Levetiracetam Tablets

レベチラセタム錠

Levetiracetam Tablets contains not less than 95.0% and not more than 105.0% of the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$: 170.21).

Method of preparation Prepare as directed under Tablets, with Levetiracetam.

Identification **(1)** To a quantity of powdered Levetiracetam Tablets, equivalent to 0.2 g of Levetiracetam, add 20 mL of methanol, shake thoroughly, filter, and use the filtrate as the sample solution. Separately, dissolve 0.01 g of Levetiracetam RS in 1 mL of methanol, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography *<2.03>*. Spot 10 μL each of the sample solution and standard solution on a plate of silica gel for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, methanol and ammonia water (28) (85:12:3) to a distance of about 8 cm, and air-dry the plate. Allow the plate to stand in iodine vapor: the principal spot from the sample solution and the spot from the standard solution show the same *R*f value.

(2) 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 the sample solution and standard solution are the same.

Operating conditions -

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

System suitability—

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

Purity **(1)** Related substances—Use the sample solution obtained in the Assay as the sample solution. Separately, weigh accurately about 10 mg of Levetiracetam Related Substance A for Purity RS, and add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 100 mL. Pipet 5 mL of this solution, and add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 100 mL. Pipet 2 mL of this solution, add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 100 mL, and use this solution as 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. Calculate the amounts of related substances by the following equations: the amount of the related substance A is not more than 0.30%, the amount of related substances other than the related substance A is not more than 0.10%, and the total amount of related substances is not more than 0.80%.

Amount (%) of the related substance A
$= M_S / M_T \times A_{T1} / A_{S1} \times M_M / C \times 25 / 2$

Amount (%) of each related substance other than the related substance A
$= A_{T2} / A_{S2} \times 100$

M_S: Amount (mg) of Levetiracetam Related Substance A for Purity RS taken
M_T: Amount (mg) of Levetiracetam Tablets taken
M_M: Average mass of 1 tablet (mg)
A_{T1}: Peak area of the related substance A from the sample solution
A_{S1}: Peak area of the related substance A from the standard solution
C : Labeled amount (mg) of levetiracetam ($C_8H_{14}N_2O_2$) in 1 tablet.
A_{T2}: Peak area of each related substance obtained from the sample solution
A_{S2}: Peak area of levetiracetam obtained from the standard solution

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 1.5 times as long as the retention time of levetiracetam, beginning after the solvent peak.

System suitability—

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

Test for required detectability: To 5 mL of the standard solution obtained in the Assay add a mixture of water and acetonitrile for liquid chromatography (19:1) to make 100 mL. To 2 mL of this solution add a mixture of water and acetonitrile for liquid chromatography (19:1) to make 100 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of levetiracetam is not less than 10.

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 the related substance A is not more than 10%.

(2) Enantiomer: To a quantity of powdered Levetiracetam Tablets, equivalent to 1.25 g of Levetiracetam, add 75 mL of ethanol (99.5) for liquid chromatography, disperse by

sonicating, and add ethanol (99.5) for liquid chromatography to make 100 mL. To 2 mL of this solution add 3 mL of ethanol (99.5) for liquid chromatography and heptane for liquid chromatography to make 25 mL. Filter through a membrane filter with a pore size not exceeding 0.45 μm, discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak area, A_2, of levetiracetam and the peak area, A_1, of the related substance B (enantiomer) having the relative retention time of about 0.8 to levetiracetam by the automatic integration method: $A_1/(A_1+A_2)$ is not more than 0.007.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with cellulose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography (10 μm particle diameter).

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

Mobile phase: A mixture of heptane for liquid chromatography and ethanol (99.5) for liquid chromatography (4:1).

Flow rate: 0.8 mL per minute.

System suitability—

Test for required detectability: Dissolve 25 mg each of Levetiracetam RS and Levetiracetam Related Substance B for System Suitability RS in 5 mL of ethanol (99.5) for liquid chromatography, add heptane for liquid chromatography to make 25 mL, and use this solution as the solution for system suitability test. Pipet 1 mL of this solution, and add the mobile phase to make exactly 100 mL. Pipet 1 mL of this solution, and add the mobile phase to make exactly 10 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, the SN ratio of the peak of the related substance B (enantiomer) is not less than 10.

