

1 Aripiprazole Tablets

2 アリピプラゾール錠

4 Aripiprazole Tablets contain not less than 95.0% and not
5 more than 105.0% of the labeled amount of aripiprazole
6 ($C_{23}H_{27}Cl_2N_3O_2$; 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 System performance: Proceed as directed in the system
24 suitability in the Assay.

25 **Purity** Related substances—This is applied to 1-mg tablets.

26 Conduct this procedure using light-resistant vessels. To a
27 quantity of powdered Aripiprazole Tablets, equivalent to 4
28 mg of Aripiprazole, add 8 mL of a mixture of water, acetonitrile
29 and acetic acid (100) (60:40:1), shake for 10 minutes,
30 and filter through a membrane filter with a pore size not ex-
31 ceeding 0.45 μ m. Discard the first 1 mL of the filtrate, and
32 use the subsequent filtrate as the sample solution. Perform the
33 test with 20 μ L of the sample solution as directed under Liq-
34 uid Chromatography <2.01> according to the following con-
35 ditions. Determine each peak area by the automatic integra-
36 tion method, and calculate their amounts by the area percent-
37 age method: the amounts of the related substance TA having
38 the relative retention times of about 0.43 and related sub-
39 stance TB having the relative retention times of about 0.48 to
40 aripiprazole, are not more than 0.2%, respectively, and the
41 amount of the peak other than aripiprazole and the peaks
42 mentioned above is not more than 0.1%.

43 *Operating conditions—*

44 Detector: An ultraviolet absorption photometer (wave-
45 length: 254 nm).

46 Column: A stainless steel column 4.6 mm in inside diam-
47 eter and 15 cm in length, packed with octadecylsilanized sil-
48 ica gel for liquid chromatography (5 μ m in particle diameter).

49 Column temperature: A constant temperature of about
50 25°C.

51 Mobile phase: Dissolve 2.88 g of sodium lauryl sulfate,
52 9.63 g of diammonium hydrogen citrate and 1.57 g of citric
53 acid monohydrate in water to make 1000 mL. To 550 mL of
54 this solution add 450 mL of acetonitrile for liquid chroma-
55 tography.

56 Flow rate: Adjust so that the retention time of aripiprazole
57 is about 21 minutes.

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

61 *System suitability—*

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

71 System performance: When the procedure is run with 20
72 μ L of the solution for system suitability test under the above
73 operating conditions, the number of theoretical plates and the
74 symmetry factor of the peak of aripiprazole are not less than
75 8000 and not more than 1.2, respectively.

76 **Uniformity of dosage unit** <6.02> Perform the test accord-
77 ing to the following method: it meets the requirement of the
78 Content uniformity test.

79 To 1 tablet of Aripiprazole Tablets add 35 mL of the mo-
80 bile phase, shake thoroughly to disintegrate. Shake thor-
81 oughly again, then add the mobile phase to make exactly 50
82 mL, and filter through a membrane filter with a pore size not
83 exceeding 0.45 μ m. Discard 1 mL of the first filtrate, pipet V
84 mL of the subsequent filtrate, add exactly $V'/20$ mL of the
85 internal standard solution, add the mobile phase to make V'
86 mL so that each mL contains about 10 μ g of aripiprazole
87 ($C_{23}H_{27}Cl_2N_3O_2$), and use this solution as the sample solution.
88 Separately, weigh accurately about 50 mg of Aripiprazole RS,
89 previously dried at 105°C for 3 hours, dissolve in the mobile
90 phase to make exactly 100 mL. Pipet 2 mL of this solution,
91 add exactly 5 mL of the internal standard solution, add the
92 mobile phase to make 100 mL, and use this solution as the
93 standard solution. Perform the test with exactly 10 μ L each
94 of the sample solution and standard solution as directed under
95 Liquid Chromatography <2.01> according to the following
96 conditions, and calculate the ratios, Q_T and Q_S , of the peak
97 area of aripiprazole to that of the internal standard.

$$\begin{aligned} & \text{Amount (mg) of aripiprazole } (C_{23}H_{27}Cl_2N_3O_2) \\ & = M_S \times Q_T / Q_S \times V' / V \times 1 / 100 \end{aligned}$$

100 M_S : Amount (mg) of Aripiprazole RS taken

101 *Internal standard solution*—A solution of propyl parahydroxybenzoate in the mobile phase (1 in 6000).

103 *Operating conditions*—

104 Proceed as directed in the operating conditions in the Assay.

106 *System suitability*—

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

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

117 **Dissolution** <6.10> (1) 1-mg and 3-mg tablets When the test is performed at 50 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 rates in 30 minutes of 1-mg and 3-mg tablets are not less than 70%.

