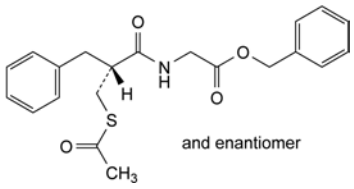
07/2008:2171
corrected 6.3

RACECADOTRIL

Racecadotrilum



$C_{21}H_{23}NO_4S$ M_r 385.5
[81110-73-8]

DEFINITION

Benzyl [[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetate.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methanol and in methylene chloride.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *racecadotril CRS*.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution Y_6 (*2.2.2, Method II*).

Dissolve 5.0 g in 10 mL of *acetone R*.

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: mobile phase A, mobile phase B (50:50 *V/V*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 mL with the solvent mixture.

Test solution (b). Dilute 5.0 mL of test solution (a) to 25.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of test solution (a) 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 (b). Dilute 500 µL of *racecadotril impurity A CRS* in *acetonitrile R* and dilute to 250.0 mL with the same solvent. Dilute 1.0 mL of the solution to 10.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 100.0 mL with the solvent mixture.

Reference solution (c). Dissolve 5 mg of *racecadotril impurity G CRS* in the solvent mixture and dilute to 50 mL with the solvent mixture. To 5 mL of this solution add 1 mL of test solution (b) and dilute to 100 mL with the solvent mixture.

Reference solution (d). Dissolve 50.0 mg of *racecadotril CRS* in the solvent mixture and dilute to 25.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 25.0 mL with the solvent mixture.

Reference solution (e). Dissolve 2 mg of *racecadotril for peak identification CRS* (containing impurities C, E and F) in 1.0 mL of the solvent mixture.

Column:

- *size*: *l* = 0.25 m, Ø = 4.0 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 30 °C.

Mobile phase:

- *mobile phase A*: dissolve 1.0 g of *potassium dihydrogen phosphate R* in *water R*, adjust to pH 2.5 with *phosphoric acid R* and dilute to 1000 mL with *water R*;
- *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	60	40
5 - 25	60 → 20	40 → 80
25 - 35	20	80

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL of the solvent mixture, test solution (a) and reference solutions (a), (b), (c) and (e).

Identification of impurities: use the chromatogram supplied with *racecadotril for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities C, E and F.

Relative retention with reference to racecadotril (retention time = about 16 min): impurity A = about 0.2; impurity C = about 0.3; impurity E = about 0.5; impurity F = about 0.9.

System suitability: reference solution (c):

- *resolution*: minimum 1.5 between the peaks due to impurity G and racecadotril.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity C = 1.4; impurity E = 0.6; impurity F = 0.7;
- *impurities C, E, F*: for each impurity, not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.1 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).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying *in vacuo* at 60 °C for 4 h.

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 modification.

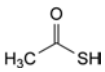
Injection: test solution (b) and reference solution (d).

Calculate the percentage content of $C_{21}H_{23}NO_4S$ from the declared content of *racecadotril CRS*.

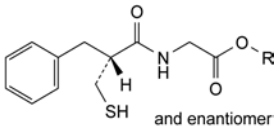
IMPURITIES

Specified impurities: A, C, E, F.

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, D, G, H.*

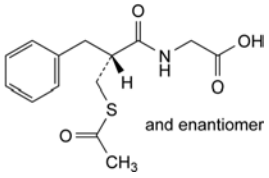


A. ethanethioic acid (thioacetic acid),

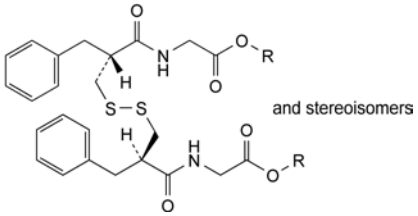


B. R = H: [[(2*RS*)-2-benzyl-3-sulfanylpropanoyl]amino]acetic acid,

G. R = CH_2-C_6H_5: benzyl [[(2*RS*)-2-benzyl-3-sulfanylpropanoyl]amino]acetate,

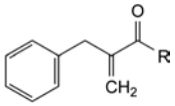


C. [[(2*RS*)-2-[(acetylsulfanyl)methyl]-3-phenylpropanoyl]amino]acetic acid,



D. R = H: 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioic acid,

H. R = CH_2-C_6H_5: dibenzyl 5,10-dibenzyl-4,11-dioxo-7,8-dithia-3,12-diazatetradecanedioate,



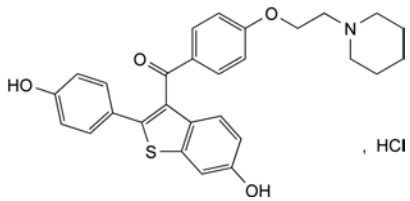
E. R = OH: 2-benzylprop-2-enoic acid (2-benzylacrylic acid),

F. R = NH-CH_2-CO-O-CH_2-C_6H_5: benzyl [(2-benzylprop-2-enoyl)amino]acetate.

01/2010:2375

RALOXIFENE HYDROCHLORIDE

Raloxifeni hydrochloridum



$C_{28}H_{28}ClNO_4S$ M_r 510.0
[82640-04-8]

DEFINITION

[6-Hydroxy-2-(4-hydroxyphenyl)-1-benzothiophen-3-yl][4-[2-(piperidin-1-yl)ethoxy]phenyl]methanone hydrochloride.

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

CHARACTERS

Appearance: almost white or pale-yellow powder.

Solubility: very slightly soluble or practically insoluble in water and in acetone, slightly soluble in ethanol (96 per cent *V/V*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *raloxifene hydrochloride CRS*.

B. Dissolve 20 mg of the substance to be examined in 2 mL of *methanol R*. The solution gives reaction (a) of chlorides (*2.3.1*).

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *acetonitrile R*, mobile phase A (30:70 *V/V*).

Test solution. Dissolve 30 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a). Dilute 1.0 mL of the test solution 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 (b). In order to produce impurity C *in situ*, to 6 mg of the substance to be examined add 15 mL of *acetonitrile R*, 3 mL of *water R* and 5 mL of stabilised *strong hydrogen peroxide solution R*. Store at 30 °C for at least 6 h then dilute to 50.0 mL with mobile phase A. To 1.0 mL of this solution add 3 mg of the substance to be examined dissolved in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (c). Dissolve 3 mg of *raloxifene for peak identification CRS* (containing impurity A) in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);
- *temperature*: 35 °C.

Mobile phase:
- *mobile phase A*: 9.0 g/L solution of *potassium dihydrogen phosphate R* adjusted to pH 3.0 with *phosphoric acid R*;
- *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 9	75	25
9 - 40	75 → 50	25 → 50

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 280 nm.

Injection: 10 µL.

Identification of impurity A: use the chromatogram supplied with *raloxifene for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention with reference to raloxifene (retention time = about 18 min): impurity A = about 0.7; impurity C = about 1.2.

System suitability:
- *resolution*: minimum 3.0 between the peaks due to raloxifene and impurity C in the chromatogram obtained with reference solution (b);
- *symmetry factor*: maximum 1.8 for the principal peak in the chromatogram obtained with reference solution (a).

Limits:
- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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);