# Sitagliptin Phosphate Tablets

シタグリプチンリン酸塩錠

Sitagliptin Phosphate Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of sitagliptin ($C_{16}H_{15}F_6N_5O$: 407.31).

**Method of preparation** Prepare as directed under Tablets, with Sitagliptin Phosphate Hydrate.

**Manufacture** In the management strategy of Sitagliptin Phosphate Tablets, setting of a target, understanding of products and processes, and process control are emphasized. The following disintegration is alternative for the dissolution, when it can be scientifically possible to explain that the disintegration ensure quality with distinguishability equal or better than the dissolution, at the foundation of systematic development methods based on quality risk management and proven science.

Disintegration *<6.09>* Perform the test for 5 minutes: it meets the requirement.

**Identification** **(1)** To 1 tablet of Sitagliptin Phosphate Tablets add water so that each mL contains about 0.2 mg of sitagliptin ($C_{16}H_{15}F_6N_5O$), and shake thoroughly to disintegrate. Centrifuge this solution, and use the supernatant liquid as the sample solution. Determine the absorption spectrum of the sample solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*: it exhibits a maximum between 265 nm and 269 nm.

**(2)** Compare the chromatograms of the sample solution and the standard solution obtained in the Assay: the retention time of the principal peaks in the chromatograms obtained from the sample solution and the standard solution is the same.

**Purity** Related substances—Use the sample solution obtained in the Assay as the sample solution. Separately, pipet 1 mL of the standard solution obtained in the Assay, add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 500 mL, and use this solution as the standard solution. Perform the test with exactly 20 $\mu$L each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine the peak areas, $A_T$, of related substances obtained from the sample solution and the peak area, $A_S$, of sitagliptin from the standard solution, and calculate the amount of related substances by the following equation: the total amount of related substances is not more than 0.2%. For this calculation the amount of related substance not more than 0.1% is excluded.

Amount (%) of related substance

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 1/50 \times 0.806$

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

$V'/V$: Dilution factor for the sample solution in the Assay

$C$: Labeled amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet

*Operating conditions*—

Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: About 5.5 times as long as the retention time of sitagliptin.

*System suitability*—

System performance and system repeatability: Proceed as directed in the system suitability in the Assay.

Test for required detectability: To 5 mL of the standard solution add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 10 mL. Confirm that the SN ratio of the peak of sitagliptin obtained with 20 $\mu$L of this solution is not less than 10.

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

To 1 tablet of Sitagliptin Phosphate Tablets add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 25 mL, and stir thoroughly. Pipet $V$ mL of this solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly $V'$ mL so that each mL contains about 80 $\mu$g of sitagliptin ($C_{16}H_{15}F_6N_5O$). Centrifuge this solution, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay.

Amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$)

$= M_S \times A_T / A_S \times V'/V \times 1/10 \times 0.806$

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

**Dissolution** *<6.10>* When the test is performed at 100 revolutions per minute according to the Basket method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of Sitagliptin Phosphate Tablets is not less than 85%.

Start the test with 1 tablet of Sitagliptin Phosphate Tablets, withdraw not less than 4 mL of the medium at the spec-

ified minute after starting the test, and filter through a membrane filter with a pore size of 0.45 $\mu$m. Discard the first 2 mL or more of the filtrate, pipet $V$ mL of the subsequent filtrate, add water to make exactly $V'$ mL so that each mL contains about 14 $\mu$g of sitagliptin ($C_{16}H_{15}F_6N_5O$), and use this solution as the sample solution. Separately, weigh accurately about 29 mg of Sitagliptin Phosphate RS (separately determine the water <*2.48*> in the same manner as Sitagliptin Phosphate Hydrate), and dissolve in a solution of sodium chloride (37 in 25,000) to make exactly 100 mL. Pipet 6 mL of this solution, and add a solution of sodium chloride (37 in 25,000) to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 $\mu$L 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 sitagliptin in each solution.

