CARBOCISTEINE 375MG CAPSULES

(Carbocisteine)

PL 18909/0364

UKPAR

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CARBOCISTEINE 375MG CAPSULES

PL 18909/0364

LAY SUMMARY

The MHRA granted Arrow Generics Limited a Marketing Authorisation (licence) for the medicinal product Carbocisteine 375mg Capsules (PL 18909/0364) on 02 March 2011. This product is available as a prescription-only medicine (POM) and is used to help treat respiratory tract problems (problems with the breathing passages) characterised by too much sticky mucus, including chronic obstructive airways disease (lung damage with restricted airways).

Carbocisteine 375mg Capsules contain carbocisteine which belongs to a group of medicines called mucolytics which cause the mucus to be less sticky and easier to cough up.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Carbocisteine 375mg Capsules outweigh the risks; hence a Marketing Authorisation has been granted.

CARBOCISTEINE 375MG CAPSULES

PL 18909/0364

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Arrow Generics Limited, a Marketing Authorisation for the medicinal product Carbocisteine 375mg Capsules (PL 18909/0364) on 02 March 2011. This product is available as a prescription-only medicine (POM) and is indicated for the adjunctive therapy of respiratory tract disorders characterised by excessive, viscous mucus, including chronic obstructive airways disease.

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC, as amended claiming to be a generic medicinal product of Mucodyne Capsules 375 mg (Sanofi-Aventis, UK), which was first authorised in March 1992.

This product contains the active ingredient carbocisteine which belongs to a pharmacotherapeutic group of drugs called mucolytic agents (ATC code: R05C B03).

Carbocisteine (5-carboxymethyl L-cysteine) has been shown in normal and bronchitic animal models to affect the nature and amount of mucus glycoprotein that 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 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 play a role in the management of disorders characterised by abnormal mucus.

No new non-clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

A single-dose, bioequivalence study was submitted to support this application, comparing the test product Carbocisteine 375mg Capsules (Arrow Generics Limited, UK) and the reference product Mucodyne 375 mg Capsules (Aventis Pharma, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were performed, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The MHRA considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for the non-submission of a Risk Management Plan.

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of taking Carbocisteine 375mg Capsules outweigh the risks; hence a Marketing Authorisation has been granted.

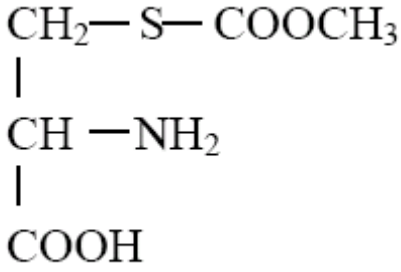
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

INN: Carbocisteine

Chemical names: (Carboxymethyl)thio- 3 –alanine Amine-2-(carboxymethyl)thio-3-propionic acid S- carboxymethyl – L – cisteine (R) – 2 – amino – 3 – [carboxymethyl) thio] propionic acid

Structure:



Molecular formula: $C_5H_9NO_4S$

Molecular weight: 179.2

Description: White crystalline powder

Solubility: Carbocisteine is practically insoluble in water, in alcohol and in ether. It dissolves in diluted mineral acids and in diluted solutions of alkali hydroxides.

Carbocisteine is the subject of a European Pharmacopoeia monograph.

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

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

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

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, macrogol, magnesium stearate, gelatin, titanium dioxide (E171), Iron Yellow Oxide (body, E172) and Brilliant Blue FCF (cap, E133).

Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients are of animal or human origin. The suppliers of gelatin have provided European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability, which covers all aspects of the manufacture and control of the excipient. No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical development

The aim of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of Mucodyne 375 mg Capsules (Aventis Pharma, UK)

Suitable data on the quality critical attributes of the product have been provided for this application.

Comparable *in vitro* dissolution and impurity profiles have been provided for the proposed and originator product.

Manufacture

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

Satisfactory batch formulae 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 specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System

The product is packaged in polyvinylchloride / aluminium blisters in pack sizes of 20, 30, 60, 100 and 120 capsules

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submit the mock-ups to the relevant regulatory authorities for approval before marketing.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 5 years with the special storage conditions 'Store below 25ºC.'

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPC, PIL and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a marketing authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed product is a generic medicinal product of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
A suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

The clinical pharmacology of carbocisteine is well-known. With the exception of the bioequivalence study, no pharmacokinetic or pharmacodynamic data were submitted for this application, and none were required for an application of this type.

