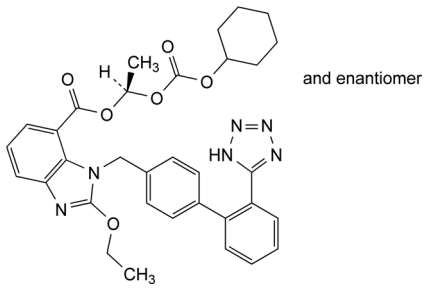
04/2021:2573

CANDESARTAN CILEXETIL

Candesartanum cilexetili



$C_{33}H_{34}N_6O_6$ M_r 611
[145040-37-5]

DEFINITION

(1*RS*)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in candesartan cilexetil should be avoided or limited as much as possible. For this reason, manufacturers of candesartan cilexetil for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in candesartan cilexetil. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance: white or almost white powder.

Solubility: practically insoluble in water, freely soluble in methylene chloride and slightly soluble in anhydrous ethanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *candesartan cilexetil CRS*.

If the spectra obtained 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.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Solvent mixture: *water R*, *acetonitrile R* (40:60 *V/V*).

Test solution. Dissolve 20 mg of the substance to be examined in 50.0 mL of 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 5 mg of *candesartan cilexetil for system suitability CRS* (containing impurities A, B and F) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Reference solution (c). Dissolve 2.5 mg of *candesartan cilexetil for peak identification CRS* (containing impurities G and H) in the solvent mixture and dilute to 5 mL with the solvent mixture.

Column:

- *size*: *l* = 0.15 m, Ø = 3.9 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (4 µm).

Mobile phase:

- *mobile phase A*: *glacial acetic acid R*, *water for chromatography R*, *acetonitrile R* (1:43:57 *V/V/V*);
- *mobile phase B*: *glacial acetic acid R*, *water for chromatography R*, *acetonitrile R* (1:10:90 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 3	100	0
3 - 33	100 → 0	0 → 100
33 - 40	0	100

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *candesartan cilexetil for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities A, B and F; use the chromatogram supplied with *candesartan cilexetil for peak identification CRS* and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities G and H.

Relative retention with reference to candesartan cilexetil (retention time = about 11 min): impurity G = about 0.2; impurity A = about 0.4; impurity B = about 0.5; impurity F = about 2.0; impurity H = about 3.5.

System suitability: reference solution (b):

- *resolution*: minimum 4.0 between the peaks due to impurities A and B.

Limits:

- *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurities A and G = 0.7; impurity H = 1.6;
- *impurity B*: not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 per cent);
- *impurities F, G*: 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);
- *impurities A, H*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 6 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.6 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).

Water (*2.5.32*): maximum 0.3 per cent, determined on 60.0 mg.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

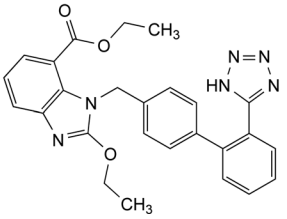
Dissolve 0.500 g in 60 mL of *glacial acetic acid R*. Titrate immediately with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*) at the 1st inflexion point.

1 mL of *0.1 M perchloric acid* is equivalent to 61.1 mg of $C_{33}H_{34}N_6O_6$.

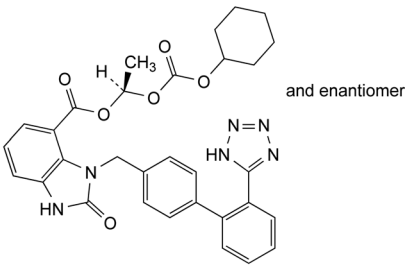
IMPURITIES

Specified impurities: A, B, F, G, H.

