Moxifloxacin Hydrochloride

Type of Posting	Revision Bulletin
Posting Date	28–Jul–2017
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Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Moxifloxacin Hydrochloride monograph. The purpose of the revision is to widen the limit for Moxifloxacin Related Compound G in *Enantiomeric Purity* test to accommodate products approved by the FDA.

The acceptance criterion in the test for *Enantiomeric Purity* is revised from NMT 0.10% to NMT 0.15%.

Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Moxifloxacin Hydrochloride Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in to the *First Supplement* to *USP 41–NF 36*.
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Should you have any questions, please contact Shankari Shivaprasad, Ph.D. Senior Scientific Liaison (301-230-7426 or sns@usp.org).

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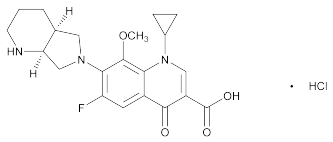
Moxifloxacin Hydrochloride



$C_{21}H_{24}FN_3O_4 \cdot HCl$ 437.89

(4a*S*-*cis*)-1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)-4-oxo-3-quinolinecarboxylic acid, monohydrochloride;

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride [186826-86-8].

DEFINITION

Moxifloxacin Hydrochloride contains NLT 98.0% and NMT 102.0% of moxifloxacin hydrochloride ($C_{21}H_{24}FN_3O_4 \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General** ⟨191⟩**,** *Chloride*
  Sample solution: To a solution (1 in 160) add diluted nitric acid, and filter.
  Acceptance criteria: Meets the requirements

ASSAY

Change to read:

- **Procedure**
  Buffer: Dissolve 0.5 g of tetrabutylammonium hydrogen sulfate and 1.0 g of monobasic potassium phosphate in water, add 2 mL of phosphoric acid, dilute with water to 1000 mL, mix, and pass through a filter of 0.45-µm pore size.
  Mobile phase: Methanol and *Buffer* (28:72)
  Diluent: Add 20 mg of anhydrous sodium sulfite to 1000 mL of *Buffer*, mix gently, and pass through a filter of 0.45-µm pore size.
  System suitability solution: 0.1 mg/mL of USP Moxifloxacin Hydrochloride RS and 1 µg/mL of USP Moxifloxacin Related Compound A RS, in *Diluent*
  Standard solution: 0.1 mg/mL of USP Moxifloxacin Hydrochloride RS in *Diluent*
  Sample solution: 0.1 mg/mL of Moxifloxacin Hydrochloride in *Diluent*
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 293 nm
  Column: 4.0-mm × 25-cm; 5-µm packing L11
  Column temperature: 45°
  Flow rate: 0.9 mL/min
  Injection volume: 25 µL
  System suitability
  Samples: *System suitability solution* and *Standard solution*
  [NOTE—The relative retention times for moxifloxacin and moxifloxacin related compound A are about 1.0 and 1.2, respectively.]
  Suitability requirements
  Resolution: NLT 1.5 between moxifloxacin and moxifloxacin related compound A, *System suitability solution*
  ▲▲*USP40*
  Tailing factor: NMT 2.0, *Standard solution*
  Relative standard deviation: ▲NMT 0.73%,▲*USP40* *Standard solution*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of moxifloxacin hydrochloride ($C_{21}H_{24}FN_3O_4 \cdot HCl$) in the portion of Moxifloxacin Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Moxifloxacin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Moxifloxacin Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition** ⟨281⟩**:** NMT 0.1%
- **Chloride and Sulfate** ⟨221⟩**,** *Sulfate*
  Sample: 0.6 g
  Acceptance criteria: 0.04%; the *Sample* shows no more sulfate than corresponds to 0.25 mL of 0.020 N sulfuric acid.

Change to read:

