Montelukast Sodium. Because there is no existing USP monograph for this drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the Assay and in the test for Organic Impurities are based on analyses performed with the Zorbax SB phenyl brand of L11 column. The typical retention time for the montelukast peak is about 6 min. The liquid chromatographic procedure in the test for Enantiomeric purity is based on analyses performed with the Chiral AGP brand of L41 column. The typical retention time for the R-enantiomer peak is about 7 min.

Montelukast Sodium is part of a USP/Ph. Eur. pilot project for prospective harmonization of monographs for drug substances. The draft monograph has been jointly prepared by the U.S. and European pharmacopeias and is now being presented for public comment in the Forums of the two pharmacopeias.

(MD-PS: E. Conikberg, M. Waddell.) RTS—C68837

Add the following:

Montelukast Sodium

Montelukast Sodium contains NLT 98.0% and NMT 102.0% of C_{35}H_{35}ClNO_{3}S, calculated on the anhydrous basis.

DEFINITION

Montelukast Sodium contains NLT 98.0% and NMT 102.0% of C_{35}H_{35}ClNO_{3}S, calculated on the anhydrous basis.

IDENTIFICATION

A. INFRARED ABSORPTION (197)

[Note—Methods described under Infrared Absorption (197K), (197M), or (197A) may be used.]

B. IDENTIFICATION TESTS—GENERAL. Sodium (191): Ignite 100 mg of Montelukast Sodium. Dissolve the residue in 2 mL of water, and filter. The filtrate meets the requirements of the pyroantimonate precipitate test.

C. Meets the requirements of the test for Enantiomeric purity.

ASSAY

[Note—Avoid exposure of the samples to moisture and light. Use low-actinic glassware.]

• PROCEDURE

Solution A: Add 1.5 mL of trifluoroacetic acid to 1 L of water.

Solution B: Add 1.5 mL of trifluoroacetic acid to 1 L of acetonitrile.

Mobile phase: See the gradient table below.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>3.0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>16.0</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>16.1</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>21.0</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

Diluent: Methanol and water (9:1)

Standard solution: 0.13 mg/mL of USP Montelukast DCHA RS in Diluent

Sample solution: 0.1 mg/mL of Montelukast Sodium in Diluent

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 238 nm

Column: 4.6-mm × 5-cm; 1.8-µm packing L11

Flow rate: 1.2 mL/min

Column temperature: 30°C

Injection size: 10 µL

System suitability

Sample: Standard solution

Suitability requirements

Relative standard deviation: NMT 0.73%

Analysis

Sample: Standard solution and Sample solution

Calculate the percentage of C_{35}H_{35}ClNO_{3}S in the portion of Montelukast Sodium taken:

\[ \text{Result} = \frac{r_U}{r_S} \times \frac{C_S}{C_U} \times \left( \frac{M_{11}}{M_{22}} \right) \times 100 \]

\[ r_S = \text{peak area response from the Standard solution} \]

\[ r_U = \text{peak area response from the Sample solution} \]

\[ C_S = \text{concentration of the Standard solution (mg/mL)} \]

\[ C_U = \text{concentration of the Sample solution (mg/mL)} \]

\[ M_{11} = \text{molecular weight of montelukast sodium, 608.17} \]

\[ M_{22} = \text{molecular weight of montelukast DCHA, 767.50} \]

Acceptance criteria: 98.0%–102.0%, on the anhydrous basis

IMPURITIES

Inorganic Impurities

• HEAVY METALS: NMT 10 ppm

Diluent: Acetone and water (4:1)

Sample solution: Dissolve 0.50 g of Montelukast Sodium in 20 mL of the Diluent.

Reference solution: Dilute 0.5 mL of the Standard Lead Solution, prepared as directed under Heavy Metals (231), with Diluent to 20 mL.

Blank solution: 20 mL of the Diluent

Procedure: To each solution, add 2 mL of pH 3.5 Acetate Buffer, prepared as directed under Heavy Metals (231). Mix, and to each solution add 1.2 mL of thioacetamide–glycerine base TS. Mix immediately, and allow to stand for 2 min. Pass the solutions through a 0.45-µm membrane filter. Compare the spots on the filters obtained from the different solutions: the brownish-black color of the spot resulting from the Sample solution is not more intense than that of the spot resulting from the Reference solution. The test is invalid if the Reference solution does not show a brownish-black color compared to the Blank solution.

Organic Impurities

• PROCEDURE [Note—Avoid exposure of the samples to moisture and light. Use low-actinic glassware.]

