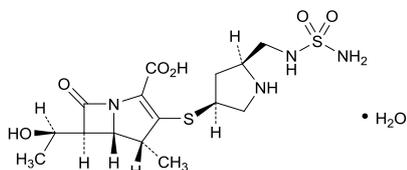


1 Doripenem Hydrate

2 ドリペネム水和物



4 $C_{15}H_{24}N_4O_6S_2 \cdot H_2O$: 438.52

5 (4*R*,5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(3*S*,5*S*-5-

6 [(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl]-1-azabicyclo

7 [3.2.0]hept-2-ene-2-carboxylic acid monohydrate

8 [364622-82-2]

9

10 Doripenem Hydrate contains not less than 970 μg
 11 (potency) and not more than 1020 μg (potency) of
 12 doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50) per mg, calcu-
 13 lated on the anhydrous basis. The potency of Dor-
 14 ipenem Hydrate is expressed as mass (potency) of
 15 doripenem ($C_{15}H_{24}N_4O_6S_2$: 420.50).

16 **Description** Doripenem Hydrate occurs as a white to
 17 pale yellow-brown-white crystalline powder.

18 It is sparingly soluble in water, slightly soluble in
 19 methanol, and practically insoluble in ethanol (99.5).

20 It is gradually colored to pale yellow-brown-white by
 21 light.

22 **Identification (1)** Determine the absorption spectrum
 23 of a solution of Doripenem Hydrate (1 in 50,000) as di-
 24 rected under Ultraviolet-visible Spectrophotometry <2.24>,
 25 and compare the spectrum with the Reference Spectrum
 26 or the spectrum of a solution of Doripenem RS prepared
 27 in the same manner as the sample solution: both spectra
 28 exhibit similar intensities of absorption at the same wave-
 29 lengths.

30 **(2)** Determine the infrared absorption spectrum of
 31 Doripenem Hydrate as directed in the potassium bromide
 32 disk method under Infrared Spectrophotometry <2.25>,
 33 and compare the spectrum with the Reference Spectrum
 34 or the spectrum of Doripenem RS: both spectra exhibit
 35 similar intensities of absorption at the same wave num-
 36 bers.

37 **Optical rotation** <2.49> $[\alpha]_D^{20}$: + 33 – + 38° (0.25 g
 38 calculated on the anhydrous basis, water, 25 mL, 100
 39 mm).

40 **pH** <2.54> Dissolve 0.3 g of Doripenem Hydrate in 30
 41 mL of water: the pH of the solution is between 4.5 and
 42 6.0.

43 **Purity (1)** Clarity and color of solution—Dissolve 0.2
 44 g of Doripenem Hydrate in 20 mL of water, and perform
 45 the test with this solution as directed under Turbidity
 46 Measurement <2.61>: the solution is clear. Perform the test
 47 with this solution according to Method 2 under Methods
 48 for Color Matching <2.65>: the solution is not more col-
 49 ored than Matching Fluid Y4.

50 **(2)** Heavy metals <1.07>—Moisten 1.0 g of Dor-
 51 ipenem Hydrate with sulfuric acid, cover loosely, and heat
 52 gently to carbonize. Then proceed according to Method 2,
 53 and perform the test. Prepare the control solution with 2.0
 54 mL of Standard Lead Solution (not more than 20 ppm).

55 **(3)** Related substances (i) — Dissolve 20 mg of
 56 Doripenem Hydrate in 10 mL of water, and use this solu-
 57 tion as the sample solution. Pipet 1 mL of the sample so-
 58 lution, add water to make exactly 100 mL, and use this
 59 solution as the standard solution. Perform the test with
 60 exactly 20 μL each of the sample solution and standard
 61 solution as directed under Liquid Chromatography <2.01>
 62 according to the following conditions. Determine each
 63 peak area by the automatic integration method: the peak
 64 areas of related substance A, having the relative retention
 65 time of about 2.2 to doripenem, related substance B, hav-
 66 ing the relative retention time of about 2.5, and related
 67 substance C, having the relative retention time of about
 68 3.2, obtained from the sample solution, are not larger than
 69 1/10 times the peak area of doripenem from the standard
 70 solution, and the area of the peak other than doripenem,
 71 the peaks mentioned above and the peak having the rela-
 72 tive retention time of about 2.1, from the sample solution,
 73 is not larger than 1/20 times the peak area of doripenem
 74 from the standard solution. Furthermore, the total area of
 75 the peaks other than doripenem and the peak having the
 76 relative retention time of about 2.1 from the sample solu-
 77 tion is not larger than 1/2 times the peak area of dor-
 78 ipenem from the standard solution.

