Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Carbocisteine 750mg/5ml sugar-free syrup

(carbocisteine)

PL 42176/0011

Lucis Pharma Ltd

LAY SUMMARY

Carbocisteine 750mg/5ml sugar-free syrup

(Carbocisteine)

This is a summary of the Public Assessment Report (PAR) for Carbocisteine 750mg/5ml sugar-free syrup. 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.

This product will be referred to as Carbocisteine sugar-free syrup in this lay summary for ease of reading.

For practical information about using Carbocisteine sugar-free syrup, patients should read the package leaflet or contact their doctor or pharmacist.

What is Carbocisteine sugar-free syrup and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Mucodyne 250mg/5ml Syrup, albeit with certain differences. In this case, Carbocisteine sugar-free syrup is a higher strength (of the active substance) from reference product.

Carbocisteine is used in adults and children from 15 years of age for problems with the breathing passages. These problems happen when too much mucus is made or the mucus is too sticky.

How does Carbocisteine sugar-free syrup work?
Carbocisteine sugar-free syrup contains the active substance carbocisteine. This belongs to a group of medicines called "mucolytics" used to treat mucus produced by infections of the breathing passages (respiratory tract). It works by making mucus (phlegm) less sticky. This makes the mucus easier to cough up.

How is Carbocisteine sugar-free syrup used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (taken by mouth).

The patient should shake the bottle before use and use the measuring cup provided (marked in 2.5 ml and 5 ml quantities).

Adults including the elderly and children from 15 years of age
The initial dose is 5ml three times a day; if symptoms improve, your doctor may lower your dose to 5ml, 2 times a day. The maximum daily dose is 15ml.

Children under 15 years
Not recommended.

For further information on how Carbocisteine sugar-free syrup is used, refer to the package leaflet and Summary of Product Characteristics 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 sugar-free syrup have been shown in studies?
No additional studies were needed as carbocisteine contains the same active substance as the reference medicine, and satisfactory data to justify the differences have been provided.

What are the possible side effects of Carbocisteine sugar-free syrup?
Because Carbocisteine sugar-free syrup is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Carbocisteine sugar-free syrup approved?
It was concluded that, in accordance with EU requirements, Carbocisteine sugar-free syrup, has been shown to be therapeutically equivalent 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 sugar-free syrup?
A Risk Management Plan (RMP) has been developed to ensure that Carbocisteine sugar-free syrup is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Carbocisteine sugar-free syrup
A Marketing Authorisation for Carbocisteine sugar-free syrup was granted in the UK on 19 February 2020.

The full PAR for Carbocisteine sugar-free syrup follows this summary.

This summary was last updated in April 2020.

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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 750mg/5ml sugar-free syrup (PL 42176/0011) could be approved.

The product is approved for the following indication:

- in adults and children over 15 years, for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

Carbocisteine is a known mucolytic agent that modifies mucous secretions. It acts during the gel phase of the mucus, most likely by breaking up the disulfide bonds of the glycoproteins, and thus favouring expectoration. Moreover, carbocisteine has effects on bronchial secretion by normalization of mucus hyperviscisity.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of a suitable originator product, Mucodyne 250mg/5ml Syrup that has been licensed within the EU for a suitable time, in line with the legal requirements.

All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP).

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

A biowaiver was submitted with this application which was accepted. No bioequivalence or therapeutic equivalence studies were required and none 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 national marketing authorisation was granted in the UK on 19 February 2019.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 750mg of carbocisteine in each 5 ml of oral solution**.**

In addition to carbocisteine, this product also contain the excipients glycerol, sodium saccharin, hydroxyethylcellulose, xanthan gum, caramel powder, raspberry flavor, sodium methyl parahydroxybenzoate, sodium hydroxide (sodium hydroxide pellets or sodium hydroxide 30 % solution) and purified water.

