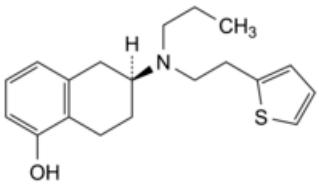
Edition: BP 2025 (Ph. Eur. 11.6 update)

Rotigotine

General Notices

(Ph. Eur. monograph 3014)



$C_{19}H_{25}NOS$ 315.5 *99755-59-6*

Action and use

Dopamine D2 receptor agonist; treatment of Parkinson's disease and restless legs syndrome.

Preparation

Rotigotine Transdermal Patches

Ph Eur

DEFINITION

(6*S*)-6-[Propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol.

Content

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

CHARACTERS

Appearance

White or light brown powder.

Solubility

Practically insoluble in water, soluble in anhydrous ethanol, very slightly soluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison rotigotine CRS.

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

B. Enantiomeric purity (see Tests).

TESTS

Enantiomeric purity

Liquid chromatography (2.2.29).

Solution A methanol R1, 2-propanol R, anhydrous ethanol R (5:5:90 *V/V/V*).

Solution B 0.1 per cent *V/V* solution of diethylamine R in solution A.

Test solution Dissolve 10 mg of the substance to be examined in solution B and dilute to 10 mL with solution B.

Reference solution Dissolve 2 mg of racemic rotigotine CRS in 1 mL of solution B.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: cellulose derivative of silica gel for chiral separation R (10 µm).

Mobile phase diethylamine R, solution A, heptane R (0.1:2:98 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 225 nm.

Injection 10 µL.

Run time 1.5 times the retention time of rotigotine.

Relative retention With reference to rotigotine (retention time = about 22 min): impurity A = about 0.9.

System suitability Reference solution:

— resolution: minimum 1.5 between the peaks due to impurity A and rotigotine.

Limit:

— *impurity A*: maximum 0.15 per cent, calculate the ratio of the area of the peak due to impurity A to the sum of the areas of the peaks due to rotigotine and impurity A.

Related substances

Liquid chromatography (2.2.29).

Solution A 0.1 per cent *V/V* solution of trifluoroacetic acid R.

Solution B 0.1 per cent *V/V* solution of trifluoroacetic acid R in acetonitrile R.

Test solution (a) Suspend 30.0 mg of the substance to be examined in 2.5 mL of solution B and add 20 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 50.0 mL with solution A.

Test solution (b) Dilute 1.0 mL of test solution (a) to 10.0 mL with solution A.

Reference solution (a) Suspend 33.0 mg of *rotigotine hydrochloride CRS* in 2.5 mL of solution B and add 20 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 50.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Reference solution (b) Suspend 3 mg of *rotigotine impurity B CRS*, 5 mg of *rotigotine impurity C CRS*, 5 mg of *rotigotine impurity G CRS* and 3 mg of *rotigotine impurity H CRS* in 5 mL of solution B and add 40 mL of solution A. Sonicate for at least 20 min, shaking vigorously at 5 min intervals, until dissolution is complete, then dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 50.0 mL with solution A.

Reference solution (c) To 1.0 mL of test solution (a) add 5 mL of solution B and dilute to 100.0 mL with solution A. Dilute 1.0 mL of this solution to 10.0 mL with solution A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped extra-dense bonded octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: *trifluoroacetic acid R*, *water for chromatography R* (0.3:1000 *V/V*);

— *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile for chromatography R* (0.2:1000 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	82	18
2 - 24	82 → 50	18 → 50

Flow rate 2.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of test solution (a) and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities B, C, G and H.

Relative retention With reference to rotigotine (retention time = about 10 min): impurity B = about 0.2; impurity C = about 0.6; impurity G = about 1.6; impurity H = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 1.5 between the peaks due to impurities G and H.

Calculation of percentage contents:

— for each impurity, use the concentration of rotigotine in reference solution (c).

Limits:

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

— *impurity B*: maximum 0.15 per cent;

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

— *total*: maximum 0.6 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.20 per cent, determined on 1.00 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 modifications.

