1 Aripiprazole Tablets

2 アリピプラゾール錠

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4 Aripiprazole Tablets contain not less than 95.0% and 5 not more than 105.0% of the labeled amount of ari-6 piprazole ($C_{23}H_{27}Cl_2N_3O_2$:448.39).

7 Method of preparation Prepare as directed under Tablets,8 with Aripiprazole .

9 **Identification** Perform the test with 10 μ L each of the sam-10 ple solution and standard solution obtained in the Assay as 11 directed under Liquid Chromatography <2.01> according to 12 the following conditions: the retention times of the principal 13 peaks in the chromatograms obtained from the sample solu-14 tion and the standard solution are the same, and both absorp-15 tion spectra of these peaks exhibit similar intensities of ab-

16 sorption at the same wavelength.

17 Operating conditions—

18 Column, column temperature, mobile phase and flow rate:19 Proceed as directed in the operating conditions in the Assay.

20 Detector: A photodiode array detector (wavelength: 254

21 nm, spectrum range of measurement: 230 – 350 nm).

22 System suitability—

23 Proceed as directed in the system suitability in the Assay.

24 Purity Related substances—This is applied to 1-mg tablets. 25 Conduct this procedure using light-resistant vessels. To a 26 quantity of powdered Aripiprazole Tablets, equivalent to 4 mg of Aripiprazole, add 8 mL of a mixture of water, acetoni-27 28 trile and acetic acid (100) (60:40:1), shake for 10 minutes, 29 and filter through a membrane filter with a pore size not ex-30 ceeding 0.45 μ m. Discard the first 1 mL of the filtrate, and 31 use the subsequent filtrate as the sample solution. Perform the 32 test with 20 μ L of the sample solution as directed under Liq-33 uid Chromatography <2.01> according to the following con-34 ditions. Determine each peak area by the automatic integra-35 tion method, and calculate their amounts by the area percentage method: the amounts of the related substances TA and 36 37 TB, having the relative retention times of about 0.43 and 38 about 0.48 to aripiprazole, are not more than 0.2%, respec-39 tively, and the amount of the peak other than aripiprazole and 40 the peaks mentioned above is not more than 0.1%. 41 Operating conditions— 42 Detector: An ultraviolet absorption photometer (wave-43 length: 254 nm).

44 Column: A stainless steel column 4.6 mm in inside diam-45 eter and 15 cm in length, packed with octadecylsilanized sil-46 ica gel for liquid chromatography (5 μ m in particle diameter). 47 Column temperature: A constant temperature of about 48 25°C. 49 Mobile phase: Dissolve 2.88 g of sodium lauryl sulfate,

50 9.63 g of diammonium hydrogen citrate and 1.57 g of citric

acid monohydrate in water to make 1000 mL. To 550 mL of
this solution add 450 mL of acetonitrile for liquid chromatography.

Flow rate: Adjust so that the retention time of aripiprazoleis about 21 minutes.

Time span of measurement: About 1.8 times as long as the
retention time of aripiprazole, beginning after the solvent
peak.

59 System suitability—

60 Test for required detectability: Pipet 1 mL of the sample solution, add a mixture of water, acetonitrile and acetic acid 61 62 (100) (60:40:1) to make exactly 100 mL, and use this solution 63 as the solution for system suitability test. Pipet 2 mL of the 64 solution for system suitability test, add a mixture of water, acetonitrile and acetic acid (100) (60:40:1) to make exactly 65 66 20 mL. Confirm that the peak area of aripiprazole obtained 67 with 20 μ L of this solution is equivalent to 7 to 13% of that 68 with 20 μ L of the solution for system suitability test.

69 System performance: When the procedure is run with 20 70 μ L of the solution for system suitability test under the above 71 operating conditions, the number of theoretical plates and the 72 symmetry factor of the peak of aripiprazole are not less than 73 8000 and not more than 1.2, respectively.

74 Uniformity of dosage unit <6.02> Perform the test accord75 ing to the following method: it meets the requirement of the
76 Content uniformity test.

