

BRIEFING

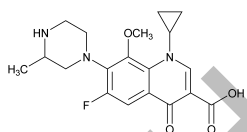
**Gatifloxacin.** This monograph has been posted on the USP Pending Standards Web page for review and public comment for more than 90 days. No comments were received. The MD-AA Expert Committee approved the monograph as an Authorized USP Pending Standard. The HPLC procedures used in the test for *Related compounds* and in the *Assay* are based on analyses performed with the XTerraRP-18 brand of L1 column. The typical retention times for gatifloxacin and gatifloxacin related compound A are about 9.5 minutes and 7 minutes, respectively.

(MD-AA: B. Davani) RTS—C44660

**Add the following:**

■ **Gatifloxacin**

*v.1 Authorized May 23, 2008*



$C_{19}H_{22}FN_3O_4$  375.39

Quinoline-3-carboxylic acid, 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydro, (±).

(±)-1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [112811-59-3].

Sesquihydrate 402.42 [180200-66-2].

Dihydrate 411.42

» Gatifloxacin contains not less than 98.0 percent and not more than 102.0 percent of  $C_{19}H_{22}FN_3O_4$ , calculated on the anhydrous basis.

**Packaging and storage**—Preserve in tight containers, protect from light, and store in a refrigerator.

**Labeling**—Label it to indicate the specific hydrated form.

**USP Reference standards** ⟨11⟩—*USP Gatifloxacin RS*. *USP Gatifloxacin Related Compound A RS*.

**Identification**—

**A:** *Infrared Absorption* ⟨197K⟩.

**B:** The retention time of the major peak for gatifloxacin in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**Water, Method I** ⟨921⟩: between 7.5% and 10.0% if labeled as dihydrate.

**Residue on ignition** ⟨281⟩: not more than 0.1%.

**Heavy metals, Method II** ⟨231⟩: 0.002%.

**Related compounds**—[NOTE—Protect solutions of gatifloxacin from light.]

*Buffer solution, Solution A, Solution B, and Diluent*—Prepare as directed in the *Assay*.

*Mobile phase*—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*.

*Standard stock solution 1*—Dissolve an accurately weighed quantity of USP Gatifloxacin RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to obtain a solution containing about 0.2 mg per mL. Dilute an aliquot of this solution with water to obtain a solution containing a known concentration of about 0.004 mg per mL.

*Standard stock solution 2*—Dissolve an accurately weighed quantity of USP Gatifloxacin Related Compound A RS in acetonitrile (about 10% final volume) using a sonicator, and dilute with water to obtain a solution containing a known concentration of about 0.2 mg per mL. Dilute an aliquot of this solution with water to obtain a solution containing a known concentration of about 0.004 mg per mL.

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*Standard solution*—Transfer 5 mL each of *Standard stock solution 1* and *Standard stock solution 2* to a 20-mL volumetric flask, and dilute with *Diluent* to volume. This solution contains about 0.001 mg per mL each of gatifloxacin and gatifloxacin related compound A.

*Test solution*—Dissolve an accurately weighed quantity of Gatifloxacin in acetonitrile (about 10% final volume) using a sonicator, and dilute quantitatively with water to obtain a solution containing a known concentration of about 1 mg per mL.

*Chromatographic system* (see *Chromatography* <621>)—Proceed as directed in the *Assay*, except that a liquid chromatograph with either a programmable variable wavelength detector or dual detectors capable of monitoring at 240 nm and 285 nm is used. The chromatograph is programmed as follows.

Time (minutes)	<i>Solution A</i> (%)	<i>Solution B</i> (%)	Elution
0–8	100	0	isocratic
8–30	100→0	0→100	linear gradient
30–30.1	0→100	100→0	step gradient
30.1–35	100	0	re-equilibration

Chromatograph the *Standard solution*, and record the peak responses for gatifloxacin and gatifloxacin related compound A at 285 nm and 240 nm, respectively. The resolution, *R*, between gatifloxacin and gatifloxacin related compound A at 285 nm is not less than 4.5; and the relative standard deviation for replicate injections for gatifloxacin related compound A peak is not more than 10.0%.

