Montelukast Sodium Tablets

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Posting Date: 29–Jan–2016
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Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the Council of Experts, the Chemicals Medicines Monographs 5 Expert Committee has revised the Montelukast Sodium Tablets monograph. The purpose for the revision is to add two dissolution tests for generic products 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 liquid chromatographic procedure in Dissolution Test 3 is based on analyses performed with a Luna C18(2) brand of L1 column. The typical retention time for montelukast is about 3.5 min.

The Montelukast Sodium Tablets 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 Tablets**

**DEFINITION**
Montelukast Sodium Tablets contain Montelukast Sodium equivalent to NLT 92.5% and NMT 107.5% of the labeled amount of montelukast (C\textsubscript{35}H\textsubscript{36}ClNO\textsubscript{3}S).

**NOTE**—Avoid exposure of samples containing montelukast to light.

**IDENTIFICATION**

**A. UV ABSORPTION (197U)**

**Diluent**: Methanol and water (3:1)

**Standard solution**: 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent

**Sample solution**: Nominally 0.02 mg/mL of USP Montelukast in Dicyclohexylamine RS in methanol.

**NOTE**—The relative retention times for the cis-isomer and montelukast are about 0.92 and 1.0, respectively.

**Suitability requirements**

**Resolution**: NLT 1.5 between the cis-isomer and montelukast, System Suitability solution

**Signal-to-noise ratio**: NMT 2% for five injections, Standard solution

**Analysis**

**Samples**: Standard solution and Sample solution

Calculate the percentage of the labeled amount of montelukast (C\textsubscript{35}H\textsubscript{36}ClNO\textsubscript{3}S) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{c_d}{c_s} \right) \times \left( \frac{C_0}{M_1} \right) \times \left( \frac{M_2}{M_3} \right) \times 100
\]

- \(c_d\) = peak response from the Sample solution
- \(c_s\) = peak response from the Standard solution
- \(C_0\) = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- \(M_1\) = molecular weight of montelukast, 586.18
- \(M_2\) = molecular weight of montelukast dicyclohexylamine, 767.50
- \(M_3\) = molecular weight of montelukast to light.

**NOTE**—Montelukast is partially converted to the cis-isomer under these conditions.

**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**: 0.52 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 \(\mu\)L of hydrogen peroxide, and mix well. Expose the flask for at least 4 h to ambient light or 10 min to a 4 kHz cool white light. [NOTE—Montelukast is partially converted to the cis-isomer under these conditions.]

**Sensitivity solution**: 0.52 \(\mu\)g/mL of USP Montelukast Dicyclohexylamine RS in Diluent from the Standard solution

**Sample solution**: Nominally 0.4 mg/mL of montelukast prepared as follows. Transfer a number of Tablets equivalent to 100 mg of montelukast to a suitable volumetric flask, add 70% of the flask volume of Diluent, and sonicate for 30 min. Shake for 30 min on a platform shaker. Dilute with Diluent to volume and stir for 30 min. Pass a portion through a suitable filter of 0.45-\(\mu\)m pore size, discarding the first mL of filtrate. Use the filtrate.

**Chromatography system**

(See Chromatography (621), System Suitability.)

**Mode**: LC

**Detector**: UV 255 nm

**Columns**

- **Guard**: 3.0-mm \(\times\) 4-mm; packing L11
- **Analytical**: 4.6-mm \(\times\) 10-cm; 3-\(\mu\)m packing L11

**Column temperature**: 50°

**Flow rate**: 1.5 mL/min

**Injection volume**: 15 \(\mu\)L

**Run time**: 2 times the retention time of montelukast

**PERFORMANCE TESTS**

**CHANGE TO READ**:

**DISOLUTION (711)**

**Test 1** (88 1-Ap6-2016)

**Medium**: 0.5% (v/v) Sodium dodecyl sulfate in water; 900 mL. Do not deaerate.

**Apparatus 2**: 50 rpm

**Time**: 20 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**: 0.35 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.27 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/Tablet of montelukast

**Sample solution**: Pass a portion of the solution under test through a suitable filter or centrifuge to obtain a clear solution.
Montelukast