77 To 1 tablet of Aripiprazole Tablets add 35 mL of the mo-78 bile phase, shake thoroughly until the tablet is disintegrated, 79 add the mobile phase to make exactly 50 mL, shake thor-80 oughly for 10 minutes, and filter through a membrane filter 81 with a pore size not exceeding 0.45 μ m. Discard 1 mL of the 82 first filtrate, pipet V mL of the subsequent filtrate, add exactly 83 V'/20 mL of the internal standard solution, add the mobile phase to make V' mL so that each mL contains about 10 μ g 84 85 of aripiprazole (C₂₃H₂₇Cl₂N₃O₂), and use this solution as the sample solution. Separately, weigh accurately about 50 mg 86 87 of Aripiprazole RS, previously dried at 105°C for 3 hours, 88 dissolve in the mobile phase to make exactly 100 mL. Pipet 89 2 mL of this solution, add exactly 5 mL of the internal 90 standard solution, add the mobile phase to make 100 mL, and 91 use this solution as the standard solution. Perform the test 92 with exactly 10 μ L each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> 93 94 according to the following conditions, and calculate the ratios, 95 $Q_{\rm T}$ and $Q_{\rm S}$, of the peak area of aripiprazole to that of the 96 internal standard.

Amount (mg) of aripiprazole (C₂₃H₂₇Cl₂N₃O₂)
=
$$M_{\rm S} \times Q_{\rm T}/Q_{\rm S} \times V'/V \times 1/100$$

99 $M_{\rm S}$: Amount (mg) of Aripiprazole RS taken

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100 Internal standard solution-A solution of propyl parahy- 150

101 droxybenzoate in the mobile phase (1 in 6000).

102 Operating conditions—

Proceed as directed in the operating conditions in the As-say.

105 System suitability—

106 System performance: When the procedure is run with 10 107 μ L of the standard solution under the above operating condi-108 tions, aripiprazole and the internal standard are eluted in this 109 order with the resolution between these peaks being not less 110 than 8.

111 System repeatability: When the test is repeated 6 times 112 with $10 \,\mu$ L of the standard solution under the above operating 113 conditions, the relative standard deviation of the ratios of the 114 peak area of aripiprazole to that of the internal standard is not 115 more than 1.0%.

116 Dissolution <6.10> (1) 1-mg and 3-mg tablets When
117 the test is performed at 50 revolutions per minute according
118 to the Paddle method, using 900 mL of a solution prepared
119 by dissolving 1.97 g of acetic acid (100) and 9.15 g of sodium
120 acetate trihydrate in water to make 1000 mL as the
121 dissolution medium, the dissolution rates in 30 minutes of 1122 mg and 3-mg tablets are not less than 70%.

123 Start the test with 1 tablet of Aripiprazole Tablets, 124 withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane 125 filter with a pore size not exceeding 0.45 μ m. Discard not less 126 127 than 10 mL of the first filtrate, pipet V mL of the subsequent 128 filtrate, add the mobile phase to make exactly V' mL so that each mL contains about 0.56 μ g of aripiprazole 129 130 $(C_{23}H_{27}Cl_2N_3O_2)$, and use this solution as the sample solution. 131 Separately, weigh accurately about 28 mg of Aripiprazole RS, 132 previously dried at 105°C for 3 hours, dissolve in the mobile 133 phase to make exactly 100 mL. Pipet 5 mL of this solution, 134 add the mobile phase to make exactly 50 mL. Pipet 2 mL of 135 this solution, add the mobile phase to make exactly 100 mL, 136 and use this solution as the standard solution. Perform the test 137 with exactly 100 μ L each of the sample solution and standard 138 solution as directed under Liquid Chromatography <2.01> 139 according to the following conditions, and determine the 140 peak areas, A_T and A_S , of aripiprazole in each solution.

141 Dissolution rate (%) with respect to the labeled amount of

142 aripiprazole (C₂₃H₂₇Cl₂N₃O₂) 143 = $M_{\rm S} \times A_{\rm T}/A_{\rm S} \times V'/V \times 1/C \times 9/5$

144 $M_{\rm S}$: Amount (mg) of Aripiprazole RS taken

145C: Labeled amount (mg) of aripiprazole $(C_{23}H_{27}Cl_2N_3O_2)$ 146in 1 tablet

147 Operating conditions—

148Detector: An ultraviolet absorption photometer (wave-199149length: 254 nm).200

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

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

Mobile phase: Dissolve 2.84 g of anhydrous sodium sulfate in water to make 1000 mL. To 500 mL of this solution add 400 mL of acetonitrile for liquid chromatography, 100 mL of methanol and 10 mL of acetic acid (100).

Flow rate: Adjust so that the retention time of aripiprazole is about 5 minutes.

System suitability—

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System performance: When the procedure is run with 100 μ L of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of aripiprazole are not less than 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 100 μ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of aripiprazole is not more than 2.0%.

