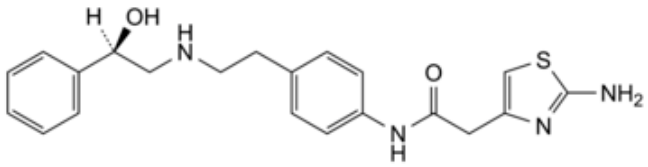
Edition: BP 2025 (Ph. Eur. 11.6 update)

Mirabegron

General Notices

(Ph. Eur. monograph 3132)



$C_{21}H_{24}N_4O_2S$ 396.5 *223673-61-8*

Action and use

$Beta_3$-adrenoceptor agonist; treatment of overactive bladder syndrome.

Ph Eur

DEFINITION

2-(2-Amino-1,3-thiazol-4-yl)-*N*-[4-[2-[[(2*R*)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide.

Content

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

CHARACTERS

Appearance

White crystalline powder.

Solubility

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

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison mirabegron CRS.

B. It complies with the limit given for impurity A in the test *Enantiomeric purity and impurity B* (see Tests).

TESTS

Enantiomeric purity and impurity B

Liquid chromatography (2.2.29). *Store the solutions protected from light*.

Solvent mixture acetonitrile R, water R (50:50 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in the solvent mixture and dilute to 25.0 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) Dissolve 4 mg of mirabegron racemate CRS in the solvent mixture and dilute to 20 mL with the solvent mixture.

Reference solution (c) Dissolve 5 mg of mirabegron impurity B CRS in the solvent mixture and dilute to 50 mL with the solvent mixture. Dilute 1 mL of this solution and 1 mL of reference solution (b) to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: beta-cyclodextrin derivative of silica gel for chiral separation R (5 µm);

— *temperature*: 50 °C.

Mobile phase Mix 200 volumes of acetonitrile for chromatography R and 750 volumes of a 6.8 g/L solution of potassium dihydrogen phosphate R, previously adjusted to pH 4.0 with a 10 per cent *V/V* solution of phosphoric acid R.

Flow rate 0.9 mL/min.

Detection Spectrophotometer at 240 nm.

Injection 20 µL of the test solution and reference solutions (a) and (c).

Run time Twice the retention time of mirabegron.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A and B.

Relative retention With reference to mirabegron (retention time = about 27 min): impurity B = about 0.7; impurity A = about 0.8.

System suitability Reference solution (c):

— *resolution*: minimum 2.5 between the peaks due to impurity A and mirabegron and minimum 2.0 between the peaks due to impurities A and B.

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity B by 1.6;

— for impurities A and B, use the concentration of mirabegron in reference solution (a).

Limits:

— *impurity A ((S)-enantiomer)*: maximum 0.2 per cent;

— *impurity B*: maximum 0.10 per cent;

— *reporting threshold for impurity B*: 0.05 per cent.

Related substances

Liquid chromatography (*2.2.29*). *Store the solutions at 2-8 °C, protected from light*.

Solvent mixture A *acetonitrile R*, *tetrahydrofuran for chromatography R* (33:67 *V/V*).

Solvent mixture B 14 g/L solution of *sodium perchlorate R*, adjusted to pH 2.0 with *perchloric acid R*.

Test solution (a) Dissolve 0.100 g of the substance to be examined in solvent mixture A and dilute to 10.0 mL with the same solvent mixture.

Test solution (b) Dilute 2.0 mL of test solution (a) to 20.0 mL with solvent mixture B.

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

Reference solution (b) Dissolve 5 mg of *mirabegron impurity C CRS* in mobile phase A and dilute to 100 mL with mobile phase A. Dilute 3 mL of this solution to 10 mL with mobile phase A. Dilute 1 mL of this solution and 1 mL of test solution (a) to 10 mL with mobile phase A.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *encapsulated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase:

— *mobile phase A*: solvent mixture A, solvent mixture B (10:80 *V/V*);

— *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 25	100	0
25 - 55	100 → 30	0 → 70
55 - 65	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

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

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention With reference to mirabegron (retention time = about 12 min): impurity C = about 1.7.

System suitability Reference solution (b):

— *resolution*: minimum 6.5 between the peaks due to mirabegron and impurity C.

