Rifaximin

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

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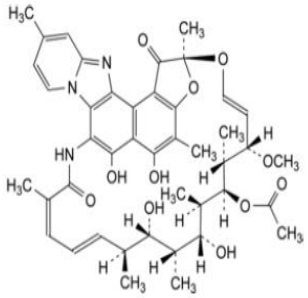
Further follow-up action as required.	

Rifaximin



$C_{43}H_{51}N_3O_{11}$ Mol. Wt. 786

Rifaximin is (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. It is a semi-synthetic product derived from a fermentation product.

Rifaximin contains not less than 97.0 per cent and not more than 102.0 per cent of $C_{43}H_{51}N_3O_{11}$, calculated on the anhydrous basis.

Category. Anti-diarrhoeal; Anti-bacterial

Description. A red-orange, crystalline powder, hygroscopic. It shows polymorphism (2.5.11).

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *rifaximin IPRS* or with the reference spectrum of rifaximin.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

Related substances. Determine by liquid chromatography (2.4.14).

Solvent mixture. 40 volumes of *acetonitrile* and 60 volumes of *water*.

Test solution. Dissolve 100 mg of the substance under examination in 8 ml of *acetonitrile* and dilute to 20.0 ml with *water*.

Reference solution (a). Dissolve 10 mg of *rifaximin IPRS* in 4 ml of *acetonitrile* and dilute to 10.0 ml with *water*. Dilute 1.0 ml of the solution to 100.0 ml with the solvent mixture.

Reference solution (b). A solution containing 0.0025 per cent w/v of *rifaximin impurity D+H IPRS* and 0.5 per cent w/v of *rifaximin IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 25 cm x 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm),
- column temperature: 40º,
- mobile phase: a mixture of 37 volumes of a buffer solution prepared by dissolving 3.16 g of *ammonium formate* in 1000 ml of *water*, adjusted to pH 7.2 with *dilute ammonia* and 63 volumes of a mixture of equal volumes of *acetonitrile* and *methanol*,
- flow rate: 1.4 ml per minute,

- spectrophotometer set at 276 nm,
- injection volume: 20 µl.

Name	Relative retention time
Rifaximin impurity D[1] and H[2]	0.7
Rifaximin (Retention time is about 12 minutes)	1.0

[1] rifaximin Y,

[2] (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).

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to impurity D+H and rifaximin is not less than 3.0.

Inject reference solution (a) and the test solution. Run the chromatogram 3 times the retention time of the principal peak. In the chromatogram obtained with the test solution, the sum of areas of the peaks corresponding to impurities D + H is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent), the area of any other secondary peak is not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent) and the sum of the areas of all the secondary peaks is not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent). Ignore any peak with an area less than 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Sulphated ash (2.3.18). Not more than 0.1 per cent.

Water (2.3.43). Not more than 4.5 per cent, determined on 0.5 g.

Assay. Determine by liquid chromatography (2.4.14), as described under Related substances using the following modifications.

Test solution. Dissolve 40 mg of the substance under examination in the solvent mixture and dilute to 100.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 50.0 ml with the solvent mixture.

Reference solution. A 0.004 per cent w/v solution of *rifaximin IPRS* in the solvent mixture.

Inject the reference solution and the test solution.

Calculate the content of $C_{43}H_{51}N_3O_{11}$.

Storage. Store protected from light and moisture.

Solubility (2.4.26). Soluble in *acetone* and in *methanol* and practically insoluble in *water*.