Temozolomide Capsules

Published on: 07 February, 2024 **Last date for comments:** 22 March, 2024

This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

Description	Details
Document version	1.0
First draft published on IPC website for public comments	February 7, 2024
Last date for comments	**March 22, 2024**
Monograph revisions proposed for inclusion in	**IP 2026**
Tentative effective date of monograph revisions	**July, 2026**
Draft revision published on IPC website for public comments	--
Further follow-up action as required.	

Temozolomide Capsules. Page 3733
Change **to**: **Temozolomide Capsules**

Temozolomide Capsules contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of temozolomide, $C_6H_6N_6O_2$.

CAUTION —Temozolomide is cytotoxic; extra care required to prevent inhaling particles and exposing the skin to it.

Usual strengths. 5 mg; 20 mg; 100 mg; 250 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (d).

Tests

Dissolution (2.5.2).
Apparatus No. 1 (Basket),
Medium.500 ml (for 5 mg capsules), 900 ml (for other strengths) of *water*,
Speed and time. 100 rpm and 30 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. A 0.1 per cent v/v solution of *glacial acetic acid* in *water*.

Test solution. Dilute the filtrate with the solvent mixture to obtain a solution having a concentration similar to that of the reference solution.

Reference solution. A 0.025 per cent w/v solution of *temozolomide IPRS* in the dissolution medium. Dilute 2.0 ml of the solution to 100.0 ml with the solvent mixture.

Chromatographic system
– a stainless steel column 25 cm × 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as X Terra RP 18),
– sample temperature: 5°,
– mobile phase: a mixture of 99 volumes of 0.04 per cent w/v of *ammonium formate* in *water* and 1 volume of *methanol*,
– flow rate: 1 ml per minute,
– spectrophotometer set at 254 nm,
– injection volume: 100 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_6H_6N_6O_2$ in the medium.

Q. Not less than 80 per cent of the stated amount of $C_6H_6N_6O_2$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE — Store the solutions containing temozolomide at 4°.

Test solution. Transfer 10 intact capsules to a suitable volumetric flask. Add mobile phase (80 per cent of the final volume) with agitation or stirring for not less than 1 hour. Ensure that the capsules are broken apart into small pieces and that

contents are adequately dissolved, dilute to volume with the mobile phase. Allow to stand for 30 minutes and mix. Centrifuge 25 ml of the solution for 10 minutes and filter. Dilute a suitable volume of the filtrate with the mobile phase to obtain a solution containing 0.01 per cent w/v of Temozolomide.

Reference solution (a). A 0.00013 per cent w/v solution of *dacarbazine related compound A IPRS* in the mobile phase. *(NOTE—Dacarbazine related compound A is the hydrochloride salt of aminoimidazole carboxamide).*

Reference solution (b). A 0.04 per cent w/v solution of *temozolomide IPRS* in the mobile phase.

Reference solution (c). Transfer 25 ml of *0.1 M hydrochloric acid* and 25 ml of reference solution (b) to a suitable glass container. Heat the container at 80° for 4 hours. *(NOTE—The preparation forms 2-azahypoxanthine, temozolomide acid and aminoimidazole carboxamide).*

Reference solution (d). Dilute 5.0 ml of reference solution (b) to 20.0 ml with the mobile phase.

Reference solution (e). Dilute 1.0 ml of reference solution (d) to 100.0 ml with the mobile phase. Further, dilute 1.0 ml of the solution to 10.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as Spherisorb ODS-2),
- sample temperature: 4°,
- mobile phase: 0.094 per cent w/v solution of *sodium 1-hexanesulphonate* in a mixture of 96 volumes of 0.5 per cent v/v solution of *glacial acetic acid* in *water* and 4 volumes of *methanol,*
- flow rate: 1 ml per minute,
- spectrophotometer set at 270 nm,
- injection volume: 20 µl.

Name	Relative retention time
2-Azahypoxanthine[1]	0.4
Temozolomide related compound A[2*]	0.5
Temozolomide acid[3]	0.9
Temozolomide	1.0
Aminoimidazolecarboxamide[4]	1.4
Cyanotemozolomide[5*]	2.3

*Process impurity included for identification only and not to be included in total degradation products.

[1] 4*a*,5-dihydro-4*H* -imidazo[4,5-*d*][1,2,3]triazin-4-one,

[2] 4-diazo-4*H* -imidazole-5-carboxamide,

[3] 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylic acid,

[4] 5-aminoimidazole-4-carboxamide,

[5] 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile.

Inject reference solution (a), (c) and (e). The test is not valid unless the resolution between the peaks due to temozolomide and aminoimidazole carboxamide is not less than 2.5 in the chromatogram obtained with reference solution (c), the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (e).

Inject reference solution (a) and the test solution. Run the chromatogram 2 times the retention time of the principal peak. The area of any peak corresponding to 2-azahypoxanthine is not more than 0.61 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.8 per cent), the area of any peak corresponding to temozolomide acid is not more than 0.2 per cent, the area of any peak corresponding to aminoimidazole carboxamide is not more than 1.2 per cent, the area of any other secondary peak is not more than 0.2 per cent, calculated by area normalization. The sum of all the secondary peaks is not more than 1.7 per cent. Ignore any peak with an area less than 0.1 per cent.

Microbial contamination (2.2.9). Total aerobic microbial count is not more than 1000 CFU per g and total fungal count is not more than 500 CFU per g and it is free from *Escherichia coli.*

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (c) and (d). The test is not valid unless the tailing factor is not more than 1.9 for temozolomide peak in the chromatogram obtained with reference solution (c) and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (d).

Inject reference solution (d) and the test solution.

Calculate the content of $C_6H_6N_6O_2$ in the capsules.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.