-∞ area under the plasma concentration-time curve form time zero to infinity

The current Guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1041/98 Rev 1) defines the confidence limits as 80% to 125% for CMax and AUC values.

As the 90% confidence intervals of the test/reference ratio for the log transformed parameters C Max, AUC 0-∞ AND AUC 0-t have been demonstrated to be within the pre specified limits bioequivalence has been demonstrated between the test product Carbocicteine 375mg capsules and the reference product Mucodyne 375mgs capsules (Aventis Pharma UK)

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

A clinical expert report has been written by an appropriate qualified person and is a suitable summary of the clinical aspects of the dossier for this application.

IV.2 Pharmacokinetics

Carbocisteine is rapidly absorbed from the GI tract. Equilibrium pharmacokinetics were established in healthy volunteers following administration of carbocisteine 375mg capsules, subjects were given 2 capsules three times per day for seven days. The mean Tmax was 2.0 hours (range 1.0-3.0), the half-life was 1.87 hours (range 1.4-2.5); Kel was 0.387 $Hours^{-1}$ (range 0.28-0.50) and $AUC_{0-7.5}$ was 39.26 mcg.hr/ml (range 26.0-62.4). Values for derived pharmacokinetic values were CL_S 331 $ml.min^{-1}$ and Volume of distribution (VD) was 105.2l and 1.4L/kg.

IV.3 Pharmacodynamics

Carbocisteine (S-carboxymethyl L-cysteine) has been shown in normal and bronchitic animal models to affect the nature and amount of mucus glycoprotein which is secreted by the respiratory tract. An increase in the acid-neutral glycoprotein ratio of the mucus and a transformation of serous cells to mucus cells is known to be the initial response to irritation and will normally be followed by hypersecretion. The administration of Carbocisteine to animals exposed to irritants indicates that the glycoprotein that is secreted remains normal; administration after exposure indicates that return to the normal state is accelerated. Studies in humans have demonstrated that Carbocisteine reduces goblet cell hyperplasia. Carbocisteine can therefore be demonstrated to have a role in the management of disorders characterised by abnormal mucus.

IV.4 Clinical Efficacy

No new efficacy data have been submitted and are not required for this application type.

IV.5 Clinical Safety

No new safety concerns were highlighted during the bioequivalence study.

Pharmacovigilance System
The marketing authorisation holder (MAH) submitted a summary of the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

Risk Management Plan

The applicant 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 Carbocisteine 375mg hard capsules. The revised RMP (version 1.3 dated final sign off 04/10/2016) is acceptable. Routine risk minimization activities are considered sufficient. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Important identified risks	Hypersensitivity Peptic ulceration
Important potential risks	None
Missing information	Use during pregnancy and lactation

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

• PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

• For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

• For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date
Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects

Bioequivalence was demonstrated between the Carbocisteine 375mg capsules (Chanelle Medical) and the reference product Mucodyne 375mg capsules (Aventis Pharma UK).

No new or unexpected safety concerns arose during assessment of this application.
Extensive clinical experience with carbocisteine is considered to have demonstrated the therapeutic value of the compound.

V. OVERALL CONCLUSIONS

Carbocisteine 375 mg capsules (Chanelle Medical) is a generic form of Mucodyne 375mg capsules (Aventis Pharma UK).

Mucodyne 375mg capsules is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been demonstrated and to be in compliance with the CHMP guidance documents. No new non clinical or clinical safety concerns have been identified. The SmPC is consistent with that of the reference product.

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

On the basis of the data submitted and considering the extensive clinical experience with use of carbocisteine the HPRA considers the benefit risk to be positive and therefore granted a marketing authorisation for Carbosisteine 375mg capsules (Chanelle Medical).

VI. REVISION DATE

24.10.2021