Montelukast Sodium Oral Granules

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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 Oral Granules. The purpose for the revision is to:

- Revise the acceptance criteria of Sulfoxide impurity from NMT 0.8% to NMT 1.0% and Total impurities from NMT 1.0% to NMT 1.5% in the Organic Impurities section to match the specification for an FDA approved drug product.
- Add Dissolution Test 4 to accommodate a drug product which was approved with different dissolution test conditions and acceptance criteria than the existing dissolution tests. The liquid chromatographic procedure used for the analysis of the standard and sample solutions in Dissolution Test 4 is based on analyses performed with the ZORBAX Eclipse XDB brand of L1 column manufactured by Agilent. The typical retention time for montelukast is about 4 min.

The Montelukast Sodium Oral Granules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the First Supplement to USP 41–NF 35.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison, (240-221-3097 or gdh@usp.org).
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 2 µg/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 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 to obtain a clear solution.
  Wavelength range: 210–400 nm
  Acceptance criteria: The Sample solution exhibits maxima 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>
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<td>23</td>
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<td>25</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>30</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>

Table 1

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 µL of hydrogen peroxide, and mix well. Expose the flask for at least 4 h to ambient light or 10 min to a 4 kW 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
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.]

Suitability requirements
Resolution: NLT 1.5 between 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

Calculate the percentage of the labeled amount of montelukast (C35H36ClNO3S) in the portion of Oral Granules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r2}}{M_{r1}} \right) \times 100
\]

\[r_U = \text{peak response from the Sample solution}\]
\[r_S = \text{peak response from the Standard solution}\]
\[C_S = \text{concentration of USP Montelukast Dicyclohexylamine RS in the Standard solution (mg/mL)}\]
\[C_U = \text{nominal concentration of montelukast in the Sample solution (mg/mL)}\]
\[M_{r1} = \text{molecular weight of montelukast, 586.18}\]
\[M_{r2} = \text{molecular weight of montelukast dicyclohexylamine, 767.50}\]

Acceptance criteria: 90.0%–108.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)
  Test 1
  Medium: 0.5% (w/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 0.23 mg/mL of montelukast)
  Standard solution: (L9000) 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.

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Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 389 nm
Column: 3.0-mm x 10-cm; 5-µm packing L11
Column temperature: 50°C
Flow rate: 0.9 mL/min
Injection volume: 25 µL
Run time: 1.5 times the retention time of montelukast

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Standard solution: 0.0065 mg/mL of USP Montelukast Dicyclohexylamine RS in Medium, 900 mL

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 an appropriate volumetric flask. Dissolve in 4% 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: 0.004 mg/mL of montelukast in Medium from the Standard stock solution

Sample solution: Place the entire contents of one packet in the basket. At the appropriate time point, 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 3-cm; 3-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
Relative standard deviation: NMT 2.0%

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

Result = \( \frac{r_0}{r_s} \times \frac{C_s \times V}{(1/L) \times 100} \)

\( r_0 \) = peak response from the Sample solution
\( r_s \) = peak response 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 85% (Q) of the labeled amount of montelukast (C35H36ClNO3S) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Standard stock solution: 0.524 mg/mL of USP Montelukast Dicyclohexylamine RS in Diluent (equivalent to 0.4 mg/mL of montelukast)

Standard solution: 0.0065 mg/mL of USP Montelukast Dicyclohexylamine RS in Medium from the Standard stock solution (equivalent to 0.005 mg/mL of montelukast)

Sample solution: Transfer the entire contents of one packet to the dissolution vessel. At the specified time point, withdraw 10 mL of sample from the dissolution vessel. Pass a portion of the solution under test through a suitable filter. Discard the first 5 mL of the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 281 nm
Column: 4.6-mm x 3-cm; 3-µm packing L1
Column temperature: 40°C
Flow rate: 0.8 mL/min
Injection volume: 25 µL
Run time: About 1.5 times the retention time of montelukast

System suitability
Samples: System suitability solution and Standard solution

[Note—The relative retention times for Z-isomer and montelukast are 0.8 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 2.0 between the Z-isomer and montelukast, System suitability solution
Tailing factor: NMT 2.0 for montelukast, System suitability solution
Relative standard deviation: NMT 2.0%, Standard solution

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Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of montelukast (C₁₈₂₆₃₅H₃₆ClNO₃S) dissolved:

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

- \( r_d \): 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)
- \( V \): volume of Medium, 900 mL
- \( L \): label claim (mg/packet)
- \( M_r \): molecular weight of montelukast, 586.18
- \( M_o \): molecular weight of montelukast dicyclohexylamine, 767.50

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₁₈₂₆₃₅H₃₆ClNO₃S) dissolved.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.