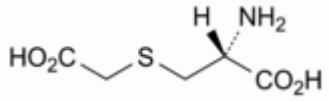
The finished product is packaged in 100 ml and 200 ml amber type III glass bottles each with a high density polyethylene (HDPE) child resistant screw cap and a polypropylene measuring cup with 2.5 ml/5 ml graduations.

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-[(carboxymethyl)sulfanyl]propanoic acid
Molecular Formula: $C_5H_9NO_4S$
Chemical Structure:



Molecular Weight: 179.2 g/mol
Appearance: A 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.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

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 finished product.

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 Specifications

The finished product specifications 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 24 months for the unopened product and one month after the product is first opened, with the storage conditions ‘Do not store above 25^{o}C.’, 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 this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase 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

In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

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 have been submitted for 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 250mg/5ml Syrup .

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 authorisation is recommended for this application.

V 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.

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.

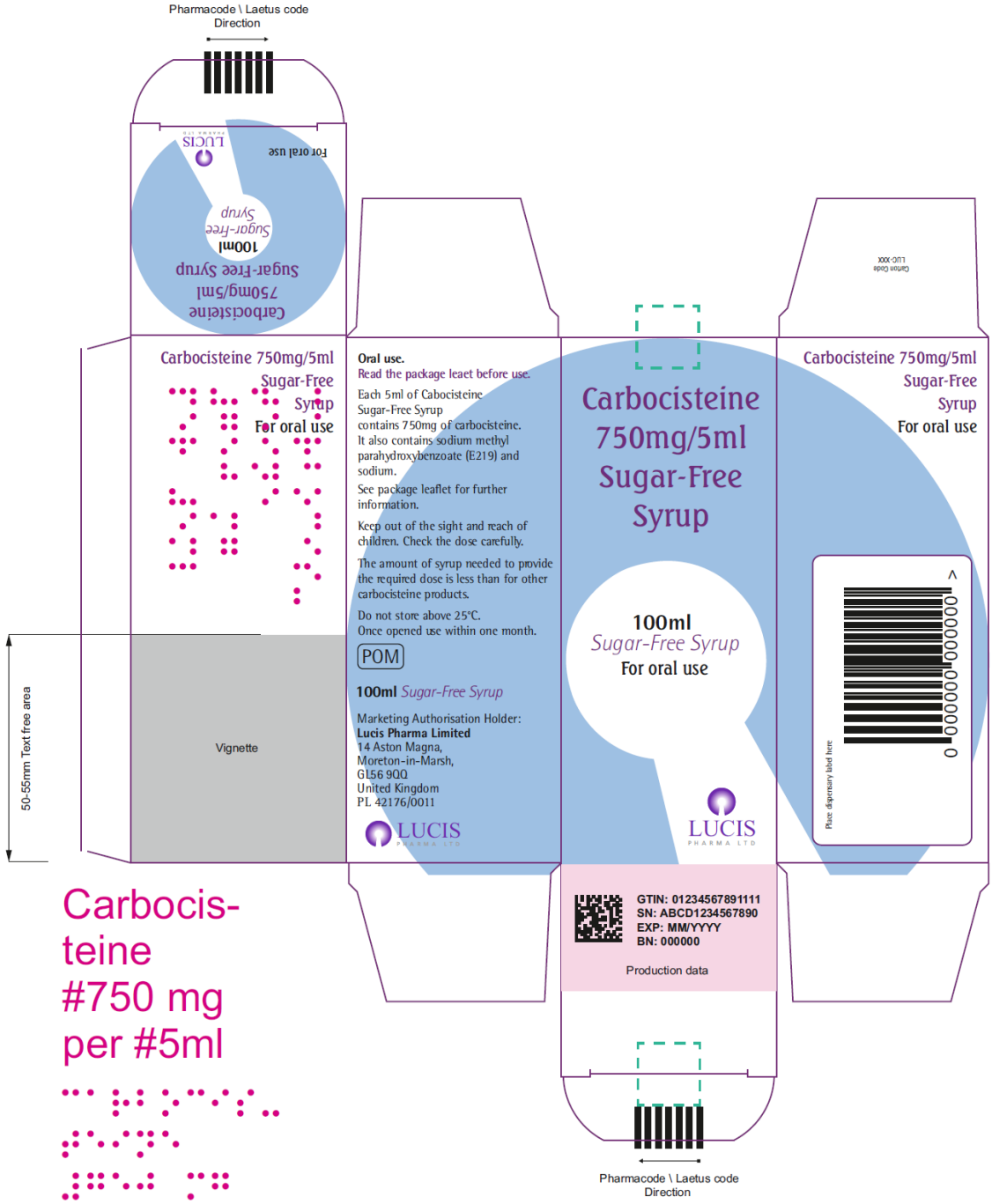
Extensive clinical experience with carbocisteine is considered to have demonstrated the therapeutic value of the product.

