Levetiracetam 1

2 レベチラセタム

4 $C_8H_{14}N_2O_2$: 170.21

5 (2S)-2-(2-Oxopyrrolidin-1-yl)butanamide

- [102767-28-2] 6
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8 Levetiracetam contains not less than 98.0% and not 9 more than 102.0% of C₈H₁₄N₂O₂, calculated on the dried basis. 10

Description Levetiracetam occurs as a white to light gray-11 ish white crystalline powder. 12

13 It is very soluble in water, freely soluble in ethanol (99.5), 14 and soluble in 2-propanol.

Optical rotation <2.49> $[\alpha]_{D}^{20}$: -76 - -82° (0.2 g, wa-15 ter, 10 mL, 100 mm). 16

17 Identification Determine the infrared absorption spectrum 18 of Levetiracetam as directed in the potassium bromide disk 19 method under Infrared Spectrophotometry <2.25>, and compare the spectrum with the Reference Spectrum or the spec-20 21 trum of Levetiracetam RS: both spectra exhibit similar inten-

22 sities of absorption at the same wave numbers. Alternatively,

23 perform the test by the ATR method, and compare the spec-

24 trum with the spectrum of Levetiracetam RS: both spectra 25 exhibit similar intensities of absorption at the same wave

numbers. 26

27 **Purity** (1) Related substances – Use the sample solution 28 obtained in the Assay as the sample solution. Weigh accu-79 29 rately about 5 mg of Levetiracetam Related Substance A for 80 Purity RS, and dissolve in a mixture of acetonitrile for liquid 30 31 chromatography and water (24:1) to make exactly 500 mL. 32 Pipet 1 mL of this solution, add a mixture of acetonitrile for 33 liquid chromatography and water (24:1) to make exactly 100 34 mL, and use this solution as the standard solution (1). Pipet 1 35 mL of the standard solution obtained in the Assay, and add a mixture of acetonitrile for liquid chromatography and water 36 (24:1) to make exactly 20 mL. Pipet 1 mL of this solution, 37 38 add a mixture of acetonitrile for liquid chromatography and 39 water (24:1) to make exactly 100 mL, and use this solution 40 as the standard solution (2). Perform the test with exactly 10 91 41 μ L each of the sample solution and standard solutions (1) and 42 (2) as directed under Liquid Chromatography <2.01> accord-43 ing to the following conditions. Determine the peak areas, A_{T1} 44 and A_{S1} , of the related substance A in the sample solution and 45 standard solution (1), the area, A_{Tn} , of each other peak in the sample solution, and the peak area, As, of levetiracetam in the 46

- 47 standard solution (2) by the automatic integration method.
- 48 Calculate the amount of each related substance by the follow-49
- ing equations: the amount of the related substance A is not
- 50 more than 0.3%, the amount of other related substances is not 51 more than 0.05%, the total amount of other related substances
- is not more than 0.1%, and the total amount of the related 52

53 substances is not more than 0.4%.

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Amount (%) of the related substance A

$$=M_{S1}/M_T \times A_{T1}/A_{S1} \times 1/2$$
Amount (%) of each of other related substances

$$=M_S/M_T \times A_{Tn}/A_S \times 1/20$$

$$M_{S1}$$
: Amount (mg) of Levetiracetam Related Substance A
for Purity RS taken

 $M_{\rm S}$: Amount (mg) of Levetiracetam RS taken, calculated on the anhydrous basis

M_T: Amount (mg) of Levetiracetam

63 Operating conditions -

64 Detector, column, column temperature, mobile phase, and 65 flow rate: Proceed as directed in the operating conditions in 66 the Assay.

Time span of measurement: About 3 times as long as the 67 68 retention time of levetiracetam, beginning after the solvent 69 peak.

70 System suitability -

71 System performance: Proceed as directed in the system 72 suitability in the Assay.

73 Test for required detectability: When the procedure is run 74 with 10 μ L of the standard solution (2) under the above op-75 erating conditions, the SN ratio of the peak of levetiracetam 76 is not less than 10.

77 System repeatability: When the test is repeated 6 times 78 with 10 μ L of the standard solution (1) under the above operating conditions, the relative standard deviation of the peak area of the related substance A is not more than 10%.

