

1 **Telmisartan and Hydrochlorothiazide** 2 **Tablets**

3 テルミサルタン・ヒドロクロロチアジド錠

4
5 Telmisartan and Hydrochlorothiazide Tablets
6 contain not less than 95.0% and not more than
7 105.0% of the labeled amount of telmisartan
8 ($C_{33}H_{30}N_4O_2$: 514.62) and hydrochlorothiazide
9 ($C_7H_8ClN_3O_4S_2$: 297.74).

10 **Method of preparation** Prepare as directed under Tab-
11 lets, with Telmisartan and Hydrochlorothiazide.

12 **Identification (1)** Telmisartan—Perform the test with
13 5 μ L each of the sample solution and standard solution
14 obtained in the Assay (1) as directed under Liquid Chro-
15 matography <2.01> according to the following conditions:
16 the retention times of the peaks of telmisartan in the
17 chromatograms obtained from the sample solution and
18 standard solution are the same, and both absorption spec-
19 tra of these peaks exhibit similar intensities of absorption
20 at the same wavelengths.

21 *Operating conditions—*

22 Column, column temperature, mobile phase, and flow
23 rate: Proceed as directed in the operating conditions in the
24 Assay (1).

25 Detector: Photodiode array detector (wavelength: 270
26 nm; spectrum range of measurement: 210 – 400 nm).

27 *System suitability—*

28 System performance: Proceed as directed in the system
29 suitability in the Assay (1).

30 **(2)** Hydrochlorothiazide—Perform the test with 5 μ L
31 each of the sample solution and standard solution obtained
32 in the Assay (2) as directed under Liquid Chromatography
33 <2.01> according to the following conditions: the retention
34 times of the peaks of hydrochlorothiazide in the chroma-
35 tograms obtained from the sample solution and standard
36 solution are the same, and both spectra of these peaks in
37 the chromatograms exhibit similar intensities of absorp-
38 tion at the same wavelengths.

39 *Operating conditions—*

40 Column, column temperature, mobile phase, and flow
41 rate: Proceed as directed in the operating conditions in the
42 Assay (1).

43 Detector: Photodiode array detector (wavelength: 270
44 nm; spectrum range of measurement: 210 – 400 nm).

45 *System suitability—*

46 System performance: Proceed as directed in the system
47 suitability in the Assay (2).

48 **Purity** Related substances—To a quantity of powdered
49 Telmisartan and Hydrochlorothiazide Tablets, equivalent

50 to 12.5 mg of Hydrochlorothiazide, add 40 mL of the dis-
51 solving solution, disperse by sonicating, add the dissolv-
52 ing solution to make exactly 50 mL. Centrifuge this solu-
53 tion, and use the supernatant liquid as the sample solution.
54 Pipet 1 mL of this solution, add the dissolving solution to
55 make exactly 100 mL, and use this solution as the stand-
56 ard solution. Perform the test with exactly 20 μ L each of
57 the sample solution and standard solution as directed un-
58 der Liquid Chromatography <2.01> according to the fol-
59 lowing conditions, and determine each peak area by the
60 automatic integration method: the area of the peak, having
61 the relative retention time of about 0.9 to hydrochlorothi-
62 azide, obtained from the sample solution is not larger than
63 the peak area of hydrochlorothiazide from the standard
64 solution.

65 Dissolving solution: Dissolve 2 g of ammonium dihy-
66 drogen phosphate in 1000 mL of water, and adjust to pH
67 1.8 with phosphoric acid. To 1000 mL of this solution add
68 1000 mL of acetonitrile.

69 *Operating conditions—*

70 Detector: An ultraviolet absorption photometer (wave-
71 length: 270 nm).

72 Column: A stainless steel column 4.0 mm in inside di-
73 ameter and 15 cm in length, packed with octylsilanized
74 silica gel for liquid chromatography (3 μ m in particle di-
75 ameter).

76 Column temperature: A constant temperature of about
77 40°C.

78 Mobile phase A: Dissolve 2 g of ammonium dihydro-
79 gen phosphate in 1000 mL of water, and adjust to pH 3.5
80 with phosphoric acid.

81 Mobile phase B: Acetonitrile.

82 Flowing of mobile phase: Control the gradient by mix-
83 ing the mobile phases A and B as directed in the following
84 table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 8	90 → 50	10 → 50
8 – 12	50	50
12 – 18	50 → 20	50 → 80
18 – 20	20	80

85 Flow rate: 1.0 mL per minute.

86 *System suitability—*

87 Test for required detectability: Pipet 5 mL of the stand-
88 ard solution and add the dissolving solution to make ex-
89 actly 50 mL. Confirm that the peak area of hydrochloro-
90 thiazide obtained with 20 μ L of this solution is equivalent
91 to 7 to 13% of that with 20 μ L of the standard solution.

