

## Montelukast Sodium Chewable Tablets

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<b>Posting Date</b>	29–Jan–2016
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<b>Expert Committee</b>	Chemical Medicines Monographs 5
<b>Reason for Revision</b>	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](mailto:mpk@usp.org)).

**Add the following:**

**▲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 (C<sub>35</sub>H<sub>36</sub>ClNO<sub>3</sub>S).

[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 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 1**

Time (min)	Solution A (%)	Solution B (%)
0	48	52
5	45	55
12	45	55
22	25	75
23	25	75
25	48	52
30	48	52

**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 klx 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 (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 × 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:** 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 (C<sub>35</sub>H<sub>36</sub>ClNO<sub>3</sub>S) in the portion of Chewable Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

*r<sub>U</sub>* = peak response from the *Sample solution*

*r<sub>S</sub>* = peak response from the *Standard solution*

*C<sub>S</sub>* = concentration of USP Montelukast Dicyclohexylamine RS in the *Standard solution* (mg/mL)

*C<sub>U</sub>* = nominal concentration of montelukast in the *Sample solution* (mg/mL)

*M<sub>r1</sub>* = molecular weight of montelukast, 586.18

*M<sub>r2</sub>* = molecular weight of montelukast dicyclohexylamine, 767.50

**Acceptance criteria:** 92.5%–107.5%

**PERFORMANCE TESTS**

**Change to read:**

• **DISSOLUTION** <711>

• **Test 1** (RB 1-May-2016)

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

## 2 Montelukast

**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 389 nm

**Column:** 3.0-mm × 10-cm; 5-μm packing L11

**Column temperature:** 50°

**Flow rate:** 0.9 mL/min

**Injection volume:** 50 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 ( $C_{35}H_{36}ClNO_3S$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

$r_U$  = 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/Chewable Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of montelukast ( $C_{35}H_{36}ClNO_3S$ ) 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 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:** 0.005 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; 1.8-μm packing L1

**Column temperature:** 35°

**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%

### Analysis

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

Calculate the percentage of the labeled amount of montelukast ( $C_{35}H_{36}ClNO_3S$ ) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

$r_U$  = 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/Chewable Tablet)

**Tolerances:** NLT 70% (Q) of the labeled amount of montelukast ( $C_{35}H_{36}ClNO_3S$ ) is dissolved. • (RB 1-May-2016)

### 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*.

• (RB 1-May-2016)

**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*, • (RB 1-May-2016) except use an *Injection volume* of 10 μL.

### Analysis

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

Calculate the percentage of the labeled amount of montelukast ( $C_{35}H_{36}ClNO_3S$ ) in the Chewable Tablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_1/M_2) \times 100$$

$r_U$  = 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)  
 $C_u$  = nominal concentration of montelukast in the *Sample solution* (mg/mL)  
 $M_{r1}$  = molecular weight of montelukast, 586.18  
 $M_{r2}$  = molecular weight of montelukast dicyclohexylamine, 767.50  
**Acceptance criteria:** Meet the requirements

**IMPURITIES**

• **ORGANIC IMPURITIES**

**Diluent, Solution A, Solution B, Mobile phase, Standard solution, System suitability solution, Sensitivity solution, Sample solution, Chromatographic system, and System suitability:** Proceed as directed in the *Assay*.

**Analysis**

**Samples:** *Standard solution* and *Sample solution*  
 Calculate the percentage of any individual degradation product in the portion of Chewable Tablets taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

- $r_u$  = 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)  
 $C_u$  = nominal concentration of montelukast in the *Sample solution* (mg/mL)  
 $M_{r1}$  = molecular weight of montelukast, 586.18  
 $M_{r2}$  = 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**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Sulfoxide impurity <sup>a,b</sup>	0.45	1.0	1.5
Montelukast ketone impurity <sup>c</sup>	0.71	1.7	0.2

<sup>a</sup> These two impurities are not resolved by the method and need to be integrated together to determine conformance.  
<sup>b</sup> 1-[[[1-[3-[(E)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>c</sup> (E)-1-[3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propan-1-one.  
<sup>d</sup> 1-[[[[(1R)-1-[3-[(Z)-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>f</sup> 1-[[[[(1R)-3-(2-Acetylphenyl)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>g</sup> 1-[[[[(1R)-1-[3-[(1R)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>h</sup> 1-[[[[(1R)-1-[3-[(1S)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>i</sup> 1-[[[[(1R)-1-[3-[(E)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

**Table 2 (Continued)**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
<i>cis</i> -Isomer <sup>d</sup>	0.92	1.0	0.2
Montelukast	1.0	—	—
Methylketone impurity <sup>e,f</sup>	1.04	—	—
Michael adduct 1 <sup>g,e</sup>	1.16	—	—
Michael adduct 2 <sup>h,e</sup>	1.18	—	—
Methylstyrene impurity <sup>i,e</sup>	1.55	—	—
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	2.0

<sup>a</sup> These two impurities are not resolved by the method and need to be integrated together to determine conformance.  
<sup>b</sup> 1-[[[1-[3-[(E)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>c</sup> (E)-1-[3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl]-3-[2-(2-hydroxypropan-2-yl)phenyl]propan-1-one.  
<sup>d</sup> 1-[[[[(1R)-1-[3-[(Z)-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>f</sup> 1-[[[[(1R)-3-(2-Acetylphenyl)-1-[3-[(E)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>g</sup> 1-[[[[(1R)-1-[3-[(1R)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>h</sup> 1-[[[[(1R)-1-[3-[(1S)-1-[[[1-(Carboxymethyl)cyclopropyl]methyl]sulfanyl]-2-(7-chloroquinolin-2-yl)ethyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.  
<sup>i</sup> 1-[[[[(1R)-1-[3-[(E)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethyl)phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

**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.

• (RB 1-May-2016)

- **USP REFERENCE STANDARDS <11>**  
 USP Montelukast Dicyclohexylamine RS  
 $C_{35}H_{36}ClNO_3S \cdot C_{12}H_{23}N$  767.50

▲ USP39