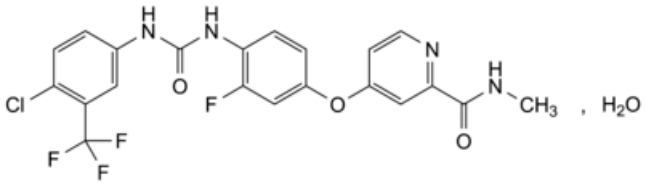
Edition: BP 2025 (Ph. Eur. 11.6 update)

Regorafenib Monohydrate

General Notices

(Ph. Eur. monograph 3012)



$C_{21}H_{15}ClF_4N_4O_3,H_2O$ 500.8 *1019206-88-2*

Action and use

Tyrosine kinase inhibitor; treatment of metastatic colorectal cancer and unresectable or metastatic gastrointestinal stromal tumours.

Preparation

Regorafenib Tablets

Ph Eur

DEFINITION

4-[4-[[[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide monohydrate.

Content

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

CHARACTERS

Appearance

White or almost white or pinkish or brownish powder.

Solubility

Practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96 per cent) and in methanol, practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison regorafenib monohydrate CRS.

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

B. Water (see Tests).

TESTS

Impurity A

Liquid chromatography (2.2.29). *Carry out the test protected from light and store the solutions at 2-8 °C.*

Test solution Dissolve 0.250 g of the substance to be examined in tetrahydrofuran R and dilute to 5.0 mL with the same solvent.

Reference solution Dissolve 5.0 mg of regorafenib impurity A CRS in tetrahydrofuran R and dilute to 50.0 mL with the same solvent. Dilute 2.5 mL of the solution to 50.0 mL with tetrahydrofuran R.

Column:

— *size*: *l* = 0.15 m, Ø = 3.0 mm;

— *stationary phase*: end-capped ethylene-bridged polar-embedded octadecylsilyl silica gel for chromatography (hybrid material) R (3.5 µm);

— *temperature*: 50 °C.

Mobile phase:

— *mobile phase A*: mix 8 volumes of acetonitrile for chromatography R and 92 volumes of a solution containing 0.5 g/L of dipotassium hydrogen phosphate R and 1.5 g/L of potassium dihydrogen phosphate R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 17	100 → 22	0 → 78

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 228 nm.

Autosampler Set at 8 °C.

Injection 3.0 µL.

Relative retention With reference to regorafenib (retention time = about 14 min): impurity A = about 0.6.

System suitability Reference solution:

— *repeatability*: maximum relative standard deviation of 10.0 per cent determined on 6 injections.

Calculation of content:

— for impurity A, use the concentration of impurity A in the reference solution.

Limit:

— *impurity A*: maximum 100 ppm.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light and store the solutions at 2-8 °C.*

Test solution (a) Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 20.0 mL with the same solvent.

Test solution (b) Dilute 15.0 mL of test solution (a) to 50.0 mL with *methanol R*.

Reference solution (a) Dissolve 30.0 mg of *regorafenib monohydrate CRS* in *methanol R* and dilute to 20.0 mL with the same solvent. Dilute 15.0 mL of the solution to 50.0 mL with *methanol R*.

Reference solution (b) Dilute 1.0 mL of test solution (a) to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (c) Dissolve 2 mg of *sorafenib CRS* in *methanol R* and dilute to 50 mL with the same solvent. Dilute 0.2 mL of the solution to 2 mL with test solution (a).

Reference solution (d) Dissolve 3 mg of *regorafenib impurity C CRS* in *methanol R* and dilute to 100 mL with the same solvent.

Reference solution (e) Dissolve 3 mg of *regorafenib impurity D CRS* in *dimethyl sulfoxide R* and dilute to 100 mL with the same solvent.

Reference solution (f) Mix 1 mL of reference solution (d) and 1 mL of reference solution (e) and dilute to 20 mL with *methanol R*.

Column:

— *size*: *l* = 0.15 m, Ø = 2.1 mm;

— *stationary phase*: *end-capped ethylene-bridged phenylsilyl silica gel for chromatography (hybrid material) R* (3.5 µm);

— *temperature*: 63 °C.

