

## 1 Irbesartan and Amlodipine Besilate Tablets

2 イルベサルタン・アムロジピンベシル酸塩錠

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4 Irbesartan and Amlodipine Besilate Tablets contain not  
5 less than 95.0% and not more than 105.0% of the labeled  
6 amount of irbesartan ( $C_{25}H_{28}N_6O$ : 428.53) and amlodipine  
7 besilate ( $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ : 567.05).

8 **Method of preparation** Prepare as directed under Tablets, with  
9 Irbesartan and Amlodipine Besilate.

10 **Identification (1)** Perform the test with 5  $\mu$ L each of the sam-  
11 ple solution and standard solution obtained in the Assay (1) as di-  
12 rected under Liquid Chromatography <2.01> according to the fol-  
13 lowing conditions: the retention time of the peak of irbesartan ob-  
14 tained from the sample solution is the same with that of the prin-  
15 cipal peak obtained from the standard solution, and both absorp-  
16 tion spectra of these peaks exhibit similar intensities of absorption  
17 at the same wavelengths.

18 *Operating conditions* –

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

21 Detector: A photodiode array detector (wavelength: 237 nm,  
22 spectrum range of measurement: 210 – 400 nm).

23 *System suitability* –

24 System performance: Proceed as directed in the system  
25 suitability in the Assay (1).

26 **(2)** Perform the test with 5  $\mu$ L each of the sample solution and  
27 standard solution obtained in the Assay (2) as directed under Liq-  
28 uid Chromatography <2.01> according to the following conditions:  
29 the retention time of the peak of amlodipine obtained from the  
30 sample solution is the same with that of the principal peak ob-  
31 tained from the standard solution and both absorption spectra of  
32 these peaks exhibit similar intensities of absorption at the same  
33 wavelengths.

34 *Operating conditions* –

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

37 Detector: A photodiode array detector (wavelength: 237 nm,  
38 spectrum range of measurement: 210 – 400 nm).

39 *System suitability* –

40 System performance: Proceed as directed in the system  
41 suitability in the Assay (2).

42 **Uniformity of dosage unit** <6.02> **(1)** Irbesartan – Perform  
43 the Mass variation test, or the Content uniformity test according  
44 to the following method: it meets the requirement.

45 To 1 tablet of Irbesartan and Amlodipine Besilate Tablets add 4  
46 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add  
47 16 mL of methanol, shake vigorously until the tablet is disinte-  
48 grated completely, and add the mobile phase to make exactly 100  
49 mL. Pipet  $V$  mL of this solution, add the mobile phase to make  
50 exactly  $V'$  mL so that each mL contains about 1 mg of irbesartan  
51 ( $C_{25}H_{28}N_6O$ ), and filter through a membrane filter with a pore size

52 not exceeding 0.45  $\mu$ m. Discard the first 5 mL of the filtrate, and  
53 use the subsequent filtrate as the sample solution. Then, proceed  
54 as directed under the Assay (1).

$$55 \quad \text{Amount (mg) of irbesartan (C}_{25}\text{H}_{28}\text{N}_6\text{O)} \\ 56 \quad = M_S \times A_T/A_S \times V'/V \times 2$$

57  $M_S$ : Amount (mg) of irbesartan for assay taken, calculated on  
58 the anhydrous basis

59 **(2)** Amlodipine besilate – Perform the test according to the  
60 following method: it meets the requirement of the Content uni-  
61 formity test.

62 To 1 tablet of Irbesartan and Amlodipine Besilate Tablets add 4  
63 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add  
64 16 mL of methanol, shake vigorously until the tablet is disinte-  
65 grated completely, and add the mobile phase to make exactly 100  
66 mL. Pipet  $V$  mL of this solution, add the mobile phase to make  
67 exactly  $V'$  mL so that each mL contains about 69  $\mu$ g of amlodipine  
68 besilate ( $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ ), and filter through a membrane  
69 filter with a pore size not exceeding 0.45  $\mu$ m. Discard the first 5  
70 mL of the filtrate, and use the subsequent filtrate as the sample  
71 solution. Then, proceed as directed under the Assay (2).

