Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Use a platinum crucible. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): maximum 1.5 per cent, determined on 0.500 g.

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*).

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

Reference solution (a). Dissolve 51.2 mg of *paroxetine hydrochloride hemihydrate CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dissolve 5.0 mg of *paroxetine hydrochloride hemihydrate CRS* and 5 mg of *paroxetine impurity A CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 3.85 g of *ammonium acetate R* in *water R*, adjust to pH 5.5 with *anhydrous acetic acid R* and dilute to 600 mL with *water R*; add 400 mL of *acetonitrile R*; slowly add, with stirring, 10 mL of *triethylamine R* and adjust to pH 5.5 with *anhydrous acetic acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 295 nm.

Injection: 10 µL.

Run time: twice the retention time of paroxetine.

System suitability: reference solution (b):

– *resolution*: minimum 2 between the peaks due to paroxetine and impurity A.

Calculate the percentage content of $C_{19}H_{21}ClFNO_3$ using the chromatogram obtained with reference solution (a) and the declared content of *paroxetine hydrochloride hemihydrate CRS*.

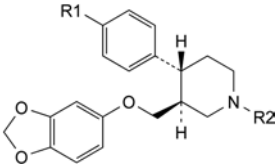
STORAGE

In an airtight container, at a temperature not exceeding 25 °C.

IMPURITIES

Specified impurities: A, C, D, F, G, H, I, J.

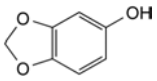
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



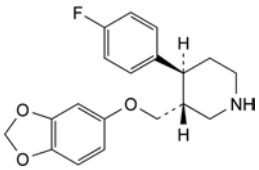
A. R1 = R2 = H: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenylpiperidine (desfluoroparoxetine),

C. R1 = F, R2 = CH_2-C_6H_5: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-1-benzyl-4-(4-fluorophenyl)piperidine (*N*-benzylparoxetine),

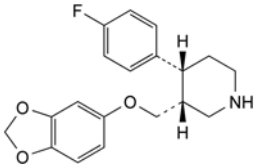
F. R1 = H, R2 = CH_2-C_6H_5: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-1-benzyl-4-phenylpiperidine (*N*-benzyldesfluoroparoxetine),



B. 1,3-benzodioxol-5-ol (sesamol),

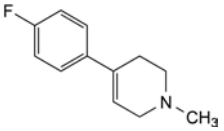


D. (3*R*,4*S*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ((+)-*trans*-paroxetine),

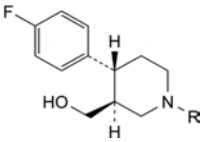


and enantiomer

E. (3*RS*,4*RS*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine (*cis*-paroxetine),

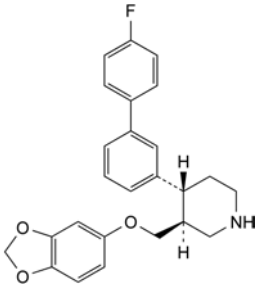


G. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine,



H. R = CH_2-C_6H_5: [(3*S*,4*R*)-1-benzyl-4-(4-fluorophenyl)-piperidin-3-yl]methanol,

I. R = H: [(3*S*,4*R*)-4-(4-fluorophenyl)piperidin-3-yl]methanol,

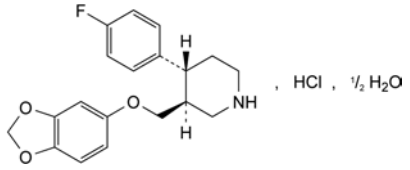


J. (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4′-fluorobiphenyl-3-yl)piperidine.

01/2008:2018

PAROXETINE HYDROCHLORIDE HEMIHYDRATE

Paroxetini hydrochloridum hemihydricum



$C_{19}H_{21}ClFNO_3,{}^1/_2H_2O$ M_r 374.8

[110429-35-1]

DEFINITION

(3*S*,4*R*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine hydrochloride hemihydrate.

Content: 97.5 per cent to 102.0 per cent (anhydrous substance).

