MOXIFLOXACIN HYDROCHLORIDE
(MOXIFLOXACINI HYDROCHLORIDUM)
Draft proposal for The International Pharmacopoeia
(January 2018)

应你有任何关于这份草案的评论，请寄送至 Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; 电子邮件: schmidht@who.int 16 March 2018.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/16.651:
Moxifloxacin hydrochloride (Moxifloxacini hydrochloridum)

<table>
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<td>Drafting of the monograph.</td>
<td>March 2016</td>
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<td>Laboratory investigations to verify and validate the analytical provision.</td>
<td>March 2016–October 2017</td>
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<td>Discussion at informal consultation on quality control laboratory tools and specifications for medicines</td>
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<td>Discussion at informal consultation on quality control laboratory tools and specifications for medicines</td>
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MOXIFLOXACIN HYDROCHLORIDE
MOXIFLOXACINI HYDROC\text{HLORIDUM}

\[\text{Note from the Secretariat.} \] The proposed monograph is based on information found in Ph.Eur. 8.0, Pharmeuropa 29.3, USP 39 and the Indian Pharmacopoeia 2014, in the scientific literature, submitted by pharmaceutical manufacturers and on laboratory investigations performed by a WHO Collaborating Centre and a collaborating laboratory. The monograph is proposed for inclusion in The International Pharmacopoeia.

Molecular formula. \( \text{C}_{21}\text{H}_{25}\text{ClF}N_3\text{O}_4\text{H}_2\text{O} \)

Relative molecular mass. 455.9.

Graphic formula

![Graphic formula](image)

Chemical name. 1-Cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid hydrochloride monohydrate; CAS Reg. No. 192927-63-2 (monohydrate).

Description. A light yellow or yellow powder or crystals.

Solubility. Sparingly soluble in water R, slightly soluble in ethanol (~760 g/L) TS, practically insoluble in acetone R.

Category. Antibacterial, antituberculosis.

Storage. Moxifloxacin hydrochloride should be kept in tightly closed containers, protected from light.

Labelling. The designation on the container of Moxifloxacin hydrochloride should state the substance is in the form of the monohydrate.

Additional information. Moxifloxacin hydrochloride may exhibit polymorphism.
Requirements

Definition. Moxifloxacin hydrochloride contains not less than 98.0% and not more than 102.0% (“Assay”, method A) or not less than 99.0% and not more than 101.0% (“Assay”, method B) of C$_{21}$H$_{25}$ClFN$_3$O$_4$, calculated with reference to the anhydrous substance.

Manufacture. The production method is validated to demonstrate the satisfactory enantiomeric purity of the final product.

Identity tests

- Either tests A, C and D or tests B, C and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from moxifloxacin hydrochloride RS or the reference spectrum of moxifloxacin hydrochloride.

If the spectra thus obtained are not concordant repeat the test using the residues obtained by separately dissolving the test substance and moxifloxacin hydrochloride RS in a small amount of methanol R and evaporating to dryness. The infrared absorption spectrum is concordant with the spectrum obtained from moxifloxacin hydrochloride RS.

B. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R6 as the coating substance and a mixture of 4 volumes of 1-butanol R, 4 volumes of methanol R and 2 volumes of ammonia (~100 g/L) TS as the mobile phase. Apply separately to the plate 10 µL of each of the following two solutions. For solution (A) dissolve a quantity of the test substance in methanol R to give a solution containing 1 mg of the test substance per mL. Dilute a portion of the solution with methanol R to give a solution containing 0.05 mg of the test substance per mL. For solution (B) use an approximately 0.05 mg/mL solution of moxifloxacin hydrochloride RS in methanol R.

Develop the plate for a distance of 15 cm. After removing the plate from the chromatographic chamber allow it to dry in air or in a current of air. Examine the chromatogram under ultraviolet light (366 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to moxifloxacin in the chromatogram obtained with solution (B).

C. Prepare a solution of 50 mg of the test substance in 5 mL of water R, add 1 mL of nitric acid (~130 g/L) TS, mix, allow to stand for 5 minutes and filter. The filtrate yields reaction A described under 2.1 General identification tests as characteristic of chlorides.

D. Determine the specific optical rotation (1.4) using a solution of 0.200 g in 20.0 mL of a mixture of equal volumes of acetonitrile R and water R. Calculate with reference to the anhydrous substance; the specific optical rotation is between -125 to -138.
Clarity and colour of solution. Dissolve 1.0 g of the test substance in 20 mL of sodium hydroxide (~85 g/L) TS. The solution is not more intensely coloured than reference solution GY2 (1.11.2, Method II).

pH value (1.13). pH of a 2 mg/mL solution in carbon-dioxide-free water R, 3.9 to 4.6.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, method A, using about 0.2 g of the substance, 30 mL anhydrous methanol and 3 minutes stirring before titration starts; the water content is not more than 45 mg/g.

Sulfated ash (2.3). Not more than 1.0 mg/g, determined on 1.0 g in a platinum crucible.

