World Health Organization

MIFEPRISTONE

(MIFEPRISTONUM)

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.
Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under "Working documents in public consultation".
If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/affiliation and email address to jonessi@who.int, nsp@who.int and your name will be added to our electronic mailing list and review platform.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/24.958

MIFEPRISTONE

(MIFEPRISTONUM)

Description	Date
Drafting of the monograph by the Secretariat based on information received from manufacturers and found in the public domain	June 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 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 on the proposed specifications and analytical procedures.

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

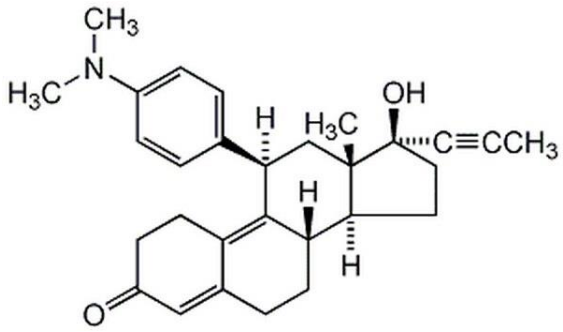
Draft monographs are subject to change.]

MIFEPRISTONE (MIFEPRISTONUM)

Molecular formula. $C_{29}H_{35}NO_2$

Relative molecular mass. 429.60

Graphic formula.



Chemical names. 11β-(4-Dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)estra-4,9-dien-3-one (*IUPAC*); (11β,17β)-11-[4-(Dimethylamino)phenyl]-17β-hydroxyl-17-(1-propynyl)-estra-4,9 dien-3-one *(CAS)*.

CAS Registry Number. 84371-65-3

Description. A white to yellowish powder.

Solubility. It is freely soluble in methanol R and dichloromethane R, soluble in dehydrated ethanol R and ethyl acetate R, and practically insoluble in water R.

Category. Uterotonics.

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

Additional information. Mifepristone may exhibit polymorphism.

Requirements

Definition. Mifepristone contains not less than 98.0% and not more than 101.0% of $C_{29}H_{35}NO_2$, calculated with reference to the dried substance.

Identity tests

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

A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from mifepristone RS or with the reference spectrum of mifepristone.

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

B. 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).

C. 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).

D. The absorption spectrum (*1.6*) of a 0.01 mg per mL solution of the test substance in methanol R, when observed between 230 nm and 350 nm, exhibits two maxima at about 260 nm and 304 nm.

E. 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 in methanol R. For solution (A), use a solution containing 0.5 mg of the test substance per mL. For solution (B), use a solution containing 0.5 mg of mifepristone RS per mL. 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).

Specific optical rotation (*1.4*)**.** Use a solution containing 5 mg per mL of the test substance in dichloromethane R. Calculate with reference to the dried substance. The specific optical rotation $[\alpha]_D^{20}$, is between +124 to +129.

Loss on drying. Dry 1.000 g of the test substance to constant weigh a 105 °C; it loses not more than 5 mg/g.

Sulfated ash (*2.3*, Method B)**.** Not more than 1.5 mg/g, determined on 1 to 2 g of the test substance.

Heavy metals. Use 1.000 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 B; not more than 20 µg/g.

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]

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 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 50 volumes of acetonitrile R and 50 volumes of water R.

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

For solution (1), transfer 25 mg of the test substance into a 25 mL volumetric flask, dissolve in about 5 mL of acetonitrile R and dilute to volume with the diluent.

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

For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL with the diluent.

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.

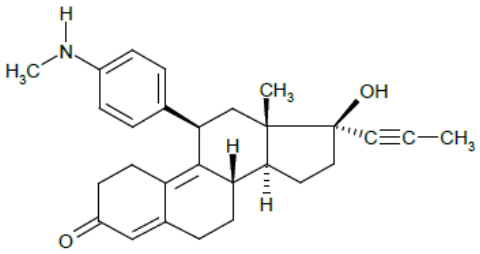
In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.53, is not greater than 0.5 times the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (0.5%);

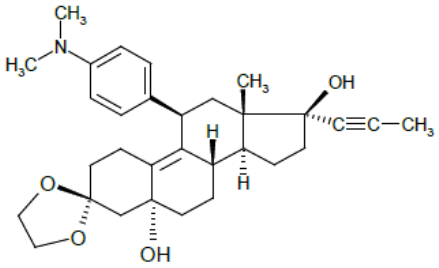
- the area of any other impurity peak is not greater than 0.1 times the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (0.10%).
- The sum of the areas of all impurity peaks, including the corrected area of any peak corresponding to impurity A, is not greater than the area of the peak due to mifepristone in the chromatogram obtained with solution (2) (1.0 %). Disregard any peaks with an area or, in the case of impurity A, a corrected area of less than the area of the peak due to mifepristone in the chromatogram obtained with solution (3) (0.05%).

Assay. Dissolve about 0.300 g in 50 mL of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/L) VS, determining the endpoint potentiometrically, as described under *2.6 Non-aqueous titration*, Method A (ii). Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 42.96 mg of $C_{29}H_{35}NO_2$.

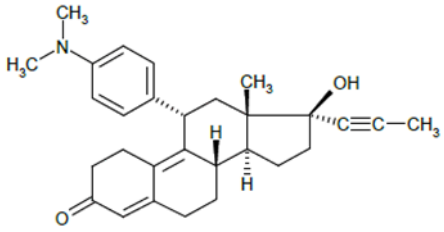
Impurities



A. 11β-[4-(Methylamino)phenyl]-17β-hydroxy-17α-(prop-1-yn-1-yl)estra-4,9-dien-3-one; 17α-propynil-17β-hydroxy-11β-((N-methyl-4´-amino)-phenyl)-19-nor-androsta-4,9-diene-3-one; (*N*-desmethyl mifepristone)(process related impurity and degradation product),



B. 11β-[4-(Dimethylamino)phenyl]-17α-(prop-1-yn-1-yl)spiro[estra-9-en-3,2'-[1,3]dioxolane]-5α,17β-diol (4,5 dihydro-5α-hydroxy-mifepristone 3-ethylene ketal)(process related impurity and degradation product),



C. 11α-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(prop-1-yn-1-yl)estra-4,9-dien-3-one (mifepristone 11α-epimer)(process related impurity).

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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