Atorvastatin Calcium

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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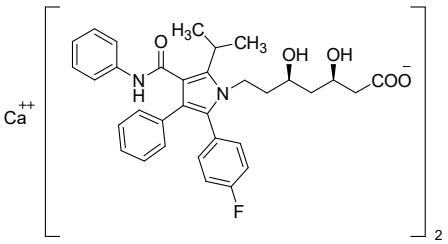

$C_{66}H_{68}CaF_2N_4O_{10}$ Mol. Wt. 1155.4 (Anhydrous)
$C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$ Mol. Wt. 1209.4 (Trihydrate)
$C_{66}H_{68}CaF_2N_4O_{10}.C_3H_8O_2$ Mol. Wt. 1231.5 (Propylene glycol solvate)

Atorvastatin Calcium is calcium salt of 1H-Pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylami no)carbonyl]-, calcium salt (2:1), [*R*- (*R**,*R**)]; Calcium (β*R*,δ*R*)-2-(p-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoate (1:2); [(3*R*,5*R*)-7-[3-(Phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt]
It may contain a suitable antioxidant.

Atorvastatin Calcium contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{66}H_{68}CaF_2N_4O_{10}$, calculated on the anhydrous, propylene glycol free (if labelled) and solvent-free basis.

Category. Antihyperlipidaemic.

Description. A white to off-white powder. It shows polymorphism.

Identification

A. Determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *atorvastatin calcium IPRS* or with the reference spectrum of atorvastatin calcium.

B. Determine by atomic absorption spectrophotometry (2.4.2). A 0.005 per cent w/v solution of the substance under examination in a mixture of 75 volumes of *methanol*, 25 volumes of *water* and 2 volumes of *hydrochloric acid* using air acetylene flame, shows absorption at the calcium emission line at 422.7 nm.

Tests

Enantiomeric purity. Not more than 0.3 per cent of atorvastatin impurity E.

Determine by liquid chromatography (2.4.14).

Test solution. Dissolve 10 mg of the substance under examination in 2.0 ml of *methanol,* add 2.0 ml of *ethanol* and dilute to10.0 ml with *hexane.*

Reference solution (a). A solution containing 0.5 per cent w/v of *atorvastatin calcium IPRS* and 0.00375 per cent w/v of *atorvastatin impurity E (3S,5S enantiomer of atorvastatin) IPRS* in *methanol*.

Reference solution (b). Transfer 2.0 ml of reference solution (a) to a 10-ml volumetric flask, add 2.0 ml of *ethanol* and dilute to volume with *hexane.*

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with amylose tris-3,5- dimethylphenylcarbamate coated with porous silica (5 µm) (Such as chiralpak AD),

- mobile phase: a mixture of 94 volumes of *hexane,* 6 volumes of *ethanol* and 0.1 volume of *trifluoroacetic acid*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 244 nm,
- injection volume: 20 µl.

NOTE—The elution order of the peaks is atorvastatin impurity E followed by atorvastatin.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to atorvastatin impurity E and atorvastatin is not less than 2.0.

Inject the test solution and calculate the content of atorvastatin impurity E in atorvastatin calcium by area normalization.

Related substances. A. Determine by liquid chromatography (2.4.14).

NOTE—On the basis of the synthetic route or of the solid state nature of the drug substance, perform either Related substances A. or Related substances B. Related substances B may be suitable when atorvastatin lactone, atorvastatin epoxy tetrahydrofuran analog, and atorvastatin acetonide are possible related compounds, and it may be suitable for an amorphous form of the drug substance.

Buffer solution. A solution prepared by dissolving 3.9 g of *ammonium acetate* in 1000 ml of *water,* adjusted to pH 5.0 with *glacial acetic acid.*

Test solution. Dissolve 50 mg of the substance under examination in *N,N-dimethylformamide* and dilute to 50.0 ml with *N,N-dimethylformamide.*

Reference solution (a). A solution containing 0.00015 per cent w/v, each of, *atorvastatin calcium IPRS, atorvastatin impurity A IPRS, atorvastatin impurity B IPRS, atorvastatin impurity C IPRS* and *atorvastatin impurity D IPRS* in *N,N-dimethylformamide*.

