## 1 Midodrine Hydrochloride Orally

## 2 **Disintegrating Tablets**

3 ミドドリン塩酸塩口腔内崩壊錠

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5 Midodrine Hydrochloride Orally Disintegrating

6 Tablets contain not less than 95.0% and not more than

7 105.0% of the labeled amount of midodrine hydrochlo-

8 ride ( $C_{12}H_{18}N_2O_4$ .HCl: 290.74).

9 Method of preparation Prepare as directed under Tablets,10 with Midodrine Hydrochloride.

Identification To a quantity of Midodrine Hydrochloride 11 12 Orally Disintegrating Tablets, equivalent to 6 mg of Mido-13 drine Hydrochloride, add 0.01 mol/L hydrochloric acid TS, 14 shake to disperse the tablets, add 0.01 mol/L hydrochloric acid TS to make 200 mL, and shake vigorously. Filter the 15 16 solution through a membrane filter with a pore size not exceeding 0.45  $\mu$ m, and determine the absorption spectrum of 17 18 the filtrate as directed under Ultraviolet-visible Spectropho-19 tometry <2.24>: it exhibits a maximum between 288 nm and 20 292 nm.

21 Purity Related substances - Weigh accurately not less 22 than 20 Midodrine Hydrochloride Orally Disintegrating Tab-23 lets, and powder. Weigh accurately a portion of the powder, 24 equivalent to about 2 mg of Midodrine Hydrochloride, add 25 exactly 10 mL of a mixture of water and acetonitrile for liquid chromatography (13:7), and disperse the particles into small 26 27 particles by sonicating with occasional shaking. Centrifuge 28 this solution, and use the supernatant liquid as the sample so-29 lution. Separately, weigh accurately about 25 mg of Mido-30 drine Hydrochloride RS, previously dried at 105°C for 2 31 hours, and dissolve in a mixture of water and acetonitrile for 32 liquid chromatography (13:7) to make exactly 25 mL. Pipet 33 2 mL of this solution, and add a mixture of water and ace-34 tonitrile for liquid chromatography (13:7) to make exactly 20 mL. Pipet 1 mL of this solution, add a mixture of water and 35 36 acetonitrile for liquid chromatography (13:7) to make exactly 37 100 mL, and use this solution as the standard solution. Per-38 form the test with exactly 10  $\mu$ L each of the sample solution 39 and standard solution as directed under Liquid Chromatog-40 raphy <2.01> according to the following conditions. Deter-41 mine each peak area by the automatic integration method, 42 and calculate the amounts of the related substances by the following formula. The amounts of the related substance hav-43 44 ing the relative retention time of about 0.25 to midodrine and the related substance A having the relative retention time of 45 46 about 1.2 are not more than 0.6%, and the amount of each of 47 other related substances is not more than 0.2%. Furthermore, 48 the total amount of the related substances is not more than 49 2.0%.

50 Amount (%) of related substances

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 $=M_{\rm S}/M_{\rm T} \times A_{\rm T}/A_{\rm S} \times M_{\rm M}/C \times 1/25$ 

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

 $M_{\rm T}$ : Amount (mg) of Midodrine Hydrochloride Orally

54 Disintegrating Tablets taken

 $M_{\rm M}$ : Average mass of 1 tablet (mg)

- $A_{\rm S}$ : Peak area of midodrine obtained from the standard solution
- $A_{\rm T}$ : Peak area of each related substance obtained from the sample solution
- *C*: Labeled amount (mg) of midodrine hydrochloride  $(C_{12}H_{18}N_2O_4.HCl)$  in 1 tablet

## 62 Operating conditions –

63 Detector: An ultraviolet absorption photometer (wave-64 length: 290 nm)

65 Column: A stainless steel column 4.6 mm in inside diam-66 eter and 15 cm in length, packed with trimethylsilanized sil-67 ica gel for liquid chromatography (5  $\mu$ m in particle diameter).

68 Column temperature: A constant temperature of about 69 35°C.

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

Flow rate: Adjust so that the retention time of midodrine isabout 10 minutes.

Time span of measurement: About 3 times as long as the
retention time of midodrine, beginning after the solvent peak. *System suitability* –

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water and acetonitrile for liquid chromatography (13:7) to make exactly 25 mL. Confirm that the peak area of midodrine obtained with 10  $\mu$ L of this solution is equivalent to 14 to 26% of that of the standard solution.

84 System performance: Dissolve 20 mg of Midodrine Hy-85 drochloride RS in dilute sodium hydroxide TS to make 20 86 mL, and allow to stand in a water bath at 80°C for 3 hours. 87 After cooling, to 1 mL of this solution add a mixture of water 88 and acetonitrile for liquid chromatography (13:7) to make 89 100 mL. When the procedure is run with 10  $\mu$ L of this solu-90 tion under the above operating conditions, midodrine and the 91 related substance A are eluted in this order with the resolution 92 between these peaks being not less than 3.

93 System reproducibility: When the test is repeated 6 times 94 using  $10 \ \mu$ L of the standard solution under the above operat-95 ing conditions, the relative standard deviation of the peak 96 area of midodrine is not more than 4.5%.

97 Uniformity of dosage units <6.02> Perform the test ac98 cording to the following method: it meets the requirement of
99 the Content uniformity test.