The following bioequivalence study was submitted:

An open-label, randomised, two-way, two-period, single dose crossover study, comparing the pharmacokinetics of the test product Carbocisteine 375mg Capsules (Arrow Generics Limited, UK) versus the reference product Mucodyne 375 mg Capsules (Aventis Pharma, UK) in healthy adult male volunteers under fasting conditions.

Subjects were administered a single oral dose of 2 x 375mg carbocisteine of the test or the reference product after an overnight fast of at least 10 hours. Blood samples were collected pre- and up to 12 hours post dose. Meals were provided at 4, 8 and 12 hours post dose. The treatment phases were separated by a washout period of at least 7 days

The main pharmacokinetic results for carbocisteine are presented below (geometric means, ratio and confidence intervals [CI]):

Treatment	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)
Test *	20363.05	21165.17	5809.40
Reference *	20632.12	21798.04	5420.21
Ratio (90% CI)	97.30 (91.24-103.76)	95.77 (90.03-101.88)	106.05 (99.50-113.05)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
90 % Confidence Interval calculated using log-transformed data

The current *Guidance on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1041/98 Rev 1) defines the confidence limits as 80% to 125% for C_{max} and AUC values. The 90% confidence intervals of the test/reference ratio for the log-transformed parameters C_{max} AUC_{0-t} and $AUC_{0-\infty}$ lie within acceptable limits. Thus the data support the claim that the test product Carbocisteine 375mg Capsules (Arrow Generics Limited, UK) is bioequivalent to the reference product Mucodyne 375 mg Capsules (Aventis Pharma, UK).

EFFICACY

No new efficacy data have been submitted and none are required for an application of this type.

SAFETY

No new safety concerns were highlighted during the pharmacokinetic study.

EXPERT REPORT

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

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)

The SmPC is clinically satisfactory and is consistent with that for the reference product.

Patient Information Leaflet (PIL)

The PIL is satisfactory and consistent with the SmPC.

Labelling

The labelling is satisfactory.

CONCLUSION

The applicant has demonstrated that this product and its reference product are bioequivalent. It is recommended that a marketing authorisation is granted for this application.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Carbocisteine 375mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of carbocisteine are well-known, no additional data were required.

EFFICACY
Bioequivalence has been demonstrated between the applicant's Carbocisteine 375mg Capsules (Arrow Generics Limited, UK) and the respective reference product, Mucodyne 375 mg Capsules (Aventis Pharma, UK).

No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. 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.

CARBOCISTEINE 375MG CAPSULES

PL 18909/0364

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 17 December 2008

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 07 January 2009

3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 15 October 2009 and 31 December 2010 and the quality dossier on 12 November 2009 and 12 August 2010.

4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 12 November 2009 and 08 December 2010 and the clinical dossier on 22 June 2010 and 07 February 2011

5 The application was determined on 02 March 2011.

CARBOCISTEINE 375MG CAPSULES

PL 18909/0364

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carbocisteine 375mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains carbocisteine 375mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.
Size 0 capsule with opaque blue cap and opaque yellow body, containing white to off-white odourless powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

For oral use.

Adults including the elderly:
Dosage is based upon an initial daily dosage of 2250 mg carbocisteine (6 capsules) in divided doses, reducing to 1500 mg (4 capsules) 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.

Children:
This formulation is not recommended for use in children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients. Active peptic ulceration.

4.4 Special warnings and precautions for use

There are no known special warnings or precautions for use.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions with other medicinal products or other forms of interaction.

4.6 Pregnancy and lactation

Pregnancy
Although tests in mammalian species have revealed no teratogenic effects, carbocisteine is not recommended during the first trimester of pregnancy.

Lactation
It is unknown whether carbocisteine and / or its metabolites are excreted in human milk. A risk to the newborn or infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from carbocisteine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

Rare (≥1/10,000 to <1/1,000)
Immune System Disorders
Anaphylactic reactions and fixed drug eruption

Gastrointestinal disorders

Gastrointestinal bleeding

Skin and subcutaneous tissue disorders
Skin rashes and allergic skin eruptions

4.9 Overdose
Gastric lavage may be beneficial, followed by observation. Gastrointestinal disturbance is the most likely symptom of carbocisteine overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Mucolytic, ATC code: R05C B03

Carbocisteine (5-carboxymethyl L-cysteine) has been shown in normal and bronchitic animal models to affect the nature and amount of mucus glycoprotein that 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 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 play a role in the management of disorders characterised by abnormal mucus.

