Montelukast Sodium Oral Granules

Type of Posting: Revision Bulletin
Posting Date: 29–Jan–2016
Official Date: 01–May–2016
Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Montelukast Sodium Oral Granules monograph. The purpose for the revision is to add a dissolution test for a generic product approved by the FDA.

- The liquid chromatographic procedure in Dissolution Test 2 is based on analyses performed with a Zorbax Eclipse XDB brand of L1 column. The typical retention time for montelukast is about 10 min.

The Montelukast Sodium Oral Granules Revision Bulletin supersedes the monograph becoming official in USP 39–NF 34. The Revision Bulletin will be incorporated in the Second Supplement to USP 39–NF 34.

Should you have any questions, please contact Mary P. Koleck, Ph.D., Scientific Liaison (301-230-7420 or mpk@usp.org).
Add the following:

## Montelukast Sodium Oral Granules

### Definition
Montelukast Sodium Oral Granules contain Montelukast Sodium equivalent to NLT 90.0% and NMT 108.0% of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S).

[Note—Avoid exposure of samples containing montelukast to light.]

### Identification

#### A. Ultraviolet Absorption (197U)

- **Diluent:** Methanol and water (3:1)
- **Standard solution:** 3.3 μg/mL of USP Montelukast Dicyclohexylamine RS in Diluent
- **Sample stock solution:** Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer the contents of one packet to a suitable volumetric flask, add 66% of the flask volume of Diluent, shake well, and sonicate for 15 min with occasional shaking. Cool to room temperature, dilute with Diluent to volume, and mix well.
- **Sample solution:** Nominally 2 μg/mL of montelukast in Diluent from the Sample stock solution. Pass a portion of the resulting solution through a suitable filter of 0.45-μm pore size or centrifuge to obtain a clear solution.

#### B. Resolution

- 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

- **Diluent:** Methanol and water (3:1)
- **Solution A:** 0.2% (v/v) Trifluoroacetic acid in water
- **Solution B:** Methanol and acetonitrile (3:2)
- **Mobile phase:** See 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>48</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>22</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>23</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>25</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>30</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>

- **Standard solution:** 0.33 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent
- **System suitability solution:** Transfer 10 mL of the Standard solution to a clear 10-mL volumetric flask, add 4 mL of hydrogen peroxide, and mix well. Expose the flask for at least 4 h to ambient light or 10 min to a 4 klx cool white light. [NOTE—Montelukast is partially converted to the cis-isomer under these conditions.]
- **Sensitivity solution:** 0.33 μg/mL of USP Montelukast Dicyclohexylamine RS in Diluent from the Standard solution
- **Sample solution:** Nominally 0.24 mg/mL of montelukast prepared as follows. Transfer the equivalent of 60 mg of montelukast from the contents of the packets (NLT 15) to a 500-mL volumetric flask, and add 250 mL of Diluent. Shake well and sonicate for 30 min, with occasional shaking. Pass a portion of the resulting solution through a suitable filter of 0.45-μm pore size or centrifuge to obtain a clear solution.

### Chromatographic System

(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 255 nm
- **Columns:** 3.0-mm × 4-mm; packing L11
- **Guard:** 0.2% (v/v) Trifluoroacetic acid in water
- **Column temperature:** 50 °C
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 20 μL

### Acceptance criteria:

- **Wavelength range:** 210–400 nm
- **Acceptance criterion:** NLT 1.5 between the cis-isomer and montelukast, System Suitability Solution
- **Resolution:** NLT 1.5 for the cis-isomer and montelukast, System Suitability Solution
- **Relative standard deviation:** NMT 2.0% for five injections, Standard solution
- **Signal-to-noise ratio:** NLT 10, Sensitivity solution

### Analysis

- **Samples:** Standard solution and Sample solution
- **Procedure:** Calculate the percentage of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) in the portion of Oral Granules taken:

  \[ \text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_d}{C_s} \right) \times \left( \frac{M_1}{M_2} \right) \times 100 \]

  \( r_d \) = peak response from the Sample solution
  \( r_s \) = peak response from the Standard solution
  \( C_s \) = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
  \( C_d \) = nominal concentration of montelukast in the Sample solution (mg/mL)
  \( M_1 \) = molecular weight of montelukast, 586.18
  \( M_2 \) = molecular weight of dicyclohexylamine, 767.50

