Ritonavir Capsules

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Posting Date: 30–Mar–2018
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Expert Committee: Chemical Medicines Monographs 1
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Ritonavir Capsules monograph. The purpose for the revision is to add Dissolution Test 2 for a drug product approved by the FDA with different dissolution conditions and tolerances than the existing dissolution tests. Labeling information has been incorporated to support the inclusion of Dissolution Test 2.

- **Dissolution Test 2** was validated using a Kromasil C8 brand of L7 column. The typical retention time for ritonavir is about 3.9 min.

In addition, the term “disregard limit” in the acceptance criteria of the test for Organic Impurities has been replaced with “reporting threshold” in the acceptance criteria of the test for Organic Impurities to be consistent with current USP style.

The revision also necessitates a change in the table numbering in the Organic Impurities section.

The Ritonavir 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 Shankari Shivaprasad, Ph.D., Senior Scientific Liaison (301-230-7426 or sns@usp.org).
Ritonavir Capsules

DEFINITION
Ritonavir Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of ritonavir (C\textsubscript{37}H\textsubscript{48}N\textsubscript{4}O\textsubscript{5}S\textsubscript{2}).

IDENTIFICATION
• A. 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
  Buffer: 4.1 g/L of monobasic potassium phosphate
  Diluent: Acetonitrile and Buffer (50:50)
  Mobile phase: Acetonitrile, methanol, tetrahydrofuran (stabilizer-free), and Buffer (7:4:4:25). Separately filter the Buffer and the pre-mixed solvents before combining to make the Mobile phase.
  Standard solution: 25 µg/mL of USP Ritonavir RS in Diluent
  Sample stock solution: Nominally 1 mg/mL of ritonavir prepared as follows. Transfer Capsules (NLT 5) equivalent to 500 mg of ritonavir into a 500-mL volumetric flask, add about 250 mL of Diluent, and shake for at least 30 min or until the Capsules have visually disintegrated. Add 150 mL of acetonitrile, allow to cool to room temperature, and dilute to volume with Diluent.
  Sample solution: Nominally 25 µg/mL of ritonavir in Diluent from the Sample stock solution

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.5 mL/min
Injection volume: 50 µL

System suitability
Sample: Standard solution
Suitability requirements
Capacity factor: NLT 15
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 ritonavir (C\textsubscript{37}H\textsubscript{48}N\textsubscript{4}O\textsubscript{5}S\textsubscript{2}) dissolved:

Result = \( \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_s}{C_d} \right) \times V \times 100 \)

\( r_d \) = peak response from the Sample solution
\( r_s \) = peak response from the Standard solution
\( C_s \) = concentration of USP Ritonavir RS in the Standard solution (mg/mL)
\( L \) = ritonavir label claim (mg/Capsule)
\( V \) = volume of Medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of ritonavir (C\textsubscript{37}H\textsubscript{48}N\textsubscript{4}O\textsubscript{5}S\textsubscript{2}) is dissolved.

Additional requirements: The retention time of the peak due to impurities does not exceed 1.2 times the retention time of the major peak of the Sample solution.

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Dissolution (711)

Medium: 0.1 N hydrochloric acid with 25 mM polyoxymethylene 10 lauryl ether, 900 mL
Apparatus 2: 50 rpm, with sinkers
Time: 30 min

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.8 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
2 Ritonavir

Official April 1, 2018

Revision Bulletin

**Table 1.**

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (min)</th>
<th>Tolerances (Q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>20%–40%</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

- **Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

Change to read:

- **Organic Impurities**

  [Note—Ritonavir is alkali sensitive. All glassware should be pre-rinsed with distilled water before use to remove residual detergent contamination.]

