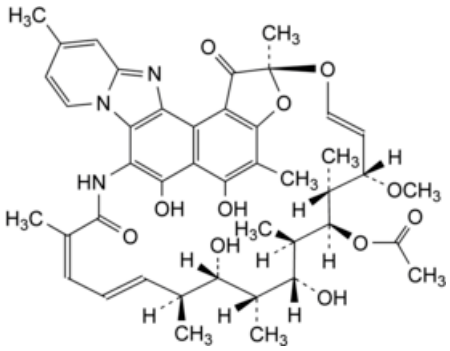
Edition: BP 2025 (Ph. Eur. 11.6 update)

Rifaximin

General Notices

(Ph. Eur. monograph 2362)



$C_{43}H_{51}N_3O_{11}$ 786 *80621-81-4*

Action and use

Antibacterial; treatment of infective diarrhoea.

Preparation

Rifaximin Tablets

Ph Eur

DEFINITION

(2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)5,6,21,23-Tetrahydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,15-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1,11,13]trienoimino)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate.

Semi-synthetic product derived from a fermentation product.

Content

97.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Red-orange, hygroscopic, crystalline powder.

Solubility

Practically insoluble in water, soluble in acetone and in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison *rifaximin CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *ethanol R*, evaporate to dryness and record new spectra using the residues.

TESTS

Related substances

Liquid chromatography (*2.2.29*).

Solvent mixture *acetonitrile R*, *water R* (40:60 *V/V*).

Test solution (a) Dissolve 0.100 g of the substance to be examined in 8 mL of *acetonitrile R* and dilute to 20 mL with *water R*.

Test solution (b) Dissolve 40.0 mg of the substance to be examined in 40.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of test solution (a) to 50.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve 5 mg of *rifaximin for system suitability CRS* (containing impurity H) in 1.6 mL of *acetonitrile R* and dilute to 4.0 mL with *water R*.

Reference solution (c) Dissolve 40.0 mg of *rifaximin CRS* in 40.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. Dilute 5.0 mL of the solution to 50.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated end-capped octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase Mix 37 volumes of a 3.16 g/L solution of *ammonium formate R* adjusted to pH 7.2 with *dilute ammonia R1* and 63 volumes of a mixture of equal volumes of *acetonitrile R* and *methanol R*.

Flow rate 1.4 mL/min.

Detection Spectrophotometer at 276 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Run time 3 times the retention time of rifaximin.

Relative retention With reference to rifaximin (retention time = about 12 min): impurities D and H = about 0.7.

System suitability Reference solution (b):

— *resolution*: minimum 3.0 between the peaks due to impurities D + H and rifaximin.

Limits:

— *sum of impurities D and H*: not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);

— *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);

— *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Water (*2.5.12*)

Maximum 4.5 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection Test solution (b) and reference solution (c).

Calculate the percentage content of $C_{43}H_{51}N_3O_{11}$ using the chromatogram obtained with reference solution (c) and the declared content of *rifaximin CRS*.

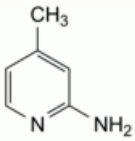
STORAGE

In an airtight container, protected from light.

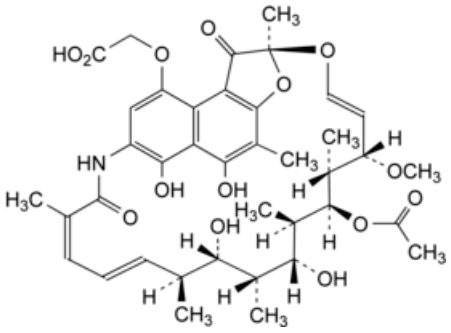
IMPURITIES

Specified impurities *D, H*.

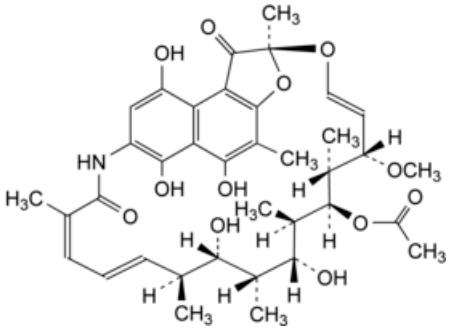
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, C, E, F, G*.