- **Organic Impurities**
  ▲Protect all solutions containing moxifloxacin from light.
  ▲*USP40*
  Mobile phase, Diluent, System suitability solution, and **Sample solution:** Prepare as directed in the *Assay*.
  Standard solution: 2 µg/mL of USP Moxifloxacin Hydrochloride RS in *Diluent*
  Sensitivity solution: 0.05 µg/mL of USP Moxifloxacin Hydrochloride RS from the *Standard solution* in *Diluent*. Store the *Sensitivity solution* under refrigeration and protected from light.
  Chromatographic system: Proceed as directed in the *Assay* with a run time of two times the retention time of moxifloxacin.
  System suitability
  Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
  Suitability requirements
  Resolution: NLT 1.5 between moxifloxacin and moxifloxacin related compound A, *System suitability solution*
  ▲▲*USP40*
  Tailing factor: NMT 2.0, *Standard solution*
  Relative standard deviation: NMT 2.0%, ▲▲*USP40* *Standard solution*
  Signal-to-noise ratio: NLT 10, *Sensitivity solution*
  Analysis
  Samples: *Sample solution* and *Standard solution*
  Calculate the percentage of each impurity in the portion of Moxifloxacin Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of moxifloxacin from the *Standard solution*
C_S = concentration of USP Moxifloxacin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Moxifloxacin Hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Moxifloxacin	1.0	—	—
Moxifloxacin related compound A[a]	1.15	1.0	0.1
▲Moxifloxacin related compound B▲*USP40*[b]	1.32	0.71	0.1
▲Moxifloxacin related compound C▲*USP40*[c]	1.48	1.0	0.1
▲Moxifloxacin related compound D▲*USP40*[d]	1.71	1.0	0.1
▲Moxifloxacin related compound E▲*USP40*[e]	1.83	0.29	0.1
Other individual impurity	—	1.0	0.1
Total impurities	—	—	0.5

[a] 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
[b] 1-Cyclopropyl-6,8-dimethoxy-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
[c] 1-Cyclopropyl-8-ethoxy-6-fluoro-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
[d] 1-Cyclopropyl-8-fluoro-6-methoxy-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
[e] 1-Cyclopropyl-6-fluoro-8-hydroxy-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.

Change to read:

▲• **ENANTIOMERIC PURITY**
Protect all solutions containing moxifloxacin from light.
Buffer: 0.47 g/L of anhydrous cupric sulfate and 1.31 g/L of L-isoleucine in water. Adjust with 0.1 N sodium hydroxide to a pH of 4.50.
Solution A: Methanol and *Buffer* (500:1500)
Solution B: Methanol and *Buffer* (225:450)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
50	100	0
51	0	100
61	0	100
62	100	0
85	100	0

System suitability solution: 8 mg/mL of USP Moxifloxacin Hydrochloride RS and 8 µg/mL of USP Moxifloxacin Related Compound G RS in *Solution A*
Sensitivity solution: 0.8 µg/mL of USP Moxifloxacin Related Compound G RS in *Solution A*
Sample solution: 8 mg/mL of Moxifloxacin Hydrochloride in *Solution A*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 295 nm
Column: 3.0-mm × 15-cm; 3-µm packing L1
Flow rate: 0.42 mL/min
Injection volume: 1.5 µL
System suitability
Samples: *System suitability solution* and *Sensitivity solution*
[NOTE—The relative retention times for moxifloxacin related compound G and moxifloxacin are 0.78 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between moxifloxacin related compound G and moxifloxacin, *System suitability solution*
Signal-to-noise ratio: NLT 5, *Sensitivity solution*
Analysis
Sample: *Sample solution*
Calculate the percentage of moxifloxacin related compound G in the portion of Moxifloxacin Hydrochloride taken:

$$\text{Result} = [r_U/(r_S + r_U)] \times 100$$

r_U = peak response of moxifloxacin related compound G from the *Sample solution*
r_S = peak response of moxifloxacin from the *Sample solution*

Acceptance criteria: •NMT 0.15%• (RB 1-Aug-2017)
▲*USP40*

SPECIFIC TESTS

Delete the following:

▲• **OPTICAL ROTATION,** *Specific Rotation* ⟨**781S**⟩
Sample: 10 mg/mL in acetonitrile and water (1:1)
Acceptance criteria: –125° to –138° at 20°
▲*USP40*

• **MICROBIAL ENUMERATION TESTS** ⟨**61**⟩ and **TESTS FOR SPECIFIED MICROORGANISMS** ⟨**62**⟩
Total aerobic microbial count: NMT 10^3 cfu/g
Total combined molds and yeasts count: NMT 10^2 cfu/g

• **pH** ⟨**791**⟩
Sample solution: 2 mg/mL
Acceptance criteria: 3.9–4.6

• **WATER DETERMINATION** ⟨**921**⟩**,** *Method I, Method Ia***:** NMT 4.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers. Store at room temperature.

Change to read:

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Moxifloxacin Hydrochloride RS
USP Moxifloxacin Related Compound A RS
1-Cyclopropyl-6,8-difluoro-1,4-dihydro-7-[(4a*S*,7a*S*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid.
$C_{20}H_{21}F_2N_3O_3$ 389.40

▲USP Moxifloxacin Related Compound G RS
1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-[(4a*R*,7a*R*)-octahydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl]-4-oxo-3-quinolinecarboxylic acid, monohydrochloride.

$C_{21}H_{24}FN_3O_4 \cdot HCl$ 437.89▲*USP40*