

1 Gatifloxacin Ophthalmic Solution

2 ガチフロキサシン点眼液

3

4 Gatifloxacin Ophthalmic Solution is an aqueous
5 ophthalmic preparation.

6 It contains not less than 95.0% and not more than
7 107.0% of the labeled amount of gatifloxacin
8 ($C_{19}H_{22}FN_3O_4$; 375.39).

9 **Method of preparation** Prepare as directed under Oph-
10 thalmic Liquids and Solutions, with Gatifloxacin Hydrate.

11 **Description** Gatifloxacin Ophthalmic Solution is a clear,
12 pale yellow liquid.

13 **Identification** To a volume of Gatifloxacin Ophthalmic
14 Solution, equivalent to 6 mg of Gatifloxacin, add diluted
15 sodium hydroxide TS (1 in 10) to make 30 mL. To 1 mL of
16 this solution add diluted sodium hydroxide TS (1 in 10) to
17 make 20 mL, and determine the absorption spectrum of this
18 solution as directed under Ultraviolet-visible Spectropho-
19 tometry <2.24>: it exhibits maxima between 238 nm and
20 242 nm, between 287 nm and 291 nm, and between 336 nm
21 and 340 nm.

22 **Osmotic pressure ratio** Being specified separately when
23 the drug is granted approval based on the Law.

24 **pH** Being specified separately when the drug is granted
25 approval based on the Law.

26 **Purity** Related substance—To a volume of Gatifloxacin
27 Ophthalmic Solution, equivalent to 6 mg of Gatifloxacin,
28 add the diluting solution to make 30 mL, and use this solu-
29 tion as the sample solution. Pipet 1 mL of the sample solu-
30 tion, add the diluting solution to make exactly 100 mL. Pi-
31 pet 2 mL of this solution, add the diluting solution to make
32 exactly 20 mL, and use this solution as the standard solu-
33 tion. Perform the test with exactly 40 μ L each of the sample
34 solution and standard solution as directed under Liquid
35 Chromatography <2.01> according to the following condi-
36 tions. Determine each peak area by the automatic integra-
37 tion method: the peak area of the related substance A, hav-
38 ing the relative retention time of about 1.2 to gatifloxacin,
39 obtained from the sample solution is not larger than 2 times
40 the peak area of gatifloxacin from the standard solution,
41 and the area of the peak other than gatifloxacin and the peak
42 mentioned above from the sample solution is not larger
43 than the peak area of gatifloxacin from the standard solu-
44 tion. Furthermore, the total area of the peaks other than gat-
45 ifloxacin from the sample solution is not larger than 3 times
46 the peak area of gatifloxacin from the standard solution.

47 Diluting solution: A mixture of diluted phosphoric acid
48 (1 in 1000) and acetonitrile (4:1).

49 **Operating conditions**—

50 Detector: An ultraviolet absorption photometer
51 (wavelength: 325 nm).

52 Column: A stainless steel column 4.6 mm in inside
53 diameter and 15 cm in length, packed with
54 octadecylsilanized silica gel for liquid chromatography (5
55 μ m in particle diameter).

56 Column temperature: A constant temperature of about
57 40°C.

58 Mobile phase A: A mixture of diluted triethylamine (1 in
59 100) and acetonitrile (22:3), adjusted to pH 4.3 with
60 phosphoric acid.

61 Mobile phase B: A mixture of diluted triethylamine (1 in
62 100) and acetonitrile (1:1), adjusted to pH 4.3 with
63 phosphoric acid.

64 Flowing of mobile phase: Control the gradient by mixing
65 the mobile phases A and B as directed in the following table.
66

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 — 15	100	0
15 — 30	100 → 0	0 → 100
30 — 40	0	100

67

68 Flow rate: 0.9 mL per minute (the retention time of
69 gatifloxacin is about 16 minutes).

70 Time span of measurement: For 40 minutes after
71 injection, beginning after the solvent peak.

72 **System suitability**—

73 Test for required detectability: Pipet 5 mL of the
74 standard solution, and add the diluting solution to make
75 exactly 10 mL. Confirm that the peak area of gatifloxacin
76 obtained with 40 μ L of this solution is equivalent to 40 to
77 60% of that with 40 μ L of the standard solution.