The benefit/risk is, therefore, considered to be positive.

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

In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product is available on the MHRA website.

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


Pharmacode \ Laetus code
Direction
Carbocisteine 750mg/5ml Sugar-Free Syrup
100ml
Sugar-Free Syrup
For oral use
Carbocisteine 750mg/5ml
Sugar-Free
Syrup
For oral use
Oral use.
Read the package leaet before use.
Each 5ml of Cabocisteine Sugar-Free Syrup contains 750mg of carbocisteine. It also contains sodium methyl parahydroxybenzoate (E219) and sodium.
See package leaflet for further information.
Keep out of the sight and reach of children. Check the dose carefully.
The amount of syrup needed to provide the required dose is less than for other carbocisteine products.
Do not store above 25°C.
Once opened use within one month.
POM
100ml Sugar-Free Syrup
Marketing Authorisation Holder:
Lucis Pharma Limited
14 Aston Magna,
Moreton-in-Marsh,
GL56 9QQ
United Kingdom
PL 42176/0011
Carbocisteine 750mg/5ml Sugar-Free Syrup
100ml
Sugar-Free Syrup
For oral use
Carbocisteine 750mg/5ml
Sugar-Free
Syrup
For oral use
Place dispensary label here
50-55mm Text free area
Vignette
GTIN: 01234567891111
SN: ABCD1234567890
EXP: MM/YYYY
BN: 000000
Production data
Pharmacode \ Laetus code
Direction
Carbocis-
teine
#750 mg
per #5ml

