PROPOSAL FOR REVISION OF MONOGRAPH IN THE FOURTH EDITION OF

The International Pharmacopoeia

MEFLOQUINE HYDROCHLORIDE
(JANUARY 2012)

DRAFT FOR COMMENT

This document was provided by a quality control expert. Should you have any comments thereon, 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 28 March 2012.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.
**SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/11.424**

*Draft proposal for revision of a published monograph in the Fourth Edition of The International Pharmacopoeia*

**MEFLOQUINE HYDROCHLORIDE**

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[Note from the Secretariat:]

- following the adoption of the text for Mefloquine tablets in October 2010, it is proposed to revised the monograph for the API accordingly;
- changes from the current monograph are indicated in the text by insert or delete.

**Mefloquinhydrochloridum**

Mefloquine hydrochloride

C\textsubscript{17}H\textsubscript{16}F\textsubscript{6}N\textsubscript{2}O.HCl

**Relative molecular mass.** 414.8

**Chemical name.** DL-erythro-\(\alpha\)-2-piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride; \((R^*,S^*)\)-(±)-\(\alpha\)-2-piperidinyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride; CAS Reg. No. 51773-92-3.

**Description.** A white to slightly yellow, crystalline powder.

**Solubility.** Very slightly soluble in water; freely soluble in methanol R; soluble in ethanol (~750 g/l) TS; sparingly soluble in dichloromethane R.

**Category.** Antimalarial.

**Storage.** Mefloquine hydrochloride should be kept in a tightly closed container, protected from light.

**Additional information.** Mefloquine hydrochloride may exhibit polymorphism. It melts at about 260 °C, with decomposition.
Requirements

Mefloquine hydrochloride contains not less than 99.0% and not more than 101.0% of C₁₇H₁₆F₆N₂O₂HCl, calculated with reference to the anhydrous and solvent-free substance.

Identity tests

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

• Either test A or tests B and C may be applied, together with test D.

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

B. See the test described below under "Related substances". The principal spot obtained with solution B corresponds in position, appearance, and intensity with that obtained with solution C. Carry out test B.1 or, where UV detection is not available, test B.2.

B.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) use 10 mg of the test substance per ml. For solution (B) use 10 mg of mefloquine hydrochloride 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.

B.2 Carry out the test as described under 1.14.1 Thin-layer chromatography, using the conditions described above under test B.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.
C. Transfer about 10 mg to a porcelain crucible, add 45 mg of magnesium oxide R, and ignite until an almost white residue is obtained. Allow to cool, add 2.0 ml of water, 0.05 ml of phenolphthalein/ethanol TS, and about 1 ml of hydrochloric acid (~70 g/l) TS. Filter, to the filtrate add a freshly prepared mixture of 0.10 ml of sodium alizarinsulfonate (1 g/l) TS and 0.10 ml of zirconyl nitrate TS, mix, and allow to stand for 5 minutes. Prepare similarly a reagent blank; a yellow colour is produced, whereas the reagent blank is red.

D. To 20 mg add about 0.2 ml of sulfuric acid (~1760 g/l) TS and view the mixture under ultraviolet light (365 nm); a blue fluorescence is observed.

C. The absorption spectrum (1.6) of a 54 µg/ml solution in methanol R, when observed between 250 nm and 290 nm, exhibits one maximum at about 283 nm.

DE. A 50 mg/ml solution yields reaction B described under 2.1 General identification tests as characteristic of chlorides.

[Note from the Secretariat: similarly as for Mefloquine tablets
- Test B has been replaced by a TLC method;
- Test C and D have been replaced by a UV method.

Choices and numbering for identity tests have been modified accordingly.]

Heavy metals. Use 1.0 g for the preparation of the test solution as described under 2.2.3 Limit test for heavy metals, Procedure 3; determine the heavy metals content according to Method A; not more than 20 µg/g.

Solution in methanol. A solution of 0.50 g in 10 ml of methanol R is clear and not more intensely coloured than standard colour solution Yw1 when compared as described under 1.11 Colour of liquids.