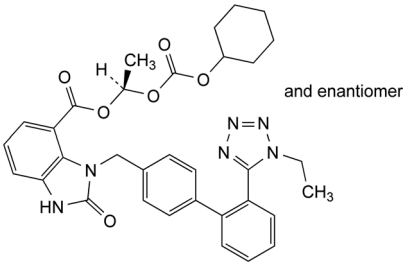
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



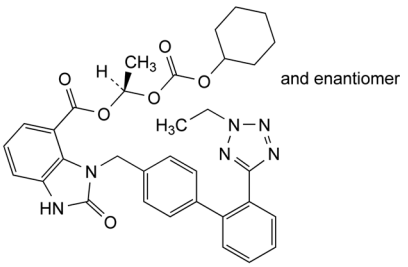
A. ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,



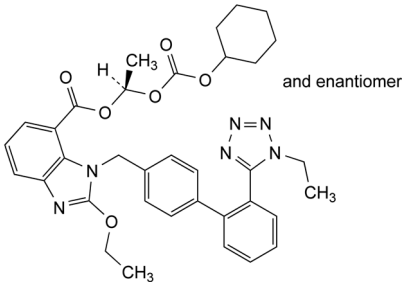
B. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-oxo-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,



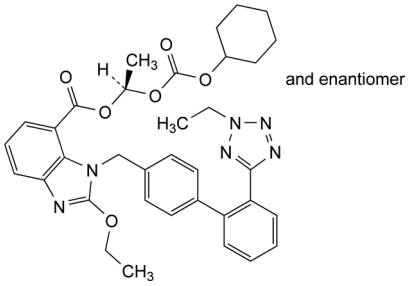
C. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 3-[[2′-(1-ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,



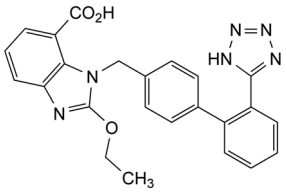
D. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 3-[[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-2-oxo-2,3-dihydro-1*H*-benzimidazole-4-carboxylate,



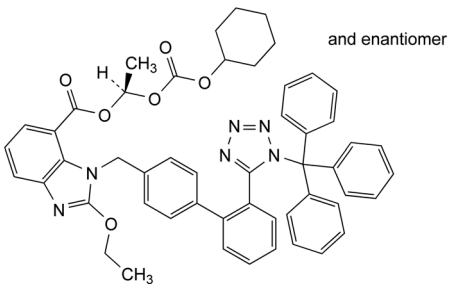
E. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1-ethyl-1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,



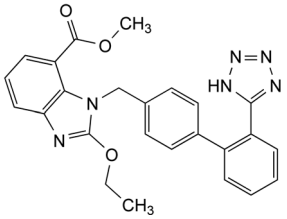
F. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(2-ethyl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate,



G. 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (candesartan),



H. (1*RS*)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-[1-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (*N*-tritylcandesartan),



I. methyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate.

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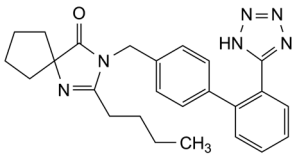
IRBESARTAN

Irbesartanum



$C_{25}H_{28}N_6O$ M_r 428.5
[138402-11-6]

DEFINITION

2-Butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-1,3-diazaspiro[4.4]non-1-en-4-one.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in irbesartan should be avoided or limited as much as possible. For this reason, manufacturers of irbesartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in irbesartan. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, sparingly soluble in methanol, slightly soluble in methylene chloride.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *irbesartan CRS*.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in *methanol R*, evaporate to dryness at 60 °C and record new spectra using the residues.

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and not more intensely coloured than reference solution B_7 (*2.2.2, Method II*).

Dissolve 0.50 g in a mixture of 1 volume of *2 M sodium hydroxide R* and 9 volumes of *methanol R2* and dilute to 10 mL with the same mixture of solvents.

Impurity B. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 0.100 g of the substance to be examined in the mobile phase and dilute to 5.0 mL with the mobile phase.

Reference solution. Dissolve 25.0 mg of *sodium azide R* (sodium salt of impurity B) in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 0.25 mL of the solution to 200.0 mL with the mobile phase.

Precolumn (used to prevent saturation of the column with irbesartan):

- *size*: *l* = 0.05 m, Ø = 4 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *strongly basic anion-exchange resin for chromatography R* (8.5 µm).

Mobile phase: 4.2 g/L solution of *sodium hydroxide R* in *carbon dioxide-free water R*.

Flow rate: 1.0 mL/min.

Detection: conductivity detector with a sensitivity of 3 µS; use a self-regenerating anion suppressor.

