MOXIFLOXACIN TABLETS
(MOXIFLOXACINI COMPRESSI)

Draft proposal for The International Pharmacopoeia
(January 2018)

DRAFT FOR COMMENT

Should you have any comments on this draft, please send these to 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; fax: (+41 22) 791 4730 or email: schmidt@who.int by 16 March 2018.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/16.650:

Moxifloxacin tablets (Moxifloxacini compressi)

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<td>March 2016</td>
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MOXIFLOXACIN TABLETS

MOXIFLOXACINI COMPRESSI

[Note from the Secretariat. The proposed monograph is based on information provided by the British Pharmacopoeia and pharmaceutical manufacturers, found in the scientific literature and on laboratory investigations. The monograph is proposed for inclusion in The International Pharmacopoeia.]

Category. Antibacterial, antituberculosis.

Labelling. The designation on the container of moxifloxacin tablets should state that the active ingredient is Moxifloxacin hydrochloride and the quantity should be indicated in terms of equivalent amount of moxifloxacin.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML) 400 mg per tablet. Strength in the current WHO EML for children: 400 mg per tablet.

Requirements

Comply with the monograph for Tablets.

Definition. Moxifloxacin tablets contain Moxifloxacin hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of moxifloxacin (C21H24FN3O4) stated on the label.

Identity tests

- Either test A or test B may be applied.

A. 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, 2 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) shake a quantity of the powdered tablets, equivalent to about 20 mg of moxifloxacin, with 20 mL of methanol R and filter. Dilute 1 mL of the filtrate to 20 mL with methanol. For solution (B) use an approximately 0.055 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).
B. Carry out the test as described under \textit{1.14.4 High-performance liquid chromatography} using the conditions given under “Assay”. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to moxifloxacin in the chromatogram obtained with solution (2).

**Dissolution.** Carry out the test as described under \textit{5.5 Dissolution test for solid oral dosage forms} using as the dissolution medium 900 mL of hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 50 revolutions per minute. At 30 minutes withdraw a sample of 10.0 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature. Measure the absorbance (\textit{I.6}) of a 1 cm layer of the resulting solution, suitably diluted with the dissolution medium, if necessary, at the maximum at about 295 nm, using the dissolution medium as the blank. Measure at the same time and under the same conditions the absorbance of a suitable solution of moxifloxacin hydrochloride RS in the dissolution medium.

For each of the tablets calculate the total amount of moxifloxacin (C\textsubscript{21}H\textsubscript{24}FN\textsubscript{3}O\textsubscript{4}) in the medium. Each mg of moxifloxacin hydrochloride (C\textsubscript{21}H\textsubscript{25}ClFN\textsubscript{3}O\textsubscript{4}) is equivalent to 0.917 mg of moxifloxacin (C\textsubscript{21}H\textsubscript{24}FN\textsubscript{3}O\textsubscript{4}).

Evaluate the results as described under \textit{5.5 Dissolution test for solid oral dosage forms}, \textit{Acceptance criteria.} The amount of moxifloxacin in solution for each tablet is not less than 75\% (Q) of the amount declared on the label.

[\textit{Note from the Secretariat.} It is intended to determine the absorptivity value of moxifloxacin during the establishment of moxifloxacin hydrochloride RS. The value will then be included in the test description.]

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

Carry out the tests as described under \textit{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).\textsuperscript{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 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.

\textsuperscript{1} A Zorbax Eclipse XDB-Phenyl column was found suitable.
Prepare the following solutions in solvent (A). For solution (1) dissolve a quantity of the powdered tablets, equivalent to about 100 mg of moxifloxacin in 100 mL of solvent (A) with sonication and filter. For solution (2) dilute 1 volume of solution (1) to 100 volumes. Dilute 1 volume of this solution to 10 volumes. 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 and E 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 A about 1.1; impurity B about 1.3; impurity E about 1.7.

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 principal peak in the chromatogram obtained with solution (2) (0.2%);

- 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 principal peak in the chromatogram obtained with solution (2) (0.2%);

- the area of any other impurity peak is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

- the sum of the areas of all impurity peaks is not greater than 10 times the area of the principal peak obtained with solution (2) (1.0%). Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay. 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) weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, accurately weighed, containing the equivalent of about 500 mg of moxifloxacin into a 500 mL volumetric flask. Add 400 mL of solvent (A), sonicate for 30 minutes, dilute to volume and filter. Dilute 1 volume of the filtrate to
10 volumes. For solution (2) use a solution containing about 0.11 mg moxifloxacin hydrochloride RS, accurately measured, per 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$_{21}$H$_{24}$FN$_3$O$_4$ in the tablets using the declared content of C$_{21}$H$_{25}$ClFN$_3$O$_4$ in moxifloxacin hydrochloride RS. Each mg of C$_{21}$H$_{25}$ClFN$_3$O$_4$ is equivalent to 0.917 mg of moxifloxacin (C$_{21}$H$_{24}$FN$_3$O$_4$).

**Impurities**

The impurities limited by the requirements of this monograph include the impurities listed in the monograph for Moxifloxacin hydrochloride.