

1 **Telmisartan and Amlodipine Besilate** 2 **Tablets**

3 テルミサルタン・アムロジピンベシル酸塩錠

4
5 Telmisartan and Amlodipine Besilate Tablets con-
6 tain not less than 95.0% and not more than 105.0% of
7 the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$:
8 514.62) and amlodipine besilate ($C_{20}H_{25}ClN_2O_5$.
9 $C_6H_6O_3S$: 567.05)

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

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

20 *Operating conditions* –

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

24 Detector: A photodiode array detector (wavelength: 270
25 nm; measuring range of spectrum: 210 – 400 nm).

26 *System suitability* –

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

29 (2) Perform the test with 5 μ L each of the sample solu-
30 tion and standard solution obtained in the Assay (2) as di-
31 rected under Liquid Chromatography <2.01> according to
32 the following conditions: the retention times of the peaks
33 of amlodipine besilate in the chromatograms obtained from
34 the sample solution and the standard solution are the same,
35 and both spectra of these peaks in the chromatograms ex-
36 hibit similar intensities of absorption at the same wave-
37 lengths.

38 *Operating conditions* –

39 Column, column temperature, mobile phase A, mobile
40 phase B, flowing of mobile phase, and flow rate: Proceed
41 as directed in the operating conditions in the Assay (2).

42 Detector: A photodiode array detector (wavelength: 237
43 nm; measuring range of spectrum: 210 – 400 nm).

44 *System suitability* –

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

47 **Uniformity of dosage unit** <6.02> Perform the test ac-
48 cording to the following method: it meets the requirement
49 of the Content uniformity test.

50 (1) Telmisartan—To 1 tablet of Telmisartan and Am-
51 lodipine Besilate Tablets add $4/5V$ mL of the dissolving so-
52 lution, disintegrate by sonicating, and add the dissolving
53 solution to make exactly V mL so that each mL contains
54 about 1.6 mg of telmisartan ($C_{33}H_{30}N_4O_2$). Centrifuge this
55 solution, pipet 5 mL of the supernatant liquid, add the
56 buffer solution to make exactly 25 mL, and use this solution
57 as the sample solution. Then, proceed as directed in the As-
58 say (1).

$$59 \quad \text{Amount (mg) of telmisartan (C}_{33}\text{H}_{30}\text{N}_4\text{O}_2\text{)} \\ 60 \quad = M_S \times A_T / A_S \times V / 50$$

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

62 Dissolving solution: Dissolve 2 g of ammonium dihydro-
63 gen phosphate in 1000 mL of water, and adjust to pH 1.8
64 with phosphoric acid. To 1000 mL of this solution add 1000
65 mL of acetonitrile.

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

69 (2) Amlodipine Besilate—To 1 tablet of Telmisartan
70 and Amlodipine Besilate Tablets add $4/5V$ mL of the dis-
71 solving solution, disintegrate by sonicating, and add the
72 dissolving solution to make exactly V mL so that each mL
73 contains about 0.138 mg of amlodipine besilate
74 ($C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$). Centrifuge this solution, pipet 5
75 mL of the supernatant liquid, add the buffer solution to
76 make exactly 25 mL, and use this solution as the sample
77 solution. Then, proceed as directed in the Assay (2).

$$78 \quad \text{Amount (mg) of amlodipine besilate} \\ 79 \quad (\text{C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S}) \\ 80 \quad = M_S \times A_T / A_S \times V / 250$$

81 M_S : Amount (mg) of Amlodipine Besilate RS taken, cal-
82 culated on the anhydrous basis

83 Dissolving solution: Dissolve 2 g of ammonium dihydro-
84 gen phosphate in 1000 mL of water, and adjust to pH 1.8
85 with phosphoric acid. To 1000 mL of this solution add 1000
86 mL of acetonitrile.

