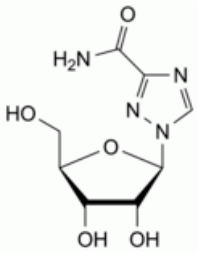
Edition: BP 2025 (Ph. Eur. 11.6 update)

Ribavirin

General Notices

(Ph. Eur. monograph 2109)



$C_8H_{12}N_4O_5$ 244.2 *36791-04-5*

Action and use

Antiviral (hepatitis C, respiratory syncytial virus).

Preparation

Ribavirin Powder for Nebuliser Solution

Ph Eur

DEFINITION

1-β-D-Ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide.

Content

98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance

White or almost white, crystalline powder.

Solubility

Freely soluble in water, slightly soluble in ethanol (96 per cent), slightly soluble or very slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison ribavirin CRS.

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

TESTS

pH (2.2.3)

4.0 to 6.5.

Dissolve 0.200 g in carbon dioxide-free water R and dilute to 10.0 mL with the same solvent.

Specific optical rotation (2.2.7)

-33 to -37 (dried substance).

Dissolve 0.250 g in water R and dilute to 25.0 mL with the same solvent. Determine the specific optical rotation within 10 min of preparing the solution.

Related substances

Liquid chromatography (2.2.29).

Test solution Dissolve 50.0 mg of the substance to be examined in water for chromatography R and dilute to 100.0 mL with the same solvent.

Reference solution (a) In order to produce impurity A *in situ*, mix 5.0 mL of the test solution and 5.0 mL of a 42 g/L solution of sodium hydroxide R and allow to stand for 90 min. Neutralise with 5.0 mL of a 103 g/L solution of hydrochloric acid R and mix well.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with water for chromatography R. Dilute 1.0 mL of this solution to 10.0 mL with water for chromatography R.

Reference solution (c) Dissolve 50.0 mg of ribavirin CRS in water for chromatography R and dilute to 100.0 mL with the same solvent.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: spherical end-capped octadecylsilyl silica gel for chromatography R (3 µm) suitable for use with highly aqueous mobile phases ;

— *temperature*: 25 °C.

Mobile phase:

— *mobile phase A*: dissolve 1.0 g of anhydrous sodium sulfate R in 950 mL of water for chromatography R, add 2.0 mL of a 5 per cent *V/V* solution of phosphoric acid R, adjust to pH 2.8 with a 5 per cent *V/V* solution of phosphoric acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: acetonitrile R1, mobile phase A (5:95 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 15	100	0

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
15 - 25	100 → 0	0 → 100
25 - 35	0	100

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 5 µL of the test solution and reference solutions (a) and (b).

Relative retention With reference to ribavirin (retention time = about 6 min): impurity A = about 0.8.

System suitability Reference solution (a):

— *resolution*: minimum 4.0 between the peaks due to impurity A and ribavirin.

Limits:

— *correction factor*: for the calculation of content, multiply the peak area of impurity A by 2.3;

— *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent);

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

— *total*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 5 h.

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 and reference solution (c).

Calculate the percentage content of $C_8H_{12}N_4O_5$ from the declared content of *ribavirin CRS*.

STORAGE

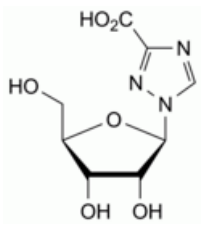
Protected from light.

IMPURITIES

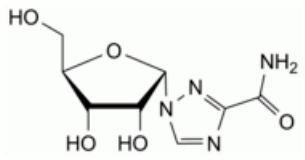
Specified impurities *A.*

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

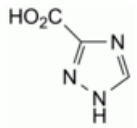
the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *B, C, D, F, G.*



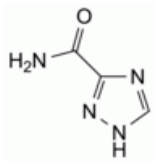
A. 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxylic acid,



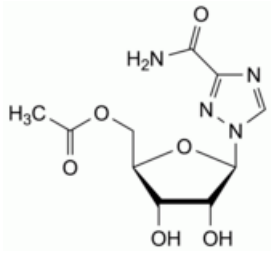
B. 1-α-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide (anomer),



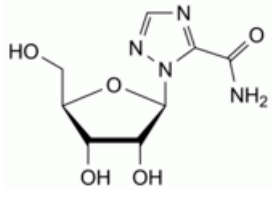
C. 1*H*-1,2,4-triazole-3-carboxylic acid,



D. 1*H*-1,2,4-triazole-3-carboxamide,



F. 1-(5-*O*-acetyl-β-D-ribofuranosyl)-1*H*-1,2,4-triazole-3-carboxamide (5′-*O*-acetylribavirin),



G. 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-5-carboxamide (*N*-isomer).