Medium: 0.5% (w/v) sodium dodecyl sulfate in water; 900 mL

Apparatus 1: 100 mesh; 50 rpm

Time: 20 min

Solution A: 3.9 g/L of sodium phosphate monobasic dihydrate in water. Adjust with dilute phosphoric acid to a pH of 3.7.

Mobile phase: Acetonitrile and Solution A (80:20)

Diluent: Medium

Standard solution: 0.005 mg/mL of montelukast in Diluent from montelukast sodium hydrate. Determine the water content of montelukast sodium hydrate at the time of use.

Sample solution: Place the entire contents of one packet in the basket. At the specified time point, withdraw 10 mL of sample from the dissolution vessel. Pass a portion of the solution under test through a suitable filter paper. Discard the first 3 mL of the filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 20°

Column: 28°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 1.5 times the retention time of montelukast

System suitability

Sample: Standard solution

Suitability requirements

- Tailing factor: NMT 2.0 for montelukast
- Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of montelukast (C₁₈₂₆₃₅H₃₆ClNO₃S) dissolved:

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

- \( r_d \): 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)
- \( V \): volume of Medium, 900 mL
- \( L \): label claim (mg/packet)
- \( M_r \): molecular weight of montelukast, 586.18
- \( M_o \): molecular weight of montelukast dicyclohexylamine, 767.50

Acceptance criteria: Meet the requirements

IMPURITIES

Change to read:


Analysis

Samples: Standard solution and Sample solution

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

\[ \text{Result} = \left( \frac{r_i}{r_s} \right) \times \frac{(C_s/C_0)}{\left( \frac{(M_r/M_o)}{100} \right)} \]

- \( r_i \): peak response of any individual degradation product 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)
- \( C_0 \): nominal concentration of montelukast in the Sample solution (mg/mL)
- \( M_r \): molecular weight of montelukast, 586.18
- \( M_o \): 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.

- **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 (C₁₈₂₆₃₅H₃₆ClNO₃S) in the packet taken:

\[ \text{Result} = \left( \frac{r_d}{r_s} \right) \times \frac{(C_s/C_0)}{\left( \frac{(M_r/M_o)}{100} \right)} \]

- \( r_d \): 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)
- \( C_0 \): nominal concentration of montelukast in the Sample solution (mg/mL)
- \( M_r \): nominal concentration of montelukast in the Sample solution (mg/mL)
- \( M_o \): molecular weight of montelukast, 586.18
- \( M_o \): molecular weight of montelukast dicyclohexylamine, 767.50

Acceptance criteria: Meet the requirements
### 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&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.45</td>
<td>1.0</td>
<td>*1.00&lt;sup&gt;•&lt;/sup&gt; (RB 1-Oct-2017)</td>
</tr>
<tr>
<td>Montelukast ketone impurity&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.71</td>
<td>1.7</td>
<td>0.2</td>
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<tr>
<td>cis-Isomer&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.92</td>
<td>1.0</td>
<td>0.2</td>
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<tr>
<td>Montelukast</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
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<td>Methylketone impurity&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td>1.04</td>
<td>—</td>
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<td>Michael adduct 1&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Michael adduct 2&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1.18</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Methylstyrene impurity&lt;sup&gt;i&lt;/sup&gt;</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>*1.50&lt;sup&gt;•&lt;/sup&gt; (RB 1-Oct-2017)</td>
</tr>
</tbody>
</table>

<sup>a</sup> These two impurities are not resolved by the method and need to be integrated together to determine conformance.


<sup>d</sup> [1-[[1-[[[1-([R])-1-[[3-[[E]-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

<sup>e</sup> This is a process impurity and is included in the table for identification only. 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.


<sup>g</sup> (1-[[[1-([R])-1-[[3-[[E]-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

<sup>h</sup> (1-[[[1-([R])-1-[[3-[[E]-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

<sup>i</sup> [1-[[1-[[[1-([R])-1-[[3-[[E]-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

### 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
  - C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> · C<sub>12</sub>H<sub>22</sub>N 767.50

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