79 **Operating conditions** —

80 **Detector:** An ultraviolet absorption photometer (wave-
 81 length: 230 nm).

82 **Column:** A stainless steel column 4.6 mm in inside di-
 83 ameter and 15 cm in length, packed with octadecylsi-
 84 lanized silica gel for liquid chromatography (5 μm in par-
 85 ticle diameter).

86 **Column temperature:** A constant temperature of about
 87 30°C.

88 **Mobile phase A:** Dissolve 2.04 g of potassium dihy-
 89 drogen phosphate in water to make 1000 mL, and adjust
 90 to pH 5.6 – 5.7 with a solution prepared by dissolving
 91 2.61 g of potassium dihydrogen phosphate in water to
 92 make 1000 mL. To 970 mL of this solution add 30 mL of
 93 acetonitrile.

94 Mobile phase B: Dissolve 2.04 g of potassium dihydrogen phosphate in water to make 1000 mL, and adjust
95 to pH 5.6 - 5.7 with a solution prepared by dissolving 2.61
96 g of potassium dihydrogen phosphate in water to make
97 1000 mL. To 700 mL of this solution add 300 mL of acetonitrile.

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

102

103

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 15	100	0
15 – 45	100 → 50	0 → 50
45 – 50	50 → 0	50 → 100
50 – 55	0	100

104

105 Flow rate: 1.0 mL per minute.

106 Time span of measurement: For 55 minutes after injection, beginning after the peak having the relative retention
107 time of about 0.2 to doripenem.

108 *System suitability*—

109 Test for required detectability: Pipet 1.5 mL of the
110 standard solution, and add water to make exactly 50 mL.
111 Confirm that the peak area of doripenem obtained with 20
112 μL of this solution is equivalent to 2.1 to 3.9% of that
113 with 20 μL of the standard solution.

114 System performance: When the procedure is run with
115 20 μL of the standard solution under the above operating
116 conditions, the number of theoretical plates and the symmetry factor of the peak of doripenem are not less than
117 5000 and not more than 1.3, respectively.

118 System repeatability: When the test is repeated 3 times
119 with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the
120 peak area of doripenem is not more than 0.95%.

121 (ii) Dissolve 20 mg of Doripenem Hydrate in 10 mL
122 of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add water to make
123 exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the
124 sample solution and standard solution as directed under
125 Liquid Chromatography <2.01> according to the following
126 conditions. Determine each peak area by the automatic
127 integration method: the peak area of related substance D,
128 having the relative retention time of about 0.5 to doripenem, obtained from the sample solution is not larger
129 than 2/5 times the peak area of doripenem from the standard solution.

130 *Operating conditions*—

131 Detector: An ultraviolet absorption photometer (wavelength: 215 nm).

140 Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecyl-strong
141 anion exchange group silanized silica gel for liquid chromatography (5 μm in particle diameter).

142 Column temperature: A constant temperature of about
143 40°C.

144 Mobile phase: To 9 mL of phosphoric acid add 200 mL
145 of water, add 20 mL of triethylamine, and add water to
146 make 2000 mL. Adjust to pH 5.7 – 5.9 with phosphoric
147 acid. To 950 mL of this solution add 50 mL of acetonitrile
148 for liquid chromatography.

149 Flow rate: Adjust so that the retention time of doripenem is about 10 minutes.

150 *System suitability*—

151 Test for required detectability: Pipet 2 mL of the standard solution, and add water to make exactly 20 mL. Confirm that the peak area of doripenem obtained with 20 μL
152 of this solution is equivalent to 7 to 13% of that with 20
153 μL of the standard solution.

154 System performance: To 1 mL of the sample solution
155 add 1 mL of 0.1 mol/L hydrochloric acid TS, allow to
156 stand at $25 \pm 5^\circ\text{C}$ for 15 minutes, and add water to make
157 100 mL. When the procedure is run with 20 μL of this
158 solution under the above operating conditions, related
159 substance D and doripenem are eluted in this order with
160 the resolution between these peaks being not less than 5.
161 The number of theoretical plates and the symmetry factor
162 of the peak of related substance D are not less than 300
163 and 0.7 to 1.3, respectively, and those of the peak of doripenem are not less than 5000 and 0.7 to 1.3, respectively.

