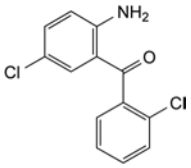
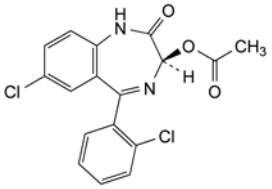
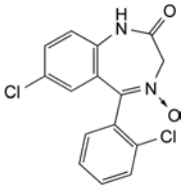


A. (2-amino-5-chlorophenyl)(2-chlorophenyl)methanone,

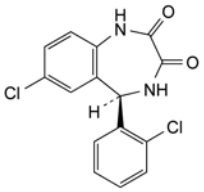


and enantiomer

B. (3*RS*)-7-chloro-5-(2-chlorophenyl)-2-oxo-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl acetate,

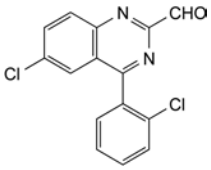


C. 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide,



and enantiomer

D. (5*RS*)-7-chloro-5-(2-chlorophenyl)-4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione,

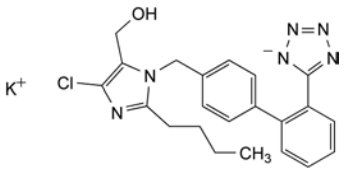


E. 6-chloro-4-(2-chlorophenyl)quinazoline-2-carbaldehyde.

04/2009:2232

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).

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 100.0 mL of *methanol R*. Dilute 1.0 mL of the solution to 100.0 mL with *methanol R*. Use 1.0 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 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).

Heavy metals: maximum 20 ppm.

Prescribed solution. Dissolve 1.0 g in 20 mL of a mixture of equal volumes of *ethanol (96 per cent) R* and *water R*.

Test solution. 12 mL of the prescribed solution.

Reference solution. Mix 1.0 mL of *lead standard solution (10 ppm Pb) R*, 2.0 mL of the prescribed solution and 9 mL of *water R*.

Blank solution. Mix 2.0 mL of the prescribed solution and 10 mL of *water R*.

To each solution, add 2 mL of *buffer solution pH 3.5 R*. Mix. The substance will precipitate. Dilute each solution to 40 mL with *ethanol (96 per cent) R*. The substance dissolves completely. Mix and add to 1.2 mL of *thioacetamide reagent R*. Mix immediately.

Filter the solutions through a membrane filter (nominal pore size 0.45 µm) (*2.4.8*). Compare the spots on the filters obtained with the different solutions. The test is invalid if the reference solution does not show a slight brownish-black colour compared to the blank solution. The substance to be examined complies with the test if the brownish-black colour of the spot resulting from the test solution is not more intense than that of the spot resulting from the reference solution.

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 $C_{22}H_{22}ClKN_6O$.

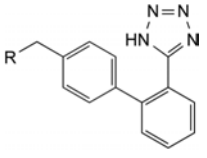
STORAGE

In an airtight container.

IMPURITIES

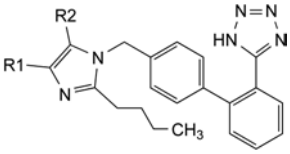
Specified impurities: *D, J, K, L, M.*

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. R = OH: [2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methanol,

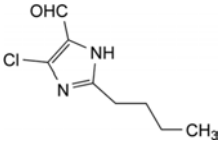
E. R = H: 5-(4′-methylbiphenyl-2-yl)-1*H*-tetrazole,



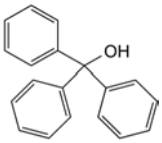
C. R1 = CH_2-OH, R2 = Cl: [2-butyl-5-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-4-yl]methanol,

F. R1 = Cl, R2 = CH_2-O-$CH(CH_3)_2$: 5-[4′-[[2-butyl-4-chloro-5-[[(1-methylethyl)oxy]methyl]-1*H*-imidazol-1-yl]methyl]biphenyl-2-yl]-1*H*-tetrazole,

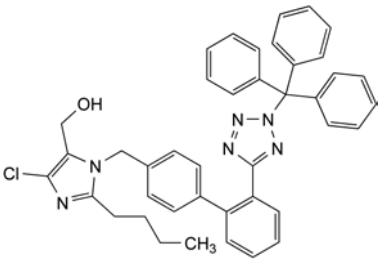
I. R1 = Cl, R2 = CH_2-O-CPh_3: 5-[4′-[[2-butyl-4-chloro-5-[[(triphenylmethyl]oxy]methyl]-1*H*-imidazol-1-yl]methyl]biphenyl-2-yl]-1*H*-tetrazole,



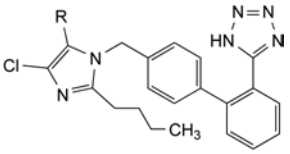
D. 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde,



