

1 Midodrine Hydrochloride Tablets

2 ミドドリン塩酸塩錠

4 Midodrine Hydrochloride Tablets contain not less
5 than 93.0% and not more than 105.0% of the labeled
6 amount of midodrine hydrochloride ($C_{12}H_{18}N_2O_4 \cdot HCl$:
7 290.74).

8 **Method of preparation** Prepare as directed under Tablets,
9 with Midodrine Hydrochloride.

10 **Identification** Weigh a quantity of powdered Midodrine
11 Hydrochloride Tablets, equivalent to 3 mg of Midodrine Hy-
12 drochloride, add 0.01 mol/L hydrochloric acid TS, shake
13 thoroughly, and add 0.01 mol/L hydrochloric acid TS to
14 make 100 mL. Centrifuge 30 mL of this solution, and deter-
15 mine the absorption spectrum of the supernatant liquid as di-
16 rected under Ultraviolet-visible Spectrophotometry <2.24>: it
17 exhibits a maximum between 288 nm and 292 nm.

18 **Purity** Related substances — Weigh accurately not less
19 than 20 Midodrine Hydrochloride Tablets, and powder.
20 Weigh accurately a portion of the powder, equivalent to
21 about 2 mg of Midodrine Hydrochloride, add exactly 10 mL
22 of a mixture of 0.01 mol/L hydrochloric acid TS and acetoni-
23 trile for liquid chromatography (13:7), and disperse the par-
24 ticles into small particles by sonicating with occasional shak-
25 ing. Centrifuge this solution, and use the supernatant liquid
26 as the sample solution. Separately, weigh accurately about 25
27 mg of Midodrine Hydrochloride RS, previously dried at
28 105°C for 2 hours, and dissolve in a mixture of 0.01 mol/L
29 hydrochloric acid TS and acetonitrile for liquid chromatog-
30 raphy (13:7) to make exactly 25 mL. Pipet 2 mL of this solu-
31 tion, and add a mixture of 0.01 mol/L hydrochloric acid TS
32 and acetonitrile for liquid chromatography (13:7) to make ex-
33 actly 20 mL. Then, pipet 1 mL of this solution, add a mixture
34 of 0.01 mol/L hydrochloric acid TS and acetonitrile for liquid
35 chromatography (13:7) to make exactly 100 mL, and use this
36 solution as the standard solution. Perform the test with ex-
37 actly 10 μ L each of the sample solution and standard solution
38 as directed under Liquid Chromatography <2.01> according
39 to the following conditions. Determine each peak area by the
40 automatic integration method, and calculate the amounts of
41 the related substances by the following formula. The amounts
42 of the related substance having the relative retention time of
43 about 0.25 to midodrine and the related substance A having
44 the relative retention time of about 1.2 are not more than
45 0.6%, and the amount of each of other related substances is
46 not more than 0.2%. Furthermore, the total amount of the re-
47 lated substances is not more than 2.0%.

48 Amount (%) of related substances

$$= M_S / M_T \times A_T / A_S \times M_M / C \times 1 / 25$$

50 M_S : Amount (mg) of Midodrine Hydrochloride RS taken
51 M_T : Amount (mg) of Midodrine Hydrochloride Tablets
52 taken
53 M_M : Average mass of 1 tablet (mg)
54 A_S : Peak area of midodrine obtained from the standard so-
55 lution
56 A_T : Peak area of each related substance obtained from the
57 sample solution
58 C : Labeled amount (mg) of midodrine hydrochloride
59 ($C_{12}H_{18}N_2O_4 \cdot HCl$) in 1 tablet

60 *Operating conditions* —

61 Detector: An ultraviolet absorption photometer (wave-
62 length: 290 nm)

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

66 Column temperature: A constant temperature of about
67 35°C.

68 Mobile phase: A mixture of a solution of sodium lauryl
69 sulfate (1 in 100), acetonitrile for liquid chromatography and
70 phosphoric acid (650:350:1).

71 Flow rate: Adjust so that the retention time of midodrine is
72 about 10 minutes.

73 Time span of measurement: About 3 times as long as the
74 retention time of midodrine, beginning after the solvent peak.