PRODUCTION

Impurity G: maximum 1 ppm, determined by a suitable, validated method.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol (96 per cent) and in methylene chloride.

It shows pseudopolymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *paroxetine hydrochloride hemihydrate CRS*.

If the spectra obtained show differences, dissolve 1 part of the substance to be examined and 1 part of the reference substance separately in 10 parts of a mixture of 1 volume of *water R* and 9 volumes of *2-propanol R* and heat to 70 °C to dissolve. Recrystallise and record new spectra using the residues.

B. Examine the chromatograms obtained in the test for impurity D.

Injection: test solution and reference solution (c).

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 (c).

C. Water (see Tests).

D. It gives reaction (b) of chlorides (*2.3.1*).

TESTS

Impurity D. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 0.1000 g of the substance to be examined in 20 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (b). Dissolve 5 mg of *paroxetine impurity D CRS* and 5 mg of *paroxetine hydrochloride hemihydrate CRS* in 2 mL of *methanol R* and dilute to 100.0 mL with the mobile phase.

Reference solution (c). Dissolve 10 mg of *paroxetine hydrochloride hemihydrate CRS* in 2 mL of *methanol R* and dilute to 10.0 mL with the mobile phase.

Column:

– *size*: *l* = 0.10 m, Ø = 4.0 mm;
– *stationary phase*: *silica gel AGP for chiral chromatography R* (5 µm).

Mobile phase: mix 2 volumes of *methanol R* and 8 volumes of a 5.8 g/L solution of *sodium chloride R*.

Flow rate: 0.5 mL/min.

Detection: spectrophotometer at 295 nm.

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

Run time: 2.5 times the retention time of paroxetine.

Retention time: paroxetine = about 30 min.

System suitability: reference solution (b):

– *resolution*: minimum 2.2 between the peaks due to impurity D and paroxetine.

Limit:

– *impurity D*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *tetrahydrofuran R, water R* (1:9 *V/V*).

Test solution. Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the same solvent mixture.

Reference solution (a). Dilute 5.0 mL of the test solution to 50.0 mL with the solvent mixture. Dilute 2.0 mL of this solution to 200.0 mL with the solvent mixture.

Reference solution (b). Dissolve 2 mg of *paroxetine for system suitability CRS* (containing impurity C) in the solvent mixture and dilute to 10 mL with the solvent mixture. Dilute 1 mL of this solution to 10 mL with the solvent mixture.

Reference solution (c). Dissolve 2 mg of *paroxetine impurity A CRS* in the solvent mixture and dilute to 20 mL with the same solvent mixture.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (5 µm);
– *temperature*: 40 °C.

Mobile phase:

– *mobile phase A*: *trifluoroacetic acid R, tetrahydrofuran R, water R* (5:100:900 *V/V/V*);
– *mobile phase B*: *trifluoroacetic acid R, tetrahydrofuran R, acetonitrile R* (5:100:900 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 30	80	20
30 - 50	80 → 20	20 → 80
50 - 60	20	80
60 - 65	20 → 80	80 → 20
65 - 70	80	20

Flow rate: 1 mL/min.

Detection: spectrophotometer at 295 nm.

Injection: 20 µL.

Relative retention with reference to paroxetine: impurity A = about 0.8.

System suitability: reference solution (b):

– *resolution*: minimum 3.5 between the peaks due to impurity C and paroxetine.

Limits:

– *impurity A*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
– *unspecified impurities*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent);
– *disregard limit*: 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 20 ppm.

1.0 g complies with test C. Use a platinum crucible. Prepare the reference solution using 2 mL of *lead standard solution (10 ppm Pb) R*.

Water (*2.5.12*): 2.2 per cent to 2.7 per cent, determined on 0.300 g.

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*).