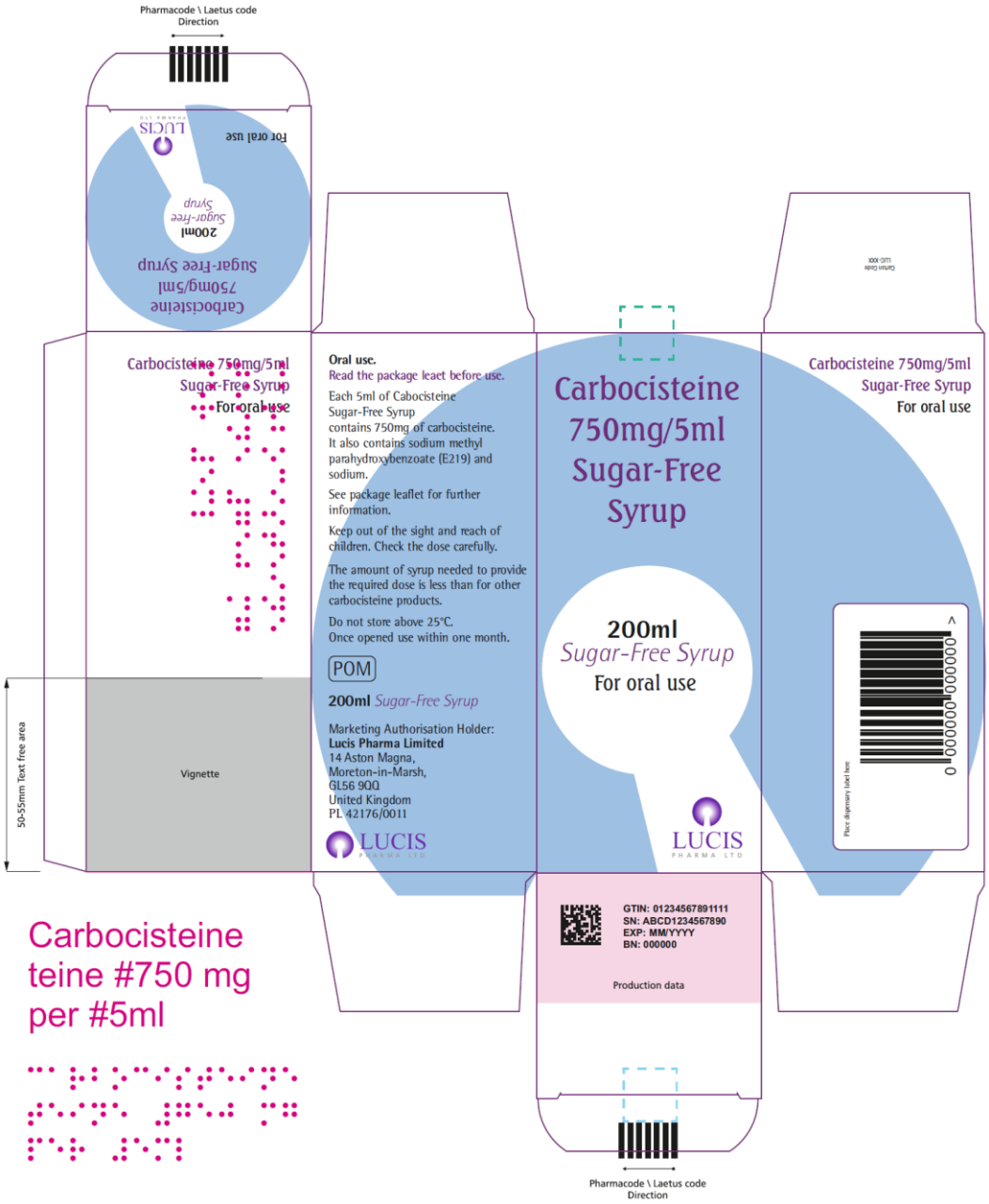

Pharmacode \ Laetus code
Direction
Carbocisteine
750mg/5ml
Sugar-Free Syrup
200ml
Sugar-Free
Syrup
For oral use
LUCIS
Carbocisteine 750mg/5ml
Sugar-Free Syrup
For oral use
Vignette
50-55mm Text free area
Oral use.
Read the package leaet before use.
Each 5ml of Cabocisteine
Sugar-Free Syrup
contains 750mg of carbocisteine.
It also contains sodium methyl
parahydroxybenzoate (E219) and
sodium.
See package leaflet for further
information.
Keep out of the sight and reach of
children. Check the dose carefully.
The amount of syrup needed to provide
the required dose is less than for other
carbocisteine products.
Do not store above 25°C.
Once opened use within one month.
POM
200ml Sugar-Free Syrup
Marketing Authorisation Holder:
Lucis Pharma Limited
14 Aston Magna,
Moreton-in-Marsh,
GL56 9QQ
United Kingdom
PL 42176/0011
LUCIS
PHARMA LTD
Carbocisteine
750mg/5ml
Sugar-Free
Syrup
200ml
Sugar-Free Syrup
For oral use
LUCIS
PHARMA LTD
Carbocisteine 750mg/5ml
Sugar-Free Syrup
For oral use
Place dispensary label here
GTIN: 01234567891111
SN: ABCD1234567890
EXP: MM/YYYY
BN: 000000
Production data
Pharmacode \ Laetus code
Direction
Carbocisteine
teine #750 mg
per #5ml

TABLE OF CONTENT OF THE PAR UPDATE

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**