Entacapone Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	29–Mar–2019
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Expert Committee	Chemical Medicines Monographs 4

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 4 Expert Committee intends to revise the Entacapone Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 4* to accommodate different dissolution conditions.

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 Heather Joyce, Ph.D., Senior Scientific Liaison–Team Leader to the Chemical Medicines Monographs 4 Expert Committee (301-998-6792 or hrj@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.

Entacapone Tablets

DEFINITION

Entacapone Tablets contain an amount of entacapone equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$).

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩**:** The sample shows a medium band at about 2216 cm^{-1} and strong bands at about 1628, 1604, 1544, 1512, 1440, 1376, 1348, 1296, 1280, and 1208 cm^{-1} similar to the reference preparation.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Protect solutions from light.

Buffer: 2.1 g/L of monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 2.1.

Diluent: Methanol and tetrahydrofuran (70:30)

Mobile phase: Methanol, tetrahydrofuran, and *Buffer* (44:2:54)

Standard solution: 0.5 mg/mL of USP Entacapone RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of entacapone prepared as follows. Finely powder NLT 20 Tablets, and transfer a suitable portion of the powder to an appropriate volumetric flask. Add NLT 30% of the final flask volume of tetrahydrofuran, and sonicate for 3 min. Add NLT 30% of the final flask volume of methanol, and shake for 5 min. Dilute with methanol to volume. Centrifuge a portion of this solution, and use the supernatant.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 300 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Flow rate: 1 mL/min

Run time: 1.5 times the retention time of the entacapone peak

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Entacapone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of entacapone in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1

Medium: pH 5.5 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water, adjusted with 1 M sodium hydroxide to a pH of 5.5); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard stock solution: 0.22 mg/mL of USP Entacapone RS, prepared as follows. Transfer a suitable quantity of USP Entacapone RS to an appropriate volumetric flask, and dissolve in 2% of the flask volume of tetrahydrofuran. Dilute with *Medium* to volume. Protect this solution from light.

Standard solution: 0.022 mg/mL of USP Entacapone RS from the *Standard stock solution* in *Medium*. Protect this solution from light.

Sample solution: Pass a portion of the solution through a suitable filter of 20-µm pore size. Dilute with *Medium*, if necessary. Protect this solution from light.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

Mode: UV

Analytical wavelength: 313 nm

Path length: 1 cm

Blank: Tetrahydrofuran and *Medium* (0.2: 99.8)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: pH 5.5 phosphate buffer (6.8 g/L of monobasic potassium phosphate in water, adjusted with 5 M sodium hydroxide to a pH of 5.5); 900 mL

Apparatus 2: 50 rpm

Time: 45 min

Standard stock solution: 0.45 mg/mL of USP Entacapone RS prepared as follows. Transfer a suitable quantity of USP Entacapone RS to an appropriate volumetric flask, and dissolve in 5% of the flask volume of methanol. Dilute with *Medium* to volume. Use this solution within 6.5 h.

Standard solution: 0.018 mg/mL of USP Entacapone RS from the *Standard stock solution* in *Medium*. Use this solution within 6.5 h.

Sample solution: Pass a portion of the solution under test through a suitable filter. Transfer 2 mL of the filtrate to a 25-mL volumetric flask, and dilute with *Medium* to volume. Pass the resulting solution through a suitable filter of 0.45-µm pore size. Use this solution within 6.5 h.

Instrumental conditions

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

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Mode: UV
Analytical wavelength: 313 nm
Path length: 1 cm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
D = dilution factor for the *Sample solution,* 12.5

Tolerances: NLT 80% (Q) of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: pH 5.5 phosphate buffer (6.8 g/L of monobasic potassium phosphate and 0.05 g/L of sodium hydroxide in water, adjusted with 5 M sodium hydroxide to a pH of 5.5); 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Standard stock solution: 0.45 mg/mL of USP Entacapone RS prepared as follows. Transfer a suitable quantity of USP Entacapone RS to an appropriate volumetric flask, and dissolve in 30% of the flask volume of methanol. Sonicate to dissolve, and allow the solution to cool to room temperature. Dilute with methanol to volume. Use this solution within 6 h.
Standard solution: 0.009 mg/mL of USP Entacapone RS from the *Standard stock solution* in *Medium*. Use this solution within 6 h.
Sample stock solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size. Use this solution within 6 h.
Sample solution: Transfer 2.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Medium* to volume. Use this solution within 6 h.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
Mode: UV
Analytical wavelength: 378 nm
Blank: *Medium*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times D \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL
D = dilution factor for the *Sample solution,* 25

Tolerances: NLT 70% (Q) of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) is dissolved.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium, Time, Instrumental conditions, and **Analysis:** Proceed as directed for *Test 3*.
Apparatus 2: 75 rpm
Standard stock solution: 0.45 mg/mL of USP Entacapone RS prepared as follows. Transfer a suitable quantity of USP Entacapone RS to an appropriate volumetric flask, and dissolve in 30% of the flask volume of methanol. Sonicate to dissolve, and allow the solution to cool to room temperature. Dilute with methanol to volume.
Standard solution: 0.009 mg/mL of USP Entacapone RS from the *Standard stock solution* in *Medium*
Sample stock solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
Sample solution: Transfer 2.0 mL of the *Sample stock solution* to a 50-mL volumetric flask, and dilute with *Medium* to volume.
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Tolerances: NLT 70% (Q) of the labeled amount of entacapone ($C_{14}H_{15}N_3O_5$) is dissolved.▲ (TBD)

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **Organic Impurities**
Protect solutions from light.
Buffer, Diluent, Mobile phase, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: 0.03 mg/mL each of USP Entacapone RS and USP Entacapone Related Compound A RS in *Diluent*
Standard solution: 0.003 mg/mL of USP Entacapone RS in *Diluent*
Sample solution: Nominally 3 mg/mL of entacapone prepared as follows. Finely powder NLT 20 Tablets, and transfer a suitable portion of the powder to an appropriate volumetric flask. Add NLT 30% of the final flask volume of tetrahydrofuran, and sonicate for 3 min. Add NLT 30% of the final flask volume of methanol, and shake for 5 min. Dilute with methanol to volume. Centrifuge a portion of this solution, and use the supernatant within 7 h.
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between entacapone related compound A and entacapone, *System suitability solution*
Relative standard deviation: NMT 10.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets 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 entacapone from the *Standard solution*
C_S = concentration of USP Entacapone RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of entacapone in the *Sample solution* (mg/mL)

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Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Entacapone related compound A	0.8	0.2
Entacapone	1.0	—
Any individual unspecified degradation product	—	0.1
Total impurities[a]	—	0.2

[a] Do not include entacapone related compound A in the calculation of total impurities.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in light-resistant containers. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Entacapone RS
  USP Entacapone Related Compound A RS
  (*Z*)-2-Cyano-3-(3,4-dihydroxy-5-nitrophenyl)-*N,N*-diethylacrylamide.
  $C_{14}H_{15}N_3O_5$ 305.29

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