System performance: When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the related substance B (enantiomer) and levetiracetam are eluted in this order with the resolution between these peaks being not less than 3.5, and the symmetry factor of the peak of levetiracetam is less than 2.0.

System repeatability: When the test is repeated 5 times with 20 μL of the solution for system suitability test under the above operating conditions, the relative standard deviations of the peak areas of the related substance B (enantiomer) and levetiracetam are not more than 1.0%.

Uniformity of dosage units <6.02> It meets the requirement of the Mass variation test.

Dissolution <6.10> When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium: the value Q in 30 minutes of Levetiracetam Tablets is 80%.

Start the test with 1 tablet of Levetiracetam Tablets, 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 0.5 μm. Discard the first 5 mL of the filtrate, pipet V mL of the subsequent filtrate, add water to make exactly V' mL so that each mL contains about 0.28 mg of levetiracetam ($C_8H_{14}N_2O_2$), and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Levetiracetam RS (separately determine the water <2.48> in the same manner as Levetiracetam), dissolve in water to make exactly 100 mL, and use this solution as the standard solution. Determine the absorbances, A_{T1} and A_{S1}, at 237 nm, and the absorbances, A_{T2} and A_{S2}, at 300 nm of the sample solution and standard solution as directed under Ultraviolet-visible Spectrophotometry <2.24>.

Dissolution rate (%) with respect to the labeled amount of levetiracetam ($C_8H_{14}N_2O_2$)

$$= M_S \times (A_{T1} - A_{T2}) / (A_{S1} - A_{S2}) \times V' / V \times 1 / C \times 900$$

M_S: Amount (mg) of Levetiracetam RS taken, calculated on the anhydrous basis

C: Labeled amount (mg) of levetiracetam ($C_8H_{14}N_2O_2$) in 1 tablet.

Assay Weigh accurately not less than 20 Levetiracetam Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 1.25 g of levetiracetam ($C_8H_{14}N_2O_2$), add 150 mL of a mixture of water and acetonitrile for liquid chromatography (19:1), disperse by sonicating, and add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 250 mL. Pipet 4 mL of this solution, and add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 200 mL. Filter this solution through a membrane filter with a pore size not exceeding 0.45 μm, discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 20 mg of Levetiracetam RS (separately determine the water <2.48> in the same manner as Levetiracetam), add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 200 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 levetiracetam in each solution.

Amount (mg) of levetiracetam ($C_8H_{14}N_2O_2$)

$$= M_S \times A_T / A_T \times 125 / 2$$

M_S: Amount (mg) of Levetiracetam RS taken, calculated on the anhydrous basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 3.9 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 20°C.

Mobile phase: Dissolve 2 g of dipotassium hydrogen phosphate in 1000 mL of water. To 950 mL of this solution add 50 mL of acetonitrile for liquid chromatography, mix, and adjust to pH 6.0 with diluted phosphoric acid (1 in 10).

Flow rate: 1.0 mL per minute.

System suitability—

System performance: To about 5 mg of Levetiracetam RS, about 5 mg of Levetiracetam Related Substance A for Purity RS and about 7.5 mg of 2-pyrrolidone add a mixture of water and acetonitrile for liquid chromatography (19:1) to make exactly 50 mL. When the procedure is run with 20 μL of this solution under the above operating conditions, 2-pyrrolidone, the related substance A and levetiracetam are eluted in this order with the resolution between 2-pyrrolidone and the related substance A being not less than 3.5, and the symmetry factor of the peak of levetiracetam is less than 2.0.

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 levetiracetam is not more than 1.0%.

Containers and storage Containers — Well-closed containers.

Others

Related substances A and B: Refer to them described in Levetiracetam.

Add the following to 9.01 Reference Standards (1):

Levetiracetam RS
Levetiracetam related substance A for Purity RS
Levetiracetam Related Substance B for System Suitability RS

Add the following to 9.42 Solid Supports/Column Packings for Chromatography:

Cellulose tris-(3,5-dimethylphenylcarbamate)-coated silica gel for liquid chromatography Prepared for liquid chromatography.