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

Temozolomide Capsules

General Notices

Action and use

Antineoplastic alkylating agent.

DEFINITION

Temozolomide Capsules contain Temozolomide.

The capsules comply with the requirements stated under Capsules and with the following requirements.

Content of temozolomide, $C_6H_6N_6O_2$

For capsules containing 5 mg or less of Temozolomide

93.0 to 105.0% of the stated amount.

For capsules containing more than 5 mg of Temozolomide

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.
(1) Stir, using a magnetic stirrer, a quantity of capsule contents with sufficient *acetonitrile* to produce a solution expected to contain 0.1% w/v of Temozolomide. Mix with the aid of ultrasound and allow to settle.
(2) 0.1% w/v of *temozolomide BPCRS* in *acetonitrile*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

15 volumes of *toluene* and 90 volumes of *acetone*.

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

Dissolution

Comply with the dissolution test for tablets and capsules, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 1, rotating the basket at 100 revolutions per minute.
(b) For capsules containing more than 5 mg of Temozolomide, use 900 mL of *water*, at a temperature of 37°, as the medium.
(c) For capsules containing 5 mg of Temozolomide, use 500 mL of *water*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 45 minutes withdraw a sample of the medium and measure the absorbance of the filtered sample, suitably diluted with the dissolution medium if necessary to produce a solution expected to contain 0.001% w/v of Temozolomide, at the maximum at 328 nm, Appendix II B, using dissolution medium in the reference cell.
(2) Measure the absorbance of a 0.001% w/v solution of *temozolomide BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of Temozolomide, $C_6H_6N_6O_2$, in the medium from the absorbances obtained and using the declared content of $C_6H_6N_6O_2$, in *temozolomide BPCRS*.

LIMITS

The amount of Temozolomide released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. *Store the solutions at 4°.*

(1) Shake 10 whole capsules with the mobile phase. Mix, centrifuge and filter (a 0.45-µm PVDF filter is suitable). Dilute with sufficient mobile phase to produce a solution containing 0.01% w/v of Temozolomide.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase.
(3) 0.1% w/v of *temozolomide for peak identification EPCRS* in the mobile phase.
(4) Dissolve 10 mg of *temozolomide BPCRS* in 25 mL of mobile phase and 25 mL of 0.1M *hydrochloric acid*. Mix and heat the solution at 80° for 4 hours (generation of impurities A, B and E).
(5) Dilute 1 volume of solution (2) to 10 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Spherisorb ODS-2 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 270 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for twice the retention time of temozolomide.

MOBILE PHASE

A 0.094% w/v solution of *sodium hexanesulfonate* in a mixture of 4 volumes of *methanol* and 96 volumes of 0.5% v/v of *glacial acetic acid*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to temozolomide (retention time, about 9 minutes) are: impurity E, about 0.4; impurity D, about 0.5; impurity 1, about 0.8; impurity B, about 0.9 and impurity A, about 1.4.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to temozolomide and impurity A is at least than 2.5.

LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurity D using the chromatogram obtained using solution (3) and identify any peaks due to impurities A and E using the chromatogram obtained using solution (4). Multiply the areas of any peaks due to impurities A and E with the corresponding correction factors: impurity A, 0.4 and impurity E, 0.6.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 1.2 times the area of the principal peak due in the chromatogram obtained with solution (2) (1.2%);

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

the area of any peak corresponding to impurity E is not greater than 0.3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

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*, excluding impurities A and D, is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

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. *Store the solutions at 4°.*

(1) Shake 10 whole capsules with the mobile phase. Mix, centrifuge and filter (a 0.45-µm PVDF filter is suitable). Dilute with sufficient mobile phase to produce a solution containing 0.01% w/v of Temozolomide.
(2) 0.01% w/v of *temozolomide BPCRS* in mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described in the test for Related substances may be used.

SYSTEM SUITABILITY

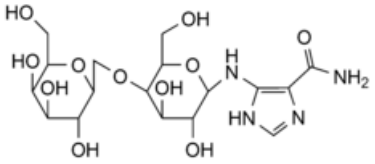
The test is not valid unless in the chromatogram obtained with solution (2), the symmetry factor is not greater than 1.9.

DETERMINATION OF CONTENT

Calculate the content of temozolomide, $C_6H_6N_6O_2$, in the capsules from the chromatograms obtained and using the declared content of $C_6H_6N_6O_2$ in *temozolomide BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Temozolomide and:



1. 4-[(β-D-galactopyranoyl-(1→4)-β-D-glucopyranosyl)amino]-1*H*-imidazole-4-carboxamide (AIC-lactose).