92 System performance: When the procedure is run with
93 20 μ L of the standard solution under the above operating

94 conditions, the number of theoretical plates and the sym-
95 metry factor of the peak of hydrochlorothiazide are not
96 less than 6000 and not more than 2.0, respectively.

97 System repeatability: When the test is repeated 6 times
98 with 20 μL of the standard solution under the above oper-
99 ating conditions, the relative standard deviation of the
100 peak area of hydrochlorothiazide is not more than 2.0%.

101 **Uniformity of dosage units** <6.02> Perform the test
102 according to the following method: it meets the require-
103 ment of the Content uniformity test.

104 (1) Telmisartan—To 1 tablet of Telmisartan and Hy-
105 drochlorothiazide Tablets add 4V/5 mL of the dissolving
106 solution, disintegrate by sonicating, add the dissolving
107 solution to make exactly V mL so that each mL contains
108 about 1.6 mg of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$). Centrifuge this
109 solution, pipet 5 mL of the supernatant liquid, add the
110 buffer solution to make exactly 25 mL, and use this solu-
111 tion as the sample solution. Proceed as directed in the
112 Assay (1).

$$113 \quad \text{Amount (mg) of telmisartan (C}_{33}\text{H}_{30}\text{N}_4\text{O}_2) \\ 114 \quad = M_S \times A_T / A_S \times V / 50$$

115 M_S : Amount (mg) of telmisartan for assay taken

116 Dissolving solution: Dissolve 2 g of ammonium dihy-
117 drogen phosphate in 1000 mL of water, and adjust to pH
118 1.8 with phosphoric acid. To 1000 mL of this solution add
119 1000 mL of acetonitrile.

120 Buffer solution: Dissolve 2 g of ammonium dihydrogen
121 phosphate in 1000 mL of water, and adjust to pH 1.8 with
122 phosphoric acid.

123 (2) Hydrochlorothiazide—To 1 tablet of Telmisartan
124 and Hydrochlorothiazide Tablets add 4V/5 mL of the dis-
125 solving solution, disintegrate by sonicating, add the dis-
126 solving solution to make exactly V mL so that each mL
127 contains about 0.25 mg of hydrochlorothiazide
128 ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$). Centrifuge this solution, pipet 5 mL of
129 the supernatant liquid, add the buffer solution to make
130 exactly 25 mL, and use this solution as the sample solu-
131 tion. Proceed as directed in the Assay (2).

$$132 \quad \text{Amount (mg) of hydrochlorothiazide (C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2) \\ 133 \quad = M_S \times A_T / A_S \times V / 50$$

134 M_S : Amount (mg) of Hydrochlorothiazide RS taken

135 Dissolving solution: Dissolve 2 g of ammonium dihy-
136 drogen phosphate in 1000 mL of water, and adjust to pH
137 1.8 with phosphoric acid. To 1000 mL of this solution add
138 1000 mL of acetonitrile.

139 Buffer solution: Dissolve 2 g of ammonium dihydrogen
140 phosphate in 1000 mL of water, and adjust to pH 1.8 with
141 phosphoric acid.

142 **Dissolution** <6.10> (1) Telmisartan—When the test is
143 performed at 50 revolutions per minute according to the
144 Paddle method, using 900 mL of 2nd fluid for dissolution
145 test as the dissolution medium, the dissolution rates in 45
146 minutes of a telmisartan 40-mg and hydrochlorothiazide
147 12.5-mg tablet and a telmisartan 80-mg and hydrochloro-
148 thiazide 12.5-mg tablet are not less than 85% and not less
149 than 80%, respectively.

150 Start the test with 1 tablet of Telmisartan and Hydro-
151 chlorothiazide Tablets, withdraw not less than 20 mL of
152 the medium at the specified minute after starting the test,
153 and filter through a membrane filter with a pore size not
154 exceeding 0.45 μm . Discard the first 15 mL or more of the
155 filtrate, pipet V mL of the subsequent filtrate, add the dis-
156 solution medium to make exactly V' mL so that each mL
157 contains about 44 μg of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$), and use
158 this solution as the sample solution. Separately, weigh
159 accurately about 44 mg of telmisartan for assay, previ-
160 ously dried at 105°C for 4 hours, dissolve in 10 mL of a
161 solution of meglumine in methanol (1 in 250), and add
162 methanol to make exactly 50 mL. Pipet 5 mL of this solu-
163 tion, add water to make exactly 100 mL, and use this so-
164 lution as the standard solution. Perform the test with ex-
165 actly 25 μL each of the sample solution and standard solu-
166 tion as directed under Liquid Chromatography <2.01>
167 according to the following conditions, and determine the
168 peak areas, A_T and A_S , of telmisartan in each solution.

