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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.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.866:

RIFAMPICIN
(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 56 th WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2021
Further follow-up action as required.	

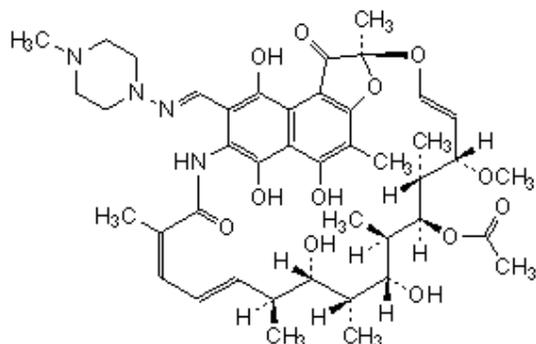
[Note from the Secretariat. Following the determination of traces of nitrosamines in some batches of rifampicin active pharmaceutical ingredient, it is proposed to revise the corresponding monograph.]

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

49

RIFAMPICIN (RIFAMPICINUM)

50



51

52

53 $C_{43}H_{58}N_4O_{12}$

54

55 **Relative molecular mass.** 822.9.

56

57 **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-
58 pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[[[(4-methylpiperazin-1-
59 yl)imino]methyl]-1,11-dioxo-1,2-dihydro-2,7-
60 (epoxypentadeca[1,11,13]trienimino)naphtho[2,1-*b*]furan-21-yl acetate; 3-[[[(4-methyl-1-
61 piperazinyl)imino]methyl]rifamycin; CAS Reg. No. 13292-46-1.

62

63 **Other name.** Rifampin.

64

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

66

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

69

70 **Category.** Antileprosy drug; antituberculosis drug.

71

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

74

75 **Additional information.** Rifampicin exhibits polymorphism.

76

77 **Requirements**

78

79 **Definition.** Rifampicin contains not less than 97.0% and not more than 102.0% of
80 $C_{43}H_{58}N_4O_{12}$, calculated with reference to the dried substance.

81

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

85

86 **Identity tests**

87

88 A. Carry out the examination as described under [1.7 Spectrophotometry in the infrared](#)
89 [region](#). The infrared absorption spectrum is concordant with the spectrum obtained
90 from rifampicin RS or with the reference spectrum of rifampicin. If the spectra thus
91 obtained are not concordant, repeat the test using the residues obtained by separately
92 dissolving the test substance and rifampicin RS in a small amount of dichloromethane
93 R and evaporating to dryness. The infrared absorption spectrum is concordant with the
94 spectrum obtained from rifampicin RS.

95

96 B. Dissolve 50 mg in 50 mL of methanol R and dilute 1 mL of this solution to 50 mL with
97 phosphate buffer, pH 7.4, TS. The absorption spectrum of the resulting solution, when
98 observed between 220 nm and 500 nm, exhibits 4 maxima at about 237 nm, 254 nm,
99 334 nm and 475 nm; the ratio of the absorbance of a 1 cm layer at the maximum at
100 about 334 nm to that at the maximum at about 475 nm is about 1.75.

101

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

106

107 **Heavy metals.** Place 1.0 g in a silica crucible and mix it with 4 mL of magnesium
108 sulfate/sulfuric acid TS. Heat cautiously to ignition and continue heating until a white or, at
109 most, greyish residue is obtained. Ignite at a temperature not exceeding 800 °C, allow to cool,
110 and moisten the residue with a few drops of sulfuric acid (~100 g/L) TS. Evaporate, ignite
111 again, and allow to cool. Next, dissolve the residue in hydrochloric acid (~70 g/L) TS, add,
112 drop by drop, a solution of ammonia (~100 g/L) PbTS, until the pH of the solution is between
113 8 and 8.5, then add, also drop by drop, acetic acid (~60 g/L) PbTS to adjust the pH to 3–4, filter,
114 dilute with water to 40 mL and mix. Determine the heavy metals content as described under
115 2.2.3 Limit test for heavy metals, according to Method A; not more than 20 µg/g.

116
117 **Sulfated ash.** Not more than 1.0 mg/g.

118
119 **Loss on drying.** Dry at 60 °C under reduced pressure (not exceeding 0.6 kPa or about 5 mm
120 of mercury) for 4 hours; it loses not more than 10 mg/g.

121
122 **pH value.** Shake 0.10 g with 10 mL of carbon-dioxide-free water R; pH of the suspension,
123 4.5–6.5.

124 125 **Related substances**

126
127 Carry out the test as described under [1.14.1 Thin-layer chromatography](#), using silica gel R1 as
128 the coating substance and preparing the slurry with phosphate/citrate buffer pH 6.0, TS. As
129 the mobile phase, use a mixture of 85 volumes of chloroform R and 15 volumes of methanol
130 R. Apply separately to the plate 20 µl of each of 4 solutions in chloroform R containing (A)
131 20 mg of the test substance per mL, (B) 0.10 mg of 3-formylrifamycin SV RS per mL, (C) 0.30
132 mg of rifampicin quinone RS per mL and (D) 0.20 mg of the test substance per mL. After
133 removing the plate from the chromatographic chamber, allow it to dry in air and examine the
134 chromatogram in daylight. Any coloured spots obtained with solution A, other than the
135 principal spot, are not more intense than the corresponding spots obtained with solutions B and
136 C. Any other spots obtained with solution A are not more intense than that obtained with
137 solution D.

138

139

140 **Assay**

141

142 Dissolve about 0.10 g, accurately weighed, in sufficient methanol R to produce 100 mL. Dilute
143 2 mL of this solution to 100 mL with phosphate buffer, pH 7.4, TS. Measure the absorbance
144 of the resulting solution in a 1 cm layer at the maximum at about 475 nm, using as the blank
145 phosphate buffer, pH 7.4, TS. Calculate the content of $C_{43}H_{58}N_4O_{12}$, using the absorptivity
146 value of 18.7 ($A_{1cm}^{1\%} = 187$).

147

148

Draft for comments