Neutralisation of the eluent: either chemical or electrochemical:

- *chemical*: by continuous countercurrent circulation in a neutralising micromembrane, performed before detection:
  - *neutralising solvent*: *0.025 M sulfuric acid*;
  - *flow rate*: 10 mL/min;
  - *pressure*: about 100 kPa.
- *electrochemical*: 300 mA (for example).

Injection: 200 µL; after each injection of the test solution, rinse the precolumn with a mixture of mobile phase and *methanol R* (40:60 *V/V*) for 10 min; equilibrate to initial conditions as necessary; a switch valve can be used to avoid disconnecting the precolumn from the column.

Run time: 25 min.

Retention time: impurity B = about 14 min.

System suitability: reference solution:

- *signal-to-noise ratio*: minimum 10 for the peak due to impurity B.

Limit:

- *impurity B*: not more than the area of the corresponding peak in the chromatogram obtained with the reference solution (10 ppm).

Related substances. Liquid chromatography (*2.2.29*).

Buffer solution pH 3.2. Mix 5.5 mL of *phosphoric acid R* and 950 mL of *water for chromatography R* and adjust to pH 3.2 with *triethylamine R*.

Test solution. Dissolve 50 mg of the substance to be examined in *methanol R2* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R2*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R2*.

Reference solution (b). Dissolve 5 mg of the substance to be examined and 5 mg of *irbesartan impurity A CRS* in *methanol R2* and dilute to 10 mL with the same solvent. Dilute 1 mL of the solution to 10 mL with *methanol R2*.

Column:

- *size*: *l* = 0.25 m, Ø = 4 mm;
- *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *acetonitrile R1*, buffer solution pH 3.2 (33:67 *V/V*).

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Run time: 1.4 times the retention time of irbesartan.

Identification of impurities: use the chromatogram obtained with reference solution (b) to identify the peak due to impurity A.

Relative retention with reference to irbesartan (retention time = about 23 min): impurity A = about 0.7.

System suitability: reference solution (b):

- *resolution*: minimum 3.0 between the peaks due to impurity A and irbesartan.

Limits:

– *impurity A*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 twice the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 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).

Water (*2.5.12*): maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

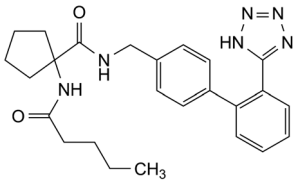
ASSAY

Dissolve 0.300 g in 50 mL of *anhydrous acetic acid R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M perchloric acid* is equivalent to 42.85 mg of $C_{25}H_{28}N_6O$.

IMPURITIES

Specified impurities: A, B.



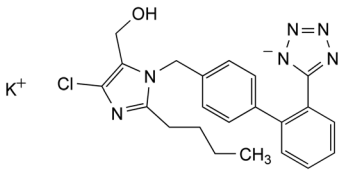
A. 1-(pentanoylamino)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]cyclopentane-1-carboxamide,

B. N_3^-: trinitride (azide).

04/2021:2232

LOSARTAN POTASSIUM

Losartanum kalicum



$C_{22}H_{22}ClKN_6O$ M_r 461.0
[124750-99-8]

DEFINITION

Potassium 5-[4′-[[2-butyl-4-chloro-5-(hydroxymethyl)-1*H*-imidazol-1-yl]methyl]biphenyl-2-yl]tetrazol-1-ide.

Content: 98.5 per cent to 101.5 per cent (dried substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in losartan potassium should be avoided or limited as much as possible. For this reason, manufacturers of losartan potassium for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in losartan potassium. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance: white or almost white, crystalline powder, hygroscopic.

Solubility: freely soluble in water and in methanol, slightly soluble in acetonitrile.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *losartan potassium CRS*.

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

B. Dissolve 25 mg in 3 mL of *water R*. The solution gives reaction (a) of potassium (*2.3.1*).

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 30.0 mg of the substance to be examined in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with *methanol R*. Dilute 1.0 mL of this solution to 10.0 mL with *methanol R*.