Related substances. Perform the test in subdued light, preferably using low-actinic glassware.

Carry out the tests as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4.6 mm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenylsilyl groups (5 µm).¹

Use the following mobile phase: Mix 28 volumes of methanol R and 72 volumes of a solution containing 0.5 g/L of tetrabutylammonium hydrogen sulfate R, 1.0 g/L of potassium dihydrogen phosphate R and 3.4 g/L of phosphoric acid (~1440 g/L) TS. Operate with a flow rate of 1.3 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 293 nm. Maintain the column temperature at 45 °C.

Prepare solvent (A) by dissolving 0.50 g of tetrabutylammonium hydrogen sulfate R and 1.0 g of potassium dihydrogen phosphate R in about 500 mL of water R. Add 2 mL of phosphoric acid (~1440 g/L) TS and 0.050 g of anhydrous sodium sulfite R, then dilute to 1000.0 mL with water R.

Prepare the following solutions in solvent (A). For solution (1) dissolve about 50.0 mg of the test substance and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) use a solution containing about 1 mg of moxifloxacin for peak identification RS (containing moxifloxacin and the impurities A, B, E and F) per mL.

Inject alternately 10 µL of solution (1), (2) and (3). Record the chromatograms for about 2.5 times the retention time of moxifloxacin.

Use the chromatogram supplied with moxifloxacin for peak identification RS and the chromatogram obtained with solution (3) to identify the peaks due to impurities A, B, E and F in the chromatogram obtained with solution (1). The impurities, if present, are eluted at the following relative retention with reference to moxifloxacin (retention time about 11 to 14 minutes): impurity F about 0.9; impurity A about 1.1; impurity B about 1.3; and impurity E about 1.7.

¹ A Inertsil Ph and a Zorbac Eclipse XDB-Phenyl column were found suitable.
The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak due to moxifloxacin and the peak due to impurity A is at least 1.5 and the chromatogram obtained is similar to the chromatogram supplied with moxifloxacin for peak identification RS.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B, when multiplied by a correction factor of 1.4, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity E, when multiplied by a correction factor of 3.5, is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any peak corresponding to impurity F is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.1%);
- the area of any other impurity peak is not greater than the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.10%);
- the sum of the corrected areas of any peak corresponding to impurity B and E and the areas of all other impurity peaks is not greater than 3 times the area of the peak due to moxifloxacin obtained with solution (2) (0.3%). Disregard any peak with an area less than 0.5 times the area of the peak due to moxifloxacin in the chromatogram obtained with solution (2) (0.05%).

Assay

- Either test A or test B may be applied.

**A.** Carry out the test as described under 1.14.4 High-performance liquid chromatography using the conditions given under “Related substances”.

Prepare the following solutions in solvent (A). For solution (1) dissolve 50.0 mg of the substance to be examined and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL. For solution (2) dissolve 50.0 mg of moxifloxacin hydrochloride RS and dilute to 50.0 mL. Dilute 2.0 mL of this solution to 20.0 mL.

Inject alternately 10 µL of solution (1) and (2).

Measure the areas of the peaks corresponding to moxifloxacin obtained in the chromatograms of solution (1) and (2) and calculate the percentage content of C<sub>21</sub>H<sub>25</sub>ClFN<sub>3</sub>O<sub>4</sub>, using the declared content of C<sub>21</sub>H<sub>25</sub>ClFN<sub>3</sub>O<sub>4</sub> in moxifloxacin hydrochloride RS.

**B.** Dissolve about 0.320 g, accurately weighed, in 50 mL of water R. Titrate with sodium hydroxide (0.1 mol/L) VS, determining the end-point potentiometrically. Read the volume added to reach the first point of inflection. Each mL of sodium hydroxide (0.1 mol/L) VS is equivalent to 43.79 mg of C<sub>21</sub>H<sub>25</sub>ClFN<sub>3</sub>O<sub>4</sub>. 
Impurities

A. 1-cyclopropyl-6,8-difluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid \( [\text{synthesis-related impurity}] \)

B. 1-cyclopropyl-6,8-dimethoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid \( [\text{synthesis-related impurity}] \)

C. 1-cyclopropyl-8-ethoxy-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid \( [\text{synthesis-related impurity}] \)

D. 1-cyclopropyl-8-fluoro-6-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid \( [\text{synthesis-related impurity}] \)
E. 1-cyclopropyl-6-fluoro-8-hydroxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [synthesis-related impurity]

F. 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-1-methyloctahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid [synthesis-related impurity]

G. methyl 1-cyclopropyl-6-fluoro-8-methoxy-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylate [synthesis-related impurity]

Reagent to be established

Sodium hydroxide (~85 g/L) TS
A solution of sodium hydroxide R in water R containing about 85 g/L of NaOH.

Sodium sulfite, anhydrous R
Anhydrous sodium sulfite of a suitable quality should be used.