Aprepitant Capsules

Type of Posting	Revision Bulletin
Posting Date	27–Apr–2018
Official Date	01–May–2018
Expert Committee	Chemical Medicines Monographs 3
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 3 Expert Committee has revised the Aprepitant Capsules monograph. The purpose for the revision is to add *Dissolution Test 3* to accommodate a drug product that was approved with different dissolution conditions and acceptance criteria.

- *Dissolution Test 3* was validated using an XTerra RP18 brand L1 column. The typical retention time for aprepitant is about 7.4 min.

Dissolution Test 2 was updated to add a note about when the test should be so labeled.

The Aprepitant Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Andrea F. Carney, Associate Scientific Liaison (301-816-8155 or afc@usp.org).

Aprepitant Capsules

DEFINITION

Aprepitant Capsules contain NLT 95.0% and NMT 105.0% of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$).

IDENTIFICATION

• **A. ULTRAVIOLET ABSORPTION ⟨197U⟩**

Wavelength range: 200–400 nm

Standard solution: 0.1 mg/mL of USP Aprepitant RS in methanol. Use sonication to dissolve.

Sample solution: Transfer the contents of Capsules, equivalent to 100 mg of aprepitant, to a 100-mL volumetric flask, add about 75 mL of methanol, and sonicate for about 5 min with intermittent shaking. Cool, dilute with methanol to volume, further dilute with methanol to obtain a solution containing 0.1 mg/mL of aprepitant, and pass through a nylon filter of 0.45-µm pore size.

Acceptance criteria: Meet the requirements

• **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**

Dilute phosphoric acid: Dilute 1 mL of phosphoric acid with water to 1 L.

Mobile phase: Acetonitrile and *Dilute phosphoric acid* (45:55)

Standard solution: 0.05 mg/mL of USP Aprepitant RS in *Mobile phase*. Use sonication as necessary to dissolve.

Sample solution: Nominally 0.05 mg/mL of aprepitant in *Mobile phase*, prepared as follows. Mix the contents of NLT 20 Capsules, and transfer a portion of the contents, equivalent to 100 mg of aprepitant, to a 100-mL volumetric flask. Add about 75 mL of *Mobile phase* and sonicate for about 10 min with intermittent shaking. Cool, dilute to volume with *Mobile phase*, further dilute with *Mobile phase* to obtain a solution containing 0.05 mg/mL of aprepitant, and pass through a nylon filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) in the portion of Capsules 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 Aprepitant RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of aprepitant in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION ⟨711⟩**

Test 1

Medium: 2.2% sodium dodecyl sulfate in water; 900 mL

Apparatus 2: 100 rpm, with sinkers. [NOTE—A suitable sinker is available from VanKel, www.chem.agilent.com, catalog number 12-3050. Proper placement of the Capsules is in the sinkers with the cap facing the fixed prong end.]

Time: 20 min

Dilute phosphoric acid: Dilute 1 mL of phosphoric acid with water to 1 L.

Mobile phase: Acetonitrile and *Dilute phosphoric acid* (50:50)

Standard solution: (*L*/900) mg/mL of USP Aprepitant RS in *Medium*, where *L* is the label claim in mg/Capsule. Dissolve first in a minimal amount of methanol (using NMT 2% of the final volume) prior to diluting with *Medium*.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 50 µL for Capsules containing 40 mg/Capsule; 10 µL for all other strengths

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Aprepitant RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Capsule)

Tolerances: NLT 80% (*Q*) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.

Test 2: ▲If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.▲ (RB 1-May-2018)

Medium: 2.2% sodium dodecyl sulfate in water; 900 mL

Apparatus 2: 100 rpm, with wire helix sinkers or other suitable sinkers

Time: 30 min

Dilute phosphoric acid and **Mobile phase:** Proceed as directed in the *Assay*.

Standard solution: (*L*/900) mg/mL of USP Aprepitant RS in *Medium,* where *L* is the label claim in mg/Capsule. Dissolve first in a minimal amount of methanol (using NMT 2% of the final volume) prior to diluting with *Medium*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system: Proceed as directed in the *Assay*, except use an autosampler temperature of 15°.
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Aprepitant RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim (mg/Capsule)

Tolerances: NLT 80% (*Q*) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.
▲**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: 2.2% sodium lauryl sulfate in water; 900 mL
Apparatus 2: 100 rpm, with suitable sinkers. Use peak vessels.
Time: 30 min
Dilute phosphoric acid: Prepare as directed in the *Assay*.
Mobile phase: *Dilute phosphoric acid* and acetonitrile (52:48)
Standard stock solution: 440 µg/mL of USP Aprepitant RS in *Mobile phase*. Sonication may be used to promote dissolution.
Standard solution: 44 µg/mL of USP Aprepitant RS from *Standard stock solution* in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.
Chromatographic system
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (1/L) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Aprepitant RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
D = dilution factor of the *Sample solution*
L = label claim (mg/Capsule)

Tolerances: NLT 75% (*Q*) of the labeled amount of aprepitant ($C_{23}H_{21}F_7N_4O_3$) is dissolved.▲ (RB 1-May-2018)

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

IMPURITIES

• **Organic Impurities**
Dilute phosphoric acid: Dilute 1 mL of phosphoric acid with water to 1 L.
Solution A: Acetonitrile and *Dilute phosphoric acid* (5:95)
Solution B: Acetonitrile and *Dilute phosphoric acid* (95:5)
Diluent: Acetonitrile and *Dilute phosphoric acid* (50:50)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
20	58	42
25	35	65
33	35	65

Return to original conditions and re-equilibrate the system for 10 min.
System suitability solution: 0.6 mg/mL of USP Aprepitant RS and 0.0012 mg/mL each of USP Desfluoro Aprepitant RS and USP Aprepitant Related Compound A RS in *Diluent*
Standard solution: 0.0012 mg/mL of USP Aprepitant RS in *Diluent*
Sample solution: Nominally 0.6 mg/mL of aprepitant, prepared as follows. Transfer the contents of Capsules, equivalent to 120 mg of aprepitant, to a 200-mL volumetric flask, add about 150 mL of *Diluent*, and sonicate for about 10 min with intermittent shaking. Cool, dilute with *Diluent* to volume, and pass through a nylon filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between the desfluoro aprepitant and aprepitant peaks, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual impurity in the portion of Capsules 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 aprepitant from the *Standard solution*

C_S = concentration of USP Aprepitant RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of aprepitant in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desfluoro aprepitant	0.85	—[a]
Aprepitant	1.0	—
Aprepitant diastereomers (*R,R,R* and *R,S,S*)[b]	1.3	—[a]
Any other individual impurity	—	0.2
Total impurities	—	0.2

[a] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.

[b] The diastereomers are not separated by this procedure and should be identified based on the retention time of aprepitant related compound A (*R,R,R*-diastereomer), which is a component of the *System suitability solution*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight 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 Aprepitant RS
  USP Aprepitant Related Compound A RS
  R,R,R-Diastereomer: 3-[[(2*R*,3*R*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl) morpholino]methyl]-1*H*-1,2,4-triazol-5(4*H*)-one.
  $C_{23}H_{21}F_7N_4O_3$ 534.43
  USP Desfluoro Aprepitant RS
  5-[[(2*R*,3*S*)-2-[(*R*)-1-[3,5-Bis(trifluoromethyl)phenyl] ethoxy]-3-phenylmorpholino]methyl]-2*H*-1,2,4-triazol-3(4*H*)-one.
  $C_{23}H_{22}F_6N_4O_3$ 516.44