TESTS

Solution S. Dissolve 20.0 ml in *carbon dioxide-free water R* and dilute to 200.0 ml with the same solvent.

Acidity. To 50.0 ml of solution S add 0.05 ml of *phenolphthalein solution R*. Not more than 1.5 ml of *0.1 M sodium hydroxide* is required to change the colour of the indicator.

Refractive index (*2.2.6*): 1.403 to 1.406.

Relative density (*2.2.5*): 0.991 to 0.996.

Distillation range (*2.2.11*): a maximum of 10 per cent distils below 123 °C and a minimum of 95 per cent distils below 126 °C.

Freezing point (*2.2.18*): 10 °C to 13 °C.

Acetaldehyde. To 5.0 ml add a mixture of 0.2 ml of *methyl orange solution R*, 5 ml of *ethanol (60 per cent V/V) R* and 5 ml of *alcoholic hydroxylamine solution R* and shake. Not more than 0.8 ml of *0.5 M sodium hydroxide* is required to change the colour of the indicator to pure yellow.

Peroxides. Place 50.0 ml of solution S in a ground-glass-stoppered flask, add 5 ml of *dilute sulphuric acid R* and 10 ml of *potassium iodide solution R*, close the flask and allow to stand protected from light for 15 min. Titrate with *0.1 M sodium thiosulphate* using 1 ml of *starch solution R* as indicator. Allow to stand for 5 min and, if necessary complete the titration. Not more than 2.0 ml of *0.1 M sodium thiosulphate* is required.

Non-volatile residue: maximum 0.6 g/l.

Heat 5.0 ml in a tared evaporating dish on a water-bath and dry at 105 °C for 1 h. The residue weighs a maximum of 3 mg.

STORAGE

In a small, well-filled, airtight container, protected from light. If the substance has solidified the whole contents of the container must be liquefied before use.

have a 2-*O*-sulpho-α-L-idopyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulpho-D-glucosamine structure at the reducing end of their chain.

Parnaparin sodium complies with the monograph Low-molecular-mass heparins (0828), with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 4000 and 6000 with a characteristic value of about 5000.

The degree of sulphatation is 2.0 to 2.6 per disaccharide unit.

The potency is not less than 75 IU and not more than 110 IU of anti-factor Xa activity per milligram calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.5 and 3.0.

IDENTIFICATION

Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *parnaparin sodium CRS*.

Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. In order to verify the suitability of the system in the lower molecular mass ranges (for example M_r 2000), a suitable reference preparation is used. The following requirements apply.

The mass-average relative molecular mass ranges between 4000 and 6000. The mass percentage of chains lower than 3000 is not more than 30 per cent. The mass percentage of chains between 3000 and 8000 ranges between 50 per cent and 60 per cent.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_5 (*2.2.2, Method II*).

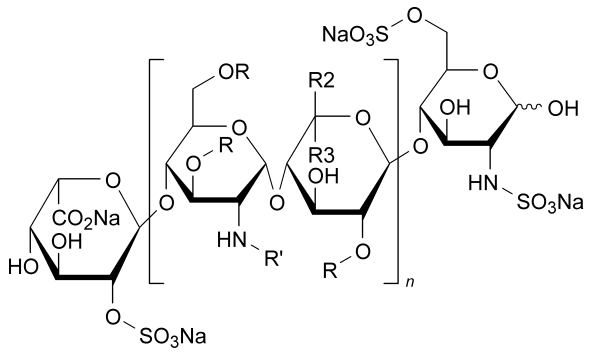
Dissolve 1.5 g in 10 ml of *water R*.

Copper: maximum 10.0 ppm, determined by atomic absorption spectrometry (*2.2.23, Method I*) and calculated with reference to the dried substance.

01/2008:1252

PARNAPARIN SODIUM

Parnaparinum natricum



n = 1 to 21 , R = H or SO_3Na , R' = SO_3Na or CO-CH_3
R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

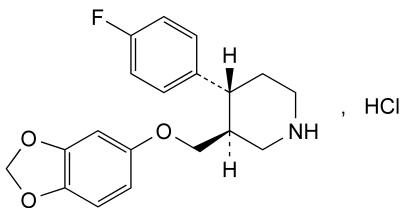
DEFINITION

Sodium salt of a low-molecular-mass heparin that is obtained by radical-catalysed depolymerisation, with hydrogen peroxide and with a cupric salt, of heparin from bovine or porcine intestinal mucosa. The majority of the components

01/2008:2283

PAROXETINE HYDROCHLORIDE, ANHYDROUS

Paroxetini hydrochloridum anhydricum



$C_{19}H_{21}ClFNO_3$ M_r 365.8
[78246-49-8]

DEFINITION

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

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, hygroscopic, crystalline powder.