Reference solution (b). Dissolve 6 mg of *triphenylmethanol R* (impurity G) in 100 mL of *methanol R*. Dilute 1 mL of the solution to 100 mL with *methanol R*. Use 1 mL of this solution to dissolve the contents of a vial of *losartan for system suitability CRS* (containing impurities J, K, L and M) and sonicate for 5 min.

Reference solution (c). Dissolve 3.0 mg of *losartan impurity D CRS* in *methanol R* and dilute to 100.0 mL with the same solvent. Dilute 1.5 mL of this solution to 100.0 mL with *methanol R*.

Column:

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

Mobile phase:

- *mobile phase A*: dilute 1.0 mL of *phosphoric acid R* to 1000 mL with *water for chromatography R*;
- *mobile phase B*: *acetonitrile R1*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	75	25
5 - 30	75 → 10	25 → 90
30 - 40	10	90

Flow rate: 1.3 mL/min.

Detection: spectrophotometer at 220 nm.

Injection: 10 µL.

Identification of impurities: use the chromatogram supplied with *losartan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G, J, K, L and M; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity D.

Relative retention with reference to losartan (retention time = about 14 min): impurity D = about 0.9; impurity J = about 1.4; impurity K = about 1.5; impurity L = about 1.6; impurity M = about 1.75; impurity G = about 1.8.

System suitability: reference solution (b):

- *peak-to-valley ratio*: minimum 2.0, where H_p = height above the baseline of the peak due to impurity M and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to impurity G.

Limits:

- *impurity D*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);
- *impurities J, K, L, M*: for each impurity, not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.15 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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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 an oven at 105 °C.

ASSAY

Dissolve 0.200 g in 75 mL of *anhydrous acetic acid R* and sonicate for 10 min. Carry out a potentiometric titration (*2.2.20*) using *0.1 M perchloric acid*.

1 mL of *0.1 M perchloric acid* is equivalent to 23.05 mg of $C_{22}H_{22}ClKN_6O$.

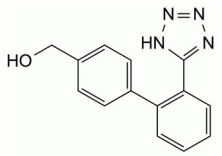
STORAGE

In an airtight container.

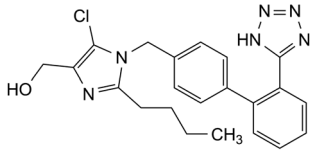
IMPURITIES

Specified impurities: D, J, K, L, M.

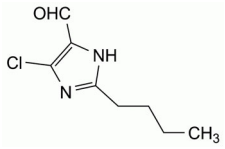
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



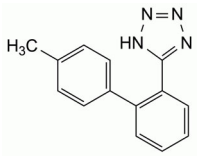
B. [2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methanol,



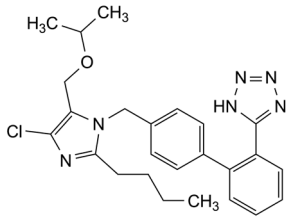
C. [2-butyl-5-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-4-yl]methanol,



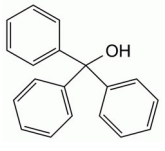
D. 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde,



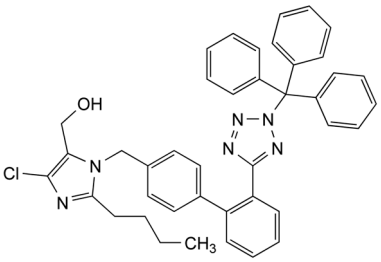
E. 5-(4′-methylbiphenyl-2-yl)-1*H*-tetrazole,



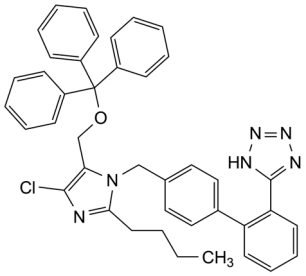
F. 5-[4′-[[2-butyl-4-chloro-5-[[(1-methylethyl)oxy]methyl]-1*H*-imidazol-1-yl]methyl]biphenyl-2-yl]-1*H*-tetrazole,



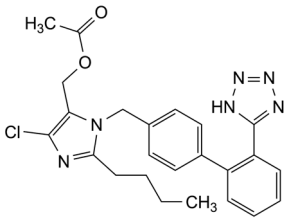
G. triphenylmethanol,



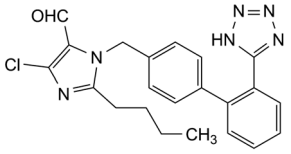
H. [2-butyl-4-chloro-1-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methanol,



