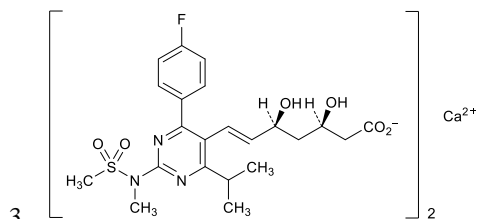


## 1 Rosuvastatin Calcium

2 ロスバスタチンカルシウム



4  $(C_{22}H_{27}FN_3O_6S)_2Ca$ : 1001.14

5 Monocalcium bis[(3*R*,5*S*,6*E*)-7-{4-(4-fluorophenyl)-6-(1-  
6 methylethyl)-2-[methyl(methylsulfonyl) amino]pyrimidin  
7 -5-yl}-3,5-dihydroxyhept-6-enoate]  
8 [147098-20-2]  
9

10 Rosuvastatin Calcium contains not less than 97.0%  
11 and not more than 102.0% of rosuvastatin calcium  
12  $[(C_{22}H_{27}FN_3O_6S)_2Ca]$ , calculated on the anhydrous  
13 basis.

14 **Description** Rosuvastatin Calcium occurs as a white  
15 powder.

16 It is freely soluble in acetonitrile, soluble in methanol,  
17 and slightly soluble in water and in ethanol (99.5).

18 It is hygroscopic.

19 **Identification** (1) Determine the absorption spectrum  
20 of a solution of Rosuvastatin Calcium in methanol (1 in  
21 100,000) as directed under Ultraviolet-visible Spectropho-  
22 tometry <2.24>, and compare the spectrum with the Refer-  
23 ence Spectrum or the spectrum of a solution of Rosuvastatin  
24 Calcium RS prepared in the same manner as the sample so-  
25 lution: both spectra exhibit similar intensities of absorp-  
26 tion at the same wavelengths.

27 (2) Determine the infrared absorption spectrum of  
28 Rosuvastatin Calcium as directed in the potassium bromide  
29 disk method under Infrared Spectrophotometry <2.25>, and  
30 compare the spectrum with the Reference Spectrum or the  
31 spectrum of Rosuvastatin Calcium RS: both spectra exhibit  
32 similar intensities of absorption at the same wave numbers.

33 (3) A solution of Rosuvastatin Calcium in a mixture of  
34 water and methanol (1:1) (1 in 125) responds to Qualitative  
35 Tests <1.09> (3) for calcium salt.

36 **Purity** (1) Inorganic impurities (chloride)—Weigh ac-  
37 curately about 0.15 g of Rosuvastatin Calcium, dissolve in  
38 60 mL of water, add 5 mL of diluted nitric acid (1 in 10),  
39 and titrate <2.50> with 0.01 mol/L silver nitrate VS (poten-  
40 tiometric titration). Perform a blank determination in the  
41 same manner, and make any necessary corrections (not  
42 more than 0.2%).

43 Each mL of 0.01 mol/L silver nitrate VS = 0.3545 mg of Cl

44 (2) Heavy metals <1.07>—Proceed with 1.0 g of Rosu-  
45 vastatin Calcium according to Method 2, and perform the  
46 test. Prepare the control solution with 2.0 mL of Standard  
47 Lead Solution (not more than 20 ppm).

48 (3) Related substances—Conduct this procedure using  
49 light-resistant vessels. Use the sample solution obtained in  
50 the Assay as the sample solution. Separately, pipet 1 mL of  
51 the standard solution obtained in the Assay, add a mixture  
52 of water and acetonitrile (3:1) to make exactly 10 mL. Pipet  
53 1 mL of this solution, add a mixture of water and acetonit-  
54 rile (3:1) to make exactly 50 mL, and use this solution as  
55 the standard solution. Perform the test with exactly 10  $\mu$ L  
56 each of the sample solution and standard solution as di-  
57 rected under Liquid Chromatography <2.01> according to  
58 the following conditions. Determine each peak area of re-  
59 lated substances,  $A_T$ , in the sample solution and the peak  
60 area of rosuvastatin,  $A_S$ , in the standard solution by the au-  
61 tomatic integration method, and calculate the amount of the  
62 related substances by the following equation: the amount of  
63 the related substance A having the relative retention time of  
64 about 0.90 to rosuvastatin is not more than 0.2%, the  
65 amount of the related substance B (diastereomer) having the  
66 relative retention time of about 1.1 is not more than 0.5%,  
67 the amount of the related substance C having the relative  
68 retention time of about 1.5 is not more than 0.7%, the  
69 amount of the related substance D having the relative reten-  
70 tion time of about 1.7 is not more than 0.15%, and each  
71 amount of other related substances is not more than 0.1%.  
72 Furthermore the total amount of the related substances is  
73 not more than 1.1%. For the area of the peak of the related  
74 substance C, multiply the relative response factor 1.4.

