

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0230/006/001

Case No: 2045998

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

UCB SA (Pharma Sector)

Allee de la Recherche 60, B-1070 Brussels, Belgium

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Pulmoclane 500, 500mg/ 5ml Oral Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **18/09/2008**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Pulmoclast 500, 500mg/ 5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Carbocysteine: 500 mg/5 ml.

Excipients: Each 5ml contains 4g sorbitol, 7.5mg parahydroxybenzoate (E218, E214, E216) and 105mg sodium hydroxide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Clear, pale yellow to colourless oral solution with a sweet and faint odour of pineapple.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As a mucolytic adjunct in the management of lower respiratory tract disorders characterised by excessive or viscous mucus.

4.2 Posology and method of administration

Adults only:

The usual dose is one 5ml teaspoonful (500mg) 3-4 times daily initially. Treatment duration should be at least 10 days at the above recommended initial dose and could then be reduced to one 5ml teaspoonful (500mg) 2-3 times daily, when a satisfactory response has been obtained.

In the elderly the normal adult dose can be used with caution.

4.3 Contraindications

Hypersensitivity to the active ingredient or any other ingredient.

4.4 Special warnings and precautions for use

Since mucolytics may disrupt the gastric mucosal barrier, Carbocysteine should be used in caution in patients with a history of gastric or duodenal ulcer.

Patients with rare hereditary problems with fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Neither hazardous nor therapeutically useful interactions have been reported.

4.6 Pregnancy and lactation

Carbocisteine should not be administered during pregnancy unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

None applicable.

4.8 Undesirable effects

Carbocisteine is generally well tolerated with skin rash, gastralgia, nausea or diarrhoea occurring with a frequency or less than 5%. Rarely gastrointestinal bleeding has been reported but a casual relationship has not been established.

Other minor adverse events have been rarely reported with Carbocisteine: headache, myalgia, dizziness, urinary incontinence, palpitations, dyspnoea and minor psychiatric disturbance.

4.9 Overdose

In acute overdose of Carbocisteine gastrointestinal disturbance is the only likely symptom and no active treatment is necessary; nevertheless symptomatic treatment may be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Carbocisteine is a mucoregulating agent and a mucolytic. Its major action is on the metabolism of mucus-producing cells.

Bronchial infection leads to hypersecretion. Repeated infections cause lesion to the mucosal. The mucosal then decreases the volume of its secretions, reducing also their proportion of sialomucins.

The mucus produced under the influence of Carbocisteine has increased sialomucin content and a decreased fucomucin content. This action reduces viscosity of bronchial secretions which results in a better clearance of the secretions. The effect on the rheological characteristics of the mucus depend on the severity of the lesions to the mucosal.

Studies of patients with otitis media with effusion, where Carbocisteine was given pre-operatively and post-operatively, have shown a favourable influence on the outcome after surgical removal of the effusion. On the other hand, through inhibition of kinins, the increased sialomucins can also reduce or prevent bronchial inflammation and bronchospasm.

5.2 Pharmacokinetic properties

Pulmoclast is rapidly and well absorbed after oral administration. Peak concentration is reached after 1.5 hour.

The apparent volume of distribution of Carbocisteine is 60 litres. The pharmacokinetics fit a one-compartment open model. No information is available on the extent of first-pass metabolism or protein binding. Carbocisteine appears to penetrate well into most organs and particularly respiratory mucus with peak concentration in the mucus at 2 hours.

There is wide variation in the pattern of metabolism in humans, the major metabolic pathways being acetylation, decarboxylation, and sulfoxidation. Sulfoxidation may be governed by genetic polymorphism; 2/3 of the patients excrete a glucuronic acid conjugate as a minor metabolite. There are no reports of pharmacologically important activity in these metabolites.

The plasma half-life of Pulmoclast is 2.5 to 3.1 hours. The majority (80%) of Carbocisteine is eliminated unchanged

by urinary excretion and 15% is excreted after sulfoxidation. Very little of the decarboxymethylated metabolite is produced.

There are no data to suggest a relevant relationship between concentration of Carbocysteine and effect.

5.3 Preclinical safety data

Tests in mammalian species have revealed no significant toxicity. No mutagenic, carcinogenic or teratogenic effects have been reported.

After oral administration the lethal dose $_{50}$ (LD $_{50}$) in rats has greater than 15g/kg.

A chronic toxicity study in rats has shown the no toxic dose to be 87.5mg/kg; no haematological or histopathological abnormalities have been observed at doses up to 700mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (non-crystallising) (E420)
Glycerol
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Ethyl parahydroxybenzoate (E214)
Pineapple flavouring
Sodium Hydroxide
Hydrochloric Acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Shake well before use.

6.5 Nature and contents of container

70 or 125 ml Type III amber glass bottle with an aluminium pilfer-proof screw cap contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

UCB S.A (Pharma Sector)
Allee de la Recherche 60
B-1070 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER

PA 230/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 August 1992

Date of last renewal: 07 August 2007

10 DATE OF REVISION OF THE TEXT

September 2008