Sitagliptin Phosphate

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In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 3 Expert Committee intends to revise the Sitagliptin Phosphate monograph. This Notice of Intent to Revise replaces a revision that was previously posted with a tighter water content limit of NMT 0.5%.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the following sections to accommodate the anhydrous form of the drug substance:

1. Chemical information: include the chemical name and molecular weight for the anhydrous form.
2. Water Determination: include the water limit of NMT 1.0% for the anhydrous form.
3. Labeling: Add a Labeling Section to accommodate the addition of the anhydrous form.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Andrea Carney, Scientific Liaison to the Chemical Medicines Monographs 3 Expert Committee (301-816-8155 or afc@usp.org).

¹ This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Sitagliptin Phosphate

Change to read:

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▲ (TBD)

C₁₆H₁₅F₆N₅O·H₃PO₄·H₂O     523.32
C₁₆H₁₅F₆N₅O·H₃PO₄     505.31
1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-( trifluoromethyl)-, phosphate (1:1) monohydrate;
7-[(R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine monophosphate monohydrate
(3R)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-4-(2,4,5-trifluorophenyl)butan-1-one phosphate monohydrate  [654671-77-9]; UNII: TS63EW8X6F.
▲7-[(R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine monophosphate  [654671-78-0]; UNII: 494P4635I6. ▲ (TBD)

DEFINITION
Sitagliptin Phosphate contains NLT 98.0% and NMT 102.0% of sitagliptin phosphate (C₁₆H₁₅F₆N₅O·H₃PO₄), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION
• A. SPECTROSCOPIC IDENTIFICATION TESTS (197), Infrared Spectroscopy: 197A, 197K, or 197M
  [Note—If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in dehydrated alcohol, evaporate to dryness, and record new spectra using the residues.]
• B. Meets the requirements of the test for Enantiomeric Purity
• C. IDENTIFICATION TESTS—GENERAL (191), Chemical Identification Tests, Phosphate: A solution containing about 40 mg/mL in water meets the requirements of test A of Orthophosphates.

ASSAY
• Procedure
  Buffer: 1.36 g/L of monobasic potassium phosphate, adjusted with phosphoric acid to a pH of 2.0
  Mobile phase: Acetonitrile and Buffer (15:85)
  Dilute phosphoric acid: Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume.
  Diluent: Acetonitrile and Dilute phosphoric acid (5:95)
  Standard solution: 0.1 mg/mL of USP Sitagliptin Phosphate RS in Diluent
  Sample solution: 0.1 mg/mL of Sitagliptin Phosphate in Diluent
Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 205 nm
Column: 4.6-mm x 15-cm; 5-μm packing L10
Column temperature: 30°
Flow rate: 1.0 mL/min
Injection volume: 20 μL

System suitability
Sample: Standard solution
Suitability requirements
Relative standard deviation: NMT 0.73%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of sitagliptin phosphate (C_{16}H_{15}F_{6}N_{5}O·H_{3}PO_{4}) in the portion of Sitagliptin Phosphate taken:

Result = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100

r_U = \text{peak area from the Sample solution}

r_S = \text{peak area from the Standard solution}

C_S = \text{concentration of USP Sitagliptin Phosphate RS in the Standard solution (mg/mL)}

C_U = \text{concentration of Sitagliptin Phosphate in the Sample solution (mg/mL)}

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES
• Organic Impurities

Buffer, Mobile phase, Dilute phosphoric acid, Diluent, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

System suitability solution: Place 10 mg of Sitagliptin Phosphate and 1 mg of sodium stearyl fumarate into a vial, add 1 mL of water, and tightly seal the vial. Heat at 80° for about 30 h to generate a fumarate adduct of sitagliptin. [Note—The chemical name of fumarate adduct of sitagliptin is 2-[[R]-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-yl]amino]succinic acid.] Transfer the content of the vial into a 100-mL volumetric flask using a small amount of Diluent, and dilute with Diluent to volume. Mix well by stirring for 1 h. Centrifuge a portion of the solution for 10 min or until the solution is clear, and use the supernatant.

Standard solution: 0.0001 mg/mL of USP Sitagliptin Phosphate RS in Diluent

System suitability
Sample: System suitability solution
[Note—The relative retention times for sitagliptin and fumarate adduct of sitagliptin are 1.0 and 1.2, respectively.]

Suitability requirements
Resolution: NLT 1.5 between sitagliptin and fumarate adduct of sitagliptin

Analysis
Samples: Sample solution and Standard solution
Calculate the percentage of each impurity in the portion of Sitagliptin Phosphate taken:

Result = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\[ r_U \] = peak response of each impurity from the Sample solution
\[ r_S \] = peak response of sitagliptin from the Standard solution
\[ C_S \] = concentration of USP Sitagliptin Phosphate in the Standard solution (mg/mL)
\[ C_U \] = concentration of Sitagliptin Phosphate in the Sample solution (mg/mL)

**Acceptance criteria:** Disregard any peak below 0.05%.

**Any individual impurity:** NMT 0.10%

**Total impurities:** NMT 0.5%

**Enantiomeric Purity**

**Mobile phase:** Dehydrated alcohol, chromatographic n-heptane, diethylamine, and water (600:400:1:1)

**Diluent:** Methanol and water (9:1)

**System suitability solution:** 8 mg/mL of USP Sitagliptin System Suitability Mixture RS in Diluent

**Sample solution:** 8 mg/mL of Sitagliptin Phosphate in Diluent

**Sensitivity solution:** 8 µg/mL of Sitagliptin Phosphate in Diluent from the Sample solution

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 268 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L51

**Column temperature:** 35°

**Flow rate:** 0.8 mL/min

**Injection volume:** 10 µL

**System suitability**

**Samples:** System suitability solution and Sensitivity solution

[Note—The relative retention times for sitagliptin, which is the R-enantiomer, and the S-enantiomer are 1.0 and 0.9, respectively.]

**Suitability requirements**

**Resolution:** NLT 1.5 between the S-enantiomer and sitagliptin, System suitability solution

**Signal-to-noise ratio:** NLT 10 for the sitagliptin peak, Sensitivity solution

**Analysis**

**Sample:** Sample solution

Calculate the percentage of S-enantiomer in the portion of Sitagliptin Phosphate taken:

\[
\text{Result} = \left( \frac{r_U}{r_T} \right) \times 100
\]

\[ r_U \] = peak response of the S-enantiomer from the Sample solution

\[ r_T \] = sum of the peak responses of the S-enantiomer and sitagliptin from the Sample solution

**Acceptance criteria:** NMT 0.5% of the S-enantiomer

**SPECIFIC TESTS**

**Change to read:**

**Water Determination (921), Method I, Method Ia:** \( ^\text{a} \) For the monohydrate form, \( ^\text{a} \) (TBD) 3.3%–3.7%. \( ^\text{a} \) For the anhydrous form, NMT 1.0%. \( ^\text{a} \) (TBD)

**ADDITIONAL REQUIREMENTS**

**Packaging and Storage:** Preserve in well-closed containers. Store at room temperature.

**Add the following:**
**LABELING:** If it is an anhydrous form, it is so labeled. (TBD)

- **USP Reference Standards (11)**
  - USP Sitagliptin Phosphate RS
  - USP Sitagliptin System Suitability Mixture RS

Sitagliptin Phosphate containing S-enantiomer.

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**Page Information:**

Not Applicable

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