Mobile phase:

— *mobile phase A*: *acetonitrile for chromatography R*, 0.1 per cent *V/V* solution of *trifluoroacetic acid R* (3:97 *V/V*);

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	100	0
2 - 15	100 → 78	0 → 22
15 - 25	78 → 60	22 → 40
25 - 33	60 → 36	40 → 64
33 - 37	36	64

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 232 nm.

Autosampler Set at 8 °C.

Injection 5 µL of test solution (a) and reference solutions (b), (c) and (f).

Identification of peaks Use the chromatogram obtained with reference solution (f) to identify the peaks due to impurities C and D; use the chromatogram obtained with reference solution (c) to identify the peak due to sorafenib.

Relative retention With reference to regorafenib (retention time = about 25 min): impurity C = about 0.4; impurity D = about 0.8; sorafenib = about 0.95.

System suitability Reference solution (c):

— *resolution*: minimum 3.0 between the peaks due to sorafenib and regorafenib.

Calculation of percentage contents:

— *correction factors*: multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 0.5; impurity D = 0.6;

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

Limits:

— *impurity D*: maximum 0.2 per cent;

— *impurity C*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.32*)

3.2 per cent to 4.0 per cent, determined on 50.0 mg using the evaporation technique at 150 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

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

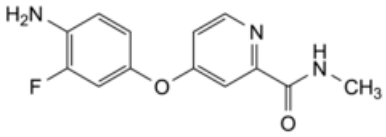
Injection Test solution (b) and reference solution (a).

Calculate the percentage content of $C_{21}H_{15}ClF_4N_4O_3$ taking into account the assigned content of *regorafenib monohydrate CRS*.

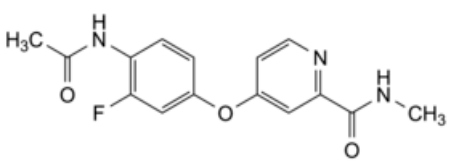
IMPURITIES

Specified impurities *A, C, D.*

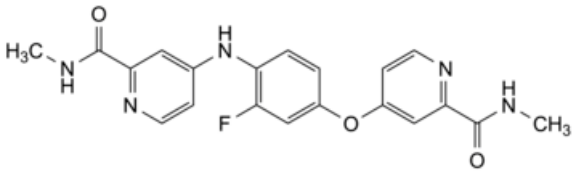
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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, E.*



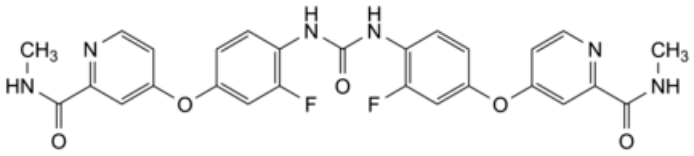
A. 4-(4-amino-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide,



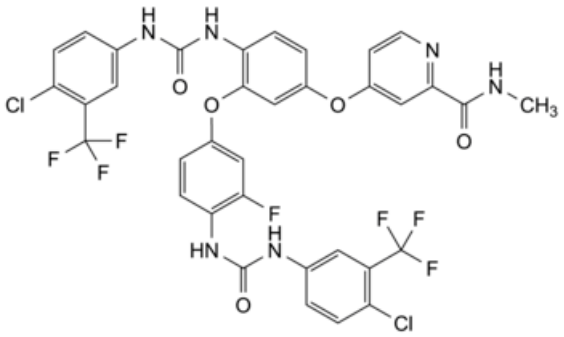
B. 4-(4-acetamido-3-fluorophenoxy)-*N*-methylpyridine-2-carboxamide,



C. 4-[3-fluoro-4-[[2-(methylcarbamoyl)pyridin-4-yl]amino]phenoxy]-*N*-methylpyridine-2-carboxamide,



D. 3^{3},7^{2}-difluoro-*N*,*N*′-dimethyl-5-oxo-2,8-dioxa-4,6-diaza-1(4),9(4)-dipyridina-3(1,4),7(1,4)-dibenzenanonaphane-1^{2},9^{2}-dicarboxamide,



E. 9^{4}-chloro-3^{4}-[[[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl]amino]-5^{3}-fluoro-*N*-methyl-7-oxo-9^{3}-(trifluoromethyl)-2,4-dioxa-6,8-diaza-1(4)-pyridina-3(1,3),5(1,4),9(1)-tribenzenanonaphane-1^{2}-carboxamide.

Ph Eur