Solution A, Solution B, Mobile phase, and Diluent: Proceed as directed in the Assay.

Sample solution: 1 mg/mL of Montelukast Sodium in Diluent

Diluted sample solution: 1 µg/mL of Montelukast Sodium in Diluent, from the Sample solution
Impurity solution: 1 mg/mL of USP Montelukast for Peak Identification RS in Diluent

System suitability solution: Transfer 1 mL of the Impurity solution to a clear glass vial, and expose to ambient light for approximately 20 min to generate the cis-isomer of montelukast.

Chromatographic system: Proceed as directed in the Assay.

System suitability
Sample: System suitability solution
Suitability requirements
Resolution: NLT 2.5 between the cis-isomer and montelukast; NLT 1.5 between montelukast and the methylketone impurity

Analysis
Samples: Sample solution and Diluted sample solution
Calculate the percentage of each impurity in the portion of Montelukast Sodium taken:

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

- \( r_U \) = peak response of each impurity from the Sample solution
- \( r_S \) = peak response for montelukast from the Diluted sample solution
- \( C_S \) = concentration of the Diluted sample solution (mg/mL)
- \( C_U \) = concentration of the Sample solution (mg/mL)

Acceptance criteria
Reporting level for impurities: 0.05%
Individual impurities: See Impurity Table 1.
Total impurities: NMT 0.6%

### Impurity Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfoxide impurity *</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>cis-isomer</td>
<td>0.8</td>
<td>0.10</td>
</tr>
<tr>
<td>Michael Adducts 1(^{+}) and 2(^{+})</td>
<td>0.9</td>
<td>0.15*</td>
</tr>
<tr>
<td>Montelukast</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Methylketone impurity(^*)</td>
<td>1.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Methylstyrone impurity(^*)</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Any other individual impurity</td>
<td>—</td>
<td>0.10</td>
</tr>
</tbody>
</table>

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

### Solution A
Add 0.6 mL of glacial acetic acid to 1 L of water. Adjust with ammonium hydroxide to a pH of 5.0.

### Mobile phase
Acetonitrile and Solution A (7:18)

### System suitability solution
0.1 mg/mL of USP Montelukast Racemate RS in methanol

### Sample solution
0.7 mg/mL of Montelukast Sodium in methanol

### Sensitivity solution
0.7 μg/mL of Montelukast Sodium in methanol, prepared from the Sample solution

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

- **Mode:** LC
- **Detector:** Fluorescence, excitation wavelength at 305 nm, emission wavelength at 370 nm
- **Column:** 4.0-mm x 15-cm; 5-μm packing L41
- **Column temperature:** 30 °C
- **Flow rate:** 1 mL/min
- **Injection size:** 5 μL
- **Run time:** 2.5 times the retention time of montelukast

### System suitability
Sample: System suitability solution and Sensitivity solution

[NOTE—Relative retention times are 1.0 for montelukast which is the R-enantiomer, and 0.7 for the S-enantiomer.]

### Suitability requirements
Resolution: NLT 2.5 between the S-enantiomer and montelukast, System suitability solution

### Tailing factor
NMT 3.0 for the S-enantiomer and montelukast peaks, System suitability solution

### Signal-to-noise ratio
NLT 6 for the montelukast peak, Sensitivity solution

### Analysis
Sample: Sample solution
Calculate the percentage of S-enantiomer in the portion of Montelukast Sodium taken:

\[ \text{Result} = \left( \frac{r_U}{r_T} \right) \times 100 \]

- \( r_U \) = peak response of the S-enantiomer from the Sample solution
- \( r_T \) = sum of the peak responses of the S-enantiomer and montelukast from the Sample solution

### Acceptance criteria
NMT 0.2% of the S-enantiomer

### ADDITIONAL REQUIREMENTS
- **Packaging and Storage:** Preserve in tight containers, protected from light. Store at room temperature.
- **USP Reference Standards** (11)
  - USP Montelukast Sodium RS
  - USP Montelukast Dicyclohexylamine (DCHA) RS
    - (C\(_{35}\)H\(_{36}\)ClNO\(_3\)S ´ C\(_{12}\)H\(_{23}\)N) 767.50
  - USP Montelukast Racemate RS
  - USP Montelukast for Peak Identification RS\(\_\text{USPNF}^{14}\)

### Specific Tests
- **Water Determination, Method Ia (921):** NMT 1.0%
- **Enantiomeric Purity:** [NOTE—Avoid exposure of the samples to light. Use low-actinic glassware.]