IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Carbocisteine 375 mg Capsules, Hard
Carbocisteine
PA0343/008/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6943/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 29th June 2021 under procedure number IE/H/1188/001/DC.

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0343/008/001
Marketing Authorisation Holder: Key Pharmaceuticals Ltd.

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Carbocisteine 375 mg Capsules, Hard (PL 34424/0048) could be approved.

Carbocisteine capsules are a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.
It is also indicated for the reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.

The Reference Member State (RMS) for this procedure was the UK and the Concerned Member State (CMS) was Republic of Ireland.

This application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic medicine of the originator medicinal product, Mucodyne 375 mg capsules (PL 04425/0203) authorised on 07 February 2009.

No new non-clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of reference product that has been licensed for over 10 years.

With the exception of three bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application is based on being a generic medicinal product of reference product that has been in clinical use for over 10 years. The bioequivalence study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of this product.

Satisfactory Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 20 January 2020. After a subsequent national phase, a marketing authorisation was granted in the UK on 18 February 2020.

II. QUALITY ASPECTS

II.1 Introduction

This product is a hard capsule. Each hard capsule contains 375 mg carbocisteine as active substance.

In addition to carbocisteine, the capsules also contain lactose monohydrate, povidone, sodium lauril sulfate and magnesium stearate making up the capsule content. The capsule shell is composed of gelatin, yellow iron oxide and titanium dioxide (E171).

The finished product is available in clear or opaque aluminium (Alu)-polyvinylchloride (PVC) blister packs. The pack sizes are 6, 18, 30 or 120 capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

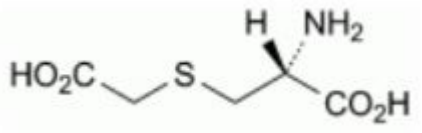
II.2 ACTIVE SUBSTANCE

rINN: Carbocisteine

Chemical Name: (2R)-2-amino-3-(carboxymethylsulfonyl)propionic acid

Molecular Formula: $C_5H_9NO_4S$

Chemical Structure:



Molecular Weight: 179/19 g/mol

Appearance: White or almost white crystalline powder.

Solubility: Practically insoluble in water and in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxide.

Carbocisteine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current European regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions is set. This is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III. NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of carbocisteine are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a generic version of already authorised product, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV. CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology, efficacy and safety of carbocisteine are well-known. With the exception of data from the bioequivalence study, no new clinical data are provided nor are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics
In support of the application, the applicant submitted the following bioequivalence study.

This study was randomised, single dose, open label, two-period, two sequence, cross-over bioequivalence study comparing the test product, Carbocisteine 375 mg capsule and the reference product, Mucodyne (carbocisteine) 375 mg capsule, hard (Sanofi, UK) in healthy adult human subjects under fasting condition.

After an overnight fast of 10 hours or more, a single oral dose of either the test product or the reference product was administered to the subjects.

Blood samples were taken pre-dose and up to 24 hours after dosing in each period.

A summary of the pharmacokinetic results are presented below:

PK Parameter	Geometric LSM		Ratio of Geometric LSM (T/R) %	90% Confidence Interval	Intra subject CV (%)	Power (%)
	Reference (R)	Test (T)				
N	32	32	-	-	-	-
C_{max} (ng/mL)	3092.66	3234.17	104.58	96.12-113.77	20.06	99.55
AUC_{0-t} (hr.ng/mL)	11859.95	12022.36	101.37	96.19-106.82	12.40	100.00
$AUC_{0-\infty}$ (hr.ng/mL)	12075.10	12208.16	101.10	96.08-106.38	12.05	100.00

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test and reference products under fasting conditions.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data were submitted with this application and none were required.

IV.5 Clinical safety
With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with this application.

The safety data from the bioequivalence study showed that the test and reference products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisations is recommended for this application.

V. OVERALL CONCLUSIONS

User consultation
The Patient Information Leaflet (PIL) 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 results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with carbocisteine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

VI. REVISION DATE

December 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6943/001/DC to IE/H/1188/001/DC	N/A	N/A	N/A	Approved