EAG/Panel/Working Party	Medicinal Chemicals 2
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Notes: New monograph If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.	

Temozolomide for Injection

Temozolomide Preparations

Action and use
Cytotoxic alkylating agent.

DEFINITION
Temozolomide for Injection is a sterile material consisting of Temozolomide with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powder for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of temozolomide, $C_6H_6N_6O_2$
95.0 to 105.0% of the stated amount.

IDENTIFICATION
A. To one vial add 40 mL of *dichloromethane* and shake for 30 minutes. Invert and allow to stand until undissolved solids settle. Filter 15 mL of the clear solution (a 0.45-µm PTFE filter is suitable). Discard the first 5 mL and evaporate the remaining filtrate to dryness under a stream of nitrogen. The *infrared absorption spectrum* of the residue, Appendix IIA, is concordant with the *infrared absorption spectrum* of *temozolomide BPCRS*.

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

TESTS

Related substances
Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing 0.2% w/v of Temozolomide. Dilute 1 volume of this solution to 20 volumes with mobile phase and mix.

(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase. Dilute 1 volume of this solution to 10 volumes with the mobile phase.

(3) 0.1% w/v of *temozolomide for peak identification EPCRS* in *dimethyl sulfoxide*.

(4) Dissolve 10 mg of *temozolomide BPCRS* in 50 mL of mobile phase and 50 mL of 0.1M *hydrochloric acid*. Mix and heat the solution at 80° for 4 hours (generation of impurities A, B and E). Store the solution at 4°.

CHROMATOGRAPHIC CONDITIONS

(a) 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 75 µL of each solution.

(g) Allow the chromatography to proceed for twice the retention time of the peak due to temozolomide.

MOBILE PHASE

1 volume of *methanol* and 24 volumes of a 0.5% v/v solution of *glacial acetic acid*, containing 0.094% w/v of *sodium hexanesulfonate*.

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 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 not less than 2.5.

LIMITS

Identify any peaks due to impurity D in the chromatogram obtained with solution (1) using the chromatogram obtained using solution (3). Identify any peaks due to impurities A and E in the chromatogram obtained with solution (1) using the chromatogram obtained using solution (4). Multiply the areas of these peaks by 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 10 times the area of the peak due to impurity A in the chromatogram obtained with solution (2) (1.0%);

the area of any peak corresponding to impurity D is not greater than 5 times 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 4 times the area of the principal peak in the chromatogram obtained with solution (2) (0.4%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any other *secondary peaks*, excluding impurities A and D, is not greater than 10 times

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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 (2) (0.1%).

ASSAY

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

(1) Dissolve the contents of a sealed container in sufficient *water* to produce a solution containing 0.2% w/v of Temozolomide. Dilute 1 volume of this solution to 20 volumes with mobile phase and mix.

(2) 0.01% w/v of *temozolomide BPCRS* in the 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 $C_6H_6N_6O_2$ in the sealed container from the chromatograms obtained using the declared content of $C_6H_6N_6O_2$ in *temozolomide BPCRS.* Repeat the procedure with a further nine sealed containers. Calculate the average content of $C_6H_6N_6O_2$ per container from the 10 individual results thus obtained.

IMPURITIES

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

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