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Atorvastatin Tablets

Details for the public consultation of this monograph are as follows:

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Notes	**NEW monograph** If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required. **BPCRS:**The British Pharmacopoeia are looking for donations of Atorvastatin Impurity H, Impurity 1 and impurities A and B for establishment of a BPCRS.

Action and use

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

DEFINITION

Atorvastatin Tablets contain Atorvastatin Calcium Trihydrate.

The Tablets comply with the requirements stated under Tablets and with the following requirements.

Content of atorvastatin, $C_{66}H_{68}F_2N_4O_{10}$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

In the Assay, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210-400 nm:

the UV spectrum of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 75 revolutions per minute.

(b) Use 900 mL of a solution containing 0.68% w/v *potassium dihydrogen phosphate* adjusted to pH 6.8 using *sodium hydroxide*, at a temperature of 37°, as the medium.

PROCEDURE

(1) After 30 minutes withdraw a sample of the medium and measure the *absorbance* of the filtered sample, suitably diluted with the dissolution medium, if necessary, to produce a solution containing the equivalent of 0.001% w/v of atorvastatin, at the maximum at 244nm, Appendix II B, using dissolution medium in the reference cell.

(2) Measure the *absorbance* of a 0.001% w/v solution of *atorvastatin calcium trihydrate BPCRS* in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of atorvastatin, $C_{33}H_{35}FN_2O_5$, in the medium from the absorbances obtained and using the declared content of $C_{33}H_{35}FN_2O_5$, in *atorvastatin calcium trihydrate BPCRS*.

Each mg of $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$ is equivalent to 0.924 mg of $C_{33}H_{35}FN_2O_5$.

LIMITS

The amount of atorvastatin released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A: Equal volumes of *acetonitrile* and a 0.96% w/v solution of *citric acid* in water, previously adjusted to pH 7.4 with *ammonium hydroxide*.

(1) Shake a quantity of the powdered tablets containing 100 mg of atorvastatin with 80 mL of solution A, shake and dilute to 100 mL and filter. Dilute the filtrate to produce a final solution containing 0.01% w/v atorvastatin.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) 0.01% w/v of *atorvastatin for system suitability BPCRS*.

(4) Dilute 1 volume of solution (2) to 10 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Ultremex C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 244 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of atorvastatin.

MOBILE PHASE

20 volumes of *tetrahydrofuran*, 27 volumes of *acetonitrile* and 53 volumes of a solution containing 0.96% w/v *citric acid*, previously adjusted to pH 4.0 using *ammonium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to atorvastatin (retention time about 9 minutes) are: impurity 1, about 0.85; impurity C, about 1.15 and impurity H, about 1.30.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between atorvastatin and impurity H is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the areas of any peaks corresponding to impurity 1, and impurity H are not greater than 0.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than 2 times the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (2.0%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.10%).

ASSAY

Weigh and powder 20 tablets. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A. *Prepare the solutions immediately before use and protect from light.*

Solution A: Equal volumes of *acetonitrile* and a 0.96% w/v solution of *citric acid* in water, previously adjusted to pH 7.4 with *ammonium hydroxide*.

(1) Shake a quantity of the powdered Tablets containing 100 mg of atorvastatin with 80 mL of solution A, shake and dilute to 100 mL and filter. Dilute the filtrate to produce a final solution containing 0.01% w/v atorvastatin.

(2) 0.01% w/v of *atorvastatin calcium trihydrate BPCRS*.

(3) 0.01% w/v of *atorvastatin for system suitability BPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *octadecylsilyl silica gel for chromatography* (5 µm) (Ultremex C18 is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.5 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 244 nm.

(f) Inject 20 µL of each solution.

(g) Allow the chromatography to proceed for 3.5 times the retention time of atorvastatin.

MOBILE PHASE

20 volumes of *tetrahydrofuran*, 27 volumes of *acetonitrile* and 53 volumes of a solution containing 0.96% w/v *citric acid*, previously adjusted to pH 4.0 using *ammonium hydroxide*.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to atorvastatin (retention time about 9 minutes) is: impurity H, about 1.30.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between atorvastatin and impurity H is at least 5.0.

DETERMINATION OF CONTENT

Calculate the total content of atorvastatin, $C_{33}H_{35}FN_2O_5$, in the Tablets from the chromatograms obtained and using the declared content of $C_{33}H_{35}FN_2O_5$, in *atorvastatin calcium trihydrate BPCRS*.

Each mg of $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$ is equivalent to 0.924 mg of $C_{33}H_{35}FN_2O_5$.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of atorvastatin.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity H listed under *Atorvastatin Calcium Trihydrate* and:

 1. Impurity 1 5-(4-Fluorophenyl)-1-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3-isopropyl-2-oxo-N,4-diphenyl-2,3-dihydro-1H-pyrrole-3-carboxamide.

1. Impurity 1 5-(4-Fluorophenyl)-1-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]ethyl}-3-isopropyl-2-oxo-N,4-diphenyl-2,3-dihydro-1H-pyrrole-3-carboxamide.