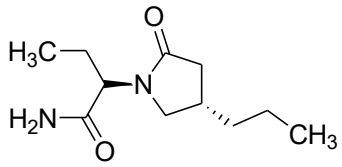
Brivaracetam



$C_{11}H_{20}N_2O_2$ Mol. Wt. 212.3

Brivaracetam is (2S)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide.

Brivaracetam contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{11}H_{20}N_2O_2$, calculated on the dried basis.

Category. Anticonvulsant.

Description. A white to off white powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *brivaracetam IPRS* or with the reference spectrum of brivaracetam.

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

Tests

Specific optical rotation (2.4.22). -65.0° to -55.0°, determined in 1.0 per cent w/v solution in *methanol*.

Related substances. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in mobile phase A and dilute to 100.0 ml with mobile phase A.

Reference solution (a). A 0.0003 per cent w/v solution of *brivaracetam IPRS* in mobile phase A.

Reference solution (b). Dilute 3.0 ml of reference solution (a) to 10.0 ml with mobile phase A.

Reference solution (c). A solution containing 0.0003 per cent w/v of *(2R,4R)-Diasteromer* (RR-isomer of brivaracetam) *IPRS* or *(2S,4S)- Diasteromer* (SS-isomer of brivaracetam) *IPRS* in mobile phase A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane with extra selectivity of penta fluoro phenyl phase bonded to porous silica (5 µm) (Such as ACE C18-PFP),
- column temperature: 35°,
- sample temperature: 10°,
- mobile phase: A. a 0.1 per cent v/v solution of *orthophosphoric acid* in *water*,
  B. a mixture of 40 volumes mobile phase A, 30 volumes of *methanol* and 30 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 15 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
5	100	0
20	50	50
50	50	50
50.1	100	0
60	100	0

The relative retention time with reference to brivaracetam for RR isomer or SS isomer of brivaracetam is about 1.02.

Inject reference solution (a) and (b). The test is not valid unless the tailing factor is not more than 1.5, the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a). The signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (c) to identify the peak due to RR isomer or SS isomer of brivaracetam.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent). Ignore any peak corresponding to RR isomer and SS isomer of brivaracetam.

The sum of all the impurities including RR isomer of brivaracetam and SS isomer of brivaracetam (determined under chiral purity test) is not more than 1.0 per cent.

Chiral purity. Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 100 mg of the substance under examination in the mobile phase and dilute to 50.0 ml with the mobile phase.

Reference solution (a). A 0.001 per cent w/v solution of *brivaracetam IPRS* in the mobile phase.

Reference solution (b). Dilute 2.0 ml of reference solution (a) to 20.0 ml with the mobile phase.

Reference solution (c). A solution containing 0.006 per cent w/v, each of, *enantiomer of brivaracetam IPRS* and *(2R,4R)-Diasteromer* (RR isomer of brivaracetam) *IPRS* and *(2S,4S)- Diasteromer* (SS isomer of brivaracetam) *IPRS* in the mobile phase.

Reference solution (d). Dissolve 20 mg of *brivaracetam IPRS* in the mobile phase, add 1.0 ml of reference solution (c) and dilute to 10.0 ml with the mobile phase.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with amylose tris-(3,5-dimethylphenylcarbamate) coated with porous silica (5 µm) (Such as chiralpack AD-H),
- column temperature:15 °,
- sample temperature:10°,
- mobile phase: a mixture of 85 volumes of *n-hexane* and 15 volumes of *ethanol.*
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 20 µl.

Name	Relative retention time
Enantiomer of brivaracetam[1]	0.39
RR-isomer of brivaracetam[2]	0.43
SS-isomer of brivaracetam[3]	0.65
Brivaracetam (Retention time is about 36 minutes)	1.0

[1](2R)-2-[(4S)-2-oxo-4-propylpyrrolidin-1-yl]butanamide
[2](2R)-2-[(4R)-2-oxo-4-propylpyrrolidin-1-yl]butanamide
[1](2S)-2-[(4S)-2-oxo-4-propylpyrrolidin-1-yl]butanamide

Inject reference solution (a), (b) and (d). The test is not valid unless the resolution between the peaks due to enantiomer of brivaracetam and (2R,4R)-Diasteromer is not less than 1.8 in the chromatogram obtained with reference solution (d), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 10.0 per cent in the chromatogram obtained with reference solution (a). The signal-to-noise ratio of the principal peak is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to enantiomer, RR-isomer and SS-isomer of brivaracetam, each of, is not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Loss on drying (2.4.19). Not more than 0.5 per cent, determined on 1.0 g in vacuum oven at 60º for 3 hours, at a pressure not exceeding 0.7 kPa.

Assay. Determine by liquid chromatography (2.4.14).

Solution A. A 0.1 per cent v/v solution of *orthophosphoric acid* in *water*.

Test solution. Dissolve 100 mg of the substance under examination in solution A and dilute to 100.0 ml with solution A. Dilute 2.0 ml of the solution to 10.0 ml with solution A.

Reference solution (a). A 0.02 per cent w/v solution of *brivaracetam IPRS* in solution A.

Reference solution (b). A solution containing 0.02 per cent w/v of *brivaracetam IPRS* and 0.00006 per cent w/v of (2R,4R)-diasteromer or (2S ,4S)-diasteromer *IPRS* in solution A.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with octadecylsilane with extra selectivity of a penta fluoro phenyl bonded to porous silica (5 µm) (Such as ACE-C18-PFP),
- mobile phase: a mixture of 64 volumes of solution A, 18 volumes of *acetronitrile* and 18 volumes of *methanol*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 15 µl.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to brivaracetam and (2R,4R)-diasteromer or (2S,4S)- diasteromer is not less than 1.8 in the chromatogram obtained with reference solution (b), the tailing factor is not more than 1.5 and the relative standard deviation for replicate injections is not more than 1.0 per cent in the chromatogram obtained with reference solution (a).

Inject reference solution (a) and the test solution.

Calculate the content of $C_{11}H_{20}N_2O_2$.

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

Solubility (2.4.26). Very soluble in *methanol,* soluble in *water* and practically insoluble in *hexane.*