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

90 **Dissolution** <6.10> (1) Telmisartan—When the test is
91 performed at 50 revolutions per minute according to the
92 Paddle method, using 900 mL of 2nd fluid for dissolution
93 test as the dissolution medium, the dissolution rate in 30
94 minutes of a telmisartan 40-mg and amlodipine besilate
95 6.93-mg tablet is not less than 80%, and that in 45 minutes
96 of a telmisartan 80-mg and amlodipine besilate 6.93-mg
97 tablet is not less than 80%.

98 Start the test with 1 tablet of Telmisartan and Amlodi-
 99 pine Besilate Tablets, withdraw not less than 20 mL of the
 100 medium at the specified minute after starting the test, and
 101 filter through a membrane filter with a pore size not ex-
 102 ceeding 0.45 μm . Discard the first 5 mL or more of the fil-
 103 trate, pipet V mL of the subsequent filtrate, add the disso-
 104 lution medium to make exactly V' mL so that each mL con-
 105 tains about 44 μg of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$), and use this
 106 solution as the sample solution. Separately, weigh accu-
 107 rately about 44 mg of telmisartan for assay, previously
 108 dried at 105°C for 4 hours, dissolve in 10 mL of a solution
 109 of meglumine in methanol (1 in 250), and add methanol to
 110 make exactly 50 mL. Pipet 5 mL of this solution, add water
 111 to make exactly 100 mL, and use this solution as the stand-
 112 ard solution. Perform the test with exactly 25 μL each of
 113 the sample solution and standard solution as directed under
 114 Liquid Chromatography <2.01> according to the following
 115 conditions, and determine the peak areas, A_T and A_S , of
 116 telmisartan in each solution.

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

$$119 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$$

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

121 C : Labeled amount (mg) of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$) in
 122 1 tablet

123 *Operating Conditions* —

124 Detector, column, column temperature, mobile phase A,
 125 mobile phase B, flowing of mobile phase, and flow rate:
 126 Proceed as directed in the operating conditions in the Assay
 127 (1).

128 *System suitability* —

129 System performance: When the procedure is run with 25
 130 μL of the standard solution under the above operating con-
 131 ditions, the number of theoretical plates and the symmetry
 132 factor of the peak of telmisartan are not less than 25,000
 133 and not more than 2.0, respectively.

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

138 (2) Amlodipine Besilate—When the test is performed
 139 at 75 revolutions per minute according to the Basket
 140 method, using 900 mL of 1st fluid for dissolution test as the
 141 dissolution medium, the dissolution rate in 30 minutes of a
 142 telmisartan 40-mg and amlodipine besilate 6.93-mg tablet
 143 is not less than 75%, and that in 45 minutes of a telmisartan
 144 80-mg and amlodipine besilate 6.93-mg tablet is not less
 145 than 80%.

146 Start the test with 1 tablet of Telmisartan and Amlodi-
 147 pine Besilate Tablets, withdraw not less than 20 mL of the
 148 medium at the specified minute after starting the test, and

149 filter through a membrane filter with a pore size not ex-
 150 ceeding 0.45 μm . Discard the first 5 mL or more of the fil-
 151 trate, pipet V mL of the subsequent filtrate, and add the dis-
 152 solution medium to make exactly V' mL so that each mL
 153 contains about 7.7 μg of amlodipine besilate
 154 ($\text{C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S}$). Pipet 2 mL of this solution, add
 155 exactly 2 mL of methanol, and use this solution as the sam-
 156 ple solution. Separately, weigh accurately about 7.5 mg of
 157 Amlodipine Besilate RS (separately determine the water
 158 <2.48> in the same manner as Amlodipine Besilate), and
 159 dissolve in methanol to make exactly 50 mL. Pipet 5 mL of
 160 this solution, and add the dissolution medium to make ex-
 161 actly 100 mL. Pipet 2 mL of this solution, add exactly 2 mL
 162 of methanol, and use this solution as the standard solution.
 163 Perform the test with exactly 50 μL each of the sample so-
 164 lution and standard solution as directed under Liquid Chro-
 165 matography <2.01> according to the following conditions,
 166 and determine the peak areas, A_T and A_S , of amlodipine in
 167 each solution.

