# Pitavastatin Calcium Orally Disintegrating Tablets

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Pitavastatin Calcium Orally Disintegrating Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$: 880.98).

**Method of preparation** Prepare as directed under Tablets, with Pitavastatin Calcium Hydrate.

**Identification** To a quantity of Pitavastatin Calcium Orally Disintegrating Tablets , equivalent to 4 mg of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$) add 10 mL of methanol, shake thoroughly, and centrifuge. To 1 mL of the supernatant liquid add methanol to make 50 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits a maximum between 243 nm and 247 nm.

**Purity** Related substances—Conduct this procedure using light-resistant vessels. To a quantity of Pitavastatin Calcium Orally Disintegrating Tablets, equivalent to 20 mg of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$), add 60 mL of a mixture of acetonitrile and water (3:2), sonicate to disintegrate, add a mixture of acetonitrile and water (3:2) to make 100 mL. Filter this solution through a membrane filter with a pore size not exceeding 0.45 $\mu$m, and use the filtrate as the sample solution. Perform the test with 10 $\mu$L of the sample solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amounts of them by the area percentage method: the amount of the related substance A having the relative retention times of about 1.1 to pitavastatin is not more than 0.5%, the amount of the related substance B having the relative retention times of about 1.5 is not more than 0.2%, the amount of the related substance TA having the relative retention times of about 1.7 is not more than 0.5%, and the amount of the peak other than pitavastatin and the peaks mentioned above is not more than 0.1%. Furthermore, the total amount of the peaks other than pitavastatin is not more than 2.0%.

*Operating conditions*—

Detector: An ultraviolet absorption photometer (wavelength: 245 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 $\mu$m in particle diameter).

Column temperature: A constant temperature of about 40ºC.

Mobile phase A: To 10 mL of dilute acetic acid add water to make 1000 mL. To 800 mL of this solution add diluted sodium acetate TS (1 in 100) to adjust to pH 3.8.

Mobile phase B: Acetonitrile for liquid chromatography.

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

| Time after injection of sample (min) | Mobile phase A (vol%) | Mobile phase B (vol%) |
|---|---|---|
| 0 — 20 | 60 | 40 |
| 20 — 40 | 60 → 30 | 40 → 70 |
| 40 — 65 | 30 | 70 |

Flow rate: Adjust so that the retention time of pitavastatin is about 23 minutes.

Time span of measurement: About 2.7 times as long as the retention time of pitavastatin, beginning after the solvent peak.

*System suitability*—

Test for required detectability: To 1 mL of the sample solution, add a mixture of acetonitrile and water (3:2) to make 100 mL, and use this solution as the solution for system suitability test. Pipet 5 mL of the solution for system suitability test, add a mixture of acetonitrile and water (3:2) to make exactly 50 mL. Confirm that the peak area of pitavastatin obtained with 10 $\mu$L of this solution is equivalent to 7 to 13% of that with 10 $\mu$L of the solution for system suitability test.

System performance: When the procedure is run with 10 $\mu$L of the solution for system suitability test under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pitavastatin are not less than 7500 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 $\mu$L of the solution for system suitability test under the above operating conditions, the relative standard deviation of the peak area of pitavastatin is not more than 2.0%.

**Uniformity of dosage units** *<6.02>* Perform the test according to the following method: it meets the requirement of the Content uniformity test.

Conduct this procedure using light-resistant vessels. To 1 tablet of Pitavastatin Calcium Orally Disintegrating Tablets add exactly *V* mL of the internal standard solution so that each mL contains about 0.2 mg of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$), and add *V* mL of a mixture of acetonitrile and water (3:2), and sonicate to disintegrate. Filter this

solution through a membrane filter with a pore size not exceeding 0.45 μm, and use the filtrate as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$)
$= M_S \times Q_T / Q_S \times V / 100 \times 0.812$

$M_S$: Amount (mg) of Pitavastatin Methylbenzylamine RS taken, calculated on the anhydrous basis

*Internal standard solution*—A solution of butyl parahydroxybenzoate in a mixture of acetonitrile and water (3:2) (3 in 10,000).