164 System repeatability: When the test is repeated 6 times
165 with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the
166 peak area of doripenem is not more than 2.0%.

167 (iii) Dissolve 20 mg of Doripenem Hydrate in 10 mL
168 of water, and use this solution as the sample solution. Pipet 1 mL of the sample solution, add water to make exactly
169 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 μL each of the sample
170 solution and standard solution as directed under Liquid Chromatography <2.01> according to the following
171 conditions. Determine each peak area by the automatic
172 integration method: the areas of the peaks, having the
173 relative retention time of about 1.8, about 2.2 and about
174 2.3 to doripenem, obtained from the sample solution are
175 not larger than 1/20, 7/100 and 1/20 times the peak area of
176 doripenem from the standard solution, respectively.

177 *Operating conditions*—

178 Detector: An ultraviolet absorption photometer (wavelength: 310 nm).

179 Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsi-

192 lanized silica gel for liquid chromatography (3 μm in par-
193 ticle diameter).

194 Column temperature: A constant temperature of about
195 30°C.

196 Mobile phase A: To 11 mL of perchloric acid add water
197 to make 500 mL. To 100 mL of this solution add water to
198 make 1000 mL. To 600 mL of this solution add 100 mL of
199 water, and adjust to pH 1.9 – 2.0 with a solution prepared
200 by adding water to 2.81 g of sodium perchlorate monohy-
201 drate to make 1000 mL. To 900 mL of this solution add
202 100 mL of acetonitrile.

203 Mobile phase B: To 11 mL of perchloric acid add water
204 to make 500 mL. To 100 mL of this solution add water to
205 make 1000 mL. To 600 mL of this solution add 100 mL of
206 water, and adjust to pH 1.9 – 2.0 with a solution prepared
207 by adding water to 2.81 g of sodium perchlorate monohy-
208 drate to make 1000 mL. To 300 mL of this solution add
209 200 mL of acetonitrile.

210 Flowing of mobile phase: Control the gradient by mix-
211 ing the mobile phases A and B as directed in the following
212 table.
213

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 25	100	0
25 – 55	100 → 0	0 → 100
55 – 60	0	100

214
215 Flow rate: 0.8 mL per minute.

216 *System suitability*—

217 Test for required detectability: Pipet 2.5 mL of the
218 standard solution, and add water to make exactly 50 mL.
219 Confirm that the peak area of doripenem obtained with 20
220 μL of this solution is equivalent to 3.5 to 6.5% of that
221 with 20 μL of the standard solution.

222 System performance: When the procedure is run with
223 20 μL of the standard solution under the above operating
224 conditions, the number of theoretical plates and the sym-
225 metry factor of the peak of doripenem are not less than
226 15,000 and not more than 1.3, respectively.

227 System repeatability: When the test is repeated 3 times
228 with 20 μL of the standard solution under the above oper-
229 ating conditions, the relative standard deviation of the
230 peak area of doripenem is not more than 0.95%.

231 **Water** <2.48> 4.0 – 5.0% (0.3 g, volumetric titration,
232 back titration).

233 **Residue on ignition** <2.44> Not more than 0.1% (1 g).

234 **Assay** Weigh accurately amounts of Doripenem Hydrate
235 and Doripenem RS (separately determine the water <2.48>
236 in the same manner as Doripenem Hydrate), equivalent to
237 about 25 mg (potency), dissolve each in water to make

238 exactly 200 mL, and use these solutions as the sample
239 solution and the standard solution, respectively. Perform
240 the test with 10 μL each of the sample solution and stand-
241 ard solution as directed under Liquid Chromatography
242 <2.01> according to the following conditions, and deter-
243 mine the peak areas, A_T and A_S , of doripenem in each so-
244 lution.

$$245 \quad \text{Amount } [\mu\text{g (potency)}] \text{ of doripenem (C}_{15}\text{H}_{24}\text{N}_4\text{O}_6\text{S}_2) \\ 246 \quad = M_S \times A_T / A_S \times 1000$$

247 M_S : Amount [mg (potency)] of Doripenem RS taken,
248 calculated on the anhydrous basis

249 *Operating conditions*—

250 Detector: An ultraviolet absorption photometer (wave-
251 length: 300 nm).

252 Column: A stainless steel column 4.6 mm in inside di-
253 ameter and 15 cm in length, packed with octadecylsi-
254 lanized silica gel for liquid chromatography (5 μm in par-
255 ticle diameter).