$$72 \quad \text{Amount (mg) of amlodipine besilate (C}_{20}\text{H}_{25}\text{ClN}_2\text{O}_5 \cdot \text{C}_6\text{H}_6\text{O}_3\text{S)} \\ 73 \quad = M_S \times A_T/A_S \times V'/V \times 1/5$$

74  $M_S$ : Amount (mg) of Amlodipine Besilate RS taken, calculated  
75 on the anhydrous basis

76 **Dissolution** <6.10> **(1)** Irbesartan – When the test is per-  
77 formed at 50 revolutions per minute according to the Paddle  
78 method, using 900 mL of 2nd fluid for dissolution test as the dis-  
79 solution medium, the dissolution rate in 30 minutes of Irbesartan  
80 and Amlodipine Besilate Tablets is not less than 70%.

81 Start the test with 1 tablet of Irbesartan and Amlodipine Besilate  
82 Tablets, withdraw not less than 15 mL of the medium at the  
83 specified minute after starting the test, and filter through a  
84 membrane filter with a pore size not exceeding 0.45  $\mu$ m. Discard  
85 the first 10 mL of the filtrate, pipet  $V$  mL of the subsequent filtrate,  
86 and add the mobile phase to make exactly  $V'$  mL so that each mL  
87 contains about 0.11 mg of irbesartan ( $C_{25}H_{28}N_6O$ ). Pipet 2 mL of  
88 this solution, add exactly 2 mL of the mobile phase, and use this  
89 solution as the sample solution. Separately, weigh accurately  
90 about 20 mg of Irbesartan for assay (separately determine the  
91 water <2.48> in the same manner as Irbesartan), dissolve in the  
92 mobile phase to make exactly 25 mL, and use this solution as the  
93 irbesartan standard stock solution. Pipet 7 mL of the standard  
94 stock solution, and add the mobile phase to make exactly 50 mL.  
95 Pipet 5 mL of this solution, add exactly 5 mL of the dissolution  
96 medium, and use this solution as the standard solution. Perform  
97 the test with exactly 10  $\mu$ L each of the sample solution and  
98 standard solution as directed under Liquid Chromatography  
99 <2.01> according to the following conditions, and determine the  
100 peak areas,  $A_T$  and  $A_S$ , of irbesartan in each solution.

101 Dissolution rate (%) with respect to the labeled amount of irbesar-  
102 tan ( $C_{25}H_{28}N_6O$ )

$$103 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 504$$

104  $M_S$ : Amount (mg) of Irbesartan for assay taken, calculated on  
105 the anhydrous basis

106  $C$ : Labeled amount (mg) of irbesartan ( $C_{25}H_{28}N_6O$ ) in 1 tablet

107 *Operating Conditions* –

108 Proceed as directed in the operating conditions in the Assay (1).

109 *System suitability* –

110 System performance: To 7 mL of the irbesartan standard stock  
111 solution and 5 mL of the amlodipine besilate standard stock  
112 solution obtained in (2) add the mobile phase to make 50 mL. To  
113 5 mL of this solution add 5 mL of the dissolution medium. When  
114 the procedure is run with 10  $\mu$ L of this solution under the above  
115 operating conditions, amlodipine and irbesartan are eluted in this  
116 order with the resolution between these peaks being not less than  
117 5.

118 System repeatability: When the test is repeated 6 times with 10  
119  $\mu$ L of the standard solution under the above operating conditions,  
120 the relative standard deviation of the peak area of irbesartan is not  
121 more than 2.0%.

122 (2) Amlodipine besilate – When the test is performed at 50  
123 revolutions per minute according to the Paddle method, using 900  
124 mL of 2nd fluid for dissolution test as the dissolution medium, the  
125 dissolution rate in 30 minutes of Irbesartan and Amlodipine  
126 Besilate Tablets is not less than 75%.