Solubility: slightly soluble in water, freely soluble in methanol, sparingly soluble in anhydrous ethanol and in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *anhydrous paroxetine hydrochloride CRS*.

If the spectra obtained in the solid state show differences, mix 1 part of the substance to be examined and 1 part of the reference substance separately with 30 parts of anhydrous *acetone R* and heat to boiling to dissolve. Recrystallise and record new spectra using the residues.

B. Water (see Tests).

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

TESTS

Impurity D. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50.0 mg of the substance to be examined in 5 ml of *methanol R* and dilute to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 5 mg of *paroxetine impurity D CRS* in 2 ml of *methanol R* and dilute to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 1.0 ml of reference solution (a) to 10.0 ml with the test solution.

Reference solution (c). Dilute 1.0 ml of reference solution (a) to 100.0 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);
– *temperature*: 30 °C.

Mobile phase: dissolve 8.7 g of *dipotassium hydrogen phosphate R* in 1000 ml of *water for chromatography R* and adjust to pH 6.5 with *phosphoric acid R*; mix 930 ml of this solution and 70 ml of *acetonitrile R*.

Flow rate: 0.9 ml/min.

Detection: spectrophotometer at 295 nm.

Injection: 20 µl of the test solution and reference solutions (b) and (c).

Run time: 2.5 times the retention time of paroxetine which is about 12 min.

System suitability:

– *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity D and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to paroxetine in the chromatogram obtained with reference solution (b);
– *signal-to-noise ratio*: minimum 3 for the principal peak in the chromatogram obtained with reference solution (c);
– *symmetry factor*: the requirements stated in chapter *2.2.46* are not applicable.

Limit:

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

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *tetrahydrofuran R, water R* (10:90 *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 solvent mixture.

Reference solution (a). Dilute 5.0 ml of the test solution to 50.0 ml with the solvent mixture.

Reference solution (b). Dissolve 5.0 mg of *anhydrous paroxetine hydrochloride impurity H CRS* in 25 ml of *tetrahydrofuran R* and dilute to 50.0 ml with *water R*.

Reference solution (c). Dissolve 5 mg of *anhydrous paroxetine hydrochloride impurity C CRS* in 25 ml of *tetrahydrofuran R* and dilute to 50.0 ml with *water R*.

Reference solution (d). To 5.0 ml of reference solution (a) add 1.0 ml of reference solution (b) and dilute to 100.0 ml with the solvent mixture.

Reference solution (e). To 5.0 ml of reference solution (a) add 5.0 ml of reference solution (b) and 5.0 ml of reference solution (c). Dilute to 100.0 ml with the solvent mixture. Dilute 1.0 ml of this solution to 10.0 ml with the solvent mixture.

Reference solution (f). Dissolve 2.5 mg of *paroxetine impurity E CRS* in the solvent mixture, add 2.5 ml of the test solution and dilute to 100.0 ml with the solvent mixture.

Reference solution (g). Dissolve 5 mg of *paroxetine impurity A CRS* in the solvent mixture and dilute to 50 ml with the solvent mixture. Use this solution to identify the peak due to impurity A.

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 - 55	20	80
55 - 60	20 → 80	80 → 20
60 - 65	80	20

Flow rate: 1.0 ml/min.

Detection: spectrophotometer at 295 nm.

Injection: 20 µl of the test solution and reference solutions (d), (e), (f) and (g).

Relative retention with reference to paroxetine (retention time = about 28 min): impurity A = about 0.8; impurity E = about 0.9; impurity C = about 1.5.

Relative retention with reference to impurity C: impurity F = about 0.97; impurity J = about 1.02.

System suitability:

– *resolution*: minimum 3.5 between the peaks due to impurity E and paroxetine in the chromatogram obtained with reference solution (f);
– *signal-to-noise ratio*: minimum 3 for the peak due to paroxetine in the chromatogram obtained with reference solution (e).