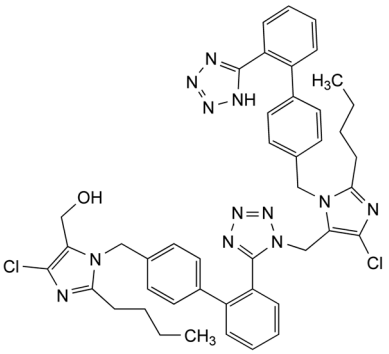
I. 5-[4′-[[2-butyl-4-chloro-5-[[(triphenylmethyl]oxy]-methyl]-1*H*-imidazol-1-yl]methyl]biphenyl-2-yl]-1*H*-tetrazole,



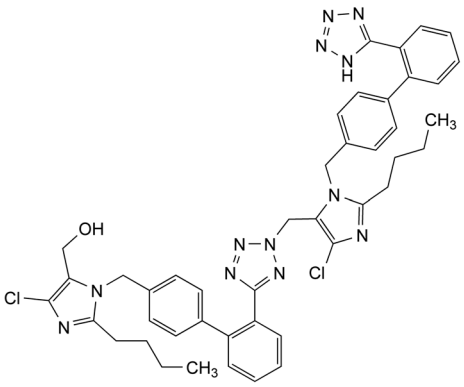
J. [2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methyl acetate,



K. 2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-carbaldehyde,



L. [2-butyl-1-[[2′-[1-[[2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methyl]-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-4-chloro-1*H*-imidazol-5-yl]methanol,

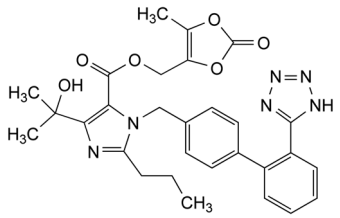


M. [2-butyl-1-[[2′-[2-[[2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methyl]-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-4-chloro-1*H*-imidazol-5-yl]methanol.

04/2021:2600

OLMESARTAN MEDOXOMIL

Olmesartanum medoxomilum



$C_{29}H_{30}N_6O_6$ M_r 558.6
[144689-63-4]

DEFINITION

(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate.

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

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in olmesartan medoxomil should be avoided or limited as much as possible. For this reason, manufacturers of olmesartan medoxomil for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in olmesartan medoxomil. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *olmesartan medoxomil CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 25 mg of the substance to be examined in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Test solution (b). Dissolve 25.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 5 mg of *olmesartan medoxomil for system suitability CRS* (containing impurities A, B and C) in *acetonitrile R* and dilute to 5 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of test solution (a) to 50.0 mL with *acetonitrile R*. Dilute 1.0 mL of this solution to 10.0 mL with *acetonitrile R*.

Reference solution (c). Dissolve 25.0 mg of *olmesartan medoxomil CRS* in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Column:

- *size*: *l* = 0.10 m, Ø = 4.6 mm;
- *stationary phase*: *end-capped octylsilyl silica gel for chromatography R* (3.5 µm);
- *temperature*: 40 °C.

Mobile phase:

- *mobile phase A*: mix 20 volumes of *acetonitrile R* and 80 volumes of a 2.04 g/L solution of *potassium dihydrogen phosphate R* previously adjusted to pH 3.4 with a 1.73 g/L solution of *phosphoric acid R*;
- *mobile phase B*: mix 20 volumes of a 2.04 g/L solution of *potassium dihydrogen phosphate R*, previously adjusted to pH 3.4 with a 1.73 g/L solution of *phosphoric acid R*, and 80 volumes of *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 10	75	25
10 - 35	75 → 0	25 → 100
35 - 45	0	100

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 250 nm.

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

Identification of impurities: use the chromatogram supplied with *olmesartan medoxomil for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities A, B and C.

Relative retention with reference to olmesartan medoxomil (retention time = about 10 min): impurity A = about 0.2; impurity B = about 0.7; impurity C = about 1.5.