Reference solution (b). A solution containing 0.005 per cent w/v of *atorvastatin calcium IPRS* and 0.006 per cent w/v of *atorvastatin impurity B* in *N,N-dimethylformamide*.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with octylsilane bonded to porous silica (5 µm),
- mobile phase: A. a mixture of 21 volumes of *acetonitrile,* 12 volumes of *tetrahydrofuran (stabilizer free)* and 67 volumes of the buffer solution,
  B. a mixture of 61 volumes of *acetonitrile,* 12 volumes of *tetrahydrofuran (stabilizer free)* and 27 volumes of the buffer solution,
- a gradient programme using the conditions given below,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 244 nm,
- injection volume: 20 µl.

NOTE- If necessary, adjust the mobile phase by increasing or decreasing the percentage of acetonitrile or the pH of the ammonium acetate solution to achieve a retention time of 26–34 minutes for the atorvastatin peak

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
40	100	0
70	20	80
85	0	100
100	0	100
105	100	0
115	100	0

Name	Relative retention time
Atorvastatin impurity A[1]	0.8
Atorvastatin impurity B [2]	0.9
Atorvastatin	1.0
Atorvastatin impurity C[3]	1.2
Atorvastatin impurity D[4,5]	2.1

[1] Desfluoro impurity,

[2] 3S,5R isomer,

[3] Difluoro impurity,

[4] Epoxide impurity,

[5] Atorvastatin impurity D may undergo a conversion to its cyclic hemiketal, which is a specified impurity as "atorvastatin epoxy tetrahydrofuran analog". The cyclic hemiketal of atorvastatin impurity D elutes about 1–2 minutes before atorvastatin impurity D. Use the sum of the areas of the two peaks as a peak response for atorvastatin impurity D in the reference solution and the test solution.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to atorvastatin impurity B and atorvastatin is not less than 1.5.

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to atorvastatin impurity A, atorvastatin impurity B and atorvastatin impurity C, each of, is not more than the twice the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.3 per cent), the area of any peak corresponding to atorvastatin impurity D, is not more than 1.33 times the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.2 per cent), the area of any other secondary peak is not more than 0.66 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

The sum of all the impurities is not more than 1.0 per cent.

B. Determine by liquid chromatography (2.4.14).

Buffer solution. A solution prepared by dissolving 2.84 g of *ammonium formate* and 0.35 g of *ammonium acetate* in 950 ml of *water* adjusted to pH 5.0 with 20 per cent v/v of *formic acid* and dilute 1000 ml with *water.*

Solvent mixture. 60 volumes of *acetonitrile,* 5 volumes of *tetrahydrofuran (stabilizer free)* and 35 volumes of *buffer solution.*

Test solution. Dissolve 50 mg of the substance under examination in the solvent mixture with the aid of ultrasound and dilute to 100.0 ml with the solvent mixture. *[NOTE—The solution is stable for 3 hours at room temperature and for 24 hours when stored at 2°–8°, protected from light.]*

Reference solution. A solution containing 0.05 per cent w/v of *atorvastatin calcium IPRS,* and 0.00025 per cent w/v, each of, *atorvastatin impurity A IPRS, atorvastatin impurity B IPRS, atorvastatin impurity H IPRS* and *atorvastatin impurity I IPRS* in the solvent mixture.

Chromatographic system
- a stainless steel column 25 cm x 4.6 mm, packed with phenyl groups bonded to porous silica (4 µm),
- column temperature: 40°,
- sample temperature: 4°,
-mobile phase: A. a mixture of 33 volumes of *acetonitrile* and 67 volumes of the buffer solution,
B. *acetonitrile,*
C. *tetrahydrofuran (stabilizer free),*
- a gradient programme using the conditions given below,
- flow rate: 1.1 ml per minute,
- spectrophotometer set at 254 nm,
- injection volume: 15 µl.

Time	Mobile phase A	Mobile phase B	Mobile phase C

(in min.)	(per cent v/v)	(per cent v/v)	(per cent v/v)
0	91	0	9
15	91	6	3
20	82	16	2
25	82	16	2
50	32	66	2
55	32	66	2
55.1	91	0	9
60	91	0	9

Name	Relative retention time	Correction factor
Atorvastatin diamino[1]	0.58	1.35
Atorvastatin impurity A[2]	0.86	---
Atorvastatin impurity B[3]	0.94	---
Atorvastatin	1.0	---
Atorvastatin impurity C[4] (if present)	1.1	---
Atorvastatin 3-deoxyhept-2-enoic acid[5]	1.45	---
Atorvastatin impurity H[6]	1.90	---
Atorvastatin epoxy tetrahydrofuran analog[7]	2.00	1.41
Atorvastatin ethyl ester[8]	2.08	---
Atorvastatin impurity D[9]	2.18	0.77
Atorvastatin impurity I[10]	2.75	---

[1](3R,5R)-7-{(3R,5R)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanamido}-3,5-dihydroxyheptanoic acid,

[2] Desfluoro impurity,

[3]3S,5R Isomer,

[4] Difluoro impurity,

[5] (S,E)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-5-hydroxyhept-2-enoic acid,

[6] Lactone impurity,

[7] 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-N,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide,

[8] (3R,5R)-Ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate,

[9] Epoxide impurity,

[10] Acetonide impurity.

