



METRONIDAZOLE ORAL SUSPENSION

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/10.346
International Pharmacopoeia monograph on Metronidazole Oral Suspension

	Date
Preparation of first draft by laboratory	February 2010
Preliminary discussion of the first draft during the tele-video-conference on Specifications for Medicines and Quality Control Laboratory Issues	4 March 2010
Discussion of the draft proposal in the consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Mailing of revised draft monograph for comment	July 2010
Collation of comments received	August 2010
Revised draft discussed during tele-/videoconference 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
Any further action as required	...

[Note from the Secretariat:

This draft text is proposed for inclusion in The International Pharmacopoeia (Ph.Int.) in the context of collaboration between WHO and the Medicines and Healthcare products Regulatory Agency of the United Kingdom of Great Britain and Northern Ireland (MHRA) hosting The British Pharmacopoeia, on which this text is based.]

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METRONIDAZOLE ORAL SUSPENSION

Category. Antibacterial.

Storage. Metronidazole oral suspension should be kept in a well-closed container, protected from light.

Labelling. The designation of the container of Metronidazole oral suspension should state that the active ingredient is in the benzoate form and the quantity should be indicated in terms of equivalent amount of metronidazole.

Additional information. Strengths in the current WHO Model list of essential medicines: 200 mg per 5 ml (40 mg per ml).

Requirements

Complies with the monograph for “Liquid preparations for oral use”.

Definition. Metronidazole oral suspension is a suspension of Metronidazole benzoate in a suitable vehicle which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of metronidazole (C₆H₉N₃O₃) stated on the label.

[Note from the Secretariat: wider limits than those stated in the BP monograph (95.0%–105.0%) are proposed, to be in line with the policy and limits applied for similar dosage forms in the Ph.Int.]

Identity tests

- Either test A or any two of tests B, C and D may be applied.
 - A. To a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole add 20 ml of water R, filter under partial vacuum and wash the residue with three quantities, each of 10 ml of water R. Dissolve the residue as completely as possible in 10 ml of acetone R, filter and evaporate the filtrate to dryness. Dry the residue at 60°C and 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 metronidazole benzoate RS or with the *reference spectrum* of metronidazole benzoate.

- B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance. Heat to activate the plate at 110°C for 1 hour and cool before use. As the mobile phase, use ethyl acetate R. Apply separately to the plate 10 µl of each of the following two solutions. For solution (A), shake and dilute a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole to 100 ml with acetone R, filter, and use the filtrate. For solution (B), use 3.2 mg of metronidazole benzoate RS per ml of acetone R. For solution (C) dissolve 20 mg of metronidazole R in 10 ml of solution (B). 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 with that obtained with solution B. The test is not valid unless the chromatogram obtained with solution (C) shows two clearly separated spots.

- C. Dilute a quantity of the oral suspension containing the equivalent of 62.2 mg of Metronidazole to 100 ml with a 103 g/l solution of hydrochloride acid R, filter, and further dilute 1 ml of the filtrate to 100 ml with the same solvent. The absorption spectrum (1.6) of this solution, when observed between 220 nm and 350 nm, exhibits two absorption maxima at 232 nm and 275 nm.
- D. See the test described below under Assay. The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to that of the principal peak in the chromatogram obtained with solution (2).

pH value. (1.13) pH of the oral suspension, 5.0 – 6.5.

Metronidazole

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

Prepare the following solutions. For solution (1), to a quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole, add 150 ml of methanol R and sufficient water R, with mixing and cooling, to produce 250.0 ml, shake and centrifuge. For solution (2), dissolve 20 mg of metronidazole RS in 150 ml of methanol R and add sufficient water R, with mixing and cooling, to produce 250.0 ml. Dilute 10.0 ml of the resulting solution to 100.0 ml with a 60% solution of methanol R. For solution (3), use 15 µg of metronidazole RS and 15 µg of metronidazole benzoate RS per ml of a 60% solution of methanol R.

Inject separately 30 µl each of solution (1), (2) and (3).

In the chromatogram obtained with solution (3), the following peak is eluted at the following relative retention, with reference to metronidazole benzoate (retention time about 6 minutes): metronidazole about 0.5. The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to metronidazole and metronidazole benzoate is at least 5.

In the chromatogram obtained with solution (1), the area of any peak corresponding to metronidazole, is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (1%).

Assay

Carry out the test as described under 1.14.4 High-performance liquid chromatography, using a stainless steel column (25 cm × 4.6 mm) packed with base deactivated 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 40 volumes of a 12.5 g/l solution of ammonium acetate R, adjusted to pH 7.0 with ammonia (~100 g/l) TS and 60 volumes of methanol R.

Prepare the following solutions. For solution (1), mix a weighed quantity of the oral suspension containing the equivalent of 200 mg of Metronidazole, add 150 ml of methanol R and sufficient water R, with mixing and cooling, to produce 250.0 ml. Shake and centrifuge. Dilute 10 ml of the resulting solution to 100.0 ml with a 60% solution of methanol R. For solution (2), dissolve 64 mg of metronidazole benzoate RS in 1 ml of dimethylformamide R and 30 ml of methanol R and add sufficient water R, with mixing and cooling, to produce 50.0 ml. Dilute 10.0 ml of the resulting solution to 100.0 ml with a 60% solution of methanol R. For solution (3), use 15 μg of metronidazole RS and 15 μg metronidazole benzoate RS per ml of 60% solution of methanol R.

Operate with a flow rate of 1.0 ml per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of about 310 nm.

Inject separately 30 μl each of solution (1), (2) and (3).

In the chromatogram obtained with solution (3), the following peak is eluted at the following relative retention, with reference to metronidazole benzoate (retention time about 6 minutes): metronidazole about 0.5. The test is not valid unless, in the chromatogram obtained with solution (3), the resolution factor between the peaks due to metronidazole and metronidazole benzoate is at least 5.

Measure the areas of the peak responses obtained in the chromatograms from solution (1) and (2).

Determine the weight per ml (1.3.1) of the oral suspension and calculate the content of metronidazole (C₆H₉N₃O₃), weight in volume, in the oral suspension using the declared content of metronidazole benzoate (C₁₃H₁₃N₃O₄) in metronidazole benzoate RS. Each mg of C₁₃H₁₃N₃O₄ is equivalent to 0.6219 mg of C₆H₉N₃O₃.

¹ Hypersil BDS C18 has been found suitable.