Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Carbocisteine 250mg/5ml Oral Solution

carbocisteine

PL 14251/0134

Manx Healthcare Ltd

LAY SUMMARY

Carbocisteine 250mg/5ml Oral Solution
carbocisteine

This is a summary of the Public Assessment Report (PAR) for Carbocisteine 250mg/5ml Oral Solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Carbocisteine 250mg/5ml Oral Solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Carbocisteine 250mg/5ml Oral Solution and what is it used for?
This application is for a generic medicine. This means that this medicine is the same as, and considered interchangeable with, a reference medicine already authorised, called Mucodyne® 250 mg/5 ml Syrup.

Carbocisteine 250mg/5ml Oral Solution belongs to a group of medicines called 'mucolytics'. It is used for problems with the breathing passages (respiratory tract). These problems happen when too much mucus is made or the mucus is too sticky.

How does Carbocisteine 250mg/5ml Oral Solution work?
It works by making mucus (phlegm) less sticky. This makes the mucus easier to cough up.

How is Carbocisteine 250mg/5ml Oral Solution used?
The pharmaceutical form of this medicine is oral solution and the route of administration is for oral use.

The patient should use the measuring syringe to measure the quantity they will need to take. The syringe is for oral administration, with graduations per 0.25 ml. Each 0.25 ml corresponds to 12.5 mg of carbocistiene.

How to use the syringe

- When the patient uses the medicine for the first time, place the adaptor in the neck of the bottle.
- Push the syringe firmly into the adaptor in the neck of the bottle.
- To fill the syringe, turn the bottle upside down. Whilst holding the syringe in place, gently pull the plunger down drawing the medicine to the correct mark on the syringe. The patient's doctor will tell you the right dose.
- Turn the bottle the right way up, remove the syringe from the adaptor by gently twisting the syringe.
- The patient should place the end of the syringe into their mouth and gently press the plunger down to slowly and gently release the medicine.
- After use, replace the bottle cap. Wash the syringe in warm water and allow to dry. Store out of reach of children.

Adults, elderly and children over 12 years
The recommended dose is 15ml, three times a day. If the patient's symptoms improve, their dose should be lowered to 10ml, three times a day.

Use in children and adolescents
Carbocisteine 250mg/5ml Oral Solution should not be given to children under 2 years of age.
For children from 2 to 5 years the dose is 1.25ml to 2.5ml, four times a day.
For children from 6 to 12 years the dose is 5ml three times a day.

For further information on how Carbocisteine 250mg/5ml Oral Solution is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Carbocisteine 250mg/5ml Oral Solution have been shown in studies?
Carbocisteine 250mg/5ml Oral Solution is a generic medicine that fulfils criteria meaning that no additional studies are required. Carbocisteine 250mg/5ml Oral Solution has been considered a generic medicine of the reference medicine based on a comparison of their physical and chemical characteristics.

What are the possible side effects of Carbocisteine 250mg/5ml Oral Solution?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Carbocisteine 250mg/5ml Oral Solution is a generic medicine, its benefits and possible side effects are considered to be the same as for the reference medicine.

Why was Carbocisteine 250mg/5ml Oral Solution approved?
It was concluded that, Carbocisteine 250mg/5ml Oral Solution has been shown to be comparable to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Carbocisteine 250mg/5ml Oral Solution?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Carbocisteine 250mg/5ml Oral Solution. The RMP details the important risks of Carbocisteine 250mg/5ml Oral Solution, how these risks can be minimised, any uncertainties about Carbocisteine 250mg/5ml Oral Solution (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Carbocisteine 250mg/5ml Oral Solution:

Summary of safety concerns	
Important identified risks	Hypersensitivity
	Peptic ulceration
Important potential risks	None
Missing information	Use during pregnancy and lactation

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Carbocisteine 250mg/5ml Oral Solution are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Carbocisteine 250mg/5ml Oral Solution
A marketing authorisation for Carbocisteine 250mg/5ml Oral Solution was granted in the United Kingdom (UK) on 07 September 2022.

The full PAR for Carbocisteine 250mg/5ml Oral Solution follows this summary.

This summary was last updated in November 2022.

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I INTRODUCTION

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 250mg/5ml Oral Solution (PL 14251/0134) could be approved.

The product is approved for the following indication:
Carbocisteine is a mucolytic agent for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

The name of the active substance is carbocisteine. 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.

This application was approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as a generic medicine of a suitable originator medicinal product, Mucodyne® 250 mg/5 ml Syrup that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a generic medicinal product of a suitable reference product.

A biowaiver was submitted with this application, which was accepted. No bioequivalence study was required and no new clinical studies were provided with this application.

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

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

A marketing authorisation for Carbocisteine 250mg/5ml Oral Solution was granted in the United Kingdom (UK) on 07 September 2022.

II QUALITY ASPECTS

II.1 Introduction

Each 5ml of oral solution contains 250mg of carbocisteine.

In addition to carbocisteine, this product also contains the excipients saccharin sodium, methyl parahydroxybenzoate (E218), raspberry flavour, carmellose sodium, sodium hydroxide, and purified water.

