Sitagliptin Phosphate

Type of Posting	Notice of Intent to Revise
Posting Date	28–Aug–2020
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 3

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).

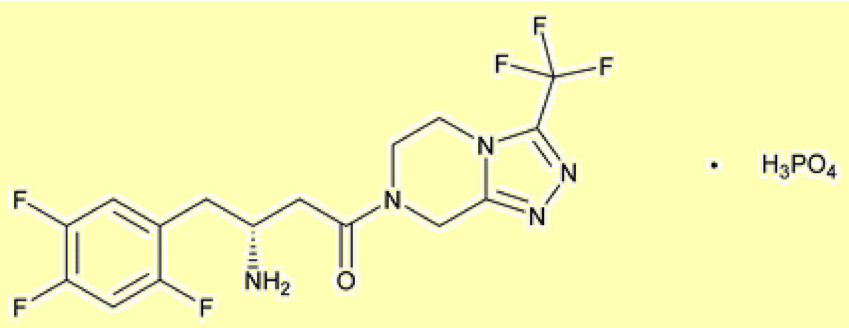
[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

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:

▲



Click image to enlarge

▲ (TBD)

$C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ 523.32
$C_{16}H_{15}F_6N_5O \cdot H_3PO_4$ 505.31

1,2,4-Triazolo[4,3-*a*]pyrazine, 7-[(3*R*)-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
(3*R*)-3-Amino-1-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8*H*)-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 ($C_{16}H_{15}F_6N_5O \cdot H_3PO_4$), 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 × 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 ($C_{16}H_{15}F_6N_5O \cdot H_3PO_4$) in the portion of Sitagliptin Phosphate taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of USP Sitagliptin Phosphate RS in the *Standard solution* (mg/mL)

C_U = 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(8*H*)-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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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:

$$\text{Result} = (r_U/r_T) \times 100$$

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*:** ▲For the monohydrate form,▲ (TBD) 3.3%–3.7%. ▲For the anhydrous form, NMT 1.0%.▲ (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.

Page Information:

Not Applicable

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