[Note from the Secretariat: proposal to delete this test, taking into account current practice.]

Sulfated ash. Not more than 1.0 mg/g.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using 1.0 g of the substance Mefloquine hydrochloride; the water content is not more than 30 mg/g.

Related substances. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R3 as the coating substance and a mixture of 8 volumes of dichloromethane R, 1 volume of glacial acetic acid R1, and 1 volume of methanol R as the mobile phase. Apply separately to the plate 5 µl of each of 4 solutions in methanol R containing (A) 8 mg of Mefloquine hydrochloride per ml, (B) 1.6 mg of Mefloquine hydrochloride per ml, (C) 1.6 mg of Mefloquine hydrochloride RS per ml, and (D)
0.04 mg of mefloquine hydrochloride RS per ml. After removing the plate from the chromatographic chamber, allow it to dry in a current of warm air for 15 minutes, and spray with a freshly prepared mixture of 1 volume of sulfuric acid (1760 g/l) TS and 40 volumes of potassium iodoplatinate TS. Then spray again with hydrogen peroxide (330 g/l) TS and examine the chromatogram in daylight.

Any spot obtained with solution A, other than the principal spot, is not more intense than that obtained with solution D (0.5%).

**Related substances**

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 the mobile phase. For solution (1) use about 2.2 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 4.4 µg of Mefloquine hydrochloride per ml. For solution (3) 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 (3). The test is not valid unless the resolution between the two principal peaks is at least 5.

Inject separately 20 µl each of solutions (1) and (2). 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 corresponding to impurity A, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%) and the area of any other peak, apart from the principal peak, is not greater than 0.5 times the area of the peak in the chromatogram obtained with solution (2) (0.1%). The sum of the areas of all peaks, other than the peak due to

\(^1\) Luna® was found suitable.
mefloquine, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

**Ethanol, methanol, and acetone.** Carry out the test as described under 1.14.5 Gas chromatography, using a stainless steel column (2 m × 2.2 mm) packed with graphitized carbon (135 – 175 µm) which is impregnated with a 0.05 g/ml solution of macrogol 20M R. Maintain the column at 70 °C, the injection port at 200 °C, and the detector at 250 °C. Use helium R as the carrier gas at a flow rate of 35 ml per minute, and a flame ionization detector.

Use the following solutions. For solution (1) dissolve 1.0 g of Mefloquine hydrochloride in 10 ml of dimethylformamide R. For solution (2) prepare a mixture of 1.0 g of methanol R, 1.0 g of dehydrated ethanol R, and 1.0 g of acetone R diluted to 100 ml with dimethylformamide R; further dilute 1.0 ml of this solution to 100 ml with dimethylformamide R.

Inject separately 1 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2), and calculate the total content of ethanol, methanol, and acetone; the total content does not exceed 5 mg/g.

*Note from the Secretariat: it is proposed to omit this specific test for residual solvents. The possibility to include under the Supplementary section of the Ph.Int., a general text on residual solvents for APIs, is under review.*

**Assay**

Dissolve about 0.31 g, accurately weighed, in 70 ml of glacial acetic acid R1, add 5 ml of mercuric acetate/acetic acid TS, and titrate with perchloric acid (0.1 mol/l) VS as described under 2.6 Non-aqueous titration, Method A.

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 41.48 mg of C_{17}H_{16}F_{6}N_{2}O, HCl.

*Note from the Secretariat: due to the toxicity of mercuric acetate/acetic acid TS, replacement of this reagent is under review.*

**Impurities**

*Note from the Secretariat: this section has been transferred from the Mefloquine tablets monograph. The latter should have instead a cross-reference to this API monograph.*
A. \((RS)-[2,8\text{-bis(trifluoromethyl)quinolin-4-yl}][2\text{RS}-piperidin-2-yl]\text{methanol (threo-mefloquine)}\)

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

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

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**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; \(C_{12}H_{14}N_4O_4S\)

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.

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