World Health Organization

MIFEPRISTONE TABLETS

(MIFEPRISTONI COMPRESSI)

Draft proposal for inclusion in *The International Pharmacopoeia*

(27 August 2024)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Bezawit Kibret (kibretb@who.int)
Comments should be submitted through the online platform by **27 October 2024**. Please note that only comments received by this deadline will be considered for the preparation of this document.
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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/24.959

MIFEPRISTONE TABLETS

(MIFEPRISTONI COMPRESSI)

Description	Date
Drafting of the monograph by the Secretariat based on information received from manufacturers and found in the public domain	June 2024
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications of Medicines	May 2024
Draft monograph sent out for public consultation.	August – October 2024
Presentation to the 58th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2024
Further follow-up action as required.	

*[**Note from the Secretariat.** The monograph on Mifepristone tablets is proposed for inclusion in* The International Pharmacopoeia*.*

Being one of the first public standards, the monographs on Mifepristone and Mifepristone tablets are expected to play an important role in ensuring access to safe, effective and acceptable abortion care. Manufacturers, regulatory authorities, procurement agencies and other stakeholders are therefore invited to provide their feedback.

The draft monograph is based on information received from manufacturers and found in the public domain and on laboratory investigations.

Draft monographs are subject to change.]

MIFEPRISTONE TABLETS (MIFEPRISTONI COMPRESSI)

Category. Uterotonics.

Storage. Mifepristone tablets should be kept in tightly closed containers and protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines: 200 mg. Additional strength available: 600 mg.

Requirements

Definition. Mifepristone tablets contain not less than 90.0% and not more than 110.0% of the amount of Mifepristone ($C_{29}H_{35}NO_2$) stated on the label.

Identity tests

- Either test A, or any two of tests B, C or D, may be applied.

A. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under "Assay" with the following modifications: As the detector, use a diode array detector to record the UV spectrum of the principal peak in each chromatogram in the range of 230 nm to 350 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and the UV spectrum of the peak due to mifepristone in the chromatogram obtained with solution (2).

B. Carry out the test as described under *1.14.1 Chromatography*, 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 mifepristone in the chromatogram obtained with solution (2).

C. Transfer a quantity of the powdered tablets, nominally containing 10 mg of Mifepristone, into a 100 mL volumetric flask, add about 60 mL of methanol R, shake with a mechanical shaker for about 30 minutes, dilute to volume with methanol R, mix and filter. Dilute 5.0 mL of this solution to 50.0 mL with the same solvent. The absorption spectrum (*1.6*) of the resulting solution, when observed between 230 nm and 350 nm, exhibits two maxima at about 260 nm and 304 nm.

D. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 7 volumes of toluene R and 3 volumes of ethyl acetate R as the mobile phase, prepared immediately before use. Apply separately to the plate 5 µL of each of the following two solutions. For solution (A), transfer a quantity of the powdered tablets, nominally containing 10 mg of mifepristone, into a 20 mL volumetric flask, add about 12 mL of methanol R, shake with a mechanical shaker for about 30 minutes, dilute to volume with methanol R, mix and filter. For solution (B), use a solution containing 0.5 mg of mifepristone RS per mL of methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air and examine under ultraviolet light (254 and 360 nm).

The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to mifepristone in the chromatogram obtained with solution (B).

Dissolution. *For 200 mg and 600 mg tablets***.** Carry out the test described under 5.*5 Dissolution test for oral dosage forms*, using as the dissolution medium 900 mL of hydrochloric acid (~0.365 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. Allow the filtered sample to cool to room temperature.

For 200 mg tablets: dilute 5.0 mL of this solution to 100.0 mL and use it as solution (1). *For 600 mg tablets:* dilute 3.0 mL of this solution to 200.0 mL and use it as solution (1).

For solution (2), transfer 44.0 mg of mifepristone RS into a 200 mL volumetric flask, dissolve in dissolution medium, dilute to volume with the same solvent and mix. Dilute 5.0 mL of this solution to 100.0 mL with the dissolution medium.

Measure the absorbance as described under *1.6 Spectrophotometry in the visible and ultraviolet regions* of solutions (1) and (2) in a cuvette with an optical pathlength of 10 mm at about 310 nm, using the dissolution buffer as the blank.

For each of the tablets tested, calculate the total amount of mifepristone ($C_{29}H_{35}NO_2$) in the medium from the results obtained.

Evaluate the results as described under *5.5 Dissolution test for solid oral dosage forms*, Acceptance criteria. The amount of mifepristone released is not less than 80% (Q) of the amount declared on the label.

