World Health Organization

RIFAMPICIN

(RIFAMPICINUM)

Draft proposal for revision for *The International Pharmacopoeia*

(November 2020)

DRAFT FOR COMMENTS

Please send any comments you may have on this draft working document to **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Claire Vogel (vogelc@who.int) by **29 January 2021**.

Our working documents are sent out electronically and they will also be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) for comments under the "*Monographs and general texts under review/revision for inclusion in The International Pharmacopoeia*". If you wish to receive our draft guidelines, please send your e-mail address to jonessi@who.int and your name will be added to our electronic mailing list.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.866:

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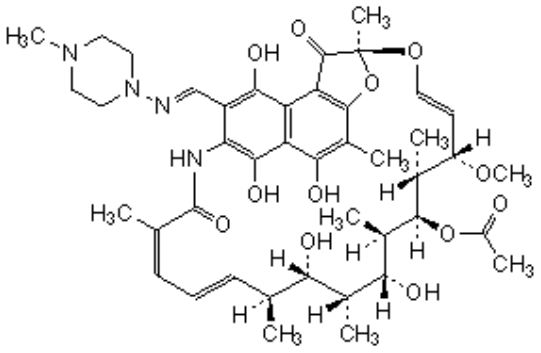
(RIFAMPICINUM)

Description	Date
Proposal drafted following discussions with the WHO Prequalification Programme.	November 2020
Draft proposal sent out for public consultation.	November 2020 - January 2021
Discussion at the Consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	May 2021
Presentation to the 56th WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2021
Further follow-up action as required.	

[Note from the Secretariat. *Following the determination of traces of nitrosamines in some batches of rifampicin active pharmaceutical ingredient, it is proposed to revise the corresponding monograph.*

Changes to the current chapter are indicated in the text by insert or ~~delete~~.]

RIFAMPICIN (RIFAMPICINUM)



$C_{43}H_{58}N_4O_{12}$

Relative molecular mass. 822.9.

Chemical name. (2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-5,6,9,17,19-pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[[(4-methylpiperazin-1-yl)imino]methyl]-1,11-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-21-yl acetate; 3-[[(4-methyl-1-piperazinyl)imino]methyl]rifamycin; CAS Reg. No. 13292-46-1.

Other name. Rifampin.

Description. A brick-red to red-brown, crystalline powder.

Solubility. Very slightly to slightly soluble in water; soluble in methanol R; slightly soluble in acetone R, ethanol (~750 g/L) TS, and ether R.

Category. Antileprosy drug; antituberculosis drug.

Storage. Rifampicin should be kept in a tightly closed container or in an atmosphere of nitrogen, protected from light.

Additional information. Rifampicin exhibits polymorphism.

Requirements

Definition. Rifampicin contains not less than 97.0% and not more than 102.0% of $C_{43}H_{58}N_4O_{12}$, calculated with reference to the dried substance.

Manufacture. The production method is validated to demonstrate to the satisfaction of the responsible regulatory authority that the probably carcinogenic nitrosamine 1-nitroso-4-methyl piperazine (MeNP) is eliminated or minimized and adequately controlled in the final product.

Identity tests

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

B. Dissolve 50 mg in 50 mL of methanol R and dilute 1 mL of this solution to 50 mL with phosphate buffer, pH 7.4, TS. The absorption spectrum of the resulting solution, when observed between 220 nm and 500 nm, exhibits 4 maxima at about 237 nm, 254 nm, 334 nm and 475 nm; the ratio of the absorbance of a 1 cm layer at the maximum at about 334 nm to that at the maximum at about 475 nm is about 1.75.

C. Suspend 25 mg in 25 mL of water, shake for 5 minutes and filter. To 5 mL of the filtrate, add 1 mL of ammonium persulfate/phosphate buffer TS and shake for a few minutes; the colour turns from orange-yellow to violet-red without the formation of a precipitate.

Heavy metals. Place 1.0 g in a silica crucible and mix it with 4 mL of magnesium sulfate/sulfuric acid TS. Heat cautiously to ignition and continue heating until a white or, at most, greyish residue is obtained. Ignite at a temperature not exceeding 800 °C, allow to cool, and moisten the residue with a few drops of sulfuric acid (~100 g/L) TS. Evaporate, ignite again, and allow to cool. Next, dissolve the residue in hydrochloric acid (~70 g/L) TS, add, drop by drop, a solution of ammonia (~100 g/L) PbTS, until the pH of the solution is between 8 and 8.5, then add, also drop by drop, acetic acid (~60 g/L) PbTS to adjust the pH to 3–4, filter, dilute with water to 40 mL and mix. Determine the heavy metals content as described under 2.2.3 Limit test for heavy metals, according to Method A; not more than 20 µg/g.

Sulfated ash. Not more than 1.0 mg/g.

Loss on drying. Dry at 60 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm of mercury) for 4 hours; it loses not more than 10 mg/g.

pH value. Shake 0.10 g with 10 mL of carbon-dioxide-free water R; pH of the suspension, 4.5–6.5.

Related substances

Carry out the test as described under *1.14.1 Thin-layer chromatography*, using silica gel R1 as the coating substance and preparing the slurry with phosphate/citrate buffer pH 6.0, TS. As the mobile phase, use a mixture of 85 volumes of chloroform R and 15 volumes of methanol R. Apply separately to the plate 20 µl of each of 4 solutions in chloroform R containing (A) 20 mg of the test substance per mL, (B) 0.10 mg of 3-formylrifamycin SV RS per mL, (C) 0.30 mg of rifampicin quinone RS per mL and (D) 0.20 mg of the test substance per mL. After removing the plate from the chromatographic chamber, allow it to dry in air and examine the chromatogram in daylight. Any coloured spots obtained with solution A, other than the principal spot, are not more intense than the corresponding spots obtained with solutions B and C. Any other spots obtained with solution A are not more intense than that obtained with solution D.

Assay

Dissolve about 0.10 g, accurately weighed, in sufficient methanol R to produce 100 mL. Dilute 2 mL of this solution to 100 mL with phosphate buffer, pH 7.4, TS. Measure the absorbance of the resulting solution in a 1 cm layer at the maximum at about 475 nm, using as the blank phosphate buffer, pH 7.4, TS. Calculate the content of $C_{43}H_{58}N_4O_{12}$, using the absorptivity value of 18.7 ($A^{1\%}_{1cm} = 187$).

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