

Montelukast Sodium Tablets

Type of Posting	Revision Bulletin
Posting Date	22–Nov–2019
Official Date	01–May–2020
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 Tablets monograph. The purpose for the revision is to widen the acceptance criteria for *cis*-isomer in *Table 2, Organic Impurities*, from NMT 0.2% to NMT 0.3% to be consistent with the FDA-approved specification.

The Montelukast Sodium Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Ren-Hwa Yeh, Senior Scientific Liaison (301-998-6818 or rhy@usp.org).

Montelukast Sodium Tablets

DEFINITION

Montelukast Sodium Tablets contain Montelukast Sodium equivalent to NLT 92.5% and NMT 107.5% of the labeled amount of montelukast ($C_{35}H_{36}ClNO_3S$).

[NOTE—Avoid exposure of samples containing montelukast to light.]

IDENTIFICATION

Change to read:

- A. [▲]SPECTROSCOPIC IDENTIFICATION TESTS** <197>, *Ultraviolet-Visible Spectroscopy*: 197U[▲] (CN 1-May-2020)
Diluent: Methanol and water (3:1)
Standard solution: 0.026 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*
Sample solution: Nominally 0.02 mg/mL of montelukast prepared as follows. Transfer one Tablet equivalent to 10 mg of montelukast to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Tablet has disintegrated. Add 60% 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: 0.52 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 μ L 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: 0.52 μ g/mL of USP Montelukast Dicyclohexylamine RS in *Diluent* from the *Standard solution*

Sample solution: Nominally 0.4 mg/mL of montelukast prepared as follows. Transfer a number of Tablets equivalent to 100 mg of montelukast to a suitable volumetric flask, add 70% of the flask volume of *Diluent*,

and sonicate for 30 min. Shake for 30 min on a platform shaker. Dilute with *Diluent* to volume and stir for 30 min. Pass a portion through a suitable filter of 0.45- μ m 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 \times 4-mm; packing L11

Analytical: 4.6-mm \times 10-cm; 3- μ m packing L11

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 15 μ L

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 ($C_{35}H_{36}ClNO_3S$) in the portion of Tablets 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: 92.5%–107.5%

PERFORMANCE TESTS

DISSOLUTION <711>

Test 1

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: 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/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*.)

2 Montelukast

Revision Bulletin
Official May 1, 2020

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: 20 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:

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

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/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) 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 a suitable volumetric flask. Dissolve in 5% 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: 0.01 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 (C₃₅H₃₆ClNO₃S) 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/Tablet)

Tolerances: NLT 80% (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*.

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

Apparatus 2: 50 rpm

Time: 30 min

Solution A: Acetonitrile and water (80:20)

Solution B: 3% Trifluoroacetic acid in *Solution A* prepared as follows. Transfer 3 mL of trifluoroacetic acid to a 100-mL volumetric flask and dilute with *Solution A* to volume.

Mobile phase: Acetonitrile, water, and *Solution B* (75: 25: 0.05).

Standard solution: (L/900) mg/mL of montelukast in *Medium* from montelukast sodium hydrate, where L is the label claim in mg/Tablet of montelukast. Determine the water content of montelukast sodium hydrate at the time of use.

Sample solution: Pass a portion of the solution under test through a suitable filter to obtain a clear solution.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 346 nm

Column: 4.6-mm × 10-cm; 3-μm packing L1

Flow rate: 1.5 mL/min

Injection volume: 25 μL

Run time: NLT 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 (C₃₅H₃₆ClNO₃S) 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/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of montelukast (C₃₅H₃₆ClNO₃S) is dissolved.

• 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: 0.052 mg/mL of USP Montelukast Dicyclohexylamine RS in *Diluent*

Sample solution: Nominally 0.04 mg/mL of montelukast prepared as follows. Transfer one Tablet equivalent to 10 mg of montelukast to a suitable volumetric flask, add 25% of the flask volume of water, and let stand for 5–10 min until the Tablet has disintegrated. Add 60% 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 μ L.

Analysis

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

Change to read:

• 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 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 ^{a,b}	0.45	1.0	2.0
Montelukast ketone impurity ^c	0.71	1.7	0.2
<i>cis</i> -Isomer ^d	0.92	1.0	▲0.3▲ (RB 1-May-2020)
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	—	—
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	3.0

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

^g 1-[[[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-(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-(1*R*)-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.
- **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
 $C_{35}H_{36}ClNO_3S \cdot C_{12}H_{23}N$ 767.50