[Note from the Secretariat: It is intended to determine the absorptivity value of mifepristone during the establishment of mifepristone RS and to use this value for the calculation of the test result.]

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (4.6 mm x 25 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (5 µm).[1]

[1] A Luna C18(2) column has been found suitable.

Prepare a phosphate buffer pH 7.0 by dissolving 4.7 g of potassium dihydrogen phosphate dihydrate R in 1000 mL of water R and adjusting the pH with at 7.0 with triethylamine R.

Use the following conditions for gradient elution:

- mobile phase A: phosphate buffer pH 7.0;
- mobile phase B: acetonitrile R.

Time (minutes)	**Mobile phase A** (% *V*/*V*)	**Mobile phase B** (% *V*/*V*)	**Comments**
0–26	50	50	Isocratic
26–30	50 to 45	50 to 55	Linear gradient
30–34	45 to 40	55 to 60	Linear gradient
34–40	40 to 35	60 to 65	Linear gradient
40–44	35 to 40	65 to 60	Linear gradient
44–48	40 to 45	60 to 55	Linear gradient
48–52	45 to 50	55 to 50	Return to initial composition
52–60	50	50	Re-equilibration

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 25 °C. Use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Prepare the following solutions, using as a diluent a mixture of 45 volumes of acetonitrile R and 55 volumes of the phosphate buffer pH 7.0.

For solution (1), transfer a quantity of the powdered tablets, nominally containing 200.0 mg of Mifepristone, into a 200 mL volumetric flask. Add about 150 mL, sonicate for 5 minutes and stir magnetically for an additional 30 minutes. Cool to room temperature, dilute to volume, mix and filter.

For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL.

For solution (3), dilute 5.0 mL of solution (2) to 50.0 mL.

For solution (4), dissolve 4 mg of mifepristone impurity B in 10 mL acetonitrile R. Dilute 1 mL of this solution to 100 mL with the diluent.

For solution (5), dilute 1 mL of solution (4) to 10 mL with solution (1).

Inject 10 µL each of solutions (1), (2), (3) and (5).

Use the chromatogram obtained with solution (5) to identify the peaks due to mifepristone and impurity B.

The impurities are eluted, if present, at the following relative retentions with reference to mifepristone (retention time about 24 minutes): impurity A about 0.57, impurity B about 0.96, and impurity C about x *[the value will be determined during the verification studies]*.The test is not valid unless, in this chromatogram obtained with solution (5), the resolution between the peaks due to impurity B and mifepristone is at least 1. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to mifepristone is obtained with a signal-to-noise ratio of at least 10.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.53, is not greater than the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (1.0 %);
- the area of any other impurity peak is not greater than 0.2 times the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (0.2 %).
- The sum of the areas of all impurity peaks, excluding the area of any peak corresponding to impurity A, is not greater than the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (1.0%).

Disregard all peaks with an area of less than the area of the peak due to mifepristone in the chromatogram obtained with solution (3) (0.10 %).

Assay. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (4.6 mm x 25 cm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm).[2]

Prepare a phosphate buffer pH 7.0 as described under "Related substances".

As the mobile phase, use a mixture of 50 volumes of the phosphate buffer pH 7.0 and 50 volumes of acetonitrile R.

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 25 °C. Use an ultraviolet spectrophotometer set at a wavelength of 260 nm.

Prepare the following solutions, using as a diluent the mobile phase.

For solution (1), weigh and powder 20 tablets. Transfer a quantity of the powdered tablets, nominally containing 200.0 mg of Mifepristone, into a 200 mL volumetric flask. Add about 150 mL, sonicate for 5 minutes, and stir magnetically for an additional 30 minutes. Cool to room temperature, dilute to volume, mix and filter. Dilute 5.0 mL of the filtered solution to 100.0 mL with mobile phase.

For solution (2), transfer 50.0 mg of mifepristone RS into a 250 mL volumetric flask, add 200 mL, sonicate for 5 minutes, cool to room temperature and dilute to volume. Dilute 5.0 mL to 20.0 mL with mobile phase.

Inject 10 µL each of solutions (1) and (2) and record the chromatogram for 45 minutes.

[2] A Luna C18(2) column has been found suitable.

Measure the areas of the peaks corresponding to mifepristone obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of mifepristone ($C_{29}H_{35}NO_2$) in the sample using the declared content of $C_{29}H_{35}NO_2$ in mifepristone RS.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Mifepristone.

Reference substances to be established.

Mifepristone RS

- *New International Chemical Reference Substance to be established.*

Mifepristone impurity B

- *New International Chemical Reference Substance to be established.*

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