75 Amount (%) of related substance  
76 
$$= M_S / M_T \times A_T / A_S \times 1 / 5$$

77  $M_S$ : Amount (mg) of Rosuvastatin Calcium RS taken,  
78 calculated on the anhydrous basis

79  $M_T$ : Amount (mg) of Rosuvastatin Calcium taken, calcu-  
80 lated on the anhydrous basis

81 **Operating conditions**—

82 Detector, column, column temperature, mobile phase,  
83 and flow rate: Proceed as directed in the operating  
84 conditions in the Assay.

85 Time span of measurement: About 2.8 times as long as  
86 the retention time of rosuvastatin, beginning after the  
87 solvent peak.

88 **System suitability**—

89 System performance: Proceed as directed in the system  
90 suitability in the Assay.

91 Test for required detectability: Pipet 5 mL of the standard  
92 solution obtained in the Assay, add 24 mL of acetonitrile,  
93 and add water to make exactly 100 mL. Pipet 1 mL of this  
94 solution, add 24 mL of acetonitrile, and add water to make

95 exactly 100 mL. Confirm that the peak area of rosuvastatin  
96 obtained with 10  $\mu\text{L}$  of this solution is equivalent to 0.025  
97 to 0.075% of that with 10  $\mu\text{L}$  of the standard solution in the  
98 Assay.

99 System repeatability: When the test is repeated 5 times  
100 with 10  $\mu\text{L}$  of the standard solution in the Assay under the  
101 above operating conditions, the relative standard deviation  
102 of the peak area of rosuvastatin is not more than 2.0%.

103 (4) Enantiomer — Dissolve 100 mg of Rosuvastatin  
104 Calcium in a mixture of water and acetonitrile (3:1) to make  
105 exactly 100 mL, and use this solution as the sample solution.  
106 Pipet 1 mL of this solution, add a mixture of water and ac-  
107 etonitrile (3:1) to make exactly 200 mL, and use this solu-  
108 tion as the standard solution. Perform the test with exactly  
109 10  $\mu\text{L}$  each of the sample solution and standard solution as  
110 directed under Liquid Chromatography <2.01> according to  
111 the following conditions, and determine each peak area by  
112 the automatic integration method: the area of related sub-  
113 stance E (enantiomer) having the relative retention time of  
114 about 0.92 to rosuvastatin from the sample solution is not  
115 larger than 1/5 times the peak area of rosuvastatin from the  
116 standard solution.

117 *Operating conditions—*

118 Detector: An ultraviolet absorption photometer  
119 (wavelength: 242 nm).

120 Column: A stainless steel column 4.6 mm in inside  
121 diameter and 15 cm in length, packed with silica gel for  
122 liquid chromatography (5  $\mu\text{m}$  in particle diameter) coated  
123 with cellulose tris(4-methylbenzoate) for liquid  
124 chromatography.

125 Column temperature: A constant temperature of about  
126 35°C.

127 Mobile phase: A mixture of diluted trifluoroacetic acid (1  
128 in 1000) and acetonitrile (3:1).

129 Flow rate: Adjust so that the retention time of  
130 rosuvastatin is 26.5 minutes.

131 Time span of measurement: About 3 times as long as the  
132 retention time of rosuvastatin, beginning after the solvent  
133 peak.

134 *System suitability—*

135 Test for required detectability: Pipet 5 mL of the standard  
136 solution, add a mixture of water and acetonitrile (3:1) to  
137 make exactly 50 mL. Confirm that the peak area of  
138 rosuvastatin obtained with 10  $\mu\text{L}$  of this solution is  
139 equivalent to 7 to 13% of that with the standard solution.

140 System performance: To 5 mg of rosuvastatin enantiomer  
141 add 12 mL of acetonitrile and 10 mL of water, sonicate to  
142 dissolve, and add water to make 50 mL. To 1 mL of this  
143 solution and 6 mL of acetonitrile add 25 mg of Rosuvastatin  
144 Calcium, sonicate to dissolve, and add water to make 25 mL.  
145 When the procedure is run with 10  $\mu\text{L}$  of this solution under  
146 the above operating conditions, rosuvastatin enantiomer

147 and rosuvastatin are eluted in this order with the resolution  
148 between these peaks being not less than 1.5, and the  
149 symmetry factor of the peak of rosuvastatin is 1.0 – 1.5.