The finished product is packaged in either a 200ml or 300ml polyethylene terephthalate (PET) amber bottle, with a white high-density polyethylene (HDPE) child resistant cap, accompanied by a syringe adaptor and a 5ml polypropylene graduated syringe (marker per 0.25ml).

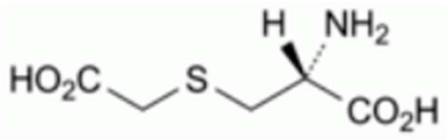
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: carbocisteine

Chemical Name: Carbocisteine contains not less than 98.5 per cent and not more than the equivalent of 101.0 per cent of (2*R*)-2-amino-3-[(carboxymethyl)sulfanyl]propanoic acid, calculated with reference to the dried substance.

Molecular Formula: $C_5H_9NO_4S$



Chemical Structure:

Molecular Weight: 179.2

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 hydroxides.

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 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 PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity 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.

No excipients of animal or human origin are used in the final products.

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.

Satisfactory batch formulation data have 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 Specifications

The finished product specifications at release and shelf-life are 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 product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years with the storage conditions do not store above 30ºC. Store in the original package in order to protect from light is acceptable. The in use shelf-life is use within 3 months after opening.

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

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 generic version of an 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. According to the regulatory requirements, the applicant has provided a suitable biowaiver and a bioequivalence study is not required for this product. An overview based on a literature review is, thus, satisfactory.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.

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
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Mucodyne® 250 mg/5 ml Syrup.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, 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 authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. 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.

VI 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.

Carbocisteine 250mg/5ml Oral Solution Carbocisteine

SUGAR FREE

Oral use. Read the package leaflet before use. **Keep out of the sight and reach of children.** Do not store above 30°C. Store in the original package in order to protect from light. Once opened, use within 3 months. Each 5ml solution contains 250mg of carbocisteine. Also contains methyl parahydroxybenzoate (E218) and sodium. See leaflet for further information.