75 *System suitability* —

76 Test for required detectability: Pipet 5 mL of the standard
77 solution, and add a mixture of 0.01 mol/L hydrochloric acid
78 TS and acetonitrile for liquid chromatography (13:7) to make
79 exactly 25 mL. Confirm that the peak area of midodrine ob-
80 tained with 10 μ L of this solution is equivalent to 14 to 26%
81 of that with the standard solution.

82 System performance: Dissolve 20 mg of Midodrine Hy-
83 drochloride RS in dilute sodium hydroxide TS to make 20
84 mL, and allow to stand in a water bath at 80°C for 3 hours.
85 After cooling, to 1 mL of this solution add a mixture of 0.01
86 mol/L hydrochloric acid TS and acetonitrile for liquid chro-
87 matography (13:7) to make 100 mL. When the procedure is
88 run with 10 μ L of this solution under the above operating
89 conditions, midodrine and the related substance A are eluted
90 in this order with the resolution between these peaks being
91 not less than 3.

92 System reproducibility: When the test is repeated 6 times
93 with 10 μ L of the standard solution under the above operating
94 conditions, the relative standard deviation of the peak area of
95 midodrine is not more than 4.5%.

96 **Uniformity of dosage units** <6.02> Perform the test ac-
97 cording to the following method: it meets the requirement of
98 the Content uniformity test.

99 To 1 tablet of Midodrine Hydrochloride Tablets add the
100 internal standard solution to make exactly V mL so that each

101 mL contains about 0.1 mg of midodrine hydrochloride
 102 ($C_{12}H_{18}N_2O_4.HCl$), warm in a water bath at 50°C for 10
 103 minutes, and stopper tightly. After shaking for 30 minutes,
 104 centrifuge this solution, and use the supernatant liquid as the
 105 sample solution. Then, proceed as directed in the Assay.

106 Amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4.HCl$)
 107 $=M_S \times Q_T/Q_S \times V/250$

108 M_S : Amount of Midodrine Hydrochloride RS taken

109 *Internal standard solution*—A solution of thymol in a mix-
 110 ture of 0.01 mol/L hydrochloric acid TS and methanol (1:1)
 111 (1 in 20,000).

112 **Dissolution** <6.10> When the test is performed at 50 revo-
 113 lutions per minute according to the Paddle method, using 900
 114 mL of water as the dissolution medium, the dissolution rate
 115 in 30 minutes of Midodrine Hydrochloride Tablets is not less
 116 than 80%.

117 Start the test with 1 tablet of Midodrine Hydrochloride
 118 Tablets, withdraw not less than 20 mL of the medium at the
 119 specified minute after starting the test, and filter through a
 120 membrane filter with a pore size not exceeding 0.45 μm . Dis-
 121 card not less than 10 mL of the first filtrate, pipet V mL of the
 122 subsequent filtrate, add water to make exactly V' mL so that
 123 each mL contains about 2.2 μg of midodrine hydrochloride
 124 ($C_{12}H_{18}N_2O_4.HCl$), and use this solution as the sample solu-
 125 tion. Separately, weigh accurately about 55 mg of Midodrine
 126 Hydrochloride RS, previously dried at 105°C for 2 hours, and
 127 dissolve in water to make exactly 50 mL. Pipet 5 mL of this
 128 solution, and add water to make exactly 100 mL. Pipet 5 mL
 129 of this solution, add water to make exactly 100 mL, and use
 130 this solution as the standard solution. Perform the test with
 131 exactly 100 μL each of the sample solution and standard so-
 132 lution as directed under Liquid Chromatography <2.01> ac-
 133 cording to the following conditions, and determine the peak
 134 areas, A_T and A_S , of midodrine in each solution.

135 Dissolution rate (%) with respect to the labeled amount
 136 of midodrine hydrochloride ($C_{12}H_{18}N_2O_4.HCl$)

137 $=M_S \times A_T/A_S \times V'/V \times 1/C \times 9/2$

138 M_S : Amount (mg) of Midodrine Hydrochloride RS taken

139 C : Labeled amount (mg) of midodrine hydrochloride
 140 ($C_{12}H_{18}N_2O_4.HCl$) in 1 tablet

141 *Operating conditions*—

142 Detector: An ultraviolet absorption photometer (wave-
 143 length: 290 nm)

144 Column: A stainless steel column 4.6 mm in inside diam-
 145 eter and 15 cm in length, packed with octadecylsilanized sil-
 146 ica gel for liquid chromatography (5 μm in particle diameter).

