Montelukast Sodium Chewable 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 Chemical Medicines Monographs 5 Expert Committee has revised the Montelukast Sodium Chewable Tablets 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 Chewable 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).
**Montelukast Sodium Chewable Tablets**

**DEFINITION**
Montelukast Sodium Chewable Tablets contain Montelukast Sodium equivalent to NLT 92.5% and NMT 107.5% 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 (for 4-mg Chewable Tablets):** 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent
  - **Standard solution (for 5-mg Chewable Tablets):** 0.033 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent
  - **Sample solution:** Nominally (L/200) mg/mL of montelukast, where L is the label claim of montelukast in mg/Chewable Tablet prepared as follows. Transfer 1 Chewable Tablet to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Chewable Tablet has disintegrated. Add 55% 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 Sample solution exhibits maximum only at the same wavelengths as the Standard solution.
  - **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>
<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>
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<tr>
<td>25</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>30</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>

**Sensitivity solution:** 0.33 µg/mL of USP Montelukast Dicyclohexylamine RS in Diluent from the Standard solution

**Sample solution (for 4-mg Chewable Tablets):** Nominally 0.24 mg/mL of montelukast prepared as follows. Transfer 12 Chewable Tablets to a suitable volumetric flask, add 75% of the flask volume of Diluent, and shake vigorously for 60 min. Dilute with Diluent to volume. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size, discarding the first mL of filtrate. Use the filtrate.

**Sample solution (for 5-mg Chewable Tablets):** Nominally 0.25 mg/mL of montelukast prepared as follows. Transfer 10 Chewable Tablets to a suitable volumetric flask, add 75% of the flask volume of Diluent, and shake vigorously for 60 min. Dilute with Diluent to volume. Pass a portion of the resulting solution 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 x 4-mm; packing L11 Analytical: 4.6-mm x 10-cm; 3-µm packing L11
- **Column temperature:** 50°
- **Flow rate:** 1.5 mL/min
- **Injection volume:** 20 µL
- **Run time:** 2 times the retention time of montelukast

**System suitability**
- **Samples:** Standard solution, System suitability solution, and Sensitivity solution
- **[NOTE—The relative retention times for the cis-isomer and montelukast are about 0.92 and 1.0, respectively.]

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- **Injection volume:** 20 µL
- **Run time:** 2 times the retention time of montelukast

**System suitability**
- **Samples:** Standard solution, System suitability solution, and Sensitivity solution
- **[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
- **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 (C35H36ClNO3S) in the portion of Chewable Tablets taken:

\[
\text{Result} = \left( \frac{f_0}{f_S} \right) \times \left( \frac{C_{EU}}{C_{UL}} \right) \times \left( \frac{M_{UL}}{M_{EU}} \right) \times 100
\]

- **f₀** = peak response from the Sample solution
- **f₅** = peak response from the Standard solution
- **Cₑu** = concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- **Cᵣ** = nominal concentration of montelukast in the Sample solution (mg/mL)
- **Mₑu** = molecular weight of montelukast, 586.18
- **Mᵣ** = molecular weight of montelukast, 767.50

**Acceptance criteria:** 92.5%–107.5%

**PERFORMANCE TESTS**

**Change to read:**

- **DISSOLUTION (711)**
  - **Test 1** (8114-May-2016)
    - **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 (for 4-mg Chewable Tablets): 0.30 mg/mL of USP Montelukast Dicyclohexylamine RS in methanol (equivalent to 0.23 mg/mL of montelukast)
Standard stock solution (for 5-mg Chewable Tablets): 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/Chewable 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.)
Mode: LC
Detector: UV 225 nm
Column: 4.6-mm × 5-cm; 1.8-µm packing L1
Column temperature: 35°C
Flow rate: 1 mL/min
Injection volume: 100 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 (C35H36ClNO3S) dissolved:
Result = (r0/rS) × (Cm/CS) × (V/L) × 100

where:
- r0 = peak response from the Sample solution
- rS = peak response from the Standard solution
- Cm = concentration of montelukast in the Sample solution (mg/mL)
- V = volume of Medium, 900 mL
- L = label claim (mg/Chewable Tablet)

Tolerances: NLT 70% (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.

  Diluent: Methanol and water (3:1)

  Standard solution (for 4-mg Chewable Tablets): 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent

  Standard solution (for 5-mg Chewable Tablets): 0.033 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent

  Sample solution: Nominally (L/200) mg/mL of montelukast, where L is the label claim of montelukast in mg/Chewable Tablet prepared as follows. Transfer 1 Chewable Tablet to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Chewable Tablet has disintegrated. Add 55% 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.

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

  Result = (r0/rS) × (Cs/mr) × (Mw/Md) × 100

  where:
- r0 = peak response from the Sample solution
- rS = peak response from the Standard solution
- Cs = concentration of montelukast in the Sample solution (mg/mL)
- m = mass of the Chewable Tablet
- Mw = molecular weight of water
- Md = molecular weight of montelukast
IMPURITIES

ORGANIC IMPURITIES


Analysis

Samples: Standard solution and Sample solution

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

\[
\text{Result} = \left( \frac{1}{\text{fs}} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_1}{M_2} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\[
\text{fs} = \left( \frac{r_0}{r_S} \right)
\]

Where:

- \( C_S \): concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)
- \( C_U \): 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: 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)(^b)</td>
<td>0.45</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Montelukast ketone impurity(^a)</td>
<td>0.71</td>
<td>1.7</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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

\(^b\): USP Reference Standards (11)

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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\(_3\)S · C\(_{12}\)H\(_{23}\)N 767.50
  USP39

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