5.2 Pharmacokinetic properties
Carbocisteine is rapidly absorbed from the GI tract. Equilibrium pharmacokinetics were established in healthy volunteers following administration of carbocisteine 375mg capsules, 2 capsules t.d.s. for seven days. The mean T_{max} was 2.0 hours (range 1.0 –3.0); T½ 1.87 hours (range 1.4 – 2.5); K_{EL} 0.387 $hour^{-1}$ (range 0.28 – 0.50) and $AUC_{0\text{-}7.5}$ was 39.26 mcg.hr/ml (range 26.0 – 62.4). Values for derived pharmacokinetic values were CL_S 331ml.min^{-1}; V_D 105.2 L and V_D 1.4 L/Kg.

5.3 Preclinical safety data
No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule contents:
Microcrystalline Cellulose
Macrogol
Magnesium Stearate

Capsule:
Gelatin
Titanium dioxide (E171)
Iron Yellow Oxide (body, E172)
Brilliant Blue FCF (cap, E133)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Store below 25ºC.

6.5 Nature and contents of container
The capsules are packed in PVC/Aluminium blisters containing 20, 30, 60, 100 and 120 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Arrow Generics Limited
Unit 2, Eastman Way,
Stevenage,
Hertfordshire, SG1 4SZ

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0364

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2011

10 DATE OF REVISION OF THE TEXT
02/03/2011

PACKAGE LEAFLET: INFORMATION FOR THE USER

Carbocisteine 375mg Capsules

(Carbocisteine)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1.WHAT CARBOCISTEINE 375MG CAPSULES ARE AND WHAT THEY ARE USED FOR

Carbocisteine 375mg Capsules are used to help treat respiratory tract problems (problems with the breathing passages) characterised by too much sticky mucus, including chronic obstructive airways disease (lung damage with restricted airways).

Carbocisteine 375mg Capsules contain carbocisteine which belongs to a group of medicines called mucolytics which cause the mucus to be less sticky and easier to cough up.

2.BEFORE YOU TAKE CARBOCISTEINE 375MG CAPSULES

Do not take Carbocisteine 375mg Capsules:
- If you are allergic (hypersensitive) to carbocisteine or any of the other ingredients of Carbocisteine 375mg Capsules (ingredients are listed in Section 6)
- If you have an active peptic (stomach) ulcer.

Before you take Carbocisteine 375mg Capsules you should tell your doctor:
- If you are pregnant or planning to become pregnant
- If you are breast feeding.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Currently carbocisteine is not known to affect or be affected by any other medicines you may be taking.

Pregnancy and breast-feeding
Carbocisteine 375mg Capsules are not recommended during the first three months of pregnancy.

If you are pregnant, think you are pregnant or are breast-feeding you must talk to your doctor before taking this medicine.

Driving and using machines
Carbocisteine 375mg Capsules are not known to affect the ability to drive or operate machinery.

3.HOW TO TAKE CARBOCISTEINE 375MG CAPSULES

Always take Carbocisteine 375mg Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual adult dose at the beginning of treatment is 2 capsules to be swallowed 3 times a day until a satisfactory improvement is seen. The dose is then reduced to 1 capsule 4 times a day.

If you take too many Carbocisteine 375mg Capsules:
If you take too many capsules contact your nearest hospital casualty department or tell your doctor IMMEDIATELY. Take the carton and this leaflet with you.

If you forget to take Carbocisteine 375mg Capsules, take the missed dose as soon as you remember. If it is almost time for your next dose, do not take the missed dose but simply take your next dose at the normal time.

Do not take a double dose to make up for the one you missed.

If you have to go to the doctor, dentist or hospital for any reason, tell them you are taking Carbocisteine 375mg Capsules.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4.POSSIBLE SIDE EFFECTS

Like all medicines, Carbocisteine 375mg Capsules can cause side effects, although not everybody gets them.

A few people can be allergic (hypersensitive) to some medicines:
Contact your doctor or go to the nearest hospital casualty department IMMEDIATELY if any of the following happen after taking your medicine:
- Wheezing, difficulty breathing or swallowing, dizziness
- Swelling of the eyelids, face, lips, tongue or throat
- Itchy skin rash affecting the whole body.

Tell your doctor if you experience any of the following:
- Skin rashes
- Bleeding from the stomach or intestine (which may be seen as black, tar-like stools).

These are rare side effects (occurring in less than 1 person in 1000).

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5.HOW TO STORE CARBOCISTEINE 375MG CAPSULES

Keep out of the reach and sight of children.