**Disintegration** Being specified separately when the drug is granted approval based on the Law.

**Dissolution** <*6.10*> When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 15 minutes of Pitavastatin Calcium Orally Disintegrating Tablets is not less than 75%.

Conduct this procedure using light-resistant vessels. Start the test with 1 tablet of Pitavastatin Calcium Orally Disintegrating Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL or more of the filtrate, pipet *V* mL of the subsequent filtrate, add the dissolution medium to make exactly *V'* mL so that each mL contains about 0.9 μg of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$), and use this solution as the sample solution. Separately, weigh accurately about 24 mg of Pitavastatin Methylbenzylamine RS (separately determine the water <*2.48*> by coulometric titration using 0.1 g) and dissolve in a mixture of acetonitrile and water (3:2) to make exactly 100 mL. Pipet 1 mL of this solution, add the dissolution medium to make exactly 200 mL, and use this solution as the standard solution. Perform the test with exactly 50 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of pitavastatin in each solution.

Dissolution rate (%) with respect to the labeled amount of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$)
$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 18 / 5 \times 0.812$

$M_S$: Amount (mg) of Pitavastatin Methylbenzylamine RS taken, calculated on the anhydrous basis
$C$: Labeled amount (mg) of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$) in 1 tablet

*Operating conditions*—
Proceed as directed in the operating conditions in the Assay.
*System suitability*—
System performance: When the procedure is run with 50 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of pitavastatin are not less than 4500 and not more than 2.0, respectively.
System repeatability: When the test is repeated 6 times with 50 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of pitavastatin is not more than 1.0%.

**Assay** Conduct this procedure using light-resistant vessels. To not less than 20 tablets of Pitavastatin Calcium Orally Disintegrating Tablets add exactly *V* mL of a mixture of acetonitrile and water (3:2) so that each mL contains about 0.2 mg of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$), and sonicate to disintegrate the tablet. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, shake, then filter through a membrane filter with a pore size not exceeding 0.45 μm, and use the filtrate as the sample solution. Separately weigh accurately about 24 mg of Pitavastatin Methylbenzylamine RS (separately determine the water <*2.48*> by coulometric titration using 0.1 g), dissolve in a mixture of acetonitrile and water (3:2) to make exactly 100 mL. Pipet 5 mL of this solution, add exactly 5 mL of the internal standard solution, and use this solution as the standard solution. Perform the test with 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and calculate the ratios, $Q_T$ and $Q_S$, of the peak area of pitavastatin to that of the internal standard.

Amount (mg) of pitavastatin calcium ($C_{50}H_{46}CaF_2N_2O_8$) in 1 tablet
$= M_S \times Q_T / Q_S \times V / N \times 1 / 100 \times 0.812$

$M_S$: Amount (mg) of Pitavastatin Methylbenzylamine RS taken, calculated on the anhydrous basis
$N$: Number of tablets taken

*Internal standard solution*—A solution of butyl parahydroxybenzoate in a mixture of acetonitrile and water (3:2) (3 in 10,000).
*Operating conditions*—
Detector: An ultraviolet absorption photometer (wavelength: 245 nm).
Column: A stainless steel column 4.6 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40ºC.

Mobile phase: To 10 mL of dilute acetic acid add water to make 1000 mL. To 350 mL of this solution add 650 mL of methanol, and add 0.29 g of sodium chloride to dissolve.

Flow rate: Adjust so that the retention time of pitavastatin is about 17 minutes.

*System suitability*—

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the internal standard and pitavastatin are eluted in this order with the resolution between these peaks being not less than 2.0.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the ratio of the peak area of pitavastatin to that of the internal standard is not more than 1.0%.

**Containers and storage** Containers—Tight containers.

Storage—Light-resistant.

**Others**

Related substances A and B: Refer to them described in Pitavastatin Calcium Hydrate.

Related substances TA:

6-{2-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl] ethenyl}-4-hydroxyoxan-2-one