127 Start the test with 1 tablet of Irbesartan and Amlodipine Besilate  
128 Tablets, withdraw not less than 15 mL of the medium at the  
129 specified minute after starting the test, and filter through a  
130 membrane filter with a pore size not exceeding 0.45  $\mu$ m. Discard  
131 the first 10 mL of the filtrate, pipet  $V$  mL of the subsequent filtrate,  
132 and add the mobile phase to make exactly  $V'$  mL so that each mL  
133 contains about 7.7  $\mu$ g of amlodipine besilate  
134 ( $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ ). Pipet 2 mL of this solution, add exactly  
135 2 mL of the mobile phase, and use this solution as the sample  
136 solution. Separately, weigh accurately about 26 mg of Amlodipine  
137 Besilate RS (separately determine the water <2.48> in the same  
138 manner as Amlodipine Besilate), dissolve in the mobile phase to  
139 make exactly 50 mL. Pipet 15 mL of this solution, add the mobile  
140 phase to make exactly 100 mL, and use this solution as the  
141 amlodipine besilate standard stock solution. Pipet 5 mL of the  
142 standard stock solution, and add the mobile phase to make exactly  
143 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the  
144 dissolution medium, and use this solution as the standard solution.  
145 Perform the test with exactly 10  $\mu$ L each of the sample solution  
146 and standard solution as directed under Liquid Chromatography  
147 <2.01> according to the following conditions, and determine the  
148 peak areas,  $A_T$  and  $A_S$ , of amlodipine in each solution.

149 Dissolution rate (%) with respect to the labeled amount of amlodi-  
150 pine besilate ( $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ )

$$151 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 27$$

152  $M_S$ : Amount (mg) of Amlodipine Besilate RS taken, calculated  
153 on the anhydrous basis

154  $C$ : Labeled amount (mg) of amlodipine besilate  
155 ( $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ ) in 1 tablet

156 *Operating Conditions* –

157 Proceed as directed in the operating conditions in the Assay (1).

158 *System suitability* –

159 System performance: To 7 mL of the irbesartan standard stock  
160 solution obtained in (1) and 5 mL of the amlodipine besilate  
161 standard stock solution add the mobile phase to make 50 mL. To  
162 5 mL of this solution add 5 mL of the dissolution medium. When  
163 the procedure is run with 10  $\mu$ L of this solution under the above  
164 operating conditions, amlodipine and irbesartan are eluted in this  
165 order with the resolution between these peaks being not less than  
166 5.

167 System repeatability: When the test is repeated 6 times with 10  
168  $\mu$ L of the standard solution under the above operating conditions,  
169 the relative standard deviation of the peak area of amlodipine is  
170 not more than 2.0%.

171 **Assay (1)** Irbesartan – To 10 tablets of Irbesartan and Amlodi-  
172 pine Besilate Tablets add 20 mL of 0.02 mol/L phosphate buffer  
173 (pH 3.0), and sonicate. Add 120 mL of methanol, shake vigorously  
174 until the tablets are disintegrated completely, and add the mobile  
175 phase to make exactly 200 mL. Pipet  $V$  mL of this solution, add  
176 the mobile phase to make exactly  $V'$  mL so that each mL contains  
177 about 1 mg of irbesartan ( $C_{25}H_{28}N_6O$ ), and filter through a mem-  
178 brane filter with a pore size not exceeding 0.45  $\mu$ m. Discard the  
179 first 5 mL of the filtrate, and use the subsequent filtrate as the sam-  
180 ple solution. Separately, weigh accurately about 50 mg of irbesar-  
181 tan for assay (separately determine the water <2.48> in the same  
182 manner as Irbesartan), dissolve in methanol to make exactly 25  
183 mL, and use this solution as the irbesartan standard stock solution.  
184 Pipet 10 mL of the standard stock solution, add 0.02 mol/L phos-  
185 phate buffer (pH 3.0) to make exactly 20 mL, and use this solution  
186 as the standard solution. Perform the test with exactly 5  $\mu$ L each  
187 of the sample solution and standard solution as directed under Liq-  
188 uid Chromatography <2.01> according to the following conditions,  
189 and determine the peak areas,  $A_T$  and  $A_S$ , of irbesartan in each so-  
190 lution.

$$191 \text{ Amount (mg) of irbesartan (} C_{25}H_{28}N_6O \text{) in 1 tablet} \\ 192 = M_S \times A_T / A_S \times V' / V \times 2 / 5$$

193  $M_S$ : Amount (mg) of irbesartan for assay taken, calculated on  
194 the anhydrous basis

195 *Operating conditions* –

196 Detector: An ultraviolet absorption photometer (wavelength:  
197 237 nm).

198 Column: A stainless steel column 3.0 mm in inside diameter and  
199 75 mm in length, packed with octadecylsilanized silica gel for  
200 liquid chromatography (2.2  $\mu$ m in particle diameter).

