

1 Sitagliptin Phosphate Tablets

2 シタグリプチンリン酸塩錠

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4 Sitagliptin Phosphate Tablets contain not less than
5 95.0% and not more than 105.0% of the labeled
6 amount of sitagliptin (C₁₆H₁₅F₆N₅O: 407.31).

7 **Method of preparation** Prepare as directed under Tab-
8 lets, with Sitagliptin Phosphate Hydrate.

9 **Manufacture** In the management strategy of Sitagliptin
10 Phosphate Tablets, setting of a target, understanding of
11 products and processes, and process control are empha-
12 sized. The following disintegration is alternative for the
13 dissolution, when it can be scientifically possible to explain
14 that the disintegration ensure quality with distinguishability
15 equal or better than the dissolution, at the foundation of sys-
16 tematic development methods based on quality risk man-
17 agement and proven science.

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

20 **Identification (1)** To 1 tablet of Sitagliptin Phosphate
21 Tablets add water so that each mL contains about 0.2 mg
22 of sitagliptin (C₁₆H₁₅F₆N₅O), and shake thoroughly to dis-
23 integrate. Centrifuge this solution, and use the supernatant
24 liquid as the sample solution. Determine the absorption
25 spectrum of the sample solution as directed under Ultravi-
26 olet-visible Spectrophotometry <2.24>: it exhibits a maxi-
27 mum between 265 nm and 269 nm.

28 (2) Compare the chromatograms of the sample solu-
29 tion and the standard solution obtained in the Assay: the
30 retention time of the principal peaks in the chromatograms
31 obtained from the sample solution and the standard solution
32 is the same.

33 **Purity** Related substances—Use the sample solution ob-
34 tained in the Assay as the sample solution. Separately, pipet
35 1 mL of the standard solution obtained in the Assay, add a
36 mixture of diluted phosphoric acid (1 in 1000) and aceton-
37 itrile for liquid chromatography (19:1) to make exactly 500
38 mL, and use this solution as the standard solution. Perform
39 the test with exactly 20 μL each of the sample solution and
40 standard solution as directed under Liquid Chromatog-
41 raphy <2.01> according to the following conditions. Deter-
42 mine the peak areas, A_T, of related substances obtained
43 from the sample solution and the peak area, A_S, of
44 sitagliptin from the standard solution, and calculate the
45 amount of related substances by the following equation: the
46 total amount of related substances is not more than 0.2%.
47 For this calculation the amount of related substance not
48 more than 0.1% is excluded.

49 Amount (%) of related substance
50 $= M_S \times A_T / A_S \times V' / V \times 1 / C \times 1 / 50 \times$
51 0.806

52 M_S: Amount (mg) of Sitagliptin Phosphate RS taken, cal-
53 culated on the anhydrous basis

54 V' / V: Dilution factor for the sample solution in the As-
55 say

56 C: Labeled amount (mg) of sitagliptin (C₁₆H₁₅F₆N₅O) in
57 1 tablet

58 *Operating conditions*—

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

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

64 *System suitability*—

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

67 Test for required detectability: To 5 mL of the standard
68 solution add a mixture of diluted phosphoric acid (1 in
69 1000) and acetonitrile for liquid chromatography (19:1) to
70 make exactly 10 mL. Confirm that the SN ratio of the peak
71 of sitagliptin obtained with 20 μL of this solution is not less
72 than 10.

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

76 To 1 tablet of Sitagliptin Phosphate Tablets add a
77 mixture of diluted phosphoric acid (1 in 1000) and
78 acetonitrile for liquid chromatography (19:1) to make
79 exactly 25 mL, and stir thoroughly. Pipet V mL of this
80 solution, and add a mixture of diluted phosphoric acid (1 in
81 1000) and acetonitrile for liquid chromatography (19:1) to
82 make exactly V' mL so that each mL contains about 80 μg
83 of sitagliptin (C₁₆H₁₅F₆N₅O). Centrifuge this solution, and
84 use the supernatant liquid as the sample solution. Then,
85 proceed as directed in the Assay.

86 Amount (mg) of sitagliptin (C₁₆H₁₅F₆N₅O)
87 $= M_S \times A_T / A_S \times V' / V \times 1 / 10 \times 0.806$

88 M_S: Amount (mg) of Sitagliptin Phosphate RS taken, cal-
89 culated on the anhydrous basis

90 **Dissolution** <6.10> When the test is performed at 100
91 revolutions per minute according to the Basket method, us-
92 ing 900 mL of water as the dissolution medium, the disso-
93 lution rate in 15 minutes of Sitagliptin Phosphate Tablets is
94 not less than 85%.

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

97 ified minute after starting the test, and filter through a mem-
 98 brane filter with a pore size of 0.45 μm . Discard the first 2
 99 mL or more of the filtrate, pipet V mL of the subsequent
 100 filtrate, add water to make exactly V' mL so that each mL
 101 contains about 14 μg of sitagliptin ($\text{C}_{16}\text{H}_{15}\text{F}_6\text{N}_5\text{O}$), and use
 102 this solution as the sample solution. Separately, weigh ac-
 103 curately about 29 mg of Sitagliptin Phosphate RS (sepa-
 104 rately determine the water <2.48> in the same manner as
 105 Sitagliptin Phosphate Hydrate), and dissolve in a solution
 106 of sodium chloride (37 in 25,000) to make exactly 100 mL.
 107 Pipet 6 mL of this solution, and add a solution of sodium
 108 chloride (37 in 25,000) to make exactly 100 mL, and use
 109 this solution as the standard solution. Perform the test with
 110 exactly 20 μL each of the sample solution and standard so-
 111 lution as directed under Liquid Chromatography <2.01> ac-
 112 cording to the following conditions, and determine the peak
 113 areas, A_T and A_S , of sitagliptin in each solution.