Store below 25°C.

Do not use Carbocisteine 375mg Capsules after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.FURTHER INFORMATION

Each Carbocisteine 375mg Capsule contains:
- The active substance: carbocisteine 375mg
- Other ingredients: microcrystalline cellulose, macrogol, magnesium stearate
- The capsules are made from gelatin, iron yellow oxide (E172), brilliant blue FCF (E133) and titanium dioxide (E171).

What Carbocisteine 375mg Capsules look like and contents of the pack
Carbocisteine 375mg Capsules are yellow and blue containing white to off-white odourless powder.
The capsules are packed in blisters, in cartons containing 20, 30, 60, 100 and 120 capsules.

Marketing Authorisation Holder
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ

Manufacturer
Arrow Pharm (Malta) Limited, HF62 Hal Far Industrial Estate, Birzebbugia, BBG 3000, Malta

This leaflet was last approved in 11/2010.

LABELLING

Carton:

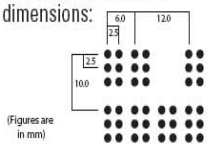
Braille text reads as follows in English:

c a r b o c i s t e i n e

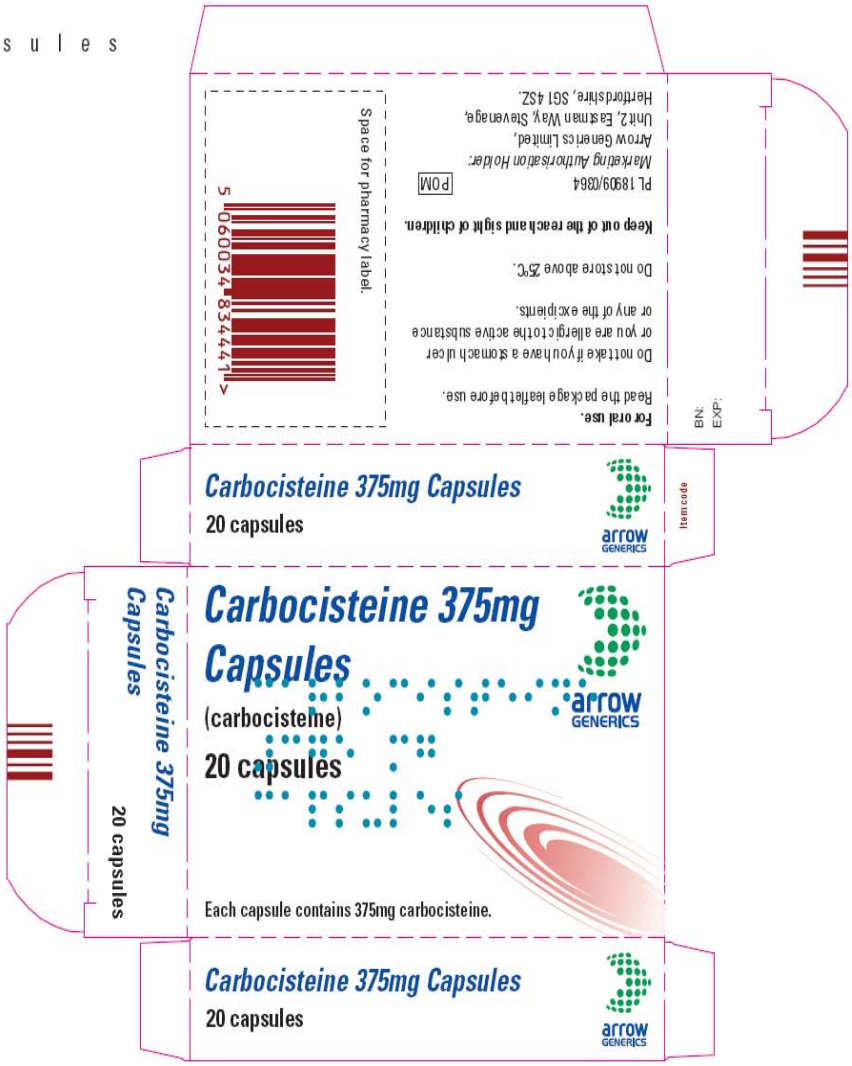
3 7 5 m g

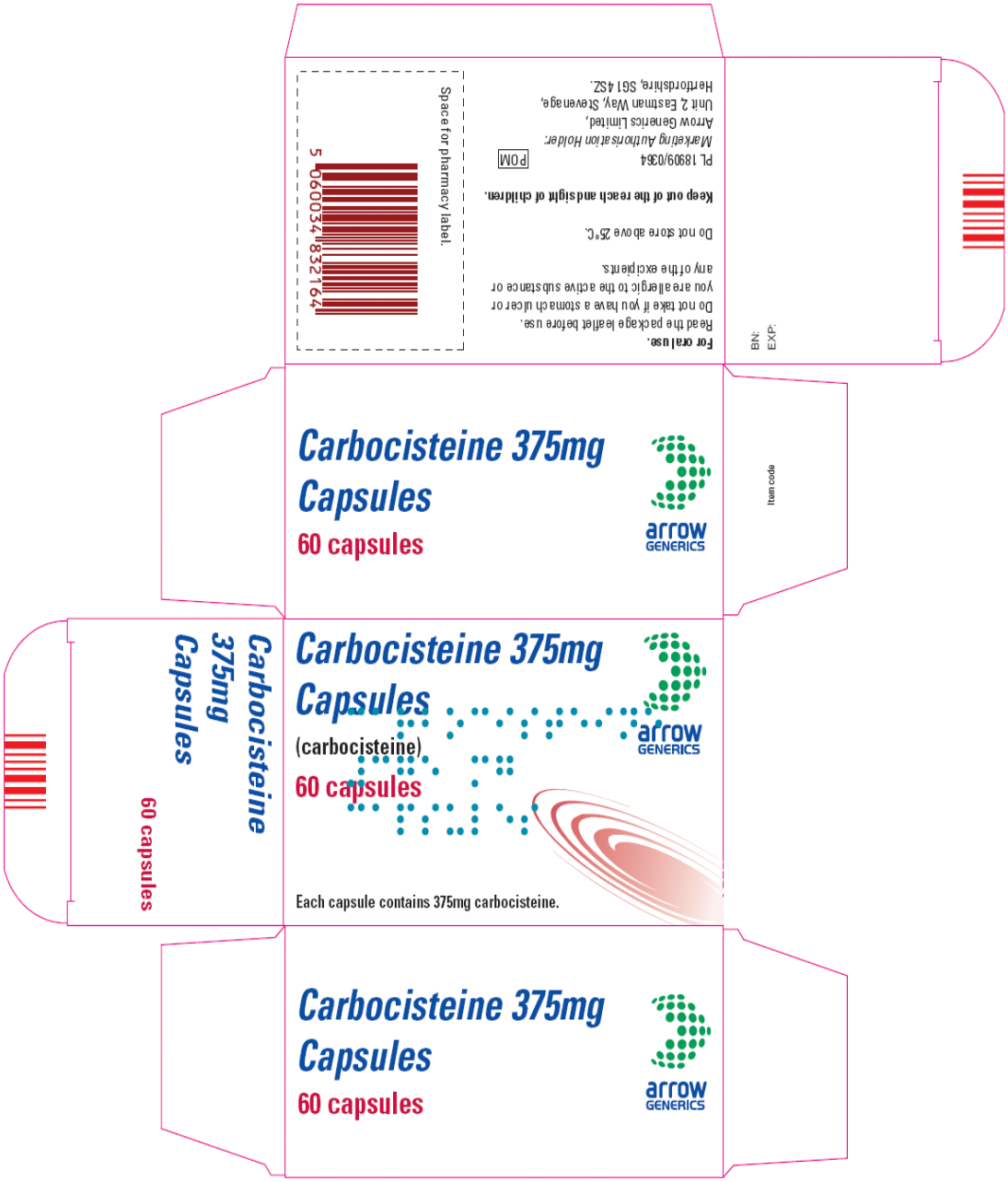
c a p s u l e s

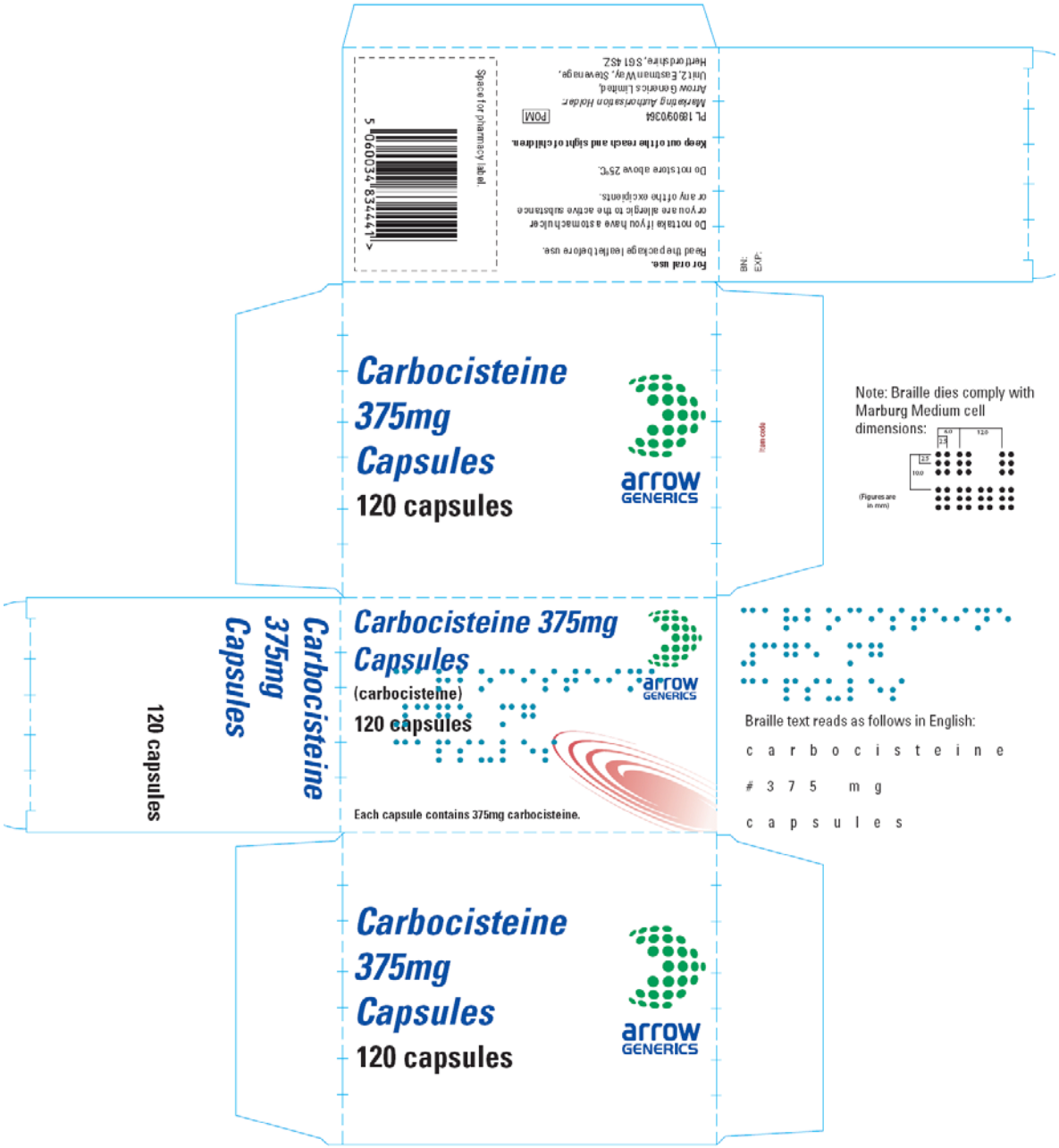
Note: Braille dies comply with Marburg Medium cell dimensions:



(Figures are in mm)




Space for pharmacy label.
5 060034 832164
For oral use.
Read the package leaflet before use.
Do not take if you have a stomach ulcer or
you are allergic to the active substance or
any of the excipients.
Do not store above 25°C.
Keep out of the reach and sight of children.
POM
PL 18909/0364
Marketing Authorisation Holder:
Arrow Generics Limited,
Unit 2 Eastman Way, Stevenage,
Hertfordshire, SG1 4SZ.
BN:
EXP:
Item code
Carbocisteine 375mg Capsules
60 capsules
arrow GENERICS
Carbocisteine 375mg Capsules
(carbocisteine)
60 capsules
Each capsule contains 375mg carbocisteine.
Carbocisteine 375mg Capsules
60 capsules


Carbocisteine
375mg
Capsules
120 capsules
arrow
GENERICS
Note: Braille dies comply with Marburg Medium cell dimensions:
Carbocisteine 375mg Capsules
(carbocisteine)
120 capsules
Each capsule contains 375mg carbocisteine.
Braille text reads as follows in English:
c a r b o c i s t e i n e
3 7 5 m g
c a p s u l e s

Blister:


Carbocisteine
375 mg Capsules
(carbocisteine)
Arrow Generics
Limited