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

Reference solution (a). Dissolve 50.0 mg of *paroxetine hydrochloride hemihydrate CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dissolve 5.0 mg of *paroxetine hydrochloride hemihydrate CRS* and 5 mg of *paroxetine impurity A CRS* in *water R* and dilute to 10.0 mL with the same solvent.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *trimethylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: dissolve 3.85 g of *ammonium acetate R* in *water R*, adjust to pH 5.5 with *anhydrous acetic acid R* and dilute to 600 mL with the same solvent; add 400 mL of *acetonitrile R*; slowly add, with stirring, 10 mL of *triethylamine R* and readjust to pH 5.5 with *anhydrous acetic acid R*.

Flow rate: 1 mL/min.

Detection: spectrophotometer at 295 nm.

Injection: 10 µL.

Run time: twice the retention time of paroxetine.

System suitability: reference solution (b):

– *resolution*: minimum 2 between the peaks due to paroxetine and impurity A.

Calculate the percentage content of paroxetine hydrochloride using the chromatogram obtained with reference solution (a).

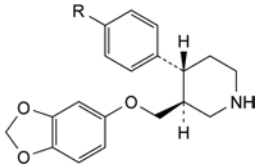
STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, D, G.

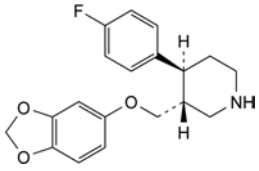
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



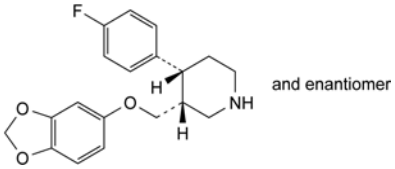
A. R = H: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenylpiperidine (desfluoroparoxetine),

B. R = OCH_3: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)piperidine,

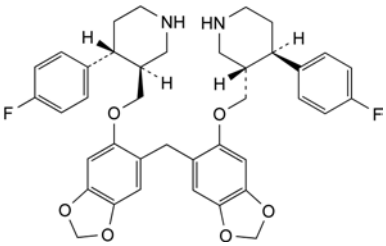
C. R = OC_2H_5: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-ethoxyphenyl)piperidine,



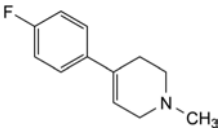
D. (3*R*,4*S*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ((+)-*trans*-paroxetine),



E. (3*RS*,4*RS*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine (*cis*-paroxetine),



F. 3,3′-[methylenebis(1,3-benzodioxole-6,5-diyloxymethylene)]bis[3*S*,4*R*)4-(4-fluorophenyl)piperidine],



G. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine.

01/2009:2403

PEA STARCH

Pisi amylum

DEFINITION

Pea starch is obtained from the seeds of *Pisum sativum* L.

CHARACTERS

Appearance: white or almost white, very fine powder.

Solubility: practically insoluble in cold water and in ethanol (96 per cent).

IDENTIFICATION

A. Examined under a microscope using equal volumes of *glycerol R* and *water R*, it presents a majority of large elliptical granules, 25-45 µm in size, sometimes irregular, or reniform. It also presents a minority of small rounded granules, 5-8 µm in size. Granules can present cracks or irregularities. Sometimes, granules show barely visible concentric striations. Exceptionally, granules show a slit along the main axis. Between orthogonally oriented polarising plates or prisms, the granules show a distinct black cross.

B. Suspend 1 g in 50 mL of *water R*, boil for 1 min and cool. A thin, cloudy mucilage is formed.

C. To 1 mL of the mucilage obtained in identification test B, add 0.05 mL of *iodine solution R1*. A dark blue colour is produced, which disappears on heating.

TESTS

pH (*2.2.3*): 5.0 to 8.0.

Shake 5.0 g with 25.0 mL of *carbon dioxide-free water R* for 60 s. Allow to stand for 15 min and shake again.

Foreign matter. Examined under a microscope using a mixture of equal volumes of *glycerol R* and *water R*, not more than traces of matter other than starch granules are present. No starch granules of any other origin are present.

Oxidising substances (*2.5.30*): maximum 20 ppm, calculated as H_2O_2.

Sulfur dioxide (*2.5.29*): maximum 50 ppm.