Temozolomide Capsules

テモゾロミドカプセル

Temozolomide Capsules contain not less than 95.0% and not more than 105.0% of the labeled amount of temozolomide ($C_6H_6N_6O_2$: 194.15).

Method of preparation Prepare as directed under Capsules, with Temozolomide.

Identification Perform the test with 20 μL each of the sample solution and standard solution obtained in the Assay as directed under Liquid Chromatography <*2.01*> according to the following conditions: the retention times of the principal peaks in the chromatograms obtained from these solutions are the same, and the absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Detector: A photodiode array detector (wavelength: 270 nm, spectrum range of measurement: 210 – 400 nm).

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Purity Related substances—Use the sample solution obtained in the Assay as the sample solution. Pipet 1 mL of the sample solution, add dimethyl sulfoxide to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine each peak area by the automatic integration method: the peak area of the related substance E, having the relative retention time of about 0.4 to temozolomide, obtained from the sample solution is not larger than 3/5 times the peak area of temozolomide from the standard solution, the peak area of the related substance CA, having the relative retention time of about 1.4, from the sample solution is not larger than the peak area of temozolomide from the standard solution, and the area of the peak other than temozolomide and the peaks mentioned above from the sample solution is not larger than 1/5 times the peak area of temozolomide from the standard solution. Furthermore, the total area of the peaks other than temozolomide from the sample solution is not larger than 1.2 times the peak area of temozolomide from the standard solution. For the peak areas of the related substances E and CA, multiply the relative response factors, 0.63 and 0.30, respectively.

Operating conditions—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 3 times as long as the retention time of temozolomide.

System suitability—

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 2 mL of the standard solution, and add the mobile phase to make exactly 20 mL. Confirm that the peak area of temozolomide obtained with 20 μL of this solution is equivalent to 7 to 13% of that with 20 μL of the standard solution.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of temozolomide is not more than 2.0%.

Uniformity of dosage units <*6.02*> Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 capsule of Temozolomide Capsules add exactly V mL of the mobile phase so that each mL contains about 1 mg of temozolomide ($C_6H_6N_6O_2$), and shake until the capsule is completely disintegrated. Shake until the content is dispersed, centrifuge for 10 minutes, and filter the supernatant liquid through a membrane filter with a pore size of 0.45 μm. Discard the first 3 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of temozolomide ($C_6H_6N_6O_2$)
$= M_S \times A_T / A_S \times V / 25$

M_S: Amount (mg) of Temozolomide RS taken

Dissolution <*6.10*> When the test is performed at 100 revolutions per minute according to the Basket method, using 900 mL of water as the dissolution medium, the Q value in 30 minutes of Temozolomide Capsules is 80%.

Start the test with 1 capsule of Temozolomide Capsules, withdraw not less than 10 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.8 μm. Discard not more than 3 mL of the first filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 22 μg of temozolomide ($C_6H_6N_6O_2$), and use this solution as the sample solution. Separately, weigh accurately about 22 mg of Temozolomide RS, and dissolve in water to make exactly 100 mL. Pipet 10 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Determine the ab-

sorbances, A_T and A_S, of the sample solution and standard solution at 328 nm as directed under Ultraviolet-visible Spectrophotometry <2.24>.

Dissolution rate (%) with respect to the labeled amount of temozolomide ($C_6H_6N_6O_2$)

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 90$

M_S: Amount (mg) of Temozolomide RS taken

C: Labeled amount (mg) of temozolomide ($C_6H_6N_6O_2$) in 1 capsule

Assay To 10 Temozolomide Capsules add the mobile phase, and shake until the capsules are completely disintegrated. Shake until the content is dispersed, and add the mobile phase to make exactly V mL so that each mL contains about 1 mg of temozolomide ($C_6H_6N_6O_2$). Centrifuge this solution for 10 minutes, and filter the supernatant liquid through a membrane filter with a pore size of 0.45 μm. Discard the first 3 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add the mobile phase to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 25 mg of Temozolomide RS, add 200 mL of the mobile phase, sonicate to dissolve, add the mobile phase to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, A_T and A_S, of temozolomide in each solution.

Amount (mg) of temozolomide ($C_6H_6N_6O_2$) in 1 capsule

$= M_S \times A_T / A_S \times V/250$

M_S: Amount (mg) of Temozolomide RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: To 5 mL of acetic acid (100) add 1000 mL of water. To 24 volumes of this solution add 1 volume of methanol. Dissolve 0.94 g of sodium 1-hexanesulfonate in 1000 mL of this solution.

Flow rate: Adjust so that the retention time of temozolomide is about 9.5 minutes.

System suitability—

System performance: Dissolve 10 mg of temozolomide in 25 mL of the mobile phase. To this solution add 25 mL of 0.1 mol/L hydrochloric acid TS, allow to stand at 80°C for 4 hours, cool to 4°C, and preserve. When the procedure is run with 20 μL of this solution under the above operating conditions, the resolution between the peaks of temozolomide and the related substance CA is not less than 2.5, and the symmetry factor of the peak of temozolomide is not more than 1.9.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of temozolomide is not more than 1.0%.

Containers and storage Containers—Tight containers.

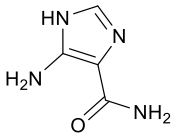
Others

Related substance E:

Refer to it described in Temozolomide.

Related substance CA:

5-Amino-1*H*-imidazole-4-carboxamide



Add the following to 9.01 Reference Standards (1):

Temozolomide RS

Add the following to 9.41 Reagents, Test Solutions:

Temozolomide $C_6H_6N_6O_2$ [Same as the namesake monograph]