168 Dissolution rate (%) with respect to the labeled amount of
 169 amlodipine besilate ($\text{C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S}$)

$$170 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 90$$

171 M_S : Amount (mg) of Amlodipine Besilate RS taken, cal-
 172 culated on the anhydrous basis

173 C : Labeled amount (mg) of amlodipine besilate
 174 ($\text{C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S}$) in 1 tablet

175 *Operating Conditions* —

176 Detector, column, column temperature, mobile phase A,
 177 mobile phase B, flowing of mobile phase, and flow rate:
 178 Proceed as directed in the operating conditions in the Assay
 179 (2).

180 *System suitability* —

181 System performance: When the procedure is run with 50
 182 μL of the standard solution under the above operating
 183 conditions, the number of theoretical plates and the
 184 symmetry factor of the peak of amlodipine are not less than
 185 25,000 and not more than 2.0, respectively.

186 System repeatability: When the test is repeated 6 times
 187 with 50 μL of the standard solution under the above
 188 operating conditions, the relative standard deviation of the
 189 peak area of amlodipine is not more than 2.0%.

190 **Assay (1)** Telmisartan—Weigh accurately the mass of
 191 not less than 20 Telmisartan and Amlodipine Besilate Tab-
 192 lets, and powder. Weigh accurately a portion of the powder,
 193 equivalent to about 80 mg of telmisartan ($\text{C}_{33}\text{H}_{30}\text{N}_4\text{O}_2$), add
 194 40 mL of the dissolving solution, disintegrate by sonicating,
 195 and add the dissolving solution to make exactly 50 mL.
 196 Centrifuge this solution, pipet 5 mL of the supernatant liq-
 197 uid, add the buffer solution to make exactly 25 mL, and use
 198 this solution as the sample solution. Separately, weigh ac-
 199 curately about 80 mg of telmisartan for assay, previously

200 dried at 105°C for 4 hours, add the dissolving solution to
 201 make exactly 50 mL, and use this solution as the telmisar-
 202 tan standard stock solution. Pipet 5 mL of the telmisar-
 203 tan standard stock solution, add the buffer solution to make ex-
 204 actly 25 mL, and use this solution as the standard solution.
 205 Perform the test with exactly 5 μ L each of the sample solu-
 206 tion and standard solution as directed under Liquid Chroma-
 207 tography <2.01> according to the following conditions,
 208 and determine the peak areas, A_T and A_S , of telmisartan in
 209 each solution.

$$210 \quad \text{Amount (mg) of telmisartan (C}_{33}\text{H}_{30}\text{N}_4\text{O}_2\text{)} \\ 211 \quad = M_S \times A_T / A_S$$

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

213 Dissolving solution: Dissolve 2 g of ammonium dihydro-
 214 gen phosphate in 1000 mL of water, and adjust to pH 1.8
 215 with phosphoric acid. To 1000 mL of this solution add 1000
 216 mL of acetonitrile.

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

220 *Operating conditions* –

221 Detector: An ultraviolet absorption photometer (wave-
 222 length: 270 nm).

223 Column: A stainless steel column 3.0 mm in inside di-
 224 ameter and 7.5 cm in length, packed with octylsilanized sil-
 225 ica gel for liquid chromatography (5 μ m in particle diame-
 226 ter).

227 Column temperature: A constant temperature of about
 228 40°C.

229 Mobile phase A: Dissolve 2 g of ammonium dihydrogen
 230 phosphate in 1000 mL of water, and adjust to pH 3.5 with
 231 phosphoric acid.

232 Mobile phase B: Acetonitrile.

233 Flowing of mobile phase: Control the gradient by mixing
 234 the mobile phases A and B as directed in the following table.
 235

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2.0	90	10
2.0 – 7.0	90 → 20	10 → 80
7.0 – 8.0	20	80

236
 237 Flow rate: 0.8 mL per minute.