  Buffer A: 4.1 g/L of monobasic potassium phosphate
  Buffer B: 3.8 g/L of monobasic potassium phosphate and 0.25 g/L of dibasic potassium phosphate
  Solution A: Acetonitrile and Buffer A (50:50)
  Solution B: Acetonitrile and Buffer A (65:35)
  Solution C: Butyl alcohol and Buffer A (8:92)
  Mobile phase: Acetonitrile, butyl alcohol, tetrahydrofuran (stabilizer-free), and Buffer B (18:5:8:69). Adjust apparent pH to 6.3 ± 0.1 with 1 M phosphoric acid or 1 M potassium hydroxide if necessary.
  Cleaning solution: Acetonitrile, butyl alcohol, tetrahydrofuran (stabilizer-free), and Buffer A (30:8:13:49)
  Standard stock solution: 0.1 mg/mL of USP Ritonavir RS in Solution A
  Standard solution: 10 µg/mL of USP Ritonavir RS in Solution C from Standard stock solution

  Peak identification solution: Transfer 5–10 g from contents of Capsules into a suitable sealed container. Add an amount of citric acid equivalent to 1% of the Capsule weight taken, and mix until dissolved. Seal the container, and heat at 60°C for about 24 h. Transfer about 2 g to a 100-mL volumetric flask, and dilute with Solution B to volume. Transfer 5.0 mL of the solution to a 50-mL centrifuge tube that has been previously rinsed with methanol and dried. Add 20.0 mL of heptane, and seal the tube with a stopper. Shake vigorously until a uniform emulsion is obtained, making sure to vent periodically. The emulsion formed yields distinct layers when centrifuged. The top layer (clear heptane) and the bottom layer (clear sample solution) are separated by a viscous white cloudy layer. The middle layer is part of the heptane layer. Carefully remove the clear heptane layer and the middle layer. Pass the bottom layer through a solid phase extraction cartridge containing strong anion-exchange packing in acetate form as described below.

  Sample stock solution: Nominally 2 mg/mL of ritonavir prepared as follows. Empty the contents of Capsules (NLT 2) into a suitable container, and accurately weigh and transfer an equivalent to 200 mg of ritonavir to a 100-mL volumetric flask. Dissolve and dilute with Solution B to volume.

  Sample solution: Nominally 1 mg/mL of ritonavir prepared as follows. Transfer 25.0 mL of Sample stock solution into a 50-mL volumetric flask, and dilute with Solution C to volume. Add 15.0 mL of this solution into a 50-mL centrifuge tube that has been previously rinsed with methanol and dried. Add 20.0 mL of heptane, and seal the tube with a stopper. Shake vigorously until a uniform emulsion is obtained, making sure to vent periodically. The emulsion formed yields distinct layers when centrifuged. The top layer (clear heptane) and the bottom layer (clear sample solution) are separated by a viscous white cloudy layer. The middle layer is part of the heptane layer. Carefully remove the clear heptane layer and the middle layer. Pass the bottom layer through a solid phase extraction cartridge containing strong anion-exchange packing in acetate form as described below. Condition a solid phase extraction cartridge with methanol and Solution B two separate times, and dry for 10 min under low vacuum. Add 5.0 mL of the clear sample solution into the reservoir. Collect the sample solution at a slow rate into a 5-mL volumetric flask using low vacuum. Dilute with Solution B to volume.

  Chromatographic system

  (See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 240 nm
  Column: 4.6-mm × 15-cm; 3-µm packing L26. Wash the column after each injection of the Peak identification solution and each injection of the Sample solution with Cleaning solution for about 26 min, and equilibrate with Mobile phase for about 30 min. Store in Cleaning solution after the analysis is completed.
  Column temperature: 60°C
  Flow rate: 1 mL/min
  Injection volume: 50 µL
  Run time: 1.8 times the retention time of ritonavir

  System suitability

  Sample: Standard solution
  Suitability requirements
  Capacity factor: NLT 13
  Tailing factor: 0.8–1.2
  Relative standard deviation: NMT 3.0%

  Analysis

  Samples: Peak identification solution, Standard solution, and Sample solution

  Calculate the percentage of each impurity in the portion of Capsules taken:

  \[
  \text{Result} = \frac{r_i}{r_u} \times \left( \frac{S_i}{C_i} \right) \times \left( \frac{1}{F} \right) \times 100
  \]

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

  \(C_i\) = concentration of USP Ritonavir RS in the Standard solution (mg/mL)

  \(S_i\) = peak response of ritonavir from the Sample solution

  \(F\) = label claim of ritonavir (mg/Capsule)

  \(NLT 80\%\) of USP Ritonavir RS

  \(r_u\) = peak response of ritonavir from the Sample solution

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When more than one revision bulletin is issued, the most recent is incorporated by reference.