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.6; impurity F = 1.7; impurity J = 1.3;
– *impurity A*: not more than 0.6 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.3 per cent);
– *impurities C, F, J*: for each impurity, not more than 0.2 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.1 per cent);
– *unspecified impurities*: for each impurity, not more than 0.2 times the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.10 per cent);
– *total*: not more than the area of the peak due to paroxetine in the chromatogram obtained with reference solution (d) (0.5 per cent);
– *disregard limit*: the area of the peak due to paroxetine in the chromatogram obtained with reference solution (e) (0.05 per cent).

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

Detection: spectrophotometer at 263 nm.

Injection: test solution and reference solutions (d) and (e).

Relative retention with reference to paroxetine (retention time = about 28 min): impurity I = about 0.2; impurity H = about 0.4.

System suitability: reference solution (e):

– *signal-to-noise ratio*: minimum 3 for the peak due to impurity H.

Limits:

– *impurities H, I*: for each impurity, not more than the area of the peak due to impurity H in the chromatogram obtained with reference solution (d) (0.1 per cent).

Acetone (*2.4.24, System B*): maximum 3.5 per cent.

2-Propanol (*2.4.24, System B*): maximum 4.3 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*): maximum 1.5 per cent, determined on 0.500 g.

Sulphated 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*.

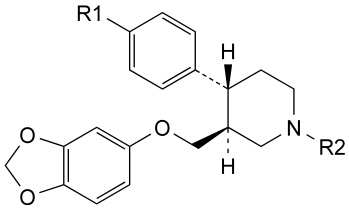
STORAGE

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

IMPURITIES

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

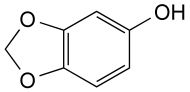
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



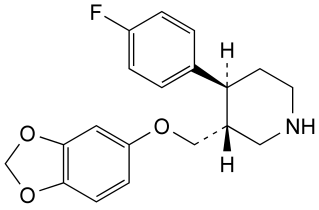
A. R1 = R2 = H: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenylpiperidine (desfluoroparoxetine),

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),

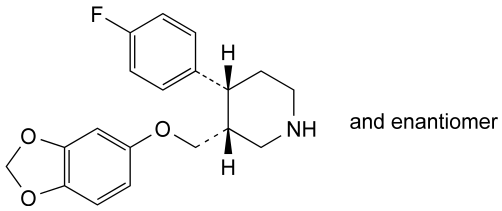
F. R1 = H, R2 = CH_2-C_6H_5: (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-1-benzyl-4-phenylpiperidine (*N*-benzyldesfluoroparoxetine),



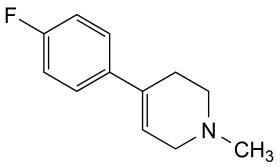
B. 1,3-benzodioxol-5-ol (sesamol),



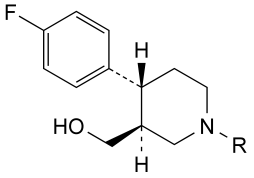
D. (3*R*,4*S*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ((+)-*trans*-paroxetine),



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

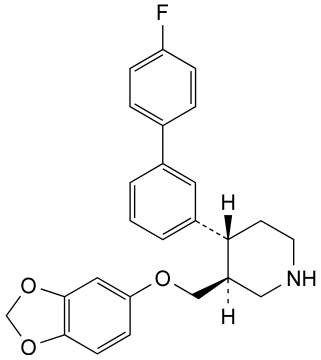


G. 4-(4-fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine,



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,

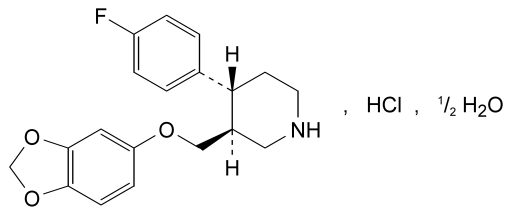


J. (3*S*,4*R*)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4′-fluorobiphenyl-3-yl)piperidine.

01/2008:2018

PAROXETINE HYDROCHLORIDE HEMIHYDRATE

Paroxetini hydrochloridum hemihydricum



$C_{19}H_{21}ClFNO_3$,½H_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.