

TESTS

Specific optical rotation (2.2.7)

-32 to -29 (anhydrous substance).

Dissolve 0.200 g in methanol R and dilute to 50.0 mL with the same solvent.

Impurity A

Thin-layer chromatography (2.2.27).

Test solution Dissolve 40.0 mg of the substance to be examined in 1.0 mL of methanol R.

Reference solution (a) Dissolve 10.0 mg of topiramate impurity A CRS in methanol R and dilute to 50.0 mL with the same solvent. Dilute 2.0 mL of the solution to 5.0 mL with methanol R.

Reference solution (b) Dissolve 40 mg of the substance to be examined in 1 mL of reference solution (a).

Plate TLC silanised silica gel plate R.

Pretreatment Wash the plate with methanol R and allow to dry in air.

Mobile phase methanol R, acetonitrile R, 29 g/L solution of sodium chloride R (15:35:50 V/V/V).

Application 5 µL.

Development Over 2/3 of the plate.

Drying In air.

Detection Spray with a solution prepared by dissolving 3 g of phenol R in 95 mL of ethanol (96 per cent) R and carefully adding 5 mL of sulfuric acid R; allow to dry in air, then heat at 125 °C for 10 min. Use transmittance mode.

Retardation factors Topiramate = about 0.43; impurity A = about 0.55.

System suitability:

— the chromatogram obtained with reference solution (b) shows 2 clearly separated spots due to topiramate and impurity A.

Limit:

— *impurity A*: any spot due to impurity A is not more intense than the corresponding spot in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R1, mobile phase A (20:80 V/V).

Test solution (a) Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Test solution (b) Dilute 1.0 mL of test solution (a) to 20.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 15.0 mg of topiramate impurity E CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 200.0 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of the substance to be examined in 1 mL of a mixture of 2 volumes of acetonitrile R1, 4 volumes of water for chromatography R and 4 volumes of anhydrous formic acid R. Incubate at 60 °C for

30 min (*in situ* preparation of impurity C). Dilute 20 µL of the solution to 1 mL with a 25 mg/L solution of [fructose R](#) (impurity E).

Reference solution (d) Dissolve 25.0 mg of [topiramate CRS](#) in 10.0 mL of the solvent mixture and dilute to 100.0 mL with the solvent mixture. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

- **size:** $l = 0.10$ m, $\varnothing = 4.6$ mm;
- **stationary phase:** [end-capped solid core pentafluorophenylpropylsilyl silica gel for chromatography R](#) (2.6 µm);
- **temperature:** 40 °C.

Mobile phase:

- **mobile phase A:** 1.93 g/L solution of [ammonium acetate R](#) adjusted to pH 3.5 with [glacial acetic acid R](#);
- **mobile phase B:** [acetonitrile R1](#);

Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 5	80	20
5 - 15	80 → 50	20 → 50
15 - 15.1	50 → 80	50 → 20

Flow rate 1.0 mL/min.

Detection Charged aerosol detector:

- **range:** 100 pA;
- **filter:** none.

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

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

Relative retention With reference to topiramate (retention time = about 5.6 min): impurity E = about 0.18; impurity C = about 0.25.

System suitability Reference solution (c):

- **resolution:** minimum 4.5 between the peaks due to impurities E and C.

Calculation of percentage contents:

- for impurity E, use the concentration of impurity E in reference solution (b) and the height of the peak due to impurity E;
- for impurities other than E, use the concentration of topiramate in reference solution (a).

Limits:

- **impurity E:** maximum 0.15 per cent;
- **unspecified impurities:** for each impurity, maximum 0.10 per cent;
- **total:** maximum 0.2 per cent;
- **reporting threshold:** 0.05 per cent.

Water (2.5.12)

Maximum 0.5 per cent, determined on 1.000 g.

Sulfated ash (2.4.14)

ASSAY

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

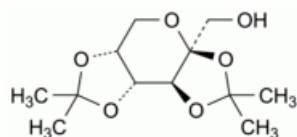
Injection Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{12}H_{21}NO_8S$ taking into account the assigned content of [topiramate CRS](#).

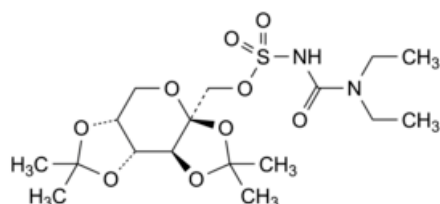
IMPURITIES

Specified impurities A, E.

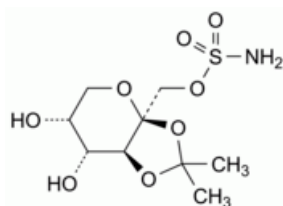
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph [Substances for pharmaceutical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



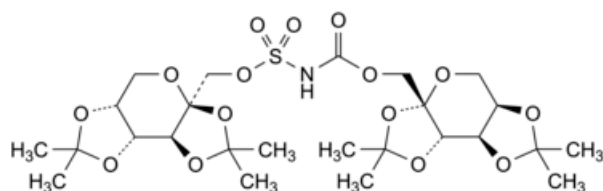
A. 2,3:4,5-bis-O-(propan-2,2-diyl)- β -D-fructopyranose,



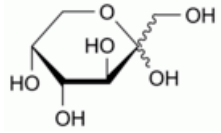
B. 2,3:4,5-bis-O-(propan-2,2-diyl)- β -D-fructopyranose 1-[N-(diethylcarbamoyl)sulfamate],



C. 2,3-O-(propan-2,2-diyl)- β -D-fructopyranose 1-sulfamate,



D. 2,3:4,5-bis-O-(propan-2,2-diyl)- β -D-fructopyranose 1-[N-[[[2,3:4,5-bis-O-(propan-2,2-diyl)- β -D-fructopyranosyl]oxy]carbamoyl]sulfamate],



E. D-fructopyranose (fructose).

Ph Eur