**Table 2**  
<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ureidovaline</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-Deacylvaline ritonavir</td>
<td>0.11</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Acetamidooxalohydroxybutyrate</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,5'-Thiazolylmethylidecarbamic</td>
<td>0.24</td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td>Hydroxylitonavir</td>
<td>0.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydantoin aminoalcohol</td>
<td>0.39</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Ritonavir hydroperoxide</td>
<td>0.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol adduct</td>
<td>0.45</td>
<td>0.66</td>
<td>0.3</td>
</tr>
<tr>
<td>Hydantoin-oxazolidinone derivati^h,^k</td>
<td>0.50</td>
<td>0.76</td>
<td>0.2</td>
</tr>
<tr>
<td>Ethyl analog</td>
<td>0.64</td>
<td>1.0</td>
<td>0.1</td>
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<tr>
<td>Geo-isomer^m</td>
<td>0.74</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>BOC-aminoalcohol^n</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Isobutoxycarbonyl aminoalcohol</td>
<td>0.81</td>
<td>0.74</td>
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<tr>
<td>Oxazolidinone derivative^p,^q</td>
<td>0.87</td>
<td>0.53</td>
<td>1.0</td>
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<tr>
<td>Ureidovaline isobutyl ester</td>
<td>0.94</td>
<td>1.0</td>
<td>0.1</td>
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<tr>
<td>Ritonavir</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4-Hydroxy isomer^r</td>
<td>1.05</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>3R-Epimer^s</td>
<td>1.11</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Aminoalcohol urea derivative^t</td>
<td>1.14</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>3,5R-Diastereomer</td>
<td>1.23</td>
<td>1.0</td>
<td>0.1</td>
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<tr>
<td>5R-Epimer^v</td>
<td>1.32</td>
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<td>0.1</td>
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<tr>
<td>Diacyl valine urea^w</td>
<td>1.70</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total process impurity</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*S* [N-Methyl(2-isopropyl-4-thiazolyl)methylamino]carboxyl-L-valine (not quantified by this method due to solvent front and placebo interferences).

^d^ Degradation impurity.

^e^ Thiazol-5-s-methyl(25,35,55)-S-acetamido-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^f^ Bis(thiazol-5-s-methyl(25,35,55)-3-hydroxy-1,6-diphenylhexan-2-yl)carbamate.

^g^ Thiazol-5-s-methyl(25,35,55)-3-hydroxy-5-{(5S)-2-[3-{2-(2-hydroxypropan-2-yl)thiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^h^ Thiazol-5-s-methyl(25,35,55)-3-hydroxy-5-{(5S)-4-isopropyl-2,5-dioxoimidazolidin-1-yl}-1,6-diphenylhexan-2-ylcarbamate.

^i^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxypropan-2-yl)thiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate (report as ethanol adduct due to possible co-elution).

^j^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^k^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate (may co-elute with isobutoxycarbonylaminoalcohol; report as isobutoxy carbonylaminoalcohol).

^l^ Thiazol-5-s-methyl(25,35,55)-5-[isobutoxycarbonylamino]-3-hydroxy-1,6-diphenylhexan-2-ylcarbamate.

^m^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-4-hydroxy-5-[((S,S)-2-ethoxycarbonylamino)-3-hydroxy-5-[((S,S)-2-hydroxy-3-methoxy)carbonylamino]-hexan-3-yl} 2-{3-[(2-isopropylthiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamide.


^o^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^p^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

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^s^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^t^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-(2-hydroxythiazol-4-yl)methyl]-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^u^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^v^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^w^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^x^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^y^ Thiazol-5-s-methyl(25,35,55)-5-{(5S)-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

^z^ Thiazol-5-s-methyl(25,35,55)-5-[isobutoxycarbonylamino]hexan-3-yl]-2-[3-{2-isopropylthiazol-4-yl(methyl)-3-methylureido}-3-methylbutanamido]-1,6-diphenylhexan-2-ylcarbamate.

▲ (RB 1-Apr-2018)