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 (C₂₃H₂₁F₇N₆O₇).

**IDENTIFICATION**
- **A. Ultraviolet Absorption (1976)**
  - 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 L7
- Column temperature: 40° C
- Flow rate: 1.0 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 (C₂₃H₂₁F₇N₆O₇) in the portion of Capsules taken:
  
  \[
  \text{Result} = \frac{r_u}{r_s} \times \frac{C_s}{C_L} \times 100
  \]

  \( r_u \) = 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)

  \( C_L \) = nominal concentration of aprepitant in the Sample solution (mg/mL)

  Tolerances: NLT 80% (Q) of the labeled amount of aprepitant (C₂₃H₂₁F₇N₆O₇) is dissolved.

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

**Dissolution (711)**

**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 (C₂₃H₂₁F₇N₆O₇) dissolved:
  
  \[
  \text{Result} = \frac{r_u}{r_s} \times \frac{C_s}{C_L} \times V/L \times 100
  \]

  \( r_u \) = 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 (C₂₃H₂₁F₇N₆O₇) is dissolved.
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 (C₂₉H₂₇F₅N₅O₁₀) dissolved:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \frac{C_t \times V \times D \times (1/L)}{100}
\]

\( r_u \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_t \) = 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 (C₂₉H₂₇F₅N₅O₁₀) 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 (C₂₉H₂₇F₅N₅O₁₀) dissolved:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \frac{C_t \times V \times D \times (1/L)}{100}
\]

\( r_u \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_t \) = 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 (C₂₉H₂₇F₅N₅O₁₀) is dissolved.

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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>58</td>
<td>42</td>
</tr>
<tr>
<td>25</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>33</td>
<td>35</td>
<td>65</td>
</tr>
</tbody>
</table>

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:

\[
\text{Result} = \left( \frac{r_u}{r_s} \right) \times \frac{C_t \times V \times D \times (1/L)}{100}
\]

\( r_u \) = peak response of aprepitant from the Sample solution
\( r_s \) = peak response of each impurity from the Standard solution

2018 The United States Pharmacopeial Convention All Rights Reserved.
\( C_1 \) = concentration of USP Aprepitant RS in the Standard solution (mg/mL)

\( C_0 \) = nominal concentration of aprepitant in the Sample solution (mg/mL)

Acceptance criteria: See Table 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desfluoro aprepitant</td>
<td>0.85</td>
<td>— (^a)</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>1.0</td>
<td>— (^a)</td>
</tr>
<tr>
<td>Aprepitant diastereomers ((R,R,R \text{ and } R,S,S))(^b)</td>
<td>1.3</td>
<td>— (^a)</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\(^a\) 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 \((R,R,R\text{-diastereomer})\), 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
    \( R,R,R\text{-Diastereomer}: 3-[(2R,3R)-2-[(R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)morpholino]methyl]-1H-1,2,4-triazol-5(4H)-one. \)\(^c\)
    \( C_{23}H_{21}F_7N_4O_3 \quad 534.43 \)
  - USP Desfluoro Aprepitant RS
    \( 5-[(2R,3S)-2-[(R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-3-phenylmorpholino]methyl]-2H-1,2,4-triazol-3(4H)-one. \)\(^c\)
    \( C_{23}H_{22}F_6N_4O_3 \quad 516.44 \)

\( ^c \) Process impurity included in the table for identification only.