

## 1 Pitavastatin Calcium Orally Disintegrating 2 Tablets

3 ピタバスタチンカルシウム口腔内崩壊錠

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5 Pitavastatin Calcium Orally Disintegrating Tablets  
6 contain not less than 95.0% and not more than  
7 105.0% of the labeled amount of pitavastatin calcium  
8 ( $C_{50}H_{46}CaF_2N_2O_8$ ; 880.98).

9 **Method of preparation** Prepare as directed under Tab-  
10 lets, with Pitavastatin Calcium Hydrate.

11 **Identification** To a quantity of Pitavastatin Calcium  
12 Orally Disintegrating Tablets, equivalent to 4 mg of  
13 pitavastatin calcium ( $C_{50}H_{46}CaF_2N_2O_8$ ) add 10 mL of meth-  
14 anol, shake thoroughly, and centrifuge. To 1 mL of the su-  
15 pernatant liquid add methanol to make 50 mL. Determine  
16 the absorption spectrum of this solution as directed under  
17 Ultraviolet-visible Spectrophotometry <2.24>: it exhibits a  
18 maximum between 243 nm and 247 nm.

19 **Purity** Related substances—Conduct this procedure us-  
20 ing light-resistant vessels. To a quantity of Pitavastatin Cal-  
21 cium Orally Disintegrating Tablets, equivalent to 20 mg of  
22 pitavastatin calcium ( $C_{50}H_{46}CaF_2N_2O_8$ ), add 60 mL of a  
23 mixture of acetonitrile and water (3:2), sonicate to disinte-  
24 grate, add a mixture of acetonitrile and water (3:2) to make  
25 100 mL. Filter this solution through a membrane filter with  
26 a pore size not exceeding 0.45  $\mu\text{m}$ , and use the filtrate as  
27 the sample solution. Perform the test with 10  $\mu\text{L}$  of the sam-  
28 ple solution as directed under Liquid Chromatography  
29 <2.01> according to the following conditions. Determine  
30 each peak area by the automatic integration method, and  
31 calculate the amounts of them by the area percentage  
32 method: the amount of the related substance A having the  
33 relative retention times of about 1.1 to pitavastatin is not  
34 more than 0.5%, the amount of the related substance B hav-  
35 ing the relative retention times of about 1.5 is not more than  
36 0.2%, the amount of the related substance TA having the  
37 relative retention times of about 1.7 is not more than 0.5%,  
38 and the amount of the peak other than pitavastatin and the  
39 peaks mentioned above is not more than 0.1%. Furthermore,  
40 the total amount of the peaks other than pitavastatin is not  
41 more than 2.0%.

42 **Operating conditions**—

43 **Detector:** An ultraviolet absorption photometer  
44 (wavelength: 245 nm).

45 **Column:** A stainless steel column 4.6 mm in inside  
46 diameter and 25 cm in length, packed with  
47 octadecylsilanized silica gel for liquid chromatography (5  
48  $\mu\text{m}$  in particle diameter).

49 **Column temperature:** A constant temperature of about  
50 40°C.

51 **Mobile phase A:** To 10 mL of dilute acetic acid add  
52 water to make 1000 mL. To 800 mL of this solution add  
53 diluted sodium acetate TS (1 in 100) to adjust to pH 3.8.

54 **Mobile phase B:** Acetonitrile for liquid chromatography.

55 **Flowing of mobile phase:** Control the gradient by mixing  
56 the mobile phases A and B as directed in the following table.  
57

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 — 20	60	40
20 — 40	60 → 30	40 → 70
40 — 65	30	70

58 **Flow rate:** Adjust so that the retention time of  
59 pitavastatin is about 23 minutes.

60 **Time span of measurement:** About 2.7 times as long as  
61 the retention time of pitavastatin, beginning after the  
62 solvent peak.

63 **System suitability**—

64 **Test for required detectability:** To 1 mL of the sample  
65 solution, add a mixture of acetonitrile and water (3:2) to  
66 make 100 mL, and use this solution as the solution for  
67 system suitability test. Pipet 5 mL of the solution for system  
68 suitability test, add a mixture of acetonitrile and water (3:2)  
69 to make exactly 50 mL. Confirm that the peak area of  
70 pitavastatin obtained with 10  $\mu\text{L}$  of this solution is  
71 equivalent to 7 to 13% of that with 10  $\mu\text{L}$  of the solution  
72 for system suitability test.

