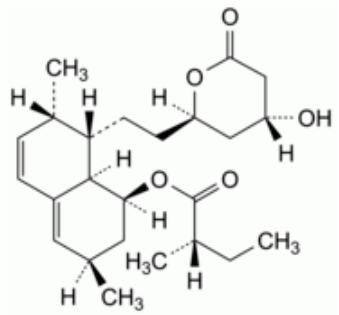
Edition: BP 2025 (Ph. Eur. 11.6 update)

Lovastatin

General Notices

(Ph. Eur Monograph 1538)



$C_{24}H_{36}O_5$ 404.5 *75330-75-5*

Action and use

HMG Co-A reductase inhibitor; lipid-regulating drug.

Ph Eur

DEFINITION

(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-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 (anhydrous 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 (anhydrous 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 25.0 mg of the substance to be examined in *acetonitrile R* 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 R*. Dilute 5.0 mL of this solution to 50.0 mL with *acetonitrile R*.

Reference solution (b) Dissolve 4 mg of *lovastatin for peak identification CRS* (containing impurities A, B, C, D, E and F) in *acetonitrile R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm);

— *temperature*: 40 °C.

Mobile phase 1.1 g/L solution of *phosphoric acid R*, *acetonitrile R1* (35:65 *V/V*).

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.

Limit:

— *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) Dissolve 4 mg of *lovastatin for peak identification CRS* (containing impurities A, B, C, D, E and F) in *acetonitrile R* and dilute to 10 mL with the same solvent.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *base-deactivated 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 for chromatography 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) and (c).

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

Relative retention With reference to lovastatin (retention time = about 7 min): impurity B = about 0.6; impurity A = about 0.8; impurity F = about 0.9; impurity C = about 1.6; impurity D = about 2.3.

System suitability Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where H_p = height above the baseline of the peak due to impurity F and H_v = height above the baseline of the lowest point of the curve separating this peak from the peak due to lovastatin.

Limits:

— *impurities A, B, C, D*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);

— *impurity F*: not more than 0.3 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.15 per cent);

— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);

— *total*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (1.0 per cent);

— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Water (*2.5.12*)

Maximum 0.5 per cent, determined on 1.00 g.

Sulfated ash (*2.4.14*)

Maximum 0.2 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 and reference solution (a).

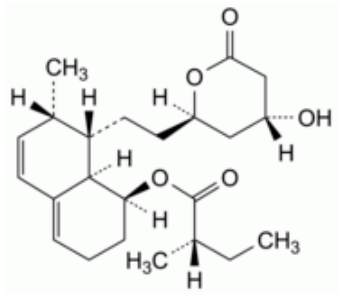
Calculate the percentage content of $C_{24}H_{36}O_5$ taking into account the assigned content of *lovastatin CRS*.

STORAGE

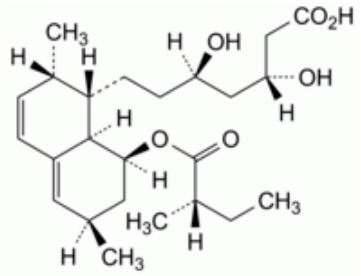
Under nitrogen, at a temperature of 2 °C to 8 °C.

IMPURITIES

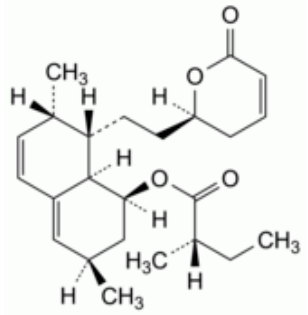
Specified impurities *A, B, C, D, E, F*.



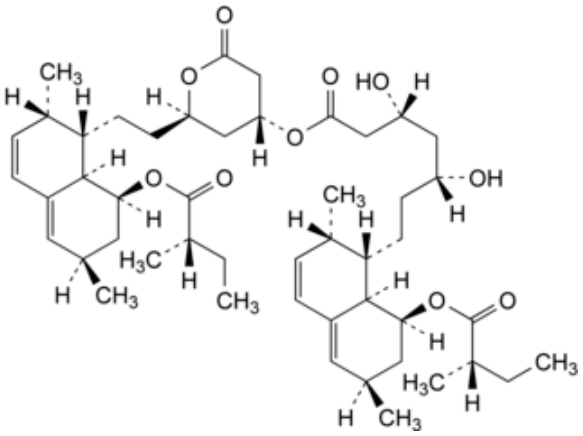
A. (1*S*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-7-methyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (mevastatin),



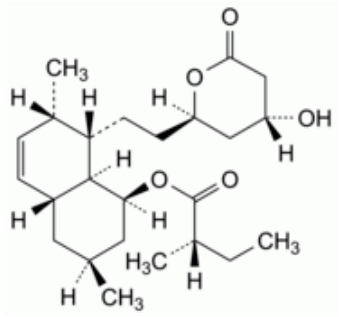
B. (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-2,6-dimethyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid (hydroxyacid lovastatin),



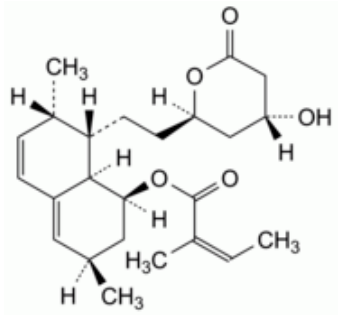
C. (1*S*,3*R*,7*S*,8*S*,8a*R*)-3,7-dimethyl-8-[2-[(2*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (dehydrolovastatin),



D. (2*R*,4*R*)-2-[2-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-2,6-dimethyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxooxan-4-yl (3*R*,5*R*)-7-[(1*S*,2*S*,6*R*,8*S*,8a*R*)-2,6-dimethyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate (lovastatin dimer),



E. (1*S*,3*S*,4a*R*,7*S*,8*S*,8a*S*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl (2*S*)-2-methylbutanoate (4,4a-dihydrolovastatin),



F. (1*S*,3*R*,7*S*,8*S*,8a*R*)-8-[2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2*Z*)-2-methylbut-2-enoate.

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