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 389 nm
Column: 4.6-mm x 10-cm; 3-µm packing L1
Column temperature: 35\(^\circ\)C
Flow rate: 1.5 mL/min
Injection volume: 3 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%
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of montelukast (C\(_{35}\)H\(_{36}\)ClNO\(_3\)S) dissolved:

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

\(r_b\) = peak response from the Standard solution
\(r_S\) = peak response from the Sample solution
\(C_S\) = concentration of montelukast in the Standard solution (mg/mL)
\(V\) = volume of Medium, 900 mL
\(L\) = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C\(_{35}\)H\(_{36}\)ClNO\(_3\)S) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
Medium: 0.5% (w/v) Sodium dodecyl sulfate in water; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Solution A: 0.07 g/L of monobasic sodium phosphate
Solution B: Acetonitrile
Mobile phase: Solution A and Solution B (45:55). Add 1.33 mL/L of triethylamine and adjust with phosphoric acid to a pH of 6.7.
Standard stock solution: 0.1 mg/mL of montelukast from montelukast sodium hydrate prepared as follows. Transfer a suitable amount of montelukast sodium hydrate to a 100-mL volumetric flask and dilute with Solution A to volume.
Standard solution: 0.01 mg/mL of montelukast in Medium from the Standard stock solution.
Sample solution: Centrifuge a portion of the solution under test.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm x 5-cm; 1.8-µm packing L1
Column temperature: 35\(^\circ\)C
Flow rate: 1.0 mL/min
Injection volume: 25 µL
Run time: NLT 1.5 times the retention time of montelukast

System suitability
Sample: Standard solution
Suitability requirements
Relative standard deviation: NMT 2%
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of montelukast (C\(_{35}\)H\(_{36}\)ClNO\(_3\)S) dissolved:

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

\(r_b\) = peak response from the Standard solution
\(r_S\) = peak response from the Sample solution
\(C_S\) = concentration of montelukast in the Standard solution (mg/mL)
\(V\) = volume of Medium, 900 mL
\(L\) = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C\(_{35}\)H\(_{36}\)ClNO\(_3\)S) 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.
Diluent: Methanol and water (3:1)
Standard solution: 0.052 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent
Sample solution: Nominally 0.04 mg/mL of montelukast prepared as follows. Transfer one Tablet equivalent to 10 mg of montelukast to a suitable volumetric flask, add 25% of the flask volume of water,
and let stand for 5–10 min until the Tablet has disintegrated. Add 60% of the flask volume of methanol, shake well, and sonicate for 70 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 or centrifuge to obtain a clear solution.

**Chromatographic system:** Proceed as directed in *Dissolution Test 1.* except use an injection volume of 10 µL.

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of any individual degradation product in the Tablet taken:

\[
\text{Result} = (r_0/r_s) \times (C_s/C_d) \times (M_1/M_2) \times 100
\]

- \( r_0 \) = 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 montelukast dicyclohexylamine, 767.50

**Acceptance criteria:** Meet the requirements

### IMPURITIES

**Organic Impurities**


**Analysis**

**Samples:** *Standard solution* and *Sample solution*

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

\[
\text{Result} = (r_0/r_s) \times (C_s/C_d) \times (M_1/M_2) \times (1/F) \times 100
\]

- \( r_0 \) = 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)
- \( C_d \) = 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(^a)</td>
<td>0.45</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Montelukast ketone impurity(^b)</td>
<td>0.71</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>cis-Isomer(^c)</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(^d)</td>
<td>1.04</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Michael adduct 1(^e)</td>
<td>1.16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Michael adduct 2(^f)</td>
<td>1.18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methylstyrene impurity(^g)</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>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>3.0</td>
</tr>
</tbody>
</table>

\(^a\)These two impurities are not resolved by the method and need to be integrated together to determine conformance.

\(^b\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

\(^c\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

\(^d\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

\(^e\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

\(^f\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

\(^g\)1-[1-(1-[3-(2-(7-Chloroquinolin-2-yl)ethenyl)phenyl]-3-[2-(1-hydroxy-1-methyl)phenyl]-propan-1-one-dicyclohexylamine, 767.50

### ADDITIONAL REQUIREMENTS

**Packaging and Storage:** Preserve in tight containers, protected from light. Store at controlled room temperature.

**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
  
  \[ C_{35}H_{36}ClNO_3S \cdot C_{12}H_{23}N \] 767.50

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