Status: Effectivity information can only be shown for content published to the website.

Update information can only be shown for content published to the website.

Carbocisteine Oral Solution

Details for the public consultation of this monograph are as follows:

EAG/Panel/Working Party	Medicinal Chemicals 2
Contact Details	helen.corns@mhra.gov.uk amelia.thomson@mhra.gov.uk
Deadline for Comment	30th September 2021
Target Publication Date (subject to change)	BP 2023/24
Notes	New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.

Action and use

Mucolytic

DEFINITION

Carbocisteine Oral Solution contains Carbocisteine in a suitable vehicle.

The Oral Solution complies with the requirements stated under Oral Liquids and with the following requirements.

Content of carbocisteine, $C_5H_9NO_4S$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions in *dilute ammonia R2*.

(1) Dilute a quantity of the oral solution containing 10 mg of Carbocisteine to 10 mL.

(2) 0.1% w/v of *carbocisteine BPCRS*.

(3) 0.04% w/v each of *carbocisteine BPCRS* and of *arginine hydrohloride BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel* pre-coated plate (Merck silica gel 60 plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 5 µL of each solution.

(d) Develop the plate to 15 cm.

(e) After removal of the plate, dry in a stream of warm air, spray with *ninhydrin solution* and heat at 105° for 15 minutes.

MOBILE PHASE

20 volumes of *glacial acetic acid* and 60 volumes of *butanol*.

SYSTEM SUITABILITY

The test is not valid unless the chromatogram obtained with solution (3) shows two clearly separated spots.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions. *Prepare the solutions immediately before use.*

Solution A 1 volume of 1M *sodium hydroxide* and 5 volumes of *water*.

(1) Disperse a volume of the oral solution containing 75 mg of Carbocisteine in 6 mL of Solution A, immediately add 8 mL of *acetonitrile R1* and dilute to 100 mL with *water*, mix and filter (a 0.2 µm nylon filter is suitable).

(2) To 1 volume of solution (1) add 8 volumes of *acetonitrile R1* and dilute to 100 volumes with *water*.

(3) Dissolve 7.5 mg of *carbocisteine BPCRS* and 7.5 mg of *carbocisteine impurity C EPCRS* in 0.5 mL of solution A and immediately dilute to 100 mL with *water*.

(4) Dissolve 7.5 mg of *carbocisteine impurity B EPCRS* and 7.5 mg of *cystine* (impurity D) in 0.5 mL solution A, immediately dilute to 10 mL with *water*. Mix 1 volume of this solution with 1 volume of solution (3) and dilute to 10 volumes with *water*.

(5) Dilute 1 volume of solution (2) to 10 volumes with *water*

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with *acidic-embedded cation-exchange resin for chromatography* (5µm) (primesep 100 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute and the gradient programme described below.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 210 nm.

(f) Use an autosampler temperature of 5°.

(g) Inject 20 µL of each solution.

MOBILE PHASE

8 volumes of acetonitrile and 92 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*.

Time (Minutes)	Flow rate (mL/min)
0-40	0.5

Time (Minutes)	Flow rate (mL/min)
40-42	0.5→0.8
42-47	0.8
47-50	0.8→0.5
50-60	0.5

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to carbocisteine (retention time about 7 minutes) are: impurity B, about 0.5; impurity C, about 0.8 and impurity D, about 2.8.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between carbocisteine and carbocisteine impurity C is at least 5.0.

LIMITS

Use the chromatogram obtained with solution (4) to identify the peaks due to impurities B, C and D in the chromatogram obtained with solution (1). Multiply the area of the peak due to impurity C by a correction factor of 0.2.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity C is not greater than 6 times the area of the principal peak in the chromatogram obtained with solution (2) (6.0%)

the area of any peak corresponding to impurity B or D is not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of all secondary peaks other than impurity C is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared immediately before use.

Solution A Use solution A from the related substances procedure.

(1) Disperse a quantity of the contents of the oral solution containing 375 mg of Carbocisteine in 6 mL solution A, add 8 mL of acetonitrile and immediately dilute to 100 mL with *water*. Dilute 1 volume of this solution to 50 volumes with *water*.

(2) 0.0075% w/v of *carbocisteine BPCRS* in a mixture of 1 volume solution A and 9 volumes of *water* (dissolve in solution A before diluting to volume with water).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm x 4.6 mm) packed with *acidic-embedded cation-exchange resin for chromatography* (5 µm) (primesep 100 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.5 mL per minute.

(d) Use a column temperature of 30°.

(e) Use a detection wavelength of 210 nm.

(f) Use an autosampler temperature of 5°.

(g) Inject 20 µL of each solution.

MOBILE PHASE

6 volumes of acetonitrile and 94 volumes of a 0.27% w/v solution of *potassium dihydrogen orthophosphate*.

DETERMINATION OF CONTENT

Calculate the content of carbocisteine, $C_5H_9NO_4S$, in the oral solution from the chromatograms obtained and using the declared content of $C_5H_9NO_4S$, in *carbocisteiene BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities B, C and D listed under *Carbocisteine*.