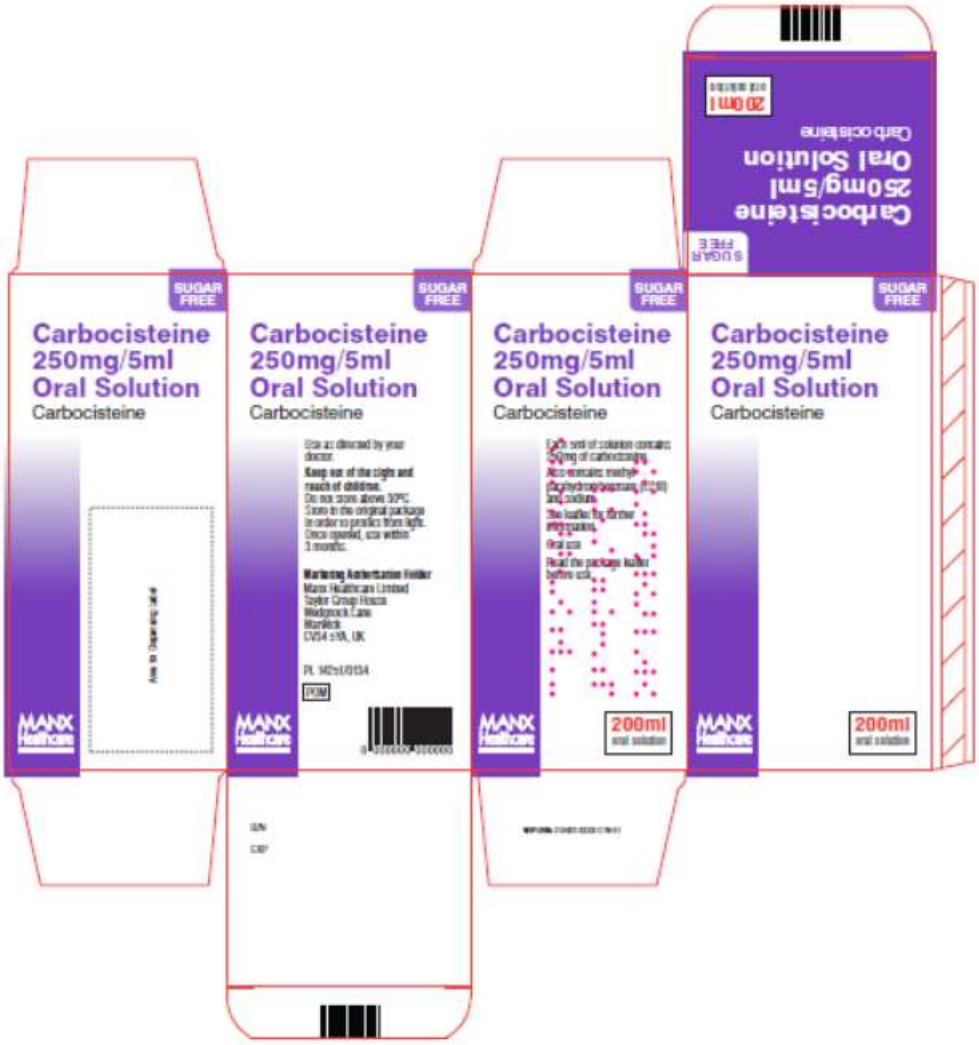
300ml oral solution

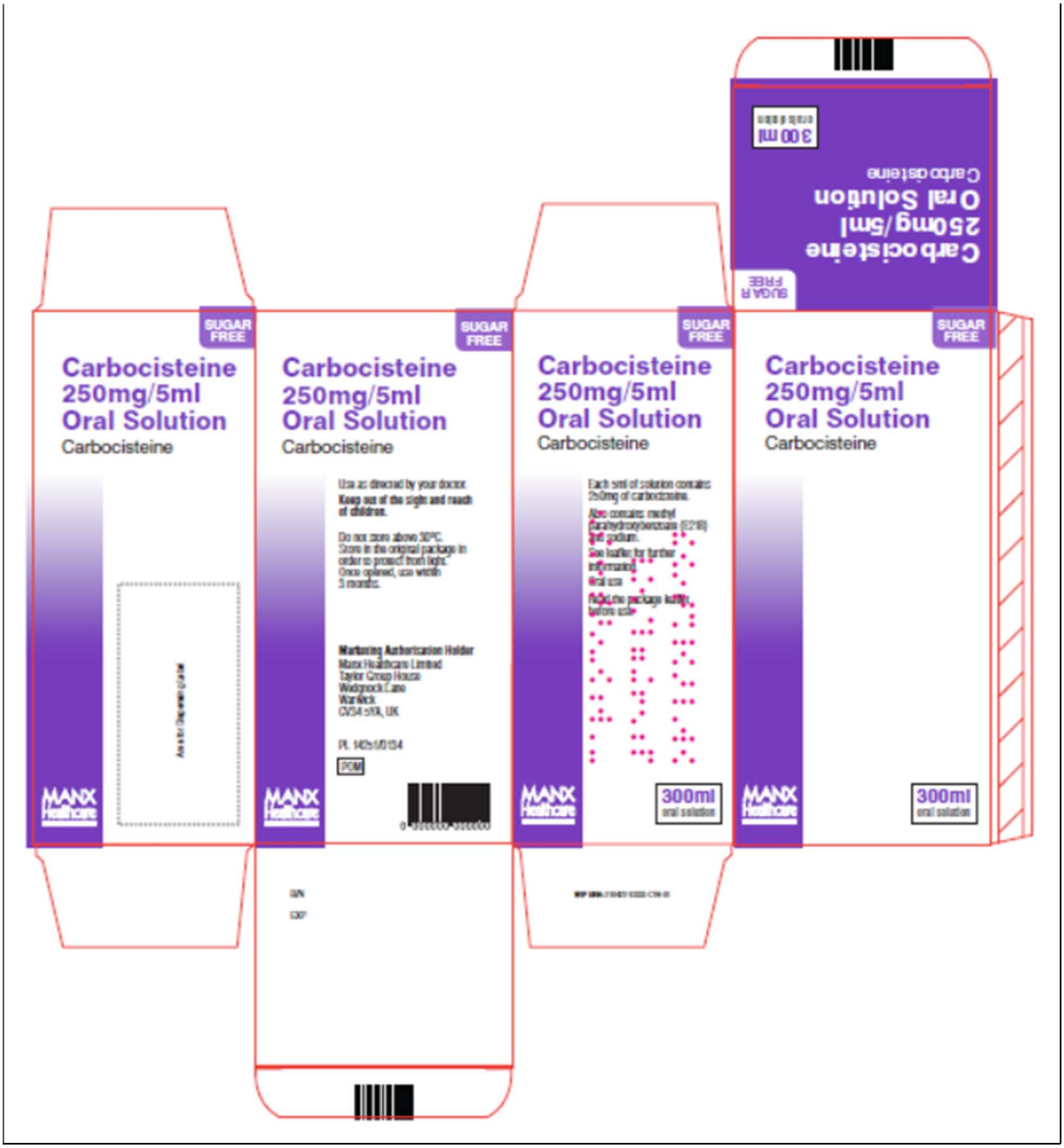
MANX Healthcare

Marketing Authorisation Holder
Manx Healthcare Limited, Taylor Group House
Wedgnock Lane, Warwick, CV34 5YA, UK

PL 14251/0134 POM **WIP URN:** 210422-XXXX-LBL-01

B/N
EXP




SUGAR FREE
Carbocisteine 250mg/5ml Oral Solution
Carbocisteine
Use as directed by your doctor.
Keep out of the sight and reach of children.
Do not store above 30°C.
Store in the original package in order to protect from light.
Once opened, use within 3 months.
Marketing Authorisation Holder
Manx Healthcare Limited
Taylor Group House
Woodcock Lane
Warwick
CV34 5TA, UK
PL 14251/0134
POM
Each 5ml of solution contains 250mg of carbocisteine.
Also contains: methyl parahydroxybenzoate (E218) and sodium.
See leaflet for further information.
Oral use
Read the package leaflet before use
300ml
oral solution
MANX HEALTHCARE

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N