Calculation of percentage contents:

— for each impurity, use the concentration of mirabegron in reference solution (a).

Limits:

— *impurity C*: maximum 0.15 per cent;

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

— *total, including impurity B* (determined in the test *Enantiomeric purity and impurity B*): maximum 0.2 per cent;

— *reporting threshold*: 0.05 per cent.

Impurities E, F, G

Liquid chromatography (*2.2.29*). *Store the solutions protected from light*.

Solvent mixture Mobile phase B, *water R* (50:50 *V/V*).

Test solution Dissolve 0.300 g of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution Dissolve 6.1 mg of *4-nitrophenethylamine hydrochloride R* (impurity E), 5.0 mg of *mirabegron impurity F CRS* and 5.0 mg of *mirabegron impurity G CRS* in the solvent mixture and dilute to 10.0 mL with the solvent mixture. Dilute 3.0 mL of the solution to 25.0 mL with the solvent mixture. Dilute 5.0 mL of this solution to 50.0 mL with the solvent mixture. Dilute 3.0 mL of the solution obtained to 20.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *encapsulated octadecylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 30 °C.

Mobile phase:

— *mobile phase A*: 14 g/L solution of *sodium perchlorate R*, adjusted to pH 2.0 with *perchloric acid R*;

— *mobile phase B*: *acetonitrile R*, *tetrahydrofuran for chromatography R* (33:67 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	85	15
10 - 15	85 → 70	15 → 30

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
15 - 30	70	30
30 - 40	70 → 35	30 → 65
40 - 50	35	65

Flow rate 1.5 mL/min.

Detection Spectrophotometer at 290 nm.

Injection 15 µL.

Identification of impurities Use the chromatogram obtained with the reference solution to identify the peaks due to impurities E, F and G.

Relative retention With reference to mirabegron (retention time = about 13 min): impurity E = about 0.7; impurity F = about 1.6; impurity G = about 1.7.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the peaks due to impurities E, F and G;

— *repeatability*: maximum relative standard deviation of 10 per cent for the areas of the peaks due to impurities E, F and G, determined on 6 injections.

Limits:

— *impurities E, F, G*: for each impurity, not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (30 ppm).

Impurity I

Gas chromatography (*2.2.28*).

Solvent mixture *N,N-diisopropylethylamine R*, *dimethylformamide R* (1:1000 *V/V*).

Test solution Dissolve 0.400 g of the substance to be examined in 1.0 mL of solvent mixture, using sonication. Add 9.0 mL of *heptane R* and shake for 45 min. Use the upper layer for injection.

Reference solution Dissolve 24.7 mg of *ethyl[(dimethylamino)propyl]carbodiimide hydrochloride R* (impurity I) in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.5 mL of this solution to 25.0 mL with the solvent mixture. Dilute 3.0 mL of this solution to 10.0 mL with the solvent mixture. To 1.0 mL of the solution obtained, add 9.0 mL of *heptane R* and shake for 45 min. Use the upper layer for injection.

Column:

— *material*: fused silica;

— *size*: *l* = 30 m, *Ø* = 0.53 mm;

— *stationary phase*: *base-deactivated phenyl(5)methyl(95)polysiloxane R* (film thickness 3 µm).

Carrier gas *helium for chromatography R*.

Flow rate 15.0 mL/min.

Split ratio 1:1.

Temperature:

	Time (min)	Temperature (°C)
Column	0 - 5	140
	5 - 10	140 → 240
	10 - 30	240
Injection port		220
Detector		250

Detection Flame ionisation.

Injection 2 µL.

Retention time Impurity I = about 4 min.

System suitability Reference solution:

— *signal-to-noise ratio*: minimum 10 for the peak due to impurity I;

— *repeatability*: maximum relative standard deviation of 10 per cent determined on 6 injections.

Limit:

— *impurity I*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (30 ppm).

Water (*2.5.32*)

Maximum 0.2 per cent determined on 0.300 g by direct sample introduction.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*). *Store the solutions at 2-8 °C, protected from light*.

Solvent mixture *acetonitrile R*, *water R* (50:50 *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. Dilute 2.5 mL of the solution to 25.0 mL with the solvent mixture.