150 System repeatability: When the test is repeated 6 times  
151 with 10  $\mu\text{L}$  of the standard solution under the above  
152 operating conditions, the relative standard deviation of the  
153 peak area of rosuvastatin is not more than 2%.

154 **Water** <2.48> Not more than 6% (20 mg, coulometric ti-  
155 tration).

156 **Assay** Conduct this procedure using light-resistant ves-  
157 sels. Weigh accurately about 35 mg each of Rosuvastatin  
158 Calcium and Rosuvastatin Calcium RS (separately deter-  
159 mine the water <2.48> in the same manner as Rosuvastatin  
160 Calcium), dissolve each in a mixture of water and acetonit-  
161 rile (3:1) to make exactly 50 mL, and use these solutions as  
162 the sample solution and the standard solution, respectively.  
163 Perform the test with exactly 10  $\mu\text{L}$  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 rosuvastatin in  
167 each solution.

$$168 \quad \text{Amount (mg) of rosuvastatin calcium} \\ 169 \quad \quad \quad [(\text{C}_{22}\text{H}_{27}\text{FN}_3\text{O}_6\text{S})_2\text{Ca}] \\ 170 \quad \quad \quad = M_S \times A_T / A_S$$

171  $M_S$ : Amount (mg) of Rosuvastatin Calcium RS taken,  
172 calculated on the anhydrous basis

173 *Operating conditions—*

174 Detector: An ultraviolet absorption photometer  
175 (wavelength: 242 nm).

176 Column: A stainless steel column 3 mm in inside  
177 diameter and 15 cm in length, packed with  
178 octadecylsilanized silica gel for liquid chromatography (3  
179  $\mu\text{m}$  in particle diameter).

180 Column temperature: A constant temperature of about  
181 40°C.

182 Mobile phase A: A mixture of water, acetonitrile and  
183 diluted trifluoroacetic acid (1 in 100) (70:29:1).

184 Mobile phase B: A mixture of acetonitrile, water, and  
185 diluted trifluoroacetic acid (1 in 100) (75:24:1).

186 Flowing of mobile phase: Control the gradient by mixing  
187 the mobile phases A and B as directed in the following table.  
188

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 30	100	0
30 – 50	100 → 60	0 → 40
50 – 60	60 → 0	40 → 100
60 – 70	0	100

189 Flow rate: 0.75 mL per minute.  
190

191 *System suitability*—

192 System performance: Dissolve 10 mg of Rosuvastatin  
193 Calcium in 10 mL of a solution of trifluoroacetic acid in  
194 acetonitrile (1 in 100), and allow to stand at 40°C for 1 hour.  
195 After cooling, add 20 mL of water, adjust to pH 6 – 8 with  
196 sodium hydroxide TS, and add water to make 50 mL. To 3  
197 mL of this solution, add water to make 50 mL. When the  
198 procedure is run with 10 µL of this solution under the above  
199 operating conditions, rosuvastatin and the related substance  
200 B (diastereomer) are eluted in this order with the resolution  
201 between these peaks being not less than 2.5, and the  
202 symmetry factor of the peak of rosuvastatin is not more than  
203 1.5.

204 System repeatability: When the test is repeated 5 times  
205 with 10 µL of the standard solution under the above  
206 operating conditions, the relative standard deviation of the  
207 peak area of rosuvastatin is not more than 2.0%.

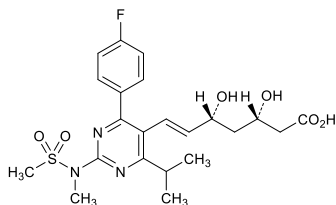
208 **Containers and storage** Containers—Tight containers.