(2) 6-mg and 12-mg tablets When the test is performed at 75 revolutions per minute according to the Paddle method, using 900 mL of a solution prepared by dissolving 1.97 g of acetic acid (100) and 9.15 g of sodium acetate trihydrate in water to make 1000 mL as the dissolution medium, the dissolution rate in 30 minutes of a 6-mg tablet is not less than 70%, and that in 60 minutes of a 12-mg tablet is not less than 70%.

Start the test with 1 tablet of Aripiprazole Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μ m. Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V' mL so that each mL contains about 6.7 μ g of aripiprazole $(C_{23}H_{27}Cl_2N_3O_2)$, and use this solution as the sample solution. Separately, weigh accurately about 56 mg of Aripiprazole RS, previously dried at 105°C for 3 hours, dissolve in ethanol (95) to make exactly 50 mL. Pipet 3 mL of this solution, add the dissolution medium to make exactly 500 mL, and use this solution as the standard solution. Determine the absorbances, $A_{\rm T}$ and $A_{\rm S}$, of the sample solution and standard solution at 249 nm as directed under Ultraviolet-visible Spectrophotometry <2.24> using the dissolution medium as the control.

Dissolution rate (%) with respect to the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$)

 $=M_{\rm S} \times A_{\rm T}/A_{\rm S} \times V'/V \times 1/C \times 54/5$

 $M_{\rm S}$: Amount (mg) of Aripiprazole RS taken

C: Labeled amount (mg) of aripiprazole (C₂₃H₂₇Cl₂N₃O₂) in 1 tablet

201 Assay Weigh accurately not less than 20 Aripiprazole Tab-202 lets, and powder. Weigh accurately a quantity of the powder, 252 203 equivalent to about 10 mg of aripiprazole (C₂₃H₂₇Cl₂N₃O₂), 204 add 20 mL of the mobile phase, add exactly 10 mL of the 205 internal standard solution, shake thoroughly for 10 minutes, then add the mobile phase to make 50 mL, and filter through 206 a membrane filter with a pore size not exceeding 0.45 μ m. 207 208 Discard 1 mL of the first filtrate, and use the subsequent 254 209 filtrate as the sample solution. Separately, weigh accurately 210 about 50 mg of Aripiprazole RS, previously dried at 105°C 255 211 for 3 hours, dissolve in the mobile phase to make exactly 50 256 212 mL. Pipet 10 mL of this solution, add exactly 10 mL of the 213 internal standard solution, add the mobile phase to make 50 214 mL, and use this solution as the standard solution. Perform 215 the test with exactly 10 μ L each of the sample solution and 216 standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and calculate 217 the ratios, $Q_{\rm T}$ and $Q_{\rm S}$, of the peak area of aripiprazole to that 218 258 219 of the internal standard.

220 Amount (mg) of aripiprazole (C₂₃H₂₇Cl₂N₃O₂) 259
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$$=M_S \times Q_T / Q_S \times 1 / 5$$

222 $M_{\rm S}$: Amount (mg) of Aripiprazole RS taken

Internal standard solution-A solution of propyl parahy-223 224 droxybenzoate in the mobile phase (1 in 3000)

225 **Operating** conditions—

226 Detector: An ultraviolet absorption photometer (wave-227 length: 254 nm).

228 Column: A stainless steel column 4.6 mm in inside diam-229 eter and 25 cm in length, packed with octadecylsilanized sil-

230 ica gel for liquid chromatography (5 μ m in particle diameter). 231 Column temperature: A constant temperature of about

232 25°C.

233 Mobile phase: Dissolve 2.84 g of anhydrous sodium sul-234 fate in water to make 1000 mL. To 560 mL of this solution 235 add 330 mL of acetonitrile for liquid chromatography, 110 236 mL of methanol and 10 mL of acetic acid (100).

237 Flow rate: Adjust so that the retention time of aripiprazole 238 is about 10 minutes.

239 System suitability-

240 System performance: When the procedure is run with 10 241 μ L of the standard solution under the above operating conditions, aripiprazole and the internal standard are eluted in this 242243 order with the resolution between these peaks being not less 244 than 8.

245 System repeatability: When the test is repeated 6 times with 10 μ L of the standard solution under the above operating 246 247 conditions, the relative standard deviation of the ratios of the 248 peak area of aripiprazole to that of the internal standard is not 249 more than 1.0%.

250 Containers and storage Containers—Tight containers.

251 Others

- Related substance TA:
- 253 8-(2,3-Dichlorophenyl)-5,8-diazaspiro[4.5]decan-5-ium



Related substance TB:

4-(2,3-Dichlorophenyl)-1-{4-[(2-0x0-1,2,3,4-

257 tetrahydroquinolin-7-yl)oxy]butyl}piperazine 1-oxide