73 **System performance:** When the procedure is run with 10  
74  $\mu\text{L}$  of the solution for system suitability test under the  
75 above operating conditions, the number of theoretical  
76 plates and the symmetry factor of the peak of pitavastatin  
77 are not less than 7500 and not more than 2.0, respectively.

78 **System repeatability:** When the test is repeated 6 times  
79 with 10  $\mu\text{L}$  of the solution for system suitability test under  
80 the above operating conditions, the relative standard  
81 deviation of the peak area of pitavastatin is not more than  
82 2.0%.  
83

84 **Uniformity of dosage units** <6.02> Perform the test ac-  
85 cording to the following method: it meets the requirement  
86 of the Content uniformity test.

87 Conduct this procedure using light-resistant vessels. To  
88 1 tablet of Pitavastatin Calcium Orally Disintegrating Tab-  
89 lets add exactly  $V$  mL of the internal standard solution so  
90 that each mL contains about 0.2 mg of pitavastatin calcium  
91 ( $C_{50}H_{46}CaF_2N_2O_8$ ), and add  $V$  mL of a mixture of acetoni-  
92 trile and water (3:2), and sonicate to disintegrate. Filter this

93 solution through a membrane filter with a pore size not ex-  
94 ceeding 0.45  $\mu\text{m}$ , and use the filtrate as the sample solution.  
95 Then, proceed as directed in the Assay.

96 Amount (mg) of pitavastatin calcium ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ )  
97  $=M_S \times Q_T/Q_S \times V/100 \times 0.812$

98  $M_S$ : Amount (mg) of Pitavastatin Methylbenzylamine  
99 RS taken, calculated on the anhydrous basis

100 *Internal standard solution*—A solution of butyl parahy-  
101 droxybenzoate in a mixture of acetonitrile and water (3:2)  
102 (3 in 10,000).

103 **Disintegration** Being specified separately when the drug  
104 is granted approval based on the Law.

105 **Dissolution** <6.10> When the test is performed at 50 rev-  
106 olutions per minute according to the Paddle method, using  
107 900 mL of 2nd fluid for dissolution test as the dissolution  
108 medium, the dissolution rate in 15 minutes of Pitavastatin  
109 Calcium Orally Disintegrating Tablets is not less than 75%.

110 Conduct this procedure using light-resistant vessels.  
111 Start the test with 1 tablet of Pitavastatin Calcium Orally  
112 Disintegrating Tablets, withdraw not less than 20 mL of the  
113 medium at the specified minute after starting the test, and  
114 filter through a membrane filter with a pore size not ex-  
115 ceeding 0.45  $\mu\text{m}$ . Discard the first 5 mL or more of the fil-  
116 trate, pipet  $V$  mL of the subsequent filtrate, add the disso-  
117 lution medium to make exactly  $V'$  mL so that each mL con-  
118 tains about 0.9  $\mu\text{g}$  of pitavastatin calcium  
119 ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ ), and use this solution as the sample so-  
120 lution. Separately, weigh accurately about 24 mg of  
121 Pitavastatin Methylbenzylamine RS (separately determine  
122 the water <2.48> by coulometric titration using 0.1 g) and  
123 dissolve in a mixture of acetonitrile and water (3:2) to make  
124 exactly 100 mL. Pipet 1 mL of this solution, add the disso-  
125 lution medium to make exactly 200 mL, and use this solu-  
126 tion as the standard solution. Perform the test with exactly  
127 50  $\mu\text{L}$  each of the sample solution and standard solution as  
128 directed under Liquid Chromatography <2.01> according to  
129 the following conditions, and determine the peak areas,  $A_T$   
130 and  $A_S$ , of pitavastatin in each solution.

131 Dissolution rate (%) with respect to the labeled amount of  
132 pitavastatin calcium ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ )

133  $=M_S \times A_T/A_S \times V'/V \times 1/C \times 18/5 \times$   
134  $0.812$

135  $M_S$ : Amount (mg) of Pitavastatin Methylbenzylamine  
136 RS taken, calculated on the anhydrous basis

137  $C$ : Labeled amount (mg) of pitavastatin calcium  
138 ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ ) in 1 tablet

139 *Operating conditions*—

140 Proceed as directed in the operating conditions in the  
141 Assay.

142 *System suitability*—

143 System performance: When the procedure is run with 50  
144  $\mu\text{L}$  of the standard solution under the above operating  
145 conditions, the number of theoretical plates and the  
146 symmetry factor of the peak of pitavastatin are not less than  
147 4500 and not more than 2.0, respectively.