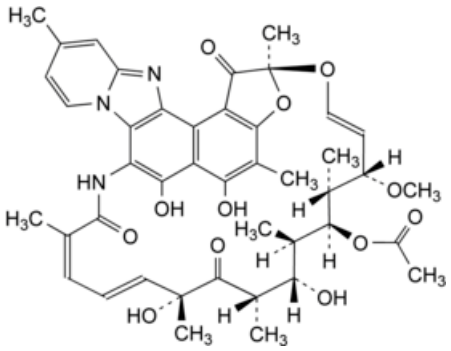
A. 4-methylpyridin-2-amine,



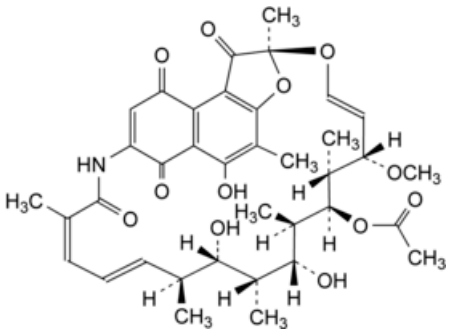
B. rifamycin B,



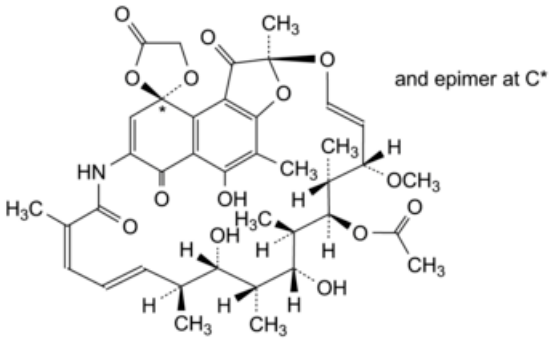
C. rifamycin SV,



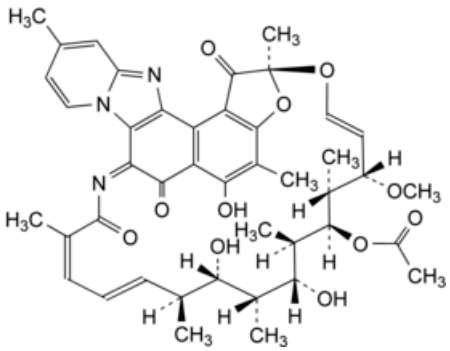
D. rifaximin Y,



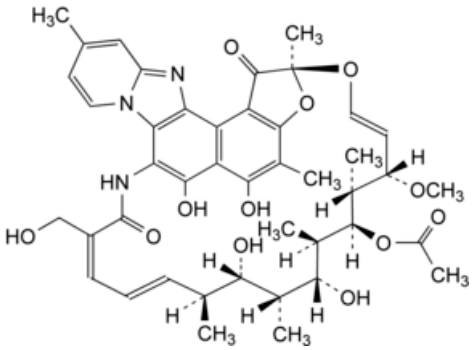
E. rifamycin S,



F. rifamycin O,



G. (2*S*,7*Z*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)-5,21,23-trihydroxy-27-methoxy-2,4,11,16,20,22,24,26-octamethyl-1,6,15-trioxo-1,2,6,7-tetrahydro-2,7-(epoxypentadeca[1,11,13]trienonitrilo)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate (6-*O*,14-didehydrorifaximin),



H. (2*S*,16*Z*,18*E*,20*S*,21*S*,22*R*,23*R*,24*R*,25*S*,26*R*,27*S*,28*E*)-5,6,21,23-tetrahydroxy-16-(hydroxymethyl)-27-methoxy-2,4,11,20,22,24,26-heptamethyl-1,15-dioxo-1,2-dihydro2,7-(epoxypentadeca[1,11,13]trienoimino)[1]benzofuro[4,5-*e*]pyrido[1,2-*a*]benzimidazol-25-yl acetate (16-desmethyl-16-(hydroxymethyl)rifaximin).

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