Montelukast Sodium Oral Granules

Type of Posting	Revision Bulletin
Posting Date	30–Sep–2016
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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 Oral Granules monograph.

The purpose for the revision is to add *Dissolution Test* 3 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* 3 is based on analyses performed with the BetaBasic 18 brand of L1 column manufactured by Thermo Scientific.

The Montelukast Sodium Oral Granules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 40–NF 35*.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison, (240-221-3097 or gdh@usp.org).

Add the following:

▲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 ($C_{35}H_{36}ClNO_3S$).

[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 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 *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 2 µg/mL of montelukast in *Diluent* from the *Sample stock solution*. Pass a portion of the resulting solution through a suitable filter of 0.45-µm pore size or centrifuge 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: 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 × 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 2.0% 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 ($C_{35}H_{36}ClNO_3S$) in the portion of Oral Granules taken:

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

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: 90.0%–108.0%

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.

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 0.25 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/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.
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: 25 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 2.0%
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 of montelukast from the *Sample solution*
r_S = peak response of montelukast 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 ($C_{35}H_{36}ClNO_3S$) 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 1: 100 mesh; 50 rpm
Time: 15 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: 0.004 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 × 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/packet)

Tolerances: NLT 80% (*Q*) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved.● (RB 1-May-2016)

•**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
Medium: 0.5% (w/v) sodium dodecyl sulfate in water; 900 mL
Apparatus 2: 50 rpm
Time: 10 min
Solution A: 2.72 g/L of monobasic potassium phosphate in water
Mobile phase: Acetonitrile and *Solution A* (70:30)
Diluent: Acetonitrile and water (50:50)
System suitability solution: Expose a portion of *Standard solution* in a clear glass vial to direct room light for about 30 min.
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 × 3-cm; 3-µm packing L1
Column temperature: 40°
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*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

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)
V = volume of *Medium*, 900 mL
L = label claim (mg/packet)
M_{r1} = molecular weight of montelukast, 586.18
M_{r2} = molecular weight of montelukast dicyclohexylamine, 767.50

Tolerances: NLT 80% (Q) of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$) is dissolved. ● (RB 1-Oct-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)
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*, ● (RB 1-May-2016) except use an *Injection volume* of 5 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 packet taken:

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

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 Oral Granules 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[a,b]	0.45	1.0	0.8
Montelukast ketone impurity[c]	0.71	1.7	0.2
cis-Isomer[d]	0.92	1.0	0.2
Montelukast	1.0	—	—
Methylketone impurity[e,f]	1.04	—	—
Michael adduct 1[g,e]	1.16	—	—
Michael adduct 2[h,e]	1.18	—	—
Methylstyrene impurity[i,e]	1.55	—	—

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

Table 2 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	1.0

[a] These two impurities are not resolved by the method and need to be integrated together to determine conformance.

[b] [1-[[[1-[3-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]sulfinyl]methyl]cyclopropyl]acetic acid.

[c] (*E*)-1-{3-[2-(7-Chloroquinolin-2-yl)vinyl]phenyl}-3-[2-(2-hydroxypropan-2-yl)phenyl]propan-1-one.

[d] [1-[[[(1*R*)-1-[3-[(*Z*)-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. 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.

[f] [1-[[[(1*R*)-3-(2-Acetylphenyl)-1-[3-[(*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl]propyl]sulfanyl]methyl]cyclopropyl]acetic acid.

[g] 1-[[[(1*R*)-1-[3-[(1*R*)-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.

[h] 1-[[[(1*R*)-1-[3-[(1*S*)-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.

[i] [1-[[[(1*R*)-1-[3-[(*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethenyl)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*