G. triphenylmethanol,

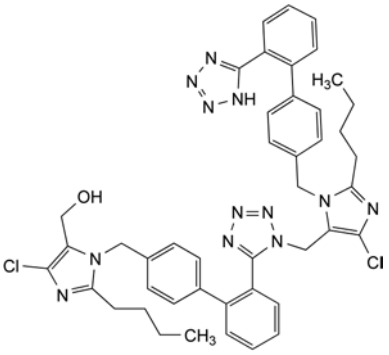


H. [2-butyl-4-chloro-1-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methanol,

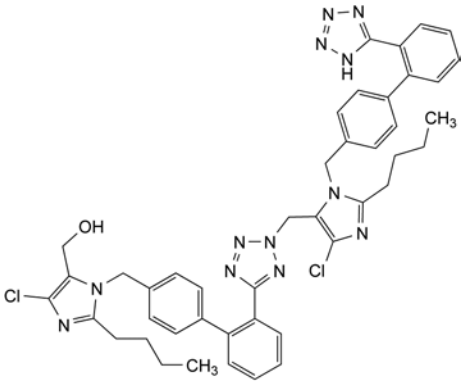


J. R = CH_2-O-CO-CH_3: [2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methyl acetate,

K. R = CHO: 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,

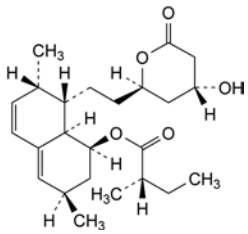


M. [2-butyl-1-[[2′-[2-[[2-butyl-4-chloro-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazol-5-yl]methyl]-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-4-chloro-1*H*-imidazol-5-yl]methanol.

07/2010:1538

LOVASTATIN

Lovastatinum



$C_{24}H_{36}O_5$ M_r 404.5
[75330-75-5]

DEFINITION

(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-Hydroxy-6-oxo-tetrahydro-2*H*-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a–hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate.

Content: 97.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, soluble in acetone, sparingly soluble in anhydrous ethanol.

IDENTIFICATION

A. Specific optical rotation (see Tests).

B. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *lovastatin CRS*.

TESTS

Specific optical rotation (*2.2.7*): + 325 to + 340 (dried substance).

Dissolve 0.125 g in *acetonitrile R* and dilute to 25.0 mL with the same solvent.

Impurity E. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 25 mg of the substance to be examined in *acetonitrile R1* and dilute to 25.0 mL with the same solvent.

Reference solution (a). Dilute 5.0 mL of the test solution to 100.0 mL with *acetonitrile R1*. Dilute 5.0 mL of this solution to 50.0 mL with *acetonitrile R1*.

Reference solution (b). Dissolve 4 mg of *lovastatin for peak identification CRS* (containing impurities A, B, C, D and E) in *acetonitrile R1* and dilute to 10.0 mL with the same solvent.

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

Mobile phase: mix 7 volumes of a 1.1 g/L solution of *phosphoric acid R* and 13 volumes of *acetonitrile R1*.

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 200 nm.

Injection: 10 µL.

Run time: 3 times the retention time of lovastatin.

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

Relative retention with reference to lovastatin (retention time = about 5 min): impurity E = about 1.3.

System suitability: reference solution (b):
- *resolution*: minimum 5.0 between the peaks due to lovastatin and impurity E.

Limits:
- *correction factor*: for the calculation of content, multiply the peak area of impurity E by 1.6;
- *impurity E*: not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.5 per cent).

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 20.0 mg of the substance to be examined in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 20.0 mg of *lovastatin CRS* in *acetonitrile R* and dilute to 50.0 mL with the same solvent.

Reference solution (b). Dilute 5.0 mL of the test solution to 100.0 mL with *acetonitrile R*. Dilute 5.0 mL of this solution to 50.0 mL with *acetonitrile R*.

Reference solution (c). To 2.5 mL of reference solution (a) add 1 mg of *simvastatin CRS* and dilute to 50.0 mL with *acetonitrile R*.

Reference solution (d). Dissolve 4 mg of *lovastatin for peak identification CRS* (containing impurities A, B, C, D and E) in *acetonitrile R* and dilute to 10.0 mL with the same solvent.

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

Mobile phase:
- *mobile phase A*: 0.1 per cent *V/V* solution of *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 - 7	40	60
7 - 9	40 → 35	60 → 65
9 - 15	35 → 10	65 → 90
15 - 20	10	90

Flow rate: 1.5 mL/min.

Detection: spectrophotometer at 238 nm.

Injection: 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities: use the chromatogram supplied with *lovastatin for peak identification CRS* and the chromatogram obtained with reference solution (d) to identify the peaks due to impurities A, B, C and D.