256 Column temperature: A constant temperature of about
257 25°C.

258 Mobile phase: Adjust the pH of 90 mL of 0.02 mol/L
259 potassium dihydrogen phosphate to pH 5.6 – 5.7 with a
260 solution prepared by dissolving 3.48 g of dipotassium
261 hydrogen phosphate in water to make 1000 mL. To 100
262 mL of this solution add water to make exactly 1000 mL.
263 To 970 mL of this solution add 30 mL of acetonitrile.

264 Flow rate: Adjust so that the retention time of dor-
265 ipenem is about 15 minutes.

266 *System suitability*—

267 System performance: When the procedure is run with
268 10 μL of the standard solution under the above operating
269 conditions, the number of theoretical plates and the sym-
270 metry factor of the peak of doripenem are not less than
271 5000 and not more than 1.3, respectively.

272 System repeatability: When the test is repeated 6 times
273 with 10 μL of the standard solution under the above oper-
274 ating conditions, the relative standard deviation of the
275 peak area of doripenem is not more than 1.0%.

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

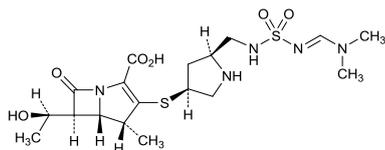
277 Storage— At a temperature between 2°C and 8°C.

278 **Others**

279 Related substance A:

280 (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-[[*N*-[*E*-(Dimethylamino)methyl
281 ene]sulfamoyl]amino)methyl]pyrrolidin-3-ylsulfanyl]-6-
282 (*1R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]
283 hepta-2-ene-2-carboxylic acid

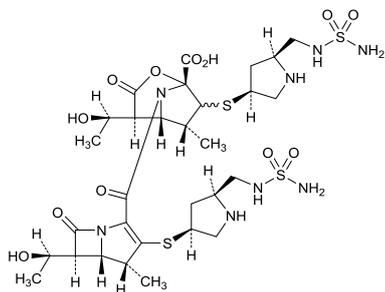
284



285 Related substance B:

286 (1*S*,4*S*,5*S*,6*R*)-4-[(1*R*)-1-Hydroxyethyl]-8-(4*R*,5*S*,6*S*)-6-[(
 287 1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(3*S*,5*S*)-5-[(sulfa
 288 moylamino)methyl]pyrrolidin-3-ylsulfanyl]-1-azabicyclo
 289 3.2.0]hepta-2-ene-2-carbonyl]-6-methyl-3-oxo-7-[(3*S*,5*S*)
 290 -5-[(sulfamoylamino)methyl]pyrrolidin-3-ylsulfanyl]-2-*o*-
 291 xa-8-azabicyclo[3.2.1]octane-1-carboxylic acid

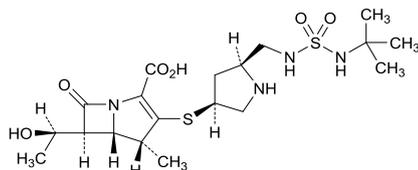
292



293 Related substance C:

294 (4*R*,5*S*,6*S*)-3-[(3*S*,5*S*)-5-[(*N*-(1,1-Dimethylethyl)sulfamo
 295 yl)amino)methyl]pyrrolidin-3-ylsulfanyl]-6-[(1*R*)-1-hydr
 296 oxyeth-
 297 yl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hepta-2-ene-2-carb
 298 oxylic acid

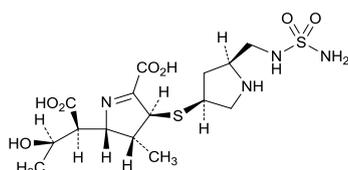
299



300 Related substance D:

301 (2*S*,3*R*,4*S*)-2-[(1*S*,2*R*)-1-Carboxy-2-hydroxypropyl]-3-me
 302 thyl-4-[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]pyrrolidin-3-*y*
 303 lsulfanyl]-3,4-dihydro-2*H*-pyrrole-5-carboxylic acid
 304

305



306

307 **Add the following to 9.01 Reference**308 **Standards (1):**309 **Doripenem RS**

310

311 **Add the following to 9.42 Solid Sup-**312 **ports/Column Packings for Chromatog-**313 **raphy:**314 **Octadecyl-strong anion exchange group silanized**315 **silica gel for liquid chromatography** Prepared for liq-

316 uid chromatography.

317

318

319