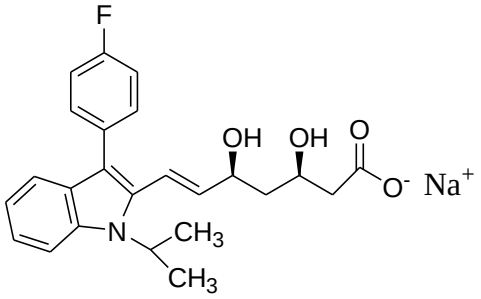
Fluvastatin Sodium



$C_{24}H_{25}FNNaO_4$ Mol. Wt. 433.5

Fluvastatin Sodium is 6-heptenoic acid,7-[3-(4-fluorophenyl)-1-(1-methyl ethyl)-1H-indol-2-yl]-3,5-dihydroxy-,monosodium salt.

Fluvastatin Sodium contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{24}H_{25}FNNaO_4$ calculated on the anhydrous basis.

Category. HMG-CoA reductase inhibitor.

Description. A white to pale yellow, brownish-pale yellow, reddish-pale yellow, hygroscopic powder.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *fluvastatin sodium RS*. If the spectra obtained show differences, dissolve the substance under examination and the reference substance in *methanol* with the aid of ultrasound, if necessary. Evaporate the solvent under nitrogen at 105° for 30 minutes and determine on the residues.

B. In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution (b).

C. It gives reaction (A) of sodium salts (2.3.1).

Tests

pH(2.4.24). 8.0 to 10.0, determine in a 1.0 per cent w/v solution, perform the test immediately after preparation.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE—Protect the solutions from light.

Test solution. Dissolve 50 mg of the substance under examination in 40 ml of the mobile phase (b) and dilute to 100.0 ml with mobile phase (a).

Reference solution (a). Dissolve 10 mg of *fluvastatin sodium for system suitability RS* in 8 ml of mobile phase (b) and dilute to 20.0 ml with mobile phase (a).

Reference solution (b). Dissolve 50 mg of *fluvastatin sodium RS* in 40 ml of mobile phase (b) and dilute to 100.0 ml with mobile phase (a).

Reference solution (c). Dilute 1.0 ml of reference solution (b) to 100.0 ml with mobile phase (a).

Reference solution (d). A 0.01 per cent w/v solution of fluvastatin related compound B RS in a mixture of 60 volumes of *methanol* and 40 volumes of *acetonitrile*. Dilute 0.5 ml of the solution to 10.0 ml with reference solution (a).

Chromatographic system

- a stainless steel column 5 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm),
- column temperature. 35°,
- mobile phase: A. a mixture of 2 volumes of 25 per cent v/v *tetramethylammonium hydroxide*, 88 volumes of *water*, adjusted to pH 7.2 with *orthophosphoric acid* and 10 volumes of a mixture of 60 volumes of *methanol* and 40 volumes of *acetonitrile*,

  B. a mixture of 2 volumes of 25 per cent v/v *tetramethylammonium hydroxide*, 8 volumes of *water*, and 90 volumes of a mixture of 60 volumes of *methanol* and 40 volumes of *acetonitrile*, adjusted to pH 7.2 with *orthophosphoric acid*
- a gradient programme using the conditions given below,
- flow rate: 3 ml per minute,
- spectrophotometer set at 365 nm for 3-hydroxy-5-keto fluvastatin and 305 nm for all other impurities,
- injection volume: 20 µl.

Time (in min)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	60	40
6	60	40

20	18	82
20.1	60	40
25.1	60	40

Name	Relative retention time	Correction factor
Fluvastatin N-ethyl analog[1]	0.7	0.83
Fluvastatin	1.0	---
Fluvastatin anti-isomer[2]	1.2	---
3-hydroxy-5-keto fluvastatin[3]	1.5	0.04
Fluvastatin hydroxydiene[4]	2.0	1.09
Fluvastatin short chain aldehyde[5]	3.0	0.71
Fluvastatin related compound B[6]	3.4	1.06

[1] Sodium (3R,5S,E)-7-[1-ethyl-3-(4-fluorophenyl)-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoate,

[2] [R*,R*-E]-(±)-7-[3-(4-fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3,5-didroxy-6-heptenoic acid monosodium salt or Sodium (3RS,5RS,E)-7-(3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl)-3,5-dihydroxyhept-6-enoate,

[3] Sodium (E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-hydroxy-5-oxohept-6-enoate,

[4] Sodium (4E,6E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-hydroxyhepta-4,6-dienoate,

[5] 3-(4-fluorophenyl)-1-isopropyl-1H-indole-2-carbaldehyde,

[6] [R*,S*-E]-(±)-7-[3-(4-fluorophenyl)-1-methylethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester or tert-butyl(3RS,5SR,E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoate.

Inject reference solution (c) and (d) at 305 nm. The test is not valid unless the resolution between the peaks due to fluvastatin anti-isomer and fluvastatin is not less than 1.6, the tailing factor is not more than 3.0 in the chromatogram obtained with the reference solution (d) and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (c).

Inject reference solution (c) and the test solution at 305 nm, In the chromatogram obtained with the test solution, the area of any peak corresponding to fluvastatin N-ethyl analog, fluvastatin hydroxydiene and fluvastatin short chain aldehyde each of is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent), the area of any peak corresponding to fluvastatin anti-isomer is not more than 0.8 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.8 per cent) , the area of any peak corresponding to fluvastatin related compound B is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.2 per cent). The area of any other secondary peak is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent).

Inject reference solution (c) and the test solution at 365 nm, the area of any peak corresponding to 3-hydroxy-5-keto fluvastatin is not more than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (c) (0.1 per cent). The sum of all the impurities is not more than 1.0 per cent.

Water (2.3.43). Not more than 4.0 per cent (for anhydrous form) and not more than 12 per cent (for hydrated form).

NOTE — The term "hydrated form" refers to several known forms of fluvastatin sodium that are not stoichiometric hydrates.

Assay. Determine by liquid chromatography (2.4.14) as described under Related substances with the following modifications.

Chromatographic system

– spectrophotometer set at 305 nm,

Inject the reference solution (a) and (b). The test is not valid unless the resolution between the peaks due to fluvastatin and fluvastatin anti-isomer peaks is not less than 1.5, the tailing factor is not more than 3.0 in the chromatogram obtained with the reference solution (a) and the relative standard deviation for replicate injections is not more than 2.0 per cent in the chromatogram obtained with the reference solution (b).

Inject the reference solution (b) and the test solution.

Calculate the content of $C_{24}H_{25}FNNaO_4$.

Storage. Store protected from light and moisture, at a temperature not exceeding 30°.

Labeling. Where it is a hydrated form, the label so indicates.

2.4.26 Solubility.

Fluvastatin Sodium. Soluble in *alcohol*, in *methanol* and in *water*.