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

System suitability Reference solution (a):

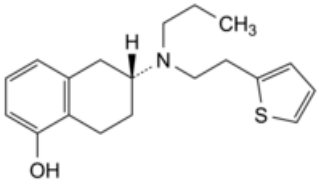
— *symmetry factor*: maximum 2.2 for the principal peak.

Calculate the percentage content of $C_{19}H_{25}NOS$ taking into account the assigned content of *rotigotine hydrochloride CRS* and a conversion factor of 0.8964.

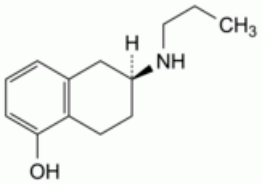
IMPURITIES

Specified impurities *A, B, C, G.*

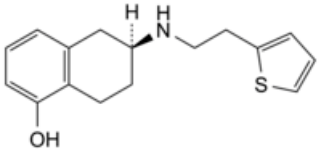
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



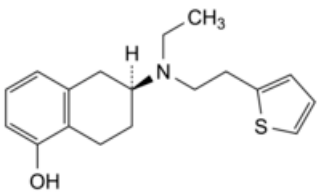
A. (6*R*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol ((*R*)-rotigotine),



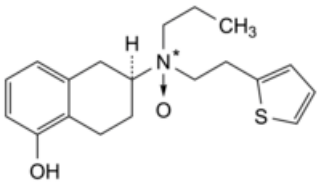
B. (6*S*)-6-(propylamino)-5,6,7,8-tetrahydronaphthalen-1-ol (desthienylethyl rotigotine),



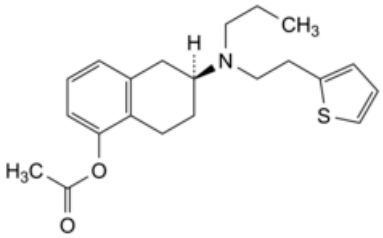
C. (6*S*)-6-[[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol (despropyl rotigotine),



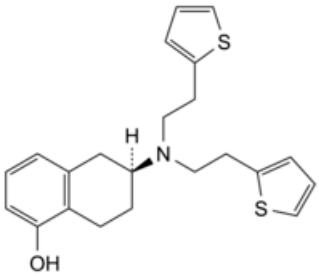
D. (6*S*)-6-[ethyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol (ethyl rotigotine),



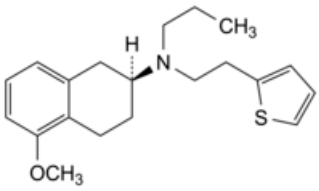
E. (2*S*)-5-hydroxy-*N*-propyl-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine *N*-oxide (rotigotine *N*-oxide),



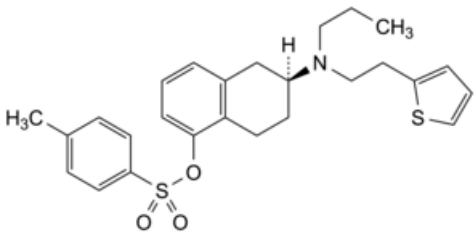
F. (6*S*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-yl acetate (acetyl rotigotine),



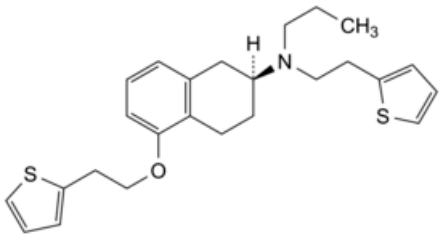
G. (6*S*)-6-[*N*,*N*-bis[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-ol,



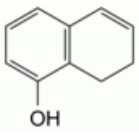
H. (2*S*)-5-methoxy-*N*-propyl-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (methoxy rotigotine),



I. (6*S*)-6-[propyl[2-(thiophen-2-yl)ethyl]amino]-5,6,7,8-tetrahydronaphthalen-1-yl 4-methylbenzenesulfonate (rotigotine toluene sulfonic acid ester),



J. (2*S*)-*N*-propyl-5-[2-(thiophen-2-yl)ethoxy]-*N*-[2-(thiophen-2-yl)ethyl]-1,2,3,4-tetrahydronaphthalen-2-amine (rotigotine thienylethyl ether),



K. 7,8-dihydronaphthalen-1-ol.

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