209 Storage—Light-resistant, at a temperature between 2°C  
210 and 8°C.

211 **Others**

212 Rosuvastatin enantiomer:

213 (3*S*,5*R*,6*E*)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-  
214 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-  
215 dihydroxyhept-6-enoic acid

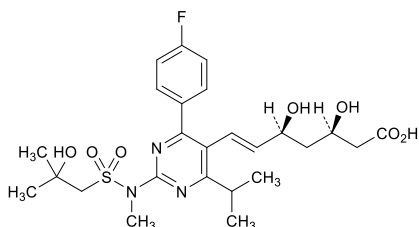


216

217

218 Related substance A:

219 (3*R*,5*S*,6*E*)-7-[4-(4-Fluorophenyl)-2-[[2-hydroxy-2-  
220 methylpropyl)sulfonyl]methylamino]-6-(1-methylethyl)  
221 pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid



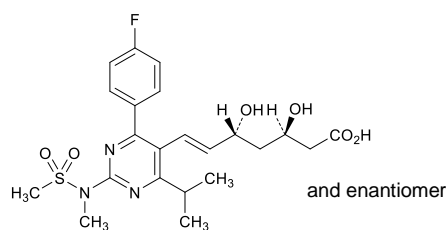
222

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224 Related substance B (diastereomer):

225 (3*RS*,5*RS*,6*E*)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-  
226 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-  
227 dihydroxyhept-6-enoic acid

228

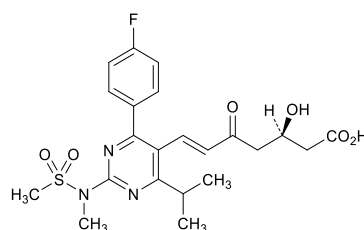


229

230

231 Related substance C:

232 (3*R*,6*E*)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-  
233 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3-hy-  
234 droxy-5-oxohept-6-enoic acid

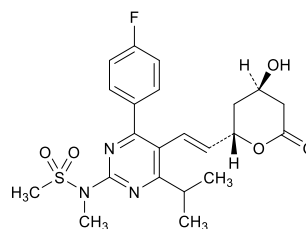


235

236

237 Related substance D:

238 *N*-[4-(4-Fluorophenyl)-5-[(1*E*)-2-[(2*S*,4*R*)-4-hydroxy-6-  
239 oxotetrahydro-2*H*-pyran-2-yl]ethenyl]-6-(1-methylethyl)  
240 pyrimidin-2-yl]-*N*-methylmethanesulfonamide

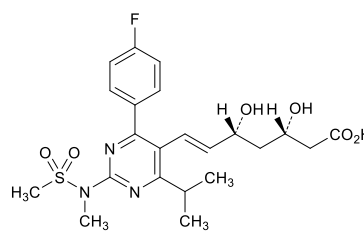


241

242

243 Related substance E (enantiomer):

244 (3*S*,5*R*,6*E*)-7-[4-(4-Fluorophenyl)-6-(1-methylethyl)-2-  
245 [methyl(methylsulfonyl)amino]pyrimidin-5-yl]-3,5-  
246 dihydroxyhept-6-enoic acid



247

248

249 **Add the following to 9.01 Reference**

250 **Standards (1):**

251 **Rosuvastatin Calcium RS**

252 **Add the following to 9.41 Reagents,**

253 **Test Solutions:**

254 **Cellulose tris(4-methylbenzoate) for liquid chroma-**  
255 **tography** Prepared for liquid chromatography.

256 **Rosuvastatin enantiomer**  $C_{22}H_{27}FN_3O_6S$  White  
257 powder.

258 *Identification—(1)* Proceed the test as directed in the  
259 system performance of the system suitability in the Purity  
260 (4) under Rosuvastatin Calcium: the relative retention time  
261 of rosuvastatin enantiomer to rosuvastatin peak is about  
262 0.92.

263 *(2)* Determine the  $^1H$  spectrum of a solution of Rosu-  
264 vastatin enantiomer in deuterated dimethyl sulfoxide for nu-  
265 clear magnetic resonance spectroscopy(3 in 100) as directed  
266 under Nuclear Magnetic Resonance Spectroscopy <2.21>,  
267 using tetramethylsilane for nuclear magnetic resonance  
268 spectroscopy as an internal reference compound: it exhibits  
269 a double triplet signal A at around  $\delta$  1.5 ppm, a multiplet  
270 signal B at around  $\delta$  4.2 ppm, a double doublet signal C at  
271 around  $\delta$  5.5 ppm, a double doublet signal D at around  $\delta$  6.5  
272 ppm, a multiplet signal E at around  $\delta$  7.3 ppm, and a multi-  
273 plet signal F at around  $\delta$  7.7 ppm. The ratio of integrated  
274 intensity of each signal, A:B:C:D:E:F, is about 1:1:1:1:2:2.

275

276