78 System performance: Dissolve 20 mg of methyl 4-
79 aminobenzoate in 100 mL of the diluting solution. To 5 mL
80 of this solution and 1 mL of the sample solution add the
81 diluting solution to make 100 mL. When the procedure is
82 run with 40 μ L of this solution under the above operating
83 conditions, gatifloxacin and methyl 4-aminobenzoate are
84 eluted in this order with the resolution between these peaks
85 being not less than 4.

86 System repeatability: When the test is repeated 6 times
87 with 40 μ L of the standard solution under the above
88 operating conditions, the relative standard deviation of the
89 peak area of gatifloxacin is not more than 3.0%.

90 **Foreign insoluble matter** <6.11> It meets the require-
91 ment.

92 **Insoluble particulate matter** <6.08> It meets the re-
93 quirement.

94 **Sterility** <4.06> Perform the test according to the Mem-
95 brane filtration method: it meets the requirement.

96 **Assay** Pipet a volume of Gatifloxacin Ophthalmic Solu-
97 tion, equivalent to 6 mg of Gatifloxacin, and add the dilut-
98 ing solution to make exactly 30 mL. Pipet 2 mL of this so-
99 lution, add exactly 3 mL of the internal standard solution,
100 add the diluting solution to make 20 mL, and use this solu-
101 tion as the sample solution. Separately, weigh accurately
102 about 22 mg of Gatifloxacin RS (separately determine the
103 water <2.48> in the same manner as Gatifloxacin Hydrate),
104 and dissolve in the diluting solution to make exactly 100
105 mL. Pipet 2 mL of this solution, add exactly 3 mL of the
106 internal standard solution, add the diluting solution to make
107 20 mL, and use this solutions as the standard solution. Per-
108 form the test with 20 μ L each of the sample solution and
109 standard solution as directed under Liquid Chromatog-
110 raphy <2.01> according to the following conditions, and
111 calculate the ratios, Q_T and Q_S , of the peak area of gatiflox-
112 acin to that of the internal standard.

$$\begin{aligned} 113 & \text{Amount (mg) of gatifloxacin (C}_{19}\text{H}_{22}\text{FN}_3\text{O}_4\text{)} \\ 114 & = M_S \times Q_T / Q_S \times 3 / 10 \end{aligned}$$

115 M_S : Amount (mg) of Gatifloxacin RS taken, calculated
116 on the anhydrous basis

117 *Internal standard solution*— A solution of methyl 4-amino-
118 benzoate in the diluting solution (1 in 10,000).

119 *Diluting solution*: A mixture of diluted phosphoric acid
120 (1 in 1000) and acetonitrile (4:1).

121 *Operating conditions*—

122 *Detector*: An ultraviolet absorption photometer (wave-
123 length: 280 nm).

124 *Column*: A stainless steel column 4.6 mm in inside di-
125 ameter and 15 cm in length, packed with octadecylsilanized
126 silica gel for liquid chromatography (5 μ m in particle di-
127 ameter).

128 *Column temperature*: A constant temperature of about
129 40°C.

130 *Mobile phase*: A mixture of water, acetonitrile and tri-
131 ethylamine (81:18:1), adjusted to pH 4.5 with phosphoric
132 acid.

133 *Flow rate*: Adjust so that the retention time of
134 gatifloxacin is about 6 minutes.

135 *System suitability*—

136 *System performance*: When the procedure is run with 20
137 μ L of the standard solution under the above operating
138 conditions, gatifloxacin and the internal standard are eluted
139 in this order with the resolution between these peaks being
140 not less than 10.

141 *System repeatability*: When the test is repeated 6 times
142 with 20 μ L of the standard solution under the above
143 operating conditions, the relative standard deviation of the

144 ratio of the peak area of gatifloxacin to that of the internal
145 standard is not more than 1.0%.

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

147 **Others**

148 Related substances A: Refer to it described in Gatifloxacin
149 Hydrate.

150 **Add the following to 9.01 Reference**
151 **Standards (1)**:

152 **Gatifloxacin RS**

153 **Add the following to 9.41 Reagents,**
154 **Test Solutions:**

155 **Methyl 4-aminobenzoate** $\text{H}_2\text{NC}_6\text{H}_4\text{COOCH}_3$ Pale
156 yellow, crystals or crystalline powder.

157 *Melting point* <2.60>: 111 – 114°C

158