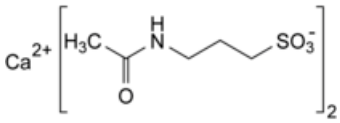
Edition: BP 2025 (Ph. Eur. 11.6 update)

Acamprosate Calcium

General Notices

(Ph. Eur. monograph 1585)



$C_{10}H_{20}CaN_2O_8S_2$ 400.5 *77337-73-6*

Action and use

Treatment of alcoholism.

Preparation

Acamprosate Gastro-resistant Tablets

Ph Eur

DEFINITION

Calcium bis(3-acetamidopropane-1-sulfonate).

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Freely soluble in water, practically insoluble in ethanol (96 per cent) and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison *acamprosate calcium CRS*.

B. It gives reaction (a) of calcium (2.3.1); use *methylene chloride R* instead of *chloroform R* for the extraction.

TESTS

Solution S

Dissolve 5.0 g in *carbon dioxide-free water R* and dilute to 100 mL with the same solvent.

Appearance of solution

Solution S is clear (2.2.1) and colourless (2.2.2, *Method II*).

pH (2.2.3)

5.5 to 7.0 for solution S.

Impurity A

Liquid chromatography (2.2.29).

Test solution Dissolve 0.400 g of the substance to be examined in *distilled water R* and dilute to 20.0 mL with the same solvent. Dilute 10.0 mL of the solution to 100.0 mL with *borate buffer solution pH 10.4 R*. Introduce 3.0 mL of this solution into a 25 mL ground-glass-stoppered tube and add 0.15 mL of a freshly prepared 5 g/L solution of *fluorescamine R* in *acetonitrile R*. Shake immediately and vigorously for 30 s. Heat in a water-bath at 50 °C for 30 min. Cool under a stream of cold water. Centrifuge and filter the supernatant through a membrane filter (nominal pore size 0.45 µm).

Reference solution Dissolve 50.0 mg of *acamprosate impurity A CRS* in *distilled water R* and dilute to 200.0 mL with the same solvent. Dilute 0.4 mL of the solution to 100.0 mL with *borate buffer solution pH 10.4 R*. Introduce 3.0 mL of this solution into a 25 mL ground-glass-stoppered tube. Proceed as described for the test solution, starting from 'and add 0.15 mL of a freshly prepared 5 g/L solution of *fluorescamine R*'.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase *acetonitrile R*, *methanol R*, *0.1 M phosphate buffer solution pH 6.5 R* (10:10:80 *V/V/V*).

Flow rate 1 mL/min.

Detection Spectrophotometer at 261 nm.

Injection 20 µL.

Run time 6 times the retention time of impurity A derivative.

Retention time Fluorescamine = about 4 min; impurity A derivative = about 8 min; acamprosate is not detected by this system.

Limit:

— *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (0.05 per cent).

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 0.100 g of the substance to be examined in 8 mL of *water R* using sonication and dilute to 10.0 mL with the same solvent.

Test solution (b) Dilute 3.0 mL of test solution (a) to 100.0 mL with *water R*.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with *water R*. Dilute 1.0 mL of this solution to 20.0 mL with *water R*.

Reference solution (b) Dissolve 30.0 mg of *acamprosate calcium CRS* in 20 mL of *water R* using sonication and dilute to 100.0 mL with the same solvent.

Reference solution (c) Dissolve 10 mg of *calcium bis(formyl homotaurine) R* (corresponding to about 9 mg of impurity B) in 1 mL of test solution (a) and dilute to 100 mL with *water R*.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography compatible with 100 per cent aqueous mobile phases R* (5 µm).

Mobile phase Mix 5 mL of *triethylamine R* and about 900 mL of *water for chromatography R*, adjust to pH 4.0 with *phosphoric acid R* and dilute to 1000 mL with *water for chromatography R*.

Flow rate 0.7 mL/min.

Detection Spectrophotometer at 210 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (c).

Run time 2.5 times the retention time of acamprosate.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B.

Relative retention With reference to acamprosate (retention time = about 9 min): calcium = about 0.4; impurity B = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity B and acamprosate.

Calculation of percentage contents:

— for each impurity, use the concentration of acamprosate calcium in reference solution (a).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.03 per cent; disregard the peak due to calcium.

Loss on drying (*2.2.32*)

Maximum 0.4 per cent, determined on 1.000 g by drying in an oven at 105 °C.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 20 µL of test solution (b) and reference solution (b).

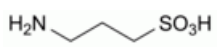
Calculate the content of $C_{10}H_{20}CaN_2O_8S_2$ taking into account the assigned content of *acamprosate calcium CRS*.

IMPURITIES

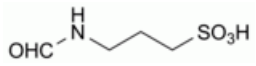
Specified impurities *A*.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by

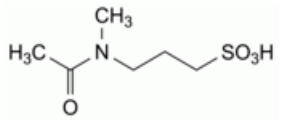
the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) B, C.



A. 3-aminopropane-1-sulfonic acid (homotaurine),



B. 3-formamidopropane-1-sulfonic acid (formyl homotaurine),



C. 3-(*N*-methylacetamido)propane-1-sulfonic acid.

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