### Performance Tests

#### Change to read:

- **Dissolution (711)**
  - **Test 1:** (88.1-M6-2016)
    - **Medium:** 0.5% (v/v) Sodium dodecyl sulfate in water; 900 mL. Do not deaerate.
    - **Apparatus 1:** 100 mesh; 50 rpm
    - **Time:** 15 min
    - **Solution A:** 0.2% (v/v) Trifluoroacetic acid in water
    - **Solution B:** 0.2% (v/v) Trifluoroacetic acid in acetonitrile
    - **Mobile phase:** Solution A and Solution B (1:1)
    - **Standard stock solution:** 0.33 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.25 mg/mL of montelukast)
    - **Standard solution:** (L/900) mg/mL of montelukast in Medium from the Standard stock solution, where L is the label claim in mg/packet of montelukast
    - **Sample solution:** Place the entire contents of one packet in the basket. At the appropriate time point, pass a portion of the solution under test through a...
suitable filter to obtain a clear solution. Discard the first 10 mL of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 389 nm
Column: 3.0-mm × 10-cm; 5-μm packing L1
Column temperature: 50°C
Flow rate: 0.9 mL/min
Injection volume: 25 μL
Run time: 1.5 times the retention time of montelukast

**System suitability**

Sample: Standard solution
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times (1/L) \times 100
\]

- \( r_U \) = peak response from the Sample solution
- \( r_S \) = peak response of montelukast from the Standard solution
- \( C_S \) = concentration of montelukast in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/packet)

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) is dissolved.

**Change to read:**

- **Uniformity of Dosage Units (905)**
  - Procedure for content uniformity
  - Solution A, Solution B, Mobile phase, and System suitability: Proceed as directed in Dissolution Test 1.
  - Standard solution: 26.4 μg/mL of USP Montelukast Dicyclohexylamine RS in methanol
  - Sample solution: Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer the contents of one packet to a suitable volumetric flask, add 66% of the flask volume of methanol, shake well, and sonicate for 15 min with occasional shaking. Cool to room temperature, dilute with methanol to volume, and mix well. Pass a portion of the resulting solution through a suitable filter of 0.45-μm pore size or centrifuge to obtain a clear solution.

**Chromatographic system**: Proceed as directed in Dissolution Test 1 except use an Injection volume of 5 μL.

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) in the packet taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_U \times (M_1/M_2) \times 100
\]

- \( r_U \) = peak response from the Sample solution
- \( r_S \) = peak response from the Standard solution
- \( C_U \) = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- \( C_S \) = nominal concentration of montelukast in the Sample solution (mg/mL)
- \( M_1 \) = molecular weight of montelukast, 586.18
- \( M_2 \) = molecular weight of montelukast dicyclohexylamine, 767.50

**Acceptance criteria**: Meet the requirements

**Impurities**

- **Organic Impurities**
Montelukast

Official May 1, 2016

Revision Bulletin

Add the following:

- **LABELING** When more than one Dissolution test is given, the labeling states the test used only if Test 1 is not used.

- **USP REFERENCE STANDARDS (11)**

  USP Montelukast Dicyclohexylamine RS

  C₁₅H₂₅CINO₅S · C₁₂H₂₂N

  767.50

  ▲USP39

## Analysis

**Samples:** Standard solution and Sample solution

Calculate the percentage of any individual degradation product in the portion of Oral Granules taken:

\[
\text{Result} = \left( \frac{r_0}{r_s} \times \left( \frac{C_s}{C_0} \right) \times \left( \frac{M_1}{M_2} \right) \times (1/F) \times 100 \right.
\]

- \( r_0 \) = peak response of any individual degradation product from the Sample solution
- \( r_s \) = peak response of montelukast from the Standard solution
- \( C_s \) = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- \( C_0 \) = nominal concentration of montelukast in the Sample solution (mg/mL)
- \( M_1 \) = molecular weight of montelukast, 586.18
- \( M_2 \) = molecular weight of montelukast dicyclohexylamine, 767.50
- \( F \) = relative response factor (see Table 2)

**Acceptance criteria:** See Table 2. Disregard any peak with an area less than that of the Sensitivity solution.

### Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfoxide impurity**</td>
<td>0.45</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Montelukast ketone impurity**</td>
<td>0.71</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>cis-Isomer**</td>
<td>0.92</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Montelukast</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylketone impurity**</td>
<td>1.04</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**These two impurities are not resolved by the method and need to be integrated together to determine conformance.

- **ADDITIONAL REQUIREMENTS**

  - **PACKAGING AND STORAGE:** Preserve in tight containers, protected from light. Store at controlled room temperature.

### Table 2 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael adduct 1**</td>
<td>1.16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Michael adduct 2**</td>
<td>1.18</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Methylstyrone impurity**</td>
<td>1.55</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any other individual degradation product</td>
<td>-</td>
<td>1.0</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Total impurities: - - 1.0

**These two impurities are not resolved by the method and need to be integrated together to determine conformance.


- **LABELING** When more than one Dissolution test is given, the labeling states the test used only if Test 1 is not used.

- **USP REFERENCE STANDARDS (11)**

  USP Montelukast Dicyclohexylamine RS

  C₁₅H₂₅CINO₅S · C₁₂H₂₂N

  767.50

  ▲USP39

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