Montelukast Sodium Tablets

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Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Montelukast Sodium Tablets monograph. The purpose for the revision is to widen the acceptance criteria for cis-isomer in Table 2, Organic Impurities, from NMT 0.2% to NMT 0.3% to be consistent with the FDA-approved specification.

The Montelukast Sodium Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).
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_{15}H_{36}ClNO_{3}S).

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

IDENTIFICATION

Change to read:
• **A. SPECTROSCOPIC IDENTIFICATION TESTS** (197), Ultraviolet-Visible Spectroscopy: 197U (CN 1-May-2020)
  
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 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. Centrifuge a portion of the resulting solution to obtain a clear solution.
  
Wavelength range: 210–400 nm
  
Acceptance criteria: The absorbance ratio for the cis-isomer and montelukast is about 0.92 and 1.0, respectively.
  
• **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**
  
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>
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<td>22</td>
<td>25</td>
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<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 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: 0.52 µg/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-µm pore size, discarding the first mL of filtrate. Use the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 255 nm
Columns
  
Guard: 3.0-mm × 4-mm; packing L11
  
Analytical: 4.6-mm × 10-cm; 3-µm packing L11
Column temperature: 50°
Flow rate: 1.5 mL/min
Injection volume: 15 µL
Run time: 2 times the retention time of montelukast

Suitability requirements
  
Resolution: NLT 1.5 between the cis-isomer and montelukast in the Sample solution.

Relative standard deviation: NMT 2% for five injections, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of montelukast (C_{15}H_{36}ClNO_{3}S) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_2}{C_1} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
\]

- \(r_d\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_1\) = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- \(C_2\) = 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: 92.5%–107.5%

PERFORMANCE TESTS

• **DISSOLUTION** (711)
  
Test 1
  
Medium: 0.5% (w/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.

Chromatographic system
(See Chromatography (621), System Suitability.)
2 Montelukast

Mode: LC
Detector: UV 389 nm
Column: 3.0-mm × 10-cm; 5-µm packing L11
Column temperature: 50°
Flow rate: 0.9 mL/min
Injection volume: 20 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 (C₁₅H₁₈ClNO₅S) dissolved:

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

\[ r_u = \text{peak response from the Sample solution} \]
\[ r_s = \text{peak response from the Standard solution} \]
\[ C_s = \text{concentration of montelukast in the Standard solution (mg/mL)} \]
\[ V = \text{volume of Medium, 900 mL} \]
\[ L = \text{label claim (mg/Tablet)} \]

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₁₅H₁₈ClNO₅S) 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 suitable volumetric flask. Dissolve in 5% of the flask volume of methanol and dilute with Medium to volume. Determine the water content of montelukast sodium hydrate at the time of use.
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 × 5-cm; 3-µm packing L1
Flow rate: 1 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 (C₁₅H₁₈ClNO₅S) dissolved:

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

\[ r_u = \text{peak response from the Sample solution} \]
\[ r_s = \text{peak response from the Standard solution} \]
\[ C_s = \text{concentration of montelukast in the Standard solution (mg/mL)} \]
\[ V = \text{volume of Medium, 900 mL} \]
\[ L = \text{label claim (mg/Tablet)} \]

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₁₅H₁₈ClNO₅S) is dissolved.

- **Uniformity of Dosage Units (905)**
  Procedure for content uniformity
  Solution A: Montelukast, 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 the labeled amount of montelukast (C13H22ClNO3S) in the Tablet taken:

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

**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:

\[
\text{Result} = \left(\frac{r_U}{r_S}\right) \times \left(\frac{C_J/C_S}\right) \times (M_1/M_2) \times (1/F) \times 100
\]

\[F = \text{relative response factor (see Table 2)}\]

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

<table>
<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)(^b)</td>
<td>0.45</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Montelukast ketone impurity(^c)</td>
<td>0.71</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>cis-Isomer(^d)</td>
<td>0.92</td>
<td>1.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Montelukast</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methylketone impurity(^e)</td>
<td>1.04</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Michael adduct 1(^b)(^e)</td>
<td>1.16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Michael adduct 2(^e)</td>
<td>1.18</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methylstyrene impurity(^f)</td>
<td>1.55</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any other individual degradation product</td>
<td>1.0</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-[[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]-3-(carboxymethyl)cyclopropyl]methyl]sulfanyl]methylacyclic acid.

\(^c\) [1-[[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropyl)-2-yl]phenyl]propyl]-1-one.

\(^d\) [1-[[3-[2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl][propyl]sulfanyl]methyl)cyclopropyl]acetic acid.

\(^e\) This is a process impurity and is included in the table for identification only.

\(^f\) This impurity is controlled in the drug substance. It is not to be reported for the drug product and should not be included in the total impurities.

**ADDITIONAL REQUIREMENTS**

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

- **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

  C13H22ClNO3S · C12H23N · 767.50