*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the major peaks. Identify the peaks using the relative retention times as shown in *Table 1*. Calculate the

percentage of all the related compounds, except gatifloxacin related compound A, gatifloxacin related compound B, and gatifloxacin related compound C, in the portion of Gatifloxacin taken by the formula:

$$100(C_s/C_T)(r_U/r_s)$$

in which *C<sub>s</sub>* is the concentration, in mg per mL, of USP Gatifloxacin RS in the *Standard solution*; *C<sub>T</sub>* is the concentration, in mg per mL, of Gatifloxacin in the *Test solution*; *r<sub>U</sub>* is the peak response for each related compound; and *r<sub>s</sub>* is the peak response for gatifloxacin obtained from the *Standard solution*, all monitored at 285 nm. Calculate the percentage of gatifloxacin related compound A, gatifloxacin related compound B, and gatifloxacin related compound C in the portion of Gatifloxacin taken by the formula:

$$100(1/F)(C_s/C_T)(r_U/r_s)$$

in which *F* is the relative response factor provided in *Table 1*; *C<sub>s</sub>* is the concentration, in mg per mL, of USP Gatifloxacin Related Compound A RS in the *Standard solution*; *C<sub>T</sub>* is the concentration, in mg per mL, of Gatifloxacin in the *Test solution*; *r<sub>U</sub>* is the peak response for each related compound obtained from the *Test solution*; and *r<sub>s</sub>* is the peak response of gatifloxacin related compound A obtained from the *Standard solution*, all monitored at 240 nm. The limits of impurities meet the requirements specified in *Table 1*.

**Assay**—

*Buffer solution*—Dissolve 6.6 mL of a 40% tetrabutylammonium hydroxide solution in water and 6.6 g of dibasic ammonium phosphate in about 500 mL of water, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 9.5, mix, and filter.

Table 1

Component	Relative Retention Time (approx.)	Relative Retention Factor (F)	Wavelength (nm)	Limit (%)
Gatifloxacin	1.0	1.0	285	—
Gatifloxacin related compound A <sup>1</sup>	0.75	1.0 (vs gatifloxacin related compound A)	240	0.15
Gatifloxacin related compound B <sup>2</sup>	1.3	2.1 (vs gatifloxacin related compound A)	240	0.10
Gatifloxacin related compound C <sup>3</sup>	2.1	1.3 (vs gatifloxacin related compound A)	240	0.10
Gatifloxacin related compound D <sup>4</sup>	0.6	1 (vs gatifloxacin)	285	0.15
Gatifloxacin related compound E <sup>5</sup>	0.88	1 (vs gatifloxacin)	285	0.15
Any other impurity	—	1 (vs gatifloxacin)	285	0.10
Total impurities	—	—	240 and 285	0.80

<sup>1</sup> 1-Cyclopropyl-6-fluoro-8-hydroxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

<sup>2</sup> 1-Cyclopropyl-6,7-difluoro-8-hydroxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

<sup>3</sup> 1-Cyclopropyl-6,7-difluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

<sup>4</sup> 1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid.

<sup>5</sup> 1-Cyclopropyl-6-fluoro-8-methoxy-7-(2-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

*Solution A*—Prepare a mixture of *Buffer solution* and acetonitrile (86 : 14).

*Solution B*—Prepare a mixture of *Buffer solution*, acetonitrile, and methanol (70 : 20 : 10).

*Mobile phase*—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

*Diluent*—Prepare a mixture of water and acetonitrile (90 : 10).

*Resolution solution*—Dissolve an accurately weighed quantity of USP Gatifloxacin RS and USP Gatifloxacin Related Compound A RS in *Diluent* to obtain a solution containing about 1 mg per mL of each component. Dilute an aliquot of this solution with water to obtain a solution containing about 0.1 mg per mL of each component.

*Standard preparation*—Dissolve an accurately weighed quantity of USP Gatifloxacin RS in acetonitrile (about 10% final volume) using a sonicator, and dilute quantitatively with

water to obtain a solution containing a known concentration of about 0.2 mg per mL. Dilute an aliquot of this solution with *Diluent* to obtain a solution containing a known concentration of about 0.02 mg per mL.

*Assay preparation*—Dissolve an accurately weighed quantity of Gatifloxacin in acetonitrile (about 10% final volume) using a sonicator, and dilute quantitatively with water to obtain a solution containing about 0.2 mg per mL. Dilute an aliquot of this solution with *Diluent* to obtain a solution containing about 0.02 mg per mL.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains 5-μm packing

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L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 38°. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0–8	100	0	isocratic
8–15	100→70	0→30	linear gradient
15–15.1	70→100	30→0	step gradient
15.1–20	100	0	re-equilibration

Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between gatifloxacin and gatifloxacin related compound A is not less than 4.5. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percentage, of C<sub>19</sub>H<sub>22</sub>FN<sub>3</sub>O<sub>4</sub> in the portion of Gatifloxacin taken by the formula:

$$100(C_s / C_u)(r_u / r_s)$$

in which *C<sub>s</sub>* and *C<sub>u</sub>* are the concentrations, in mg per mL, of gatifloxacin in the *Standard preparation* and the *Assay preparation*, respectively; and *r<sub>u</sub>* and *r<sub>s</sub>* are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■