169 Dissolution rate (%) with respect to the labeled amount of
170 telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$)

$$171 \quad = M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$$

172 M_S : Amount (mg) of telmisartan for assay taken

173 C : Labeled amount (mg) of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$) in
174 1 tablet

175 *Operating conditions*—

176 Detector, column, column temperature, mobile phase
177 and flow rate: Proceed as directed in the operating condi-
178 tions in the Assay (1).

179 *System suitability*—

180 System performance: When the procedure is run with
181 25 μL of the standard solution under the above operating
182 conditions, the number of theoretical plates and the sym-
183 metry factor of the peak of telmisartan are not less than
184 25,000 and not more than 2.0, respectively.

185 System repeatability: When the test is repeated 6 times
186 with 25 μL of the standard solution under the above oper-
187 ating conditions, the relative standard deviation of the
188 peak area of telmisartan is not more than 2.0%.

189 (2) Hydrochlorothiazide—When the test is performed
190 at 75 revolutions per minute according to the Paddle
191 method, using 900 mL of 2nd fluid for dissolution test as
192 the dissolution medium, the dissolution rate in 45 minutes

193 of Telmisartan and Hydrochlorothiazide Tablets is not less
194 than 80%.

195 Start the test with 1 tablet of Telmisartan and Hydro-
196 chlorothiazide Tablets, withdraw not less than 20 mL of
197 the medium at the specified minute after starting the test,
198 and filter through a membrane filter with a pore size not
199 exceeding 0.45 μm . Discard the first 15 mL or more of the
200 filtrate, pipet V mL of the subsequent filtrate, add the dis-
201 solution medium to make exactly V' mL so that each mL
202 contains about 14 μg of hydrochlorothiazide
203 ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$), and use this solution as the sample solu-
204 tion. Separately, weigh accurately about 14 mg of Hydro-
205 chlorothiazide RS, previously dried at 105°C for 2 hours,
206 and add methanol to make exactly 50 mL. Pipet 5 mL of
207 this solution, add water to make exactly 100 mL, and use
208 this solution as the standard solution. Perform the test
209 with exactly 25 μL each of the sample solution and stand-
210 ard solution as directed under Liquid Chromatography
211 <2.01> according to the following conditions, and deter-
212 mine the peak areas, A_T and A_S , of hydrochlorothiazide in
213 each solution.

214 Dissolution rate (%) with respect to the labeled amount of
215 hydrochlorothiazide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$)

$$216 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$$

217 M_S : Amount (mg) of Hydrochlorothiazide RS taken

218 C : Labeled amount (mg) of hydrochlorothiazide
219 ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$) in 1 tablet

220 *Operating conditions*—

221 Detector, column, column temperature, mobile phase
222 and flow rate: Proceed as directed in the operating condi-
223 tions in the Assay (1).

224 *System suitability*—

225 System performance: When the procedure is run with
226 25 μL of the standard solution under the above operating
227 conditions, the number of theoretical plates and the sym-
228 metry factor of the peak of hydrochlorothiazide are not
229 less than 1000 and not more than 2.0, respectively.

230 System repeatability: When the test is repeated 6 times
231 with 25 μL of the standard solution under the above oper-
232 ating conditions, the relative standard deviation of the
233 peak area of hydrochlorothiazide is not more than 2.0%.

234 **Assay (1)** Telmisartan—Weigh accurately the mass of
235 not less than 20 Telmisartan and Hydrochlorothiazide
236 Tablets, and powder. Weigh accurately a portion of the
237 powder, equivalent to about 80 mg of telmisartan
238 ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$), add 40 mL of the dissolving solution, soni-
239 cate, and add the dissolving solution to make exactly 50
240 mL. Centrifuge this solution, pipet 5 mL of the superna-
241 tant liquid, add the buffer solution to make exactly 25 mL,
242 and use this solution as the sample solution. Separately,

243 weigh accurately about 80 mg of telmisartan for assay,
244 previously dried at 105°C for 4 hours, and add the dis-
245 solving solution to make exactly 50 mL. Pipet 5 mL of
246 this solution, add the buffer solution to make exactly 25
247 mL, and use this solution as the standard solution. Per-
248 form the test with exactly 5 μL each of the sample solu-
249 tion and standard solution as directed under Liquid Chro-
250 matography <2.01> according to the following conditions,
251 and determine the peak areas, A_T and A_S , of telmisartan in
252 each solution.

$$253 \text{ Amount (mg) of telmisartan (C}_{33}\text{H}_{30}\text{N}_4\text{O}_2\text{)} \\ 254 = M_S \times A_T / A_S$$

255 M_S : Amount (mg) of telmisartan for assay taken

256 Dissolving solution: Dissolve 2 g of ammonium dihy-
257 drogen phosphate in 1000 mL of water, and adjust to pH
258 1.8 with phosphoric acid. To 1000 mL of this solution add
259 1000 mL of acetonitrile.