201 Column temperature: A constant temperature of about 40°C.

202 Mobile phase: A mixture of methanol and 0.02 mol/L phosphate  
203 buffer (pH 3.0) (3:2).

204 Flow rate: Adjust so that the retention time of irbesartan is about  
205 3 minutes.

206 *System suitability* —

207 System performance: To 10 mL of the irbesartan standard stock  
208 solution and 2 mL of the amlodipine besilate standard stock  
209 solution obtained in (2) add 0.02 mol/L phosphate buffer (pH 3.0)  
210 to make 20 mL. When the procedure is run with 5  $\mu$ L of this  
211 solution under the above operating conditions, amlodipine and  
212 irbesartan are eluted in this order with the resolution between these  
213 peaks being not less than 5.

214 System repeatability: When the test is repeated 6 times with 5  
215  $\mu$ L of the standard solution under the above operating conditions,  
216 the relative standard deviation of the peak area of irbesartan is not  
217 more than 1.0%.

218 (2) Amlodipine besilate — To 10 tablets of Irbesartan and Am-  
219 lodipine Besilate Tablets add 20 mL of 0.02 mol/L phosphate  
220 buffer (pH 3.0), and sonicate. Add 120 mL of methanol, shake  
221 vigorously until the tablets are disintegrated completely, and add  
222 the mobile phase to make exactly 200 mL. Pipet  $V$  mL of this so-  
223 lution, add the mobile phase to make exactly  $V'$  mL so that each  
224 mL contains about 69  $\mu$ g of amlodipine besilate  
225 ( $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ ), and filter through a membrane filter  
226 with a pore size not exceeding 0.45  $\mu$ m. Discard the first 5 mL of  
227 the filtrate, and use the subsequent filtrate as the sample solution.  
228 Separately, weigh accurately about 35 mg of Amlodipine Besilate  
229 RS (separately determine the water <2.48> in the same manner as  
230 Amlodipine Besilate), dissolve in methanol to make exactly 50  
231 mL, and use this solution as the amlodipine besilate standard stock  
232 solution. Pipet 2 mL of the standard stock solution, add 0.02 mol/L  
233 phosphate buffer (pH 3.0) to make exactly 20 mL, and use this  
234 solution as the standard solution. Perform the test with exactly 5  
235  $\mu$ L each of the sample solution and standard solution as directed  
236 under Liquid Chromatography <2.01> according to the following  
237 conditions, and determine the peak areas,  $A_T$  and  $A_S$ , of amlodipine  
238 in each solution.

239 Amount (mg) of amlodipine besilate ( $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ ) in  
240 1 tablet

$$241 = M_S \times A_T / A_S \times V' / V \times 1 / 25$$

242  $M_S$ : Amount (mg) of Amlodipine Besilate RS taken, calculated  
243 on the anhydrous basis

244 *Operating conditions* —

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

246 *System suitability* —

247 System performance: To 10 mL of the irbesartan standard stock  
248 solution obtained in (1) and 2 mL of the amlodipine besilate  
249 standard stock solution add 0.02 mol/L phosphate buffer (pH 3.0)  
250 to make 20 mL. When the procedure is run with 5  $\mu$ L of this  
251 solution under the above operating conditions, amlodipine and  
252 irbesartan are eluted in this order with the resolution between these  
253 peaks being not less than 5.

254 System repeatability: When the test is repeated 6 times with 5  
255  $\mu$ L of the standard solution under the above operating conditions,  
256 the relative standard deviation of the peak area of amlodipine is  
257 not more than 1.0%.

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

259 **Add the following to 9.41 Reagents, Test**  
260 **Solutions:**

261 **Irbesartan for assay**  $C_{25}H_{28}N_6O$  [Same as the monograph  
262 Irbesartan]

263