238 *System suitability* –

239 System performance: To each 5 mL of the telmisartan
 240 standard stock solution and the amlodipine besilate stand-
 241 ard stock solution obtained in (2) add the buffer solution to
 242 make 25 mL. When the procedure is run with 5 μ L of this
 243 solution under the above operating conditions, amlodipine
 244 and telmisartan are eluted in this order with the resolution
 245 between these peaks being not less than 5.

246 System repeatability: When the test is repeated 6 times
 247 with 5 μ L of the standard solution under the above operat-
 248 ing conditions, the relative standard deviation of the peak
 249 area of telmisartan is not more than 1.0%.

250 (2) Amlodipine Besilate—Weigh accurately the mass
 251 of not less than 20 Telmisartan and Amlodipine Besilate
 252 Tablets, and powder. Weigh accurately a portion of the
 253 powder, equivalent to about 6.9 mg of amlodipine besilate
 254 (C₂₀H₂₅ClN₂O₅·C₆H₆O₃S), add 40 mL of the dissolving so-
 255 lution, disintegrate by sonicating, and add the dissolving
 256 solution to make exactly 50 mL. Centrifuge this solution,
 257 pipet 5 mL of the supernatant liquid, add the buffer solution
 258 to make exactly 25 mL, and use this solution as the sample
 259 solution. Separately, weigh accurately about 35 mg of Am-
 260 lodipine Besilate RS (separately determine the water <2.48>
 261 in the same manner as Amlodipine Besilate) and add the
 262 dissolving solution to make exactly 100 mL. Pipet 20 mL
 263 of this solution, add the dissolving solution to make exactly
 264 50 mL, and use this solution as the amlodipine besilate
 265 standard stock solution. Pipet 5 mL of the amlodipine be-
 266 silate standard stock solution, add the buffer solution to
 267 make exactly 25 mL, and use this solution as the standard
 268 solution. Perform the test with exactly 5 μ L each of the
 269 sample solution and standard solution as directed under
 270 Liquid Chromatography <2.01> according to the following
 271 conditions, and determine the peak areas, A_T and A_S , of am-
 272 lodipine in each solution.

$$273 \quad \text{Amount (mg) of amlodipine besilate} \\ 274 \quad (\text{C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S}) \\ 275 \quad = M_S \times A_T / A_S \times 1 / 5$$

276 M_S : Amount (mg) of Amlodipine Besilate RS taken, cal-
 277 culated on the anhydrous basis

278 Dissolving solution: Dissolve 2 g of ammonium dihydro-
 279 gen phosphate in 1000 mL of water, and adjust to pH 1.8
 280 with phosphoric acid. To 1000 mL of this solution add 1000
 281 mL of acetonitrile.

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

285 *Operating conditions* –

286 Detector: An ultraviolet absorption photometer (wave-
 287 length: 237 nm).

288 Column: A stainless steel column 3.0 mm in inside di-
 289 ameter and 7.5 cm in length, packed with octylsilanized sil-
 290 ica gel for liquid chromatography (5 μ m in particle diame-
 291 ter).

292 Column temperature: A constant temperature of about
 293 40°C.

294 Mobile phase A: Dissolve 2 g of ammonium dihydrogen
 295 phosphate in 1000 mL of water, and adjust to pH 3.5 with
 296 phosphoric acid.

297 Mobile phase B: Acetonitrile.
298 Flowing of mobile phase: Control the gradient by mixing
299 the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 2.0	90	10
2.0 – 7.0	90 → 20	10 → 80
7.0 – 8.0	20	80

300

301 Flow rate: 0.8 mL per minute.

302 *System suitability* –

303 System performance: To 5 mL each of the telmisartan
304 standard stock solution obtained in (1) and the amlodipine
305 besilate standard stock solution add the buffer solution to
306 make 25 mL. When the procedure is run with 5 μL of this
307 solution under the above operating conditions, amlodipine
308 and telmisartan are eluted in this order with the resolution
309 between these peaks being not less than 5.

310 System repeatability: When the test is repeated 6 times
311 with 5 μL of the standard solution under the above operat-
312 ing conditions, the relative standard deviation of the peak
313 area of telmisartan is not more than 1.0%.

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