



MEFLOQUINE TABLETS

Draft proposal for *The International Pharmacopoeia*

(September 2010)

REVISED DRAFT FOR COMMENT

This document was provided by a quality control expert and was discussed at the recent WHO consultation on specifications for medicines and quality control laboratory issues. Previous comments received have been incorporated into this revised draft. Should you have any comments, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mails: kopps@who.int with a copy to Ms C. Mendy mendyc@who.int by 11 October 2010.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/10.370

International Pharmacopoeia monograph on Mefloquine tablets

	Date
Preparation of first draft by laboratory	September 2009–May 2010
Discussion at consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Draft monograph mailed out for comments	July 2010
Collation of comments	August 2010
Comments discussed during video-/teleconference on specifications for medicines	25 August 2010
Revised draft mailed out for comments	September 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Further action as necessary	

MEFLOQUINE TABLETS

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Category. Antimalarial.

Storage. Mefloquine tablets should be kept in a well-closed container, protected from light.

Labelling. The designation of the container of Mefloquine tablets should state that the active ingredient is in the hydrochloride form and the quantity should be indicated in terms of the equivalent amount of mefloquine.

Additional information. Strength in the current WHO Model list of essential medicines: 250 mg.
Strength in the current WHO Model list of essential medicines for children: 250 mg.

Requirements

Comply with the monograph for "Tablets".

Definition. Mefloquine tablets contain Mefloquine hydrochloride. They contain not less than 90.0% and not more than 110.0% of the amount of mefloquine (C₁₇H₁₆F₆N₂O) stated on the label.

Identity tests

- Any two of tests A, B or C may be applied together with test D.

A. Carry out test A.1 or, where UV detection is not available, test A.2.

A.1 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 70 volumes of toluene R, 30 volumes of ethanol R and 2 volumes of 25% ammonia solution R as the mobile phase. Apply separately to the plate 10 µl of each of the following two solutions in methanol R. For solution (A) sonicate, with intermittent shaking, a quantity of the powdered tablets containing the equivalent of about 250 mg of mefloquine for 5 minutes with 25 ml, filter, and use the filtrate. For solution (B) use 10 mg of mefloquine RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of air and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance and intensity to that obtained with solution B.

A.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test A.1 but using silica gel R5 as the coating substance. Stain the plate with iodine vapours. Examine the chromatogram in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity to that obtained with solution B.

- B. See the test described under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that in the chromatogram obtained with solution (2).
- C. To a quantity of the powdered tablets containing the equivalent of 50 mg of mefloquine add 100 ml of methanol R, shake and filter. Dilute 5 ml of the filtrate to 50 ml with the same solvent. The absorption spectrum (1.6) of the resulting solution, when observed between 250 nm and 290 nm, exhibits one maximum at about 283 nm.
- D. To a quantity of powdered tablets containing the equivalent of about 0.5 g of mefloquine add 10 ml of water R, sonicate for 10 minutes and filter. The filtrate yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

Dissolution. Carry out the test as described under 5.5 Dissolution test for solid oral dosage forms, using as the dissolution medium, 900 ml of hydrochloric acid (~4 g/l) TS and rotating the paddle at 75 revolutions per minute. At 30 minutes withdraw a sample of 10 ml of the medium through an in-line filter. Measure the absorbance (1.6) of a 1-cm layer of the filtered sample, suitably diluted if necessary, at the maximum at about 283 nm. At the same time measure the absorbance at the maximum at about 283 nm of a suitable solution of mefloquine hydrochloride RS, initially dissolved in methanol R and then diluted in 0.1 mol/l hydrochloric acid, using hydrochloric acid (~4 g/l) TS as the blank. Each mg of mefloquine hydrochloride ($C_{17}H_{16}F_6N_2O \cdot HCl$) is equivalent to 0.912 mg of mefloquine ($C_{17}H_{16}F_6N_2O$).

For each of the six tablets tested, calculate the total amount of mefloquine ($C_{17}H_{16}F_6N_2O$) in the medium. The amount in solution for each tablet is not less than 80% of the amount declared on the label. If the amount obtained for one of the six tablets is less than 80%, repeat the test using a further six tablets; the average amount for all 12 tablets tested is not less than 75% and no tablet contains less than 60%.

Related substances

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using the conditions described under Assay.

Use solutions (1) and (4) as described under Assay. For solution (5) transfer 1 ml of solution (1) as prepared for the assay, to a 50-ml volumetric flask and make up to volume with the mobile phase. Dilute 2 ml of this solution to 20 ml with the mobile phase.