System suitability: reference solution (a):

- *resolution*: minimum 3.5 between the peaks due to impurity B and olmesartan medoxomil.

Limits:

- *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.4 per cent);
- *impurity C*: not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
- *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
- *total*: not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.7 per cent);
- *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Acetone. Head-space gas chromatography (*2.2.28*): use the direct calibration method.

Internal standard solution. Dilute 1.0 mL of *butanol R* to 100.0 mL with *dimethyl sulfoxide R*.

Test solution. Dissolve 0.250 g of the substance to be examined in *dimethyl sulfoxide R*, add 2.0 mL of the internal standard solution and dilute to 10.0 mL with *dimethyl sulfoxide R*.

Reference solution. Dilute 0.50 mL of *acetone R* to 200.0 mL with *dimethyl sulfoxide R*. Dilute 15.0 mL of the solution to 100.0 mL with *dimethyl sulfoxide R*. To 25.0 mL of this solution add 10.0 mL of the internal standard solution and dilute to 50.0 mL with *dimethyl sulfoxide R*.

Column:

- *material*: fused silica;
- *size*: *l* = 30 m, Ø = 0.53 mm;
- *stationary phase*: *macrogol 20 000 R* (film thickness 1 µm).

Carrier gas: *nitrogen for chromatography R* or *helium for chromatography R*.

Flow rate: 4.0 mL/min.

Split ratio: 1:5.

Static head-space conditions that may be used:

– *equilibration temperature*: 80 °C;

– *equilibration time*: 30 min.

Temperature:

	Time (min)	Temperature (°C)
Column	5	50
	5 - 18	50 → 180
	18 - 23	180
Injection port		200
Detection		200

Detection: flame ionisation.

Injection: 1 mL.

Calculate the content of acetone, taking its relative density to be 0.79 at 20 °C.

Limit:

– *acetone*: maximum 0.6 per cent.

Water (*2.5.32*): maximum 0.5 per cent, determined on 0.500 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.

Mobile phase: mobile phase B, mobile phase A (25:75 *V/V*).

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

Retention time: olmesartan medoxomil = about 10 min.

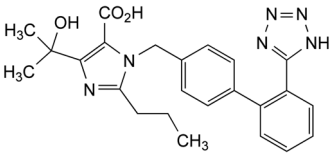
Run time: 1.5 times the retention time of olmesartan medoxomil.

Calculate the percentage content of $C_{29}H_{30}N_6O_6$ taking into account the assigned content of *olmesartan medoxomil CRS*.

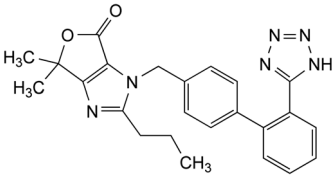
IMPURITIES

Specified impurities: A, C.

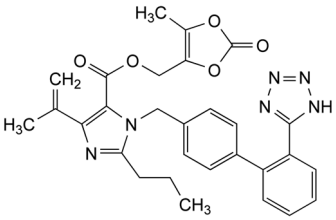
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



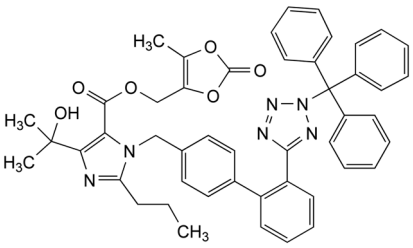
A. 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylic acid (olmesartan),



B. 6,6-dimethyl-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3,6-dihydro-4*H*-furo[3,4-*d*]imidazol-4-one,



C. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-methylethenyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate,

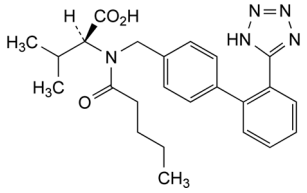


D. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-[(2-triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazole-5-carboxylate.

04/2021:2423

VALSARTAN

Valsartanum



$C_{24}H_{29}N_5O_3$ M_r 435.5
[137862-53-4]

DEFINITION

(2*S*)-3-Methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid.

Content: 99.0 per cent to 101.0 per cent (anhydrous substance).