147 Column temperature: A constant temperature of about
 148 50°C.

149 Mobile phase: A mixture of a solution of sodium lauryl
 150 sulfate (1 in 100), acetonitrile for liquid chromatography and
 151 phosphoric acid (600:400:1).

152 Flow rate: Adjust so that the retention time of midodrine is
 153 about 6 minutes.

154 *System suitability*—

155 System performance: When the procedure is run with 100
 156 μL of the standard solution under the above operating condi-
 157 tions, the number of theoretical plates and the symmetry fac-
 158 tor of the peak of midodrine are not less than 5000 and not
 159 more than 2.0, respectively.

160 System repeatability: When the test is repeated 6 times
 161 with 100 μL of the standard solution under the above operat-
 162 ing conditions, the relative standard deviation of the peak
 163 area of midodrine is not more than 2.0%.

164 **Assay** Weigh accurately not less than 20 Midodrine Hydro-
 165 chloride Tablets, and powder. Weigh accurately a portion of
 166 the powder equivalent to about 2 mg of midodrine hydrochlo-
 167 ride ($C_{12}H_{18}N_2O_4.HCl$), add exactly 20 mL of the internal
 168 standard solution, warm in a water bath at 50°C for 10
 169 minutes, and stopper tightly. After shaking for 30 minutes,
 170 centrifuge this solution, and use the supernatant liquid as the
 171 sample solution. Separately, weigh accurately about 25 mg
 172 of Midodrine Hydrochloride RS, previously dried at 105°C
 173 for 2 hours, and dissolve in the internal standard solution to
 174 make exactly 25 mL. Pipet 2 mL of this solution, add the in-
 175 ternal standard solution to make exactly 20 mL, and use this
 176 solution as the standard solution. Perform the test with 10 μL
 177 each of the sample solution and standard solution as directed
 178 under Liquid Chromatography <2.01> according to the fol-
 179 lowing conditions, and calculate the ratios, Q_T and Q_S , of the
 180 peak area of midodrine to that of the internal standard.

181 Amount (mg) of midodrine hydrochloride ($C_{12}H_{18}N_2O_4.HCl$)
 182 $=M_S \times Q_T/Q_S \times 2/25$

183 M_S : Amount (mg) of Midodrine Hydrochloride RS taken

184 *Internal standard solution*—A solution of thymol in a mix-
 185 ture of 0.01 mol/L hydrochloric acid TS and methanol (1:1)
 186 (1 in 20,000).

187 *Operating conditions*—

188 Detector: An ultraviolet absorption photometer (wave-
 189 length: 220 nm)

190 Column: A stainless steel column 4.6 mm in inside diam-
 191 eter and 15 cm in length, packed with octadecylsilanized sil-
 192 ica gel for liquid chromatography (5 μm in particle diameter).

193 Column temperature: A constant temperature of about
 194 45°C.

195 Mobile phase: A mixture of a solution of sodium lauryl
 196 sulfate (1 in 100), acetonitrile for liquid chromatography and
 197 phosphoric acid (550:450:1).

198 Flow rate: Adjust so that the retention time of midodrine is
199 about 5 minutes.

200 *System suitability*—

201 System performance: When the procedure is run with 10
202 μL of the standard solution under the above operating condi-
203 tions, midodrine and the internal standard are eluted in this
204 order with the resolution between these peaks being not less
205 than 1.5.

206 System repeatability: When the test is repeated 6 times
207 with 10 μL of the standard solution under the above operating
208 conditions, the relative standard deviation of the ratio of the
209 peak area of midodrine to that of the internal standard is not
210 more than 1.0%.

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

212 **Others**

213 Related substance A: Refer to it described in Midodrine Hy-
214 drochloride.

215 **9.01 Add the following to Reference**
216 **Standards (1) section.**

217 Midodrine Hydrochloride RS
218