148 System repeatability: When the test is repeated 6 times  
149 with 50  $\mu\text{L}$  of the standard solution under the above  
150 operating conditions, the relative standard deviation of the  
151 peak area of pitavastatin is not more than 1.0%.

152 **Assay** Conduct this procedure using light-resistant ves-  
153 sels. To not less than 20 tablets of Pitavastatin Calcium  
154 Orally Disintegrating Tablets add exactly  $V$  mL of a mix-  
155 ture of acetonitrile and water (3:2) so that each mL contains  
156 about 0.2 mg of pitavastatin calcium ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ ),  
157 and sonicate to disintegrate the tablet. Pipet 5 mL of this  
158 solution, add exactly 5 mL of the internal standard solution,  
159 shake, then filter through a membrane filter with a pore size  
160 not exceeding 0.45  $\mu\text{m}$ , and use the filtrate as the sample  
161 solution. Separately weigh accurately about 24 mg of  
162 Pitavastatin Methylbenzylamine RS (separately determine  
163 the water <2.48> by coulometric titration using 0.1 g), dis-  
164 solve in a mixture of acetonitrile and water (3:2) to make  
165 exactly 100 mL. Pipet 5 mL of this solution, add exactly 5  
166 mL of the internal standard solution, and use this solution  
167 as the standard solution. Perform the test with 10  $\mu\text{L}$  each  
168 of the sample solution and standard solution as directed un-  
169 der Liquid Chromatography <2.01> according to the fol-  
170 lowing conditions, and calculate the ratios,  $Q_T$  and  $Q_S$ , of  
171 the peak area of pitavastatin to that of the internal standard.

172 Amount (mg) of pitavastatin calcium ( $\text{C}_{50}\text{H}_{46}\text{CaF}_2\text{N}_2\text{O}_8$ ) in  
173 1 tablet

174  $=M_S \times Q_T/Q_S \times V/N \times 1/100 \times 0.812$

175  $M_S$ : Amount (mg) of Pitavastatin Methylbenzylamine  
176 RS taken, calculated on the anhydrous basis

177  $N$ : Number of tablets taken

178 *Internal standard solution*—A solution of butyl parahy-  
179 droxybenzoate in a mixture of acetonitrile and water (3:2)  
180 (3 in 10,000).

181 *Operating conditions*—

182 Detector: An ultraviolet absorption photometer  
183 (wavelength: 245 nm).

184 Column: A stainless steel column 4.6 mm in inside  
185 diameter and 25 cm in length, packed with  
186 octadecylsilanized silica gel for liquid chromatography (5  
187  $\mu\text{m}$  in particle diameter).

188 Column temperature: A constant temperature of about  
189 40°C.

190 Mobile phase: To 10 mL of dilute acetic acid add water  
191 to make 1000 mL. To 350 mL of this solution add 650 mL  
192 of methanol, and add 0.29 g of sodium chloride to dissolve.

193 Flow rate: Adjust so that the retention time of  
194 pitavastatin is about 17 minutes.

195 *System suitability*—

196 System performance: When the procedure is run with 10  
197  $\mu\text{L}$  of the standard solution under the above operating  
198 conditions, the internal standard and pitavastatin are eluted  
199 in this order with the resolution between these peaks being  
200 not less than 2.0.

201 System repeatability: When the test is repeated 6 times  
202 with 10  $\mu\text{L}$  of the standard solution under the above  
203 operating conditions, the relative standard deviation of the  
204 ratio of the peak area of pitavastatin to that of the internal  
205 standard is not more than 1.0%.

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

207 Storage—Light-resistant.

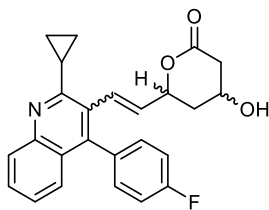
208 **Others**

209 Related substances A and B: Refer to them described in  
210 Pitavastatin Calcium Hydrate.

211 Related substances TA:

212 6-{2-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]

213 ethenyl}-4-hydroxyoxan-2-one



214