PRODUCTION

As *N*-nitrosamines are classified as probable human carcinogens, their presence in valsartan should be avoided or limited as much as possible. For this reason, manufacturers of valsartan for human use are expected to perform an assessment of the risk of *N*-nitrosamine formation and contamination during their manufacturing process; if this assessment identifies a potential risk, the manufacturing process should be modified to minimise contamination and a control strategy implemented to detect and control *N*-nitrosamine impurities in valsartan. The general chapter *2.5.42. N-Nitrosamines in active substances* is available to assist manufacturers.

CHARACTERS

Appearance: white or almost white, hygroscopic powder.

Solubility: practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in methylene chloride.

IDENTIFICATION

Carry out either tests A, B or tests A, C.

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

B. Enantiomeric purity (see Tests).

C. Specific optical rotation (*2.2.7*): – 69.0 to – 64.0 (anhydrous substance).
   Dissolve 0.200 g in *methanol R* and dilute to 20.0 mL with the same solvent.

TESTS

Enantiomeric purity. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in the mobile phase and dilute to 50.0 mL with the mobile phase.

Reference solution (a). Dissolve 5 mg of *valsartan for peak identification CRS* (containing impurity A) in the mobile phase and dilute to 5 mL with the mobile phase.

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

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (5 µm).

Mobile phase: *trifluoroacetic acid R*, *2-propanol R*, *hexane R* (0.1:15:85 *V/V/V*).

Flow rate: 0.8 mL/min.

Detection: spectrophotometer at 230 nm.

Injection: 10 µL.

Run time: 1.5 times the retention time of valsartan.

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

Relative retention with reference to valsartan (retention time = about 13 min): impurity A = about 0.6.

System suitability: reference solution (a):

– *resolution*: minimum 2.0 between the peaks due to impurity A and valsartan.

Limit:

– *impurity A*: not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 50 mg of the substance to be examined in the mobile phase 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 the contents of a vial of *valsartan for system suitability CRS* (containing impurity C) in 1 mL of the mobile phase.

Column:

– *size*: *l* = 0.125 m, Ø = 3.0 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: *glacial acetic acid R*, *acetonitrile R1*, *water for chromatography R* (1:500:500 *V/V/V*).

Flow rate: 0.4 mL/min.

Detection: spectrophotometer at 225 nm.

Injection: 10 µL.

Run time: 6 times the retention time of valsartan.

Identification of impurities: use the chromatogram supplied with *valsartan for system suitability CRS* and the chromatogram obtained with reference solution (b) to identify the peak due to impurity C.

Relative retention with reference to valsartan (retention time = about 5 min): impurity C = about 0.8.

System suitability: reference solution (b):

– *resolution*: minimum 3.0 between the peaks due to impurity C and valsartan.

Limits:

– *impurity C*: 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 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.3 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).

Water (*2.5.12*): maximum 2.0 per cent, determined on 0.500 g.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.170 g in 70 mL of *2-propanol R*. Titrate with *0.1 M tetrabutylammonium hydroxide in 2-propanol*, determining the endpoint potentiometrically (*2.2.20*). Perform all operations under nitrogen.

1 mL of *0.1 M tetrabutylammonium hydroxide in 2-propanol* is equivalent to 21.78 mg of $C_{24}H_{29}N_5O_3$.

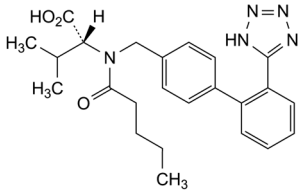
STORAGE

In an airtight container.

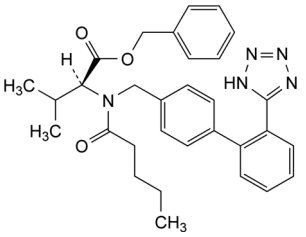
IMPURITIES

Specified impurities: A, C.

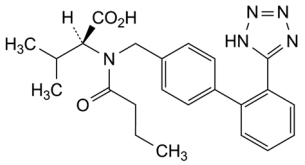
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical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



A. (2*R*)-3-methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoic acid,



B. benzyl (2*S*)-3-methyl-2-[pentanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]butanoate,



C. (2*S*)-2-[butanoyl[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-3-methylbutanoic acid.