Dissolution rate (%) with respect to the labeled amount of sitagliptin ($C_{16}H_{15}F_6N_5O$)

$= M_S \times A_T / A_S \times V' / V \times 1 / C \times 54 \times 0.806$

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

$C$: Labeled amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet

*Operating conditions*—

Column, column temperature and flow rate: Proceed as directed in the operating conditions in the Assay.

Detector: An ultraviolet absorption photometer (wavelength: 267 nm).

Mobile phase: Dissolve 1.36 g of sodium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 750 mL of this solution add 250 mL of acetonitrile for liquid chromatography.

*System suitability*—

System performance: When the procedure is run with 20 $\mu$L of the standard solution under the above operating conditions, the theoretical plates and the symmetry factor of the peak of sitagliptin are not less than 5000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 $\mu$L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

**Assay** To 10 Sitagliptin Phosphate Tablets add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 250 mL, and stir thoroughly. Pipet $V$ mL of this solution, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly $V'$ mL so that each mL contains about 80 $\mu$g of sitagliptin ($C_{16}H_{15}F_6N_5O$). Centrifuge this solution, and use the supernatant liquid as the sample solution. Separately, weigh accurately about 26 mg of Sitagliptin Phosphate RS (separately determine the water <*2.48*> in the same manner as Sitagliptin Phosphate Hydrate), dissolve in a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make exactly 250 mL, and use this solution as the standard solution. Perform the test with exactly 20 $\mu$L 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 sitagliptin in each solution.

Amount (mg) of sitagliptin ($C_{16}H_{15}F_6N_5O$) in 1 tablet of Sitagliptin Phosphate Tablets

$= M_S \times A_T / A_S \times V' / V \times 1 / 10 \times 0.806$

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

*Operating conditions*—

Detector: An ultraviolet absorption photometer (wavelength: 205 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with cyanopropylsilanized silica gel for liquid chromatography (5 $\mu$m in particle diameter).

Column temperature: A constant temperature of about 30℃.

Mobile phase: Dissolve 1.36 g of sodium dihydrogen phosphate in 900 mL of water, adjust to pH 2.0 with phosphoric acid, and add water to make 1000 mL. To 850 mL of this solution add 150 mL of acetonitrile for liquid chromatography.

Flow rate: 1.0 mL per minute.

*System suitability*—

System performance: Proceed as directed in the system suitability in the Assay. The following method can be applied when sodium stearyl fumarate is contained in the additive of the tablet.

Crush 1 tablet of Sitagliptin Phosphate Tablets, transfer to a vial, and add 1 mL of water. Stopper the vial tightly, and heat at 80℃ for 20 to 48 hours. Take out the contents of the vial, wash the vial 3 times with a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1), combine the washings and the content, and add a mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1) to make 100 mL. Stir this solution for 1 hour, and centrifuge for 10 minutes or until the solution becomes clear. When the procedure is run with 20 $\mu$L of the supernatant liquid under the above operating conditions, the resolution

between sitagliptin and the peak having the relative retention time of about 1.2 to sitagliptin is not less than 1.5.

System repeatability: When the test is repeated 6 times with 20 $\mu$L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of sitagliptin is not more than 1.0%.

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

***Add the following to 9.01 Reference Standards (1):***

**Sitagliptin Phosphate RS**

***Add the following to 9.41 Reagents, Test Solutions:***

**Sodium stearyl fumarate** $C_{22}H_{39}NaO_4$ A white crystalline powder.

*Content*: not less than 99.0% and not more than 101.5%, calculated on the anhydrous basis. Assay—Weigh accurately about 0.6 g of sodium stearyl fumarate, add 8 mL of chloroform and 140 mL of acetic acid (100), and warm to dissolve. After cooling, titrate <*2.50*> with 0.1 mol/L perchloric acid VS (potentiometric titration). Perform a blank determination in the same manner, and make any necessary correction.

Each mL of 0.1 mol/L perchloric acid VS
= 39.05 mg of $C_{22}H_{39}NaO_4$