260 Buffer solution: Dissolve 2 g of ammonium dihydrogen
261 phosphate in 1000 mL of water, and adjust to pH 1.8 with
262 phosphoric acid.

263 *Operating conditions*—

264 Detector: An ultraviolet absorption photometer (wave-
265 length: 270 nm).

266 Column: A stainless steel column 3.0 mm in inside di-
267 ameter and 7.5 cm in length, packed with octylsilanized
268 silica gel for liquid chromatography (5 μm in particle di-
269 ameter).

270 Column temperature: A constant temperature of about
271 40°C.

272 Mobile phase A: Dissolve 2 g of ammonium dihydro-
273 gen phosphate in 1000 mL of water, and adjust to pH 3.5
274 with phosphoric acid.

275 Mobile phase B: Acetonitrile.

276 Flowing of the mobile phase: Control the gradient by
277 mixing the mobile phases A and B as directed in the fol-
278 lowing table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2	90	10
2 – 7	90 → 20	10 → 80
7 – 8	20	80

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281 Flow rate: 0.8 mL per minute.

282 *System suitability*—

283 System performance: When the procedure is run with 5
284 μL of the standard solution under the above operating
285 conditions, the number of theoretical plates and the sym-
286 metry factor of the peak of telmisartan are not less than
287 15,000 and not more than 2.0, respectively.

288 System repeatability: When the test is repeated 6 times
289 with 5 μL of the standard solution under the above oper-
290 ating conditions, the relative standard deviation of the
291 peak area of telmisartan is not more than 1.0%.

292 (2) Hydrochlorothiazide—Weigh accurately the mass
293 of not less than 20 Telmisartan and Hydrochlorothiazide
294 Tablets, and powder. Weigh accurately a portion of the
295 powder, equivalent to about 12.5 mg of hydrochlorothia-
296 zide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$), add 40 mL of the dissolving solu-
297 tion, sonicate, and add the dissolving solution to make
298 exactly 50 mL. Centrifuge this solution, pipet 5 mL of the
299 supernatant liquid, add the buffer solution to make exactly
300 25 mL, and use this solution as the sample solution. Sep-
301 arately, weigh accurately about 12.5 mg of Hydrochloro-
302 thiazide RS, previously dried at 105°C for 2 hours, and
303 add the dissolving solution to make exactly 50 mL. Pipet
304 5 mL of this solution, add the buffer solution to make
305 exactly 25 mL, and use this solution as the standard solu-
306 tion. Perform the test with exactly 5 μL each of the sam-
307 ple solution and standard solution as directed under Liq-
308 uid Chromatography <2.01> according to the following
309 conditions, and determine the peak areas, A_T and A_S , of
310 hydrochlorothiazide in each solution.

311 Amount (mg) of hydrochlorothiazide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$)
312 $=M_S \times A_T/A_S$

313 M_S : Amount (mg) of Hydrochlorothiazide RS taken

314 Dissolving solution: Dissolve 2 g of ammonium dihy-
315 drogen phosphate in 1000 mL of water, and adjust to pH
316 1.8 with phosphoric acid. To 1000 mL of this solution add
317 1000 mL of acetonitrile.

318 Buffer solution: Dissolve 2 g of ammonium dihydrogen
319 phosphate in 1000 mL of water, and adjust to pH 1.8 with
320 phosphoric acid.

321 *Operating conditions*—

322 Proceed as directed in the operating conditions in (1).

323 *System suitability*—

324 System performance: When the procedure is run with 5
325 μL of the standard solution under the above operating
326 conditions, the number of theoretical plates and the sym-
327 metry factor of the peak of hydrochlorothiazide are not
328 less than 15,000 and not more than 2.0, respectively.

329 System repeatability: When the test is repeated 6 times
330 with 5 μL of the standard solution under the above oper-
331 ating conditions, the relative standard deviation of the
332 peak area of hydrochlorothiazide is not more than 1.0%.

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