Reference solution Dissolve 50.0 mg of *mirabegron CRS* in the solvent mixture and dilute to 50.0 mL with the solvent mixture. Dilute 2.5 mL of the solution to 25.0 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: *encapsulated octadecylsilyl silica gel for chromatography R* (3 µm);

— *temperature*: 45 °C.

Mobile phase Mix 800 volumes of a 14 g/L solution of *sodium perchlorate R*, previously adjusted to pH 2.0 with *perchloric acid R*, and 100 volumes of a mixture of *acetonitrile R* and *tetrahydrofuran for chromatography R* (33:67 *V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Autosampler Set at 5 °C.

Injection 10 µL.

Run time Twice the retention time of mirabegron.

Retention time Mirabegron = about 13 min.

Calculate the percentage content of $C_{21}H_{24}N_4O_2S$ taking into account the assigned content of *mirabegron CRS*.

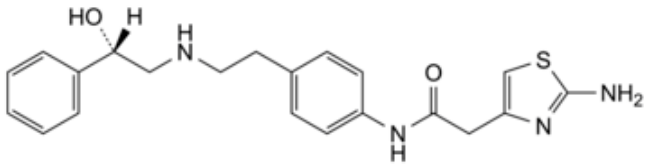
STORAGE

Protected from light.

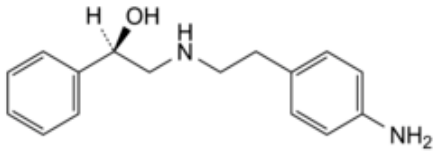
IMPURITIES

Specified impurities *A, B, C, E, F, G, I*.

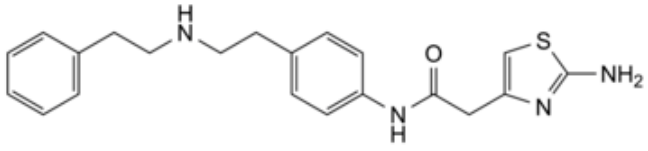
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



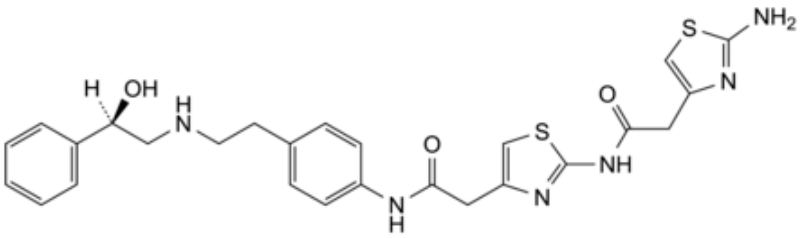
A. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[[(2*S*)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]acetamide ((*S*)-enantiomer of mirabegron),



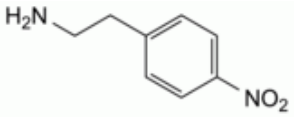
B. (1*R*)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethan-1-ol,



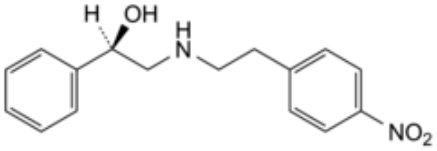
C. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[(2-phenylethyl)amino]ethyl]phenyl]acetamide,



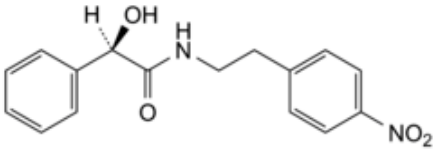
D. 2-(2-amino-1,3-thiazol-4-yl)-*N*-[4-[2-[4-[2-[[(2*R*)-2-hydroxy-2-phenylethyl]amino]ethyl]anilino]-2-oxoethyl]-1,3-thiazol-2-yl]acetamide,



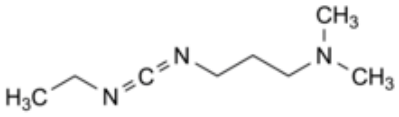
E. 2-(4-nitrophenyl)ethan-1-amine,



F. (1*R*)-2-[[2-(4-nitrophenyl)ethyl]amino]-1-phenylethan-1-ol,



G. (2*R*)-2-hydroxy-*N*-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide,



I. N^1-[(ethylimino)methylidene]-N^3,N^3-dimethylpropan-1,3-diamine.

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