Inject the reference solution to identify the impurity peaks due to atorvastatin impurity A, B, H and I.

Inject the reference solution. The test is not valid unless the peak-to-valley ratio between the peaks for atorvastatin impurity B and atorvastatin is not less than 2.

Inject the test solution. The area of any peak corresponding to atorvastatin diamino, atorvastatin impurity H, atorvastatin epoxy tetrahydrofuran analog, atorvastatin ethyl ester, atorvastatin impurity D and atorvastatin impurity I, each of, is not more than 0.15 per cent, the area of any peak corresponding to atorvastatin impurity A, B and C, each of, is not more than 0.3 per cent, the area of any peak corresponding to atorvastatin 3-deoxyhept-2-enoic acid is not more than 0.10 per cent, the area of any other secondary peak is not more than 0.10 per cent and the sum of areas of all the secondary peaks is not more than 1.0 per cent (excluding impurity E as controlled in enantiomeric test), calculated by area normalization. Ignore any peak eluting before 2 minutes and the peaks with an area less than 0.05 per cent.

Propylene Glycol Content. (If labelled as a propylene glycol solvate) Not less than 5.4 per cent and not more than 7.3 per cent.

Determine by gas chromatography (2.3.13).

Test solution. Dissolve 50 mg of the substance under examination in *dimethylsulfoxide* with the aid of ultrasound and dilute to 20.0 ml with *dimethylsulfoxide.*

Reference solution. A 0.0125 per cent w/v solution of *propylene glycol IPRS* in *dimethylsulfoxide.*

Chromatographic system

- a capillary column 75 m x 0.53 mm, coated with 6 per cent cyanopropylphenyl and 94 per cent dimethylpolysiloxane (film thickness 3 µm),
- temperature
  column. 100° for 1 minute, 100 ° to 140° @ 10° per minute and hold at 140° for 5 minutes, 140° to 225° @ 30° per minutes and hold at 225° for 3 minutes,
- inlet port at 230° and detector at 250°,
- splitless using a suitable inlet liner,
- flame ionization detector,
- flow rate: 6 ml per minute, using helium as the carrier gas,
- injection volume: 1 µl.

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0, the relative standard deviation for replicate injections is not more than 5.0 per cent.

Inject the reference solution and the test solution. Calculate the content of propylene glycol.

Heavy metals (2.3.13). 1.0 g complies with the limit test for heavy metals, Method B (20 ppm).

Water (2.3.43). Not less than 3.5 per cent and not more than 5.5 per cent for trihydrate form; not more than 6.0 per cent for amorphous or semicrystalline form and not more than 1.0 per cent for propylene glycol solvate form.

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

Test solution. Dissolve 20 mg of the substance under examination in *N,N-dimethylformamide* with the aid of ultrasound and dilute to 50.0 ml with *N,N-dimethylformamide*.

Reference solution (a). A 0.04 per cent w/v solution of *atorvastatin calcium IPRS* in *N,N-dimethylformamide*.

Reference solution (b). A solution containing 0.005 per cent w/v of *atorvastatin calcium IPRS,* and 0.006 per cent w/v of *atorvastatin impurity B IPRS* in *N,N-dimethylformamide*.

Inject reference solution (a) and (b). The test is not valid unless the resolution between the peak due to atorvastatin impurity B and atorvastatin is not less than 1.5 in the chromatogram obtained with reference solution (b) and the tailing factor is not more than 1.6 and the relative standard deviation for replicate injections is not more than 0.6 per cent in the chromatogram obtained with reference solution (a).

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

Calculate the content of $C_{66}H_{68}CaF_2N_4O_{10}$.

Storage. Store protected from light and moisture at a temperature not exceeding 30° (trihydrate form), if labeled as amorphous or semicrystalline or as a propylene glycol solvate, store as per labeling instructions.

Labeling. The label states (1) it is an amorphous form; (2) it is a semicrystalline form, (3) it is a propylene glycol solvate form (4) if a test for related substance other than method A is used, the test with which the article complies.