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

Riociguat Tablets

General Notices

(Ph. Eur. monograph 3079)

Action and use

Guanylate cyclase stimulator; treatment of pulmonary hypertension.

Ph Eur

DEFINITION

Tablets containing *Riociguat (3078)*, for human use.

They comply with the monograph Tablets (0478) and the following additional requirements.

Content

95.0 per cent to 105.0 per cent of the content of riociguat ($C_{20}H_{19}FN_8O_2$) stated on the label.

IDENTIFICATION

A. Record the UV spectrum of the principal peak in the chromatograms obtained with the solutions used in the assay, with a diode array detector in the range of 210-400 nm.

Results The UV spectrum of the principal peak in the chromatogram obtained with the test solution is similar to the UV spectrum of the principal peak in the chromatogram obtained with reference solution (a).

B. Examine the chromatograms obtained in the assay.

Results The principal peak in the chromatogram obtained with the test solution is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a).

TESTS

Protect the solutions from light throughout the tests.

Related substances

Liquid chromatography (*2.2.29*).

Solution A Mix about 5.5 mL of *phosphoric acid R* and 1000 mL of *water for chromatography R* and adjust to pH 1.6 with *phosphoric acid R*.

Solvent mixture *acetonitrile R*, solution A (20:80 *V/V*).

Test solution To an appropriate number of tablets (at least 5) add a volume of the solvent mixture equivalent to about 2/3 of the final volume. Shake for at least 15 min or sonicate for at least 30 min, until the tablets have disintegrated completely. Dilute with the solvent mixture to obtain a concentration of riociguat of 0.10 mg/mL, shake, centrifuge and use the clear supernatant.

Reference solution (a) Dissolve 5.0 mg of *riociguat CRS* in the solvent mixture using sonication and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of *riociguat for FP system suitability CRS* (containing impurities A and C) in the solvent mixture using sonication and dilute to 20 mL with the solvent mixture.

Column:

— *size*: *l* = 0.10 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (3.5 µm);

— *temperature*: 40 °C.

Mobile phase *acetonitrile R1*, solution A (23:77 *V/V*).

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 210 nm.

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

Run time 4 times the retention time of riociguat.

Identification of impurities Use the chromatogram supplied with *riociguat for FP system suitability CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and C.

Relative retention With reference to riociguat (retention time = about 3 min): impurity A = about 0.7; impurity C = about 2.4.

System suitability Reference solution (c):

— *resolution*: minimum 5.0 between the peaks due to impurity A and riociguat.

Calculation of percentage contents:

— for each impurity, use the concentration of riociguat in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.2 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.1 per cent; disregard the peak due to impurity C.

Dissolution[1] (*2.9.3, Apparatus 2*).

Dissolution medium Dissolve 4.75 g of *citric acid monohydrate R* and 27.47 g of *disodium hydrogen phosphate dihydrate R* in *water R*, add 1 L of a 10 g/L solution of *sodium laurilsulfate R* and dilute to 10 L with *water R*; adjust to pH 6.8 with a solution of *sodium hydroxide R* or *phosphoric acid R*. Use 900 mL of the medium.

Rotation speed 75 r/min.

Time 30 min.

Analysis Liquid chromatography (*2.2.29*).

Test solutions The samples withdrawn from the dissolution vessel and filtered.

Reference solution Dissolve 55.6 mg of *riociguat CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *methanol R*. Dilute a suitable volume of this solution with the dissolution medium to obtain a concentration of riociguat corresponding to the theoretical concentration of riociguat in the test solution, based on the labelled content of the tablets.

Column:

— *size*: *l* = 0.06 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 45 volumes of *acetonitrile R* and 55 volumes of a 1.54 g/L solution of *ammonium acetate R* previously adjusted to pH 4.0 with *glacial acetic acid R*.

Flow rate 2.3 mL/min.

Detection Spectrophotometer at 326 nm.

Injection 100 µL.

Run time Twice the retention time of riociguat.

Retention time Riociguat = about 1 min.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

Calculate the amount of dissolved riociguat ($C_{20}H_{19}FN_8O_2$), expressed as a percentage of the content stated on the label, taking into account the assigned content of *riociguat CRS*.

Acceptance criterion:

— *Q* = 80 per cent after 30 min.

ASSAY

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

Injection Test solution and reference solution (a).

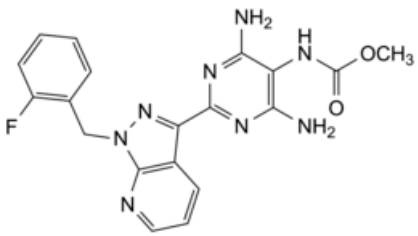
System suitability Reference solution (a):

— *repeatability*: maximum relative standard deviation of 1.0 per cent determined on 6 injections.

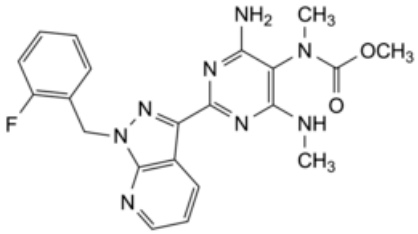
Calculate the percentage content of riociguat ($C_{20}H_{19}FN_8O_2$) taking into account the assigned content of *riociguat CRS*.

IMPURITIES

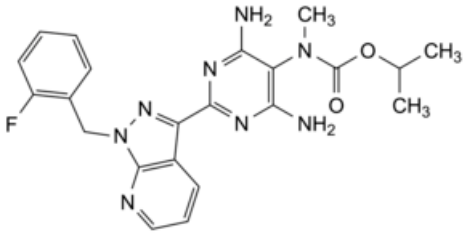
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph)*: A, C, D*.



A. methyl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl]carbamate,



C. methyl [4-amino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-(methylamino)pyrimidin-5-yl](methyl)carbamate,



D. propan-2-yl [4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl](methyl)carbamate.

Ph Eur

[1] The test approved in the marketing authorisation is to be used for routine quality control to confirm batch-to-batch consistency. For more information please consult Ph. Eur. *1. General Notices*.