114 Dissolution rate (%) with respect to the labeled amount of
 115 sitagliptin ($\text{C}_{16}\text{H}_{15}\text{F}_6\text{N}_5\text{O}$)
 116 $= M_S \times A_T / A_S \times V' / V \times 1 / C \times 54 \times$
 117 0.806

118 M_S : Amount (mg) of Sitagliptin Phosphate RS taken, cal-
 119 culated on the anhydrous basis

120 C : Labeled amount (mg) of sitagliptin ($\text{C}_{16}\text{H}_{15}\text{F}_6\text{N}_5\text{O}$) in
 121 1 tablet

122 *Operating conditions*—

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

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

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

132 *System suitability*—

133 System performance: When the procedure is run with 20
 134 μL of the standard solution under the above operating
 135 conditions, the theoretical plates and the symmetry factor
 136 of the peak of sitagliptin are not less than 5000 and not
 137 more than 1.5, respectively.

138 System repeatability: When the test is repeated 6 times
 139 with 20 μL of the standard solution under the above
 140 operating conditions, the relative standard deviation of the
 141 peak area of sitagliptin is not more than 1.0%.

142 **Assay** To 10 Sitagliptin Phosphate Tablets add a mixture
 143 of diluted phosphoric acid (1 in 1000) and acetonitrile for
 144 liquid chromatography (19:1) to make exactly 250 mL, and
 145 stir thoroughly. Pipet V mL of this solution, and add a mix-
 146 ture of diluted phosphoric acid (1 in 1000) and acetonitrile

147 for liquid chromatography (19:1) to make exactly V' mL so
 148 that each mL contains about 80 μg of sitagliptin
 149 ($\text{C}_{16}\text{H}_{15}\text{F}_6\text{N}_5\text{O}$). Centrifuge this solution, and use the super-
 150 natant liquid as the sample solution. Separately, weigh ac-
 151 curately about 26 mg of Sitagliptin Phosphate RS (sepa-
 152 rately determine the water <2.48> in the same manner as
 153 Sitagliptin Phosphate Hydrate), dissolve in a mixture of di-
 154 luted phosphoric acid (1 in 1000) and acetonitrile for liquid
 155 chromatography (19:1) to make exactly 250 mL, and use
 156 this solution as the standard solution. Perform the test with
 157 exactly 20 μL each of the sample solution and standard so-
 158 lution as directed under Liquid Chromatography <2.01> ac-
 159 cording to the following conditions, and determine the peak
 160 areas, A_T and A_S , of sitagliptin in each solution.

161 Amount (mg) of sitagliptin ($\text{C}_{16}\text{H}_{15}\text{F}_6\text{N}_5\text{O}$) in 1 tablet of
 162 Sitagliptin Phosphate Tablets

$$163 = M_S \times A_T / A_S \times V' / V \times 1 / 10 \times 0.806$$

164 M_S : Amount (mg) of Sitagliptin Phosphate RS taken, cal-
 165 culated on the anhydrous basis

166 *Operating conditions*—

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

169 Column: A stainless steel column 4.6 mm in inside
 170 diameter and 15 cm in length, packed with
 171 cyanopropylsilanized silica gel for liquid chromatography
 172 (5 μm in particle diameter).

173 Column temperature: A constant temperature of about
 174 30°C.

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

180 Flow rate: 1.0 mL per minute.

181 *System suitability*—

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

186 Crush 1 tablet of Sitagliptin Phosphate Tablets, transfer
 187 to a vial, and add 1 mL of water. Stopper the vial tightly,
 188 and heat at 80°C for 20 to 48 hours. Take out the contents
 189 of the vial, wash the vial 3 times with a mixture of diluted
 190 phosphoric acid (1 in 1000) and acetonitrile for liquid
 191 chromatography (19:1), combine the washings and the
 192 content, and add a mixture of diluted phosphoric acid (1 in
 193 1000) and acetonitrile for liquid chromatography (19:1) to
 194 make 100 mL. Stir this solution for 1 hour, and centrifuge
 195 for 10 minutes or until the solution becomes clear. When
 196 the procedure is run with 20 μL of the supernatant liquid
 197 under the above operating conditions, the resolution

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

200 System repeatability: When the test is repeated 6 times
201 with 20 μL of the standard solution under the above
202 operating conditions, the relative standard deviation of the
203 peak area of sitagliptin is not more than 1.0%.

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

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

207 **Sitagliptin Phosphate RS**

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

210 **Sodium stearyl fumarate** $\text{C}_{22}\text{H}_{39}\text{NaO}_4$ A white crys-
211 talline powder.

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

220 Each mL of 0.1 mol/L perchloric acid VS
221 = 39.05 mg of $\text{C}_{22}\text{H}_{39}\text{NaO}_4$

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