100 To 1 tablet of Midodrine Hydrochloride Orally Disinte-

101 grating Tablets add the internal standard solution to make ex-

102 actly V mL so that each mL contains about 0.1 mg of mido-

103 drine hydrochloride (C12H18N2O4.HCl), and disperse the par-

104 ticles into small particles by sonicating with occasional shak-

ing. Centrifuge this solution, and use the supernatant liquid 105 153 154

as the sample solution. Then, proceed as directed in the Assay. 106

107 Amount (mg) of midodrine hydrochloride (C12H18N2O4.HCl)  $=M_{\rm S} \times Q_{\rm T}/Q_{\rm S} \times V/250$ 108

M<sub>S</sub>: Amount of Midodrine Hydrochloride RS taken 109

110 Internal standard solution-A solution of thymol in a mixture of 0.01 mol/L hydrochloric acid TS and methanol (1:1) 111 112 (1 in 20,000).

**Disintegration** Being specified separately when the drug is 113 granted approval based on the Law. 114

**Dissolution** <6.10> When the test is performed at 50 revo-115 lutions per minute according to the Paddle method, using 900 116 117 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Midodrine Hydrochloride Orally Disinte-118 grating Tablets is not less than 85%. 119 120 Start the test with 1 tablet of Midodrine Hydrochloride

- 121 Orally Disintegrating Tablets, withdraw not less than 10 mL 171 122 of the medium at the specified minute after starting the test, 172 and filter through a membrane filter with a pore size not ex-123 173 124 ceeding 0.45  $\mu$ m. Discard not less than 5 mL of the first fil-174 125 trate, pipet V mL of the subsequent filtrate, add water to make 175 126 exactly V' mL so that each mL contains about 2.2  $\mu$ g of mido-176 127 drine hydrochloride (C12H18N2O4.HCl), and use this solution 177 128 as the sample solution. Separately, weigh accurately about 50 178 129 mg of Midodrine Hydrochloride RS, previously dried at 179 105°C for 2 hours, and dissolve in water to make exactly 50 130 180 131 mL. Pipet 5 mL of this solution, and add water to make ex-181 132 actly 100 mL. Pipet 5 mL of this solution, add water to make 182 133 exactly 100 mL, and use this solution as the standard solution. 183 134 Perform the test with exactly 100  $\mu$ L each of the sample so-184 lution and standard solution as directed under Liquid Chro-135 136 matography <2.01> according to the following conditions, and determine the peak areas,  $A_{\rm T}$  and  $A_{\rm S}$ , of midodrine in each 137
- 138 solution.

139 Dissolution rate (%) with respect to the labeled amount 140 of midodrine hydrochloride (C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>.HCl)  $\times$  A /A  $\times$  W/W  $\times$  1 /C  $\times$  0 /2 1 / 1

$$141 \qquad -M_{\rm S} \wedge A_{\rm T}/A_{\rm S} \wedge V/V \wedge 1/C \wedge 9/2$$

142 M<sub>S</sub>: Amount (mg) of Midodrine Hydrochloride RS taken

143 C: Labeled amount (mg) of midodrine hydrochloride 144 (C12H18N2O4.HCl) in 1 tablet

145 Operating conditions –

146 Detector: An ultraviolet absorption photometer (wave-

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5  $\mu$ m in particle diameter).

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

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

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

System suitability-

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System performance: When the procedure is run with 100  $\mu$ L of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of midodrine are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 100  $\mu$ L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of midodrine is not more than 1.5%.

Assay Weigh accurately not less than 20 Midodrine Hydrochloride Orally Disintegrating Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 2 mg of midodrine hydrochloride (C12H18N2O4.HCl), add exactly 20 mL of the internal standard solution, and disperse the particles into small particles by sonicating with occasional shaking. Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 25 mg of Midodrine Hydrochloride RS, previously dried at 105°C for 2 hours, and dissolve in the internal standard solution to make exactly 25 mL. Pipet 2 mL of this solution, add the internal standard solution to make exactly 20 mL, and use this solution as the standard solution. Perform the test with 10  $\mu$ L each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and calculate the ratios,  $Q_{\rm T}$  and  $Q_{\rm S}$ , of the peak area of midodrine to that of the internal standard.

Amount (mg) of midodrine hydrochloride (C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>.HCl)  $=M_{\rm S} \times Q_{\rm T}/Q_{\rm S} \times 2/25$ 

M<sub>S</sub>: Amount (mg) of Midodrine Hydrochloride RS taken

188 Internal standard solution-A solution of thymol in a mixture of 0.01 mol/L hydrochloric acid TS and methanol (1:1) 190 (1 in 20,000).

191 Operating conditions –

192 Detector: An ultraviolet absorption photometer (wave-193 length: 220 nm)

194 Column: A stainless steel column 4.6 mm in inside diam-195 eter and 15 cm in length, packed with octadecylsilanized sil-196 ica gel for liquid chromatography (5  $\mu$ m in particle diameter).

147 length: 290 nm)

197	Column temperature: A constant temperature of about
198	45°C.
199	Mobile phase: A mixture of a solution of sodium lauryl
200	sulfate (1 in 100), acetonitrile for liquid chromatography and
201	phosphoric acid (550:450:1).
202	Flow rate: Adjust so that the retention time of midodrine is
203	about 5 minutes.
204	System suitability—
205	System performance: When the procedure is run with 10
206	$\mu$ L of the standard solution under the above operating condi-
207	tions, midodrine and the internal standard are eluted in this
208	order with the resolution between these peaks being not less
209	than 1.5.
210	System repeatability: When the test is repeated 6 times
211	with 10 $\mu$ L of the standard solution under the above operating
212	conditions, the relative standard deviation of the ratio of the
213	peak area of midodrine to that of the internal standard is not
214	more than 1.0%.
215	<b>Containers and storage</b> Containers – Tight containers
216	(Moisture-proof packaging).
217	Storage—Light-resistant.
218	Others
219	Related substance A: Refer to it described in Midodrine Hy-
220	drochloride.

- 221 9.01 Add the following to Reference
- 222 Standards (1) section.
- 223 Midodrine Hydrochloride RS

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