124 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 μm . Discard not less than 10 mL of the first filtrate, pipet V mL of the subsequent filtrate, add the mobile phase to make exactly V' mL so that each mL contains about 0.56 μg of aripiprazole ($\text{C}_{23}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$), and use this solution as the sample solution. Separately, weigh accurately about 28 mg of Aripiprazole RS, previously dried at 105°C for 3 hours, dissolve in the mobile phase to make exactly 100 mL. Pipet 5 mL of this solution, add the mobile phase to make exactly 50 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 100 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 aripiprazole in each solution.

142 Dissolution rate (%) with respect to the labeled amount of aripiprazole ($\text{C}_{23}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$)

$$144 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 9 / 5$$

145 M_S : Amount (mg) of Aripiprazole RS taken

146 C : Labeled amount (mg) of aripiprazole ($\text{C}_{23}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$) in 1 tablet

148 *Operating conditions*—

149 Detector: An ultraviolet absorption photometer (wavelength: 254 nm).

151 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 μm in particle diameter).

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

156 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).

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

162 *System suitability*—

163 System performance: When the procedure is run with 100 μL 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.

168 System repeatability: When the test is repeated 6 times with 100 μL 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%.

172 (2) 6-mg, 12-mg and 24-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 those in 60 minutes of a 12-mg and 24-mg tablets are not less than 70%.

180 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 μm . 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 μg of aripiprazole ($\text{C}_{23}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$), 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_T and A_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.

196 Dissolution rate (%) with respect to the labeled amount of aripiprazole ($\text{C}_{23}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_2$)

$$198 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 54 / 5$$

199 M_S : Amount (mg) of Aripiprazole RS taken
 200 C: Labeled amount (mg) of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$)
 201 in 1 tablet

202 **Assay** Weigh accurately not less than 20 Aripiprazole Tab-
 203 lets, and powder. Weigh accurately a quantity of the powder,
 204 equivalent to about 10 mg of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$),
 205 add 20 mL of the mobile phase, add exactly 10 mL of the
 206 internal standard solution, shake thoroughly, then add the
 207 mobile phase to make 50 mL, and filter through a membrane
 208 filter with a pore size not exceeding $0.45\ \mu\text{m}$. Discard 1 mL
 209 of the first filtrate, and use the subsequent filtrate as the
 210 sample solution. Separately, weigh accurately about 50 mg
 211 of Aripiprazole RS, previously dried at 105°C for 3 hours,
 212 dissolve in the mobile phase to make exactly 50 mL. Pipet 10
 213 mL of this solution, add exactly 10 mL of the internal stand-
 214 ard solution, add the mobile phase to make 50 mL, and use
 215 this solution as the standard solution. Perform the test with
 216 exactly $10\ \mu\text{L}$ each of the sample solution and standard solu-
 217 tion as directed under Liquid Chromatography <2.01> ac-
 218 cording to the following conditions, and calculate the ratios,
 219 Q_T and Q_S , of the peak area of aripiprazole to that of the
 220 internal standard.

$$\begin{aligned} & \text{Amount (mg) of aripiprazole } (C_{23}H_{27}Cl_2N_3O_2) \\ & = M_S \times Q_T / Q_S \times 1/5 \end{aligned}$$

223 M_S : Amount (mg) of Aripiprazole RS taken

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

226 *Operating conditions*—

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

229 Column: A stainless steel column 4.6 mm in inside diam-
 230 eter and 25 cm in length, packed with octadecylsilanized sil-
 231 ica gel for liquid chromatography ($5\ \mu\text{m}$ in particle diameter).

232 Column temperature: A constant temperature of about
 233 25°C .

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

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

240 *System suitability*—

241 System performance: When the procedure is run with 10
 242 μL of the standard solution under the above operating condi-
 243 tions, aripiprazole and the internal standard are eluted in this
 244 order with the resolution between these peaks being not less
 245 than 8.

246 System repeatability: When the test is repeated 6 times
 247 with $10\ \mu\text{L}$ of the standard solution under the above operating
 248 conditions, the relative standard deviation of the ratios of the

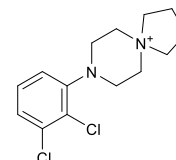
249 peak area of aripiprazole to that of the internal standard is not
 250 more than 1.0%.

251 **Containers and storage** Containers—Tight containers.

252 **Others**

253 Related substance TA:

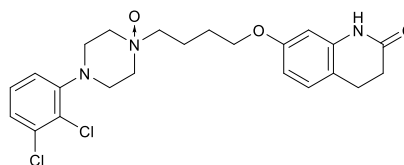
254 8-(2,3-Dichlorophenyl)-5,8-diazaspiro[4.5]decan-5-ium



255

256 Related substance TB:

257 4-(2,3-Dichlorophenyl)-1-{4-[(2-oxo-1,2,3,4-
 258 tetrahydroquinolin-7-yl)oxy]butyl}piperazine 1-oxide



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260