81 (2) Enantiomer-Dissolve 0.20 g of Levetiracetam in 2-82 propanol for liquid chromatography to make 10 mL. To 1 mL 83 of this solution add the mobile phase to make 20 mL, and use this solution as the sample solution. Perform the test with 20 84 85 μ L of the sample solution as directed under Liquid Chroma-86 tography <2.01> according to the following conditions. De-87 termine the peak area, A_2 , of levetiracetam and the peak area, A_1 of the related substance B (enantiomer) having the relative 88 89 retention time of about 0.8 to levetiracetam by the automatic 90 integration method: $A_1/(A_1+A_2)$ is not more than 0.007. Operating conditions –

92 Detector: An ultraviolet absorption photometer (wave-93 length: 205 nm).

94 Column: A stainless steel column 4.6 mm in inside diam-95 eter and 25 cm in length, packed with cellulose tris-(3,5-

- 96 dimethylphenylcarbamate)-coated silica gel for liquid chro-145 97 matography (10 μ m particle diameter). 146
- 98 Column temperature: A constant temperature of about 99 20°C.
- 100 Mobile phase: A mixture of hexane for liquid chromatog-149
- raphy and 2-propanol for liquid chromatography (41:9). 101
- 102 Flow rate: 0.8 mL per minute.
- 103 System suitability-

104 Test for required detectability: Dissolve 25 mg each of Levetiracetam RS and Levetiracetam Related Substance B for 105 106 System Suitability RS in the mobile phase to make 25 mL, 107 and use this solution as the solution for system suitability test. 108 Pipet 1 mL of the solution for system suitability test, and add 109 the mobile phase to make exactly 10 mL. Pipet 1 mL of this 110 solution, and add the mobile phase to make exactly 25 mL. When the procedure is run with 20 μ L of this solution under 111

- the above operating conditions, the SN ratio of the peak of 112
- the related substance B (enantiomer) is not less than 10. 113

114 System performance: When the procedure is run with 20 115 μ L of the solution for system suitability test under the above 116 operating conditions, the resolution between the peaks of le-

117 vetiracetam and the related substance B (enantiomer) is not

118 less than 1.5, and the symmetry factor of the peak of le-

119 vetiracetam is not more than 2.3. 120

- System repeatability: When the test is repeated 5 times 121 with 20 μ L of the solution for system suitability test under 122 the above operating conditions, the relative standard devia-
- 123 tion of the peak area of levetiracetam is not more than 1.0%.

124 Water <2.48> Not more than 0.5% (0.3 g, coulometric ti-125 tration).

Residue on ignition $\langle 2.44 \rangle$ Not more than 0.1% (1 g). 126

- Assay Weigh accurately about 50 mg each of Levetirace-127 128 tam and Levetiracetam RS (separately determine the water 129 <2.48> in the same manner as Levetiracetam), dissolve each 174
- 130 in a mixture of acetonitrile for liquid chromatography and
- 131 water (24:1) to make exactly 250 mL, and use these solutions
- as the sample solution and the standard solution, respectively. 132

Perform the test with exactly 10 μ L each of the sample solu-133 134 tion and standard solution as directed under Liquid Chroma-135 tography <2.01> according to the following conditions, and

136 determine the peak areas, $A_{\rm T}$ and $A_{\rm S}$, of levetiracetam in each 137 solution.

138 Amount (mg) of levetiracetam (C₈H₁₄N₂O₂)
139 =
$$M_S \times A_T / A_S$$

140 $M_{\rm S}$: Amount (mg) of Levetiracetam RS taken, calculated 141 on the anhydrous basis

142 Operating conditions –

143 Detector: An ultraviolet absorption photometer (wave-144 length: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with silica gel for liquid chromatography (5 μ m in particle diameter).

Column temperature: A constant temperature of about 20°C.

Mobile phase: A mixture of acetonitrile for liquid chromatography and diluted sulfuric acid (11 in 10,000) (24:1).

Flow rate: 1.0 mL per minute.

System suitability-

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System performance: Dissolve 5 mg each of Levetiracetam RS and 2-pyrrolidone in 25 mL of a mixture of acetonitrile for liquid chromatography and water (24:1). When the procedure is run with 10 μ L of this solution under the above operating conditions, levetiracetam and 2-pyrrolidone are eluted in this order with the resolution between these peaks being not less than 1.5, and the symmetry factor of the peak of levetiracetam is not more than 1.4.

System repeatability: When the test is repeated 6 times with 10 μ L 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%.

166 **Containers and storage** Containers - Well-closed con-167 tainers

168 Others

169 Related Substance A:

(2RS)-2-(2-Oxopyrrolidin-1-yl)butanoic acid 170

$$N$$
 CO_2H and enantiomer

172 Related Substance B:

173 (2R)-2-(2-Oxopyrrolidin-1-yl)butanamide



Add the following to 9.01 Reference 175 176 Standards (1):

177 Levetiracetam Reference Standard

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

181 Add the following to 9.42 Solid Sup-182 ports/Column Packings for Chromatog-183 raphy:

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