Inject 20 μ l of solution (4). The test is not valid unless the resolution between the two principal peaks is at least 5.

Inject separately 20 μ l each of solutions (1) and (5). Record the chromatograms for about 10 times the retention time of mefloquine.

In the chromatogram obtained with solution (1) the following impurities, if present, are eluted at the following relative retention with reference to mefloquine (retention time about 3.9 minutes): impurity A about 0.9, impurity C about 3.6 and impurity B about 7.4.

In the chromatogram obtained with solution (1) the area of any peak, other than the peak due to mefloquine, is not greater than the area of the principal peak in the chromatogram obtained with solution (5) (0.2%). The sum of the areas of all peaks, other than the peak due to mefloquine, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.5%). Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

[Note from Secretariat. The limit of 0.2% for individual related substances in this test is tighter than the limit of 0.5% in the current Ph.Int. monograph for mefloquine hydrochloride API, as determined by TLC. It is therefore intended to revise accordingly the Related substances test of the API monograph (list of impurities, limits).]

Assay

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

As the mobile phase, use a mixture of 22 volumes of methanol R, 38 volumes of acetonitrile R and 40 volumes of buffer pH 3.5 prepared as follows: dissolve 13.6 g potassium dihydrogen phosphate in about 900 ml of water R, adjust the pH to 3.5 by addition of 10% phosphoric acid and dilute to 1000 ml.

Prepare the following solutions in mobile phase. For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powder containing the equivalent of about 200 mg of mefloquine, accurately weighed, into a 100-ml volumetric flask. Add 70 ml of mobile phase and sonicate for about 10 minutes. Allow to cool to room temperature and make up to volume with mobile phase. Filter a portion of this solution through a 0.45-µm filter, discarding the first few ml of the filtrate. For solution (2) dilute 5 ml of solution (1) to 50 ml with mobile phase. For solution (3), use 0.22 mg of mefloquine hydrochloride RS per ml. For solution (4) use about 0.22 mg of mefloquine hydrochloride RS and about 0.04 mg of sulfadoxine R per ml.

Operate with a flow rate of 1.5 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 283 nm.

Inject 20 µl of solution (4). The assay is not valid unless the resolution between the two principal peaks is at least 5.

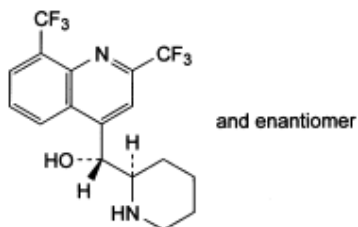
Inject separately 20 µl each of solutions (2) and (3).

Measure the areas of the peaks responses obtained in the chromatograms from solutions (2) and (3) and calculate the content of mefloquine (C₁₇H₁₆F₆N₂O) in the tablets, using the declared content of mefloquine hydrochloride (C₁₇H₁₆F₆N₂O.HCl) in mefloquine hydrochloride RS. Each mg of mefloquine hydrochloride (C₁₇H₁₆F₆N₂O.HCl) is equivalent to 0.912 mg of mefloquine (C₁₇H₁₆F₆N₂O).

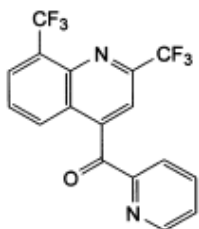
¹ Luna® was found suitable.

Impurities

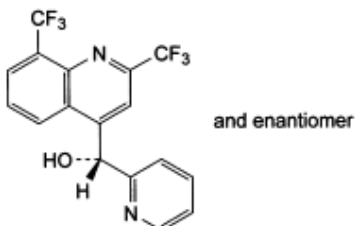
The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.



A. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl][(2RS)-piperidin-2-yl]methanol (*threo*-mefloquine)



B. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl)methanone



C. (RS)-[2,8-bis(trifluoromethyl)quinolin-4-yl](pyridin-2-yl)methanol

New reagents to be added to Ph.Int.

Hydrochloric acid (~4 g/l) TS

Dilute 10 ml of hydrochloric acid (~420 g/l) TS with sufficient water to produce 1000 ml (approximately 0.1 mol/l).

Sulfadoxine R. *N*¹-(5,6-Dimethoxy-4-pyrimidinyl)sulfanilamide; 4-amino-*N*-(5,6-dimethoxy-4-pyrimidinyl)benzenesulfonamide; C₁₂H₁₄N₄O₄S

A commercially available reagent of suitable grade.

Description. A white or creamy white, crystalline powder.

Solubility. Very slightly soluble in water; slightly soluble in ethanol (~750 g/l) TS and in methanol R; practically insoluble in ether R.
