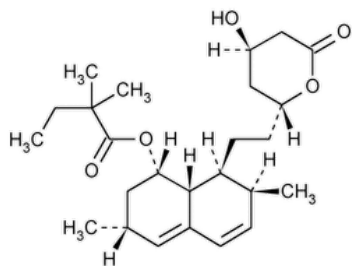


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Simvastatin



$C_{25}H_{38}O_5$ 418.57

Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1 α ,3 α ,7 β ,8 β -(2S*,4S*),8a β]].

2,2-Dimethylbutyric acid, 8-ester with (4R,6R)-6-2-[(1S,2S,6R,8S,8 α R)-1,2,6,7,8,8a-hexahydro-8-hydroxy-2,6-dimethyl-1-naphthyl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one CAS RN®: 79902-63-9; UNII: AGG2FN16EV.

» Simvastatin contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{38}O_5$, calculated on the dried basis. It may contain a suitable antioxidant.

Packaging and storage—Preserve in well-closed containers. Store between 15° and 30°, or under refrigeration.

USP REFERENCE STANDARDS (11).—

[USP Lovastatin RS](#)

[USP Simvastatin RS](#)

Identification—

Change to read:

A: ▲ [Spectroscopic Identification Tests \(197\)](#), [Infrared Spectroscopy: 197M](#) ▲ (CN 1-May-2020) .

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the Assay.

SPECIFIC ROTATION (781S): between +285° and +298°.

Test solution: 5 mg per mL, in acetonitrile.

LOSS ON DRYING (731).—Dry it in vacuum at 60° for 3 hours: it loses not more than 0.5% of its weight.

RESIDUE ON IGNITION (281): not more than 0.1%.

Chromatographic purity—[NOTE—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]

Mobile phase, Diluent, and Chromatographic system—Proceed as directed in the Assay.

Test solution—Use the *Assay preparation*.

Procedure—Inject about 5 μ L of the *Test solution* into the chromatograph, record the chromatogram, identify the specified impurities listed in [Table 1](#), and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Simvastatin taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak area for each impurity; and r_s is the sum of the areas of all the peaks. Reporting level for impurities is 0.05%.

Table 1

Name	Relative Retention Time	Limit %
Simvastatin hydroxyacid ¹	0.45	0.4
Epilovastatin ² and Lovastatin	0.60	1.0 ³
Methylene simvastatin ⁴	0.80	0.4
Simvastatin	1.0	n/a
Acetyl simvastatin ⁵	2.38	0.4
Anhydro simvastatin ⁶	2.42	0.4
Simvastatin dimer ⁷	3.80	0.4
Any other individual impurity	—	0.1
Total impurities other than lovastatin and epilovastatin	—	1.0

¹ (3R,5R)-7-[(1S,2S,6R,8S,8aR)-8-[(2,2-Dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid.

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

³ If present, lovastatin and epilovastatin may not be completely resolved by the method. These peaks are integrated together to determine conformance.

⁴ (1S,7S,8S,8aR)-8-[2-[(2R,4R)-4-Hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbut-3-enoate.

⁵ (1S,3R,7S,8S,8aR)-8-[2-[(2R,4R)-4-(Acetyloxy)-6-oxotetrahydro-2H-pyran-2-yl]ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

⁶ (1S,3R,7S,8S,8aR)-3,7-Dimethyl-8-[2-[(2R)-6-oxo-3,6-dihydro-2H-pyran-2-yl]ethyl]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate.

⁷ (2R,4R)-2-[[[(1S,2S,6R,8S,8aR)-8-[(2,2-Dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]ethyl]-6-oxotetrahydro-2H-pyran-4-yl (3R,5R)-7-[(1S,2S,6R,8S,8aR)-8-[(2,2-dimethylbutanoyl)oxy]-2,6-dimethyl-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoate.

Assay—[NOTE—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]

Dilute phosphoric acid—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume.

Solution A—Prepare a mixture of acetonitrile and *Dilute phosphoric acid* (50:50).

Solution B—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with acetonitrile to volume.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B*, as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under [Chromatography \(621\)](#)).

Buffer solution—Prepare a solution containing 1.4 g of monobasic potassium phosphate per L, and adjust with phosphoric acid to a pH of 4.0.

Diluent—Prepare a mixture of acetonitrile and *Buffer solution* (3:2).

System suitability preparation—Dissolve accurately weighed quantities of [USP Simvastatin RS](#) and [USP Lovastatin RS](#) in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 1.5 mg per mL of [USP Simvastatin RS](#) and 0.015 mg per mL of [USP Lovastatin RS](#).

Standard preparation—Dissolve an accurately weighed quantity of [USP Simvastatin RS](#) in *Diluent* to obtain a solution having a known concentration of about 1.5 mg per mL.

Assay preparation—Transfer about 75 mg of Simvastatin, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see [CHROMATOGRAPHY \(621\)](#))—The liquid chromatograph is equipped with a 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. The chromatograph is programmed as follows.