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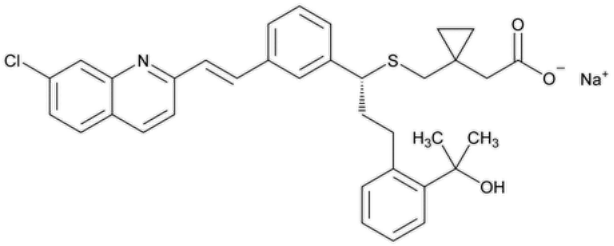
Montelukast Sodium



$C_{35}H_{35}ClNNaO_3S$ 608.17

Cyclopropaneacetic acid, 1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]-, sodium salt, [*R*-,(*E*)]-;

Sodium 1-[[[(*R*)-*m*-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]-α-[*o*-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio]-methyl]cyclopropaneacetate CAS RN®: 151767-02-1; UNII: U1O3J18SFL.

$C_{35}H_{36}ClNO_3S$ 586.18

Montelukast CAS RN®: 158966-92-8; UNII: MHM278SD3E.

DEFINITION

Montelukast Sodium contains NLT 98.0% and NMT 102.0% of $C_{35}H_{35}ClNNaO_3S$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

- **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A, 197K, or 197M▲ (CN 1-May-2020)
- **B.** **Identification Tests—General, *Sodium*⟨191⟩**

  Sample: 100 mg

  Analysis: Ignite the *Sample* in a crucible until an almost white residue is obtained. Take up the residue in 2 mL of water, and filter.

  Acceptance criteria: The filtrate meets the requirements of test *A*.
- **C.** Meets the requirements of the test for *Enantiomeric Purity*.

ASSAY

[Note—Avoid exposure of the samples to 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 *Table 1*. Return to original conditions and re-equilibrate the column.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
3.0	60	40
16.0	49	51

Diluent: Methanol and water (9:1)

Standard solution: 0.13 mg/mL of USP Montelukast Dicyclohexylamine 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

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of montelukast sodium ($C_{35}H_{35}ClNNaO_3S$) in the portion of Montelukast Sodium taken:

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

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

M_{r1} = molecular weight of montelukast sodium, 608.17

M_{r2} = molecular weight of montelukast dicyclohexylamine, 767.50

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Organic Impurities**

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

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

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 colorless glass vial, and expose to ambient light for approximately 20 min to generate the *cis*-isomer of montelukast.

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

Sensitivity solution: 0.5 µg/mL of Montelukast Sodium in *Diluent* from the *Sample solution*

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.5 between the *cis*-isomer and montelukast; NLT 1.5 between montelukast and the methylketone impurity, *System suitability solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Montelukast Sodium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

Acceptance criteria: See *Table 2*.

Reporting level for impurities: 0.05%

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Sulfoxide impurity[a]	0.4	0.2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Cis-isomer[b]	0.8	0.15
Michael Adducts 1[c] and 2[d]	0.9	0.15[*]
Montelukast	1.0	—
Methylketone impurity[e]	1.2	0.15
Methylstyrene impurity[f]	1.9	0.3
Any other individual impurity	—	0.10
Total impurities	—	0.6

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

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

[b] [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.

[c] 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.

[d] 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.

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

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

• **Enantiomeric Purity**

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

Solution A: 2.3 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 5.7.

Solution B: Methanol and acetonitrile (60:40)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	70	30
30	60	40
35	60	40

Diluent: Acetonitrile and water (1:1)

System suitability solution: 0.1 mg/mL of USP Montelukast Racemate RS in *Diluent*

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

Sensitivity solution: 1 µg/mL of Montelukast Sodium in *Diluent* from the *Sample solution*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 15-cm; 5-µm packing L41

Column temperature: 30°

Flow rate: 0.9 mL/min

Injection size: 10 µL

System suitability

Samples: *System suitability solution* and *Sensitivity solution*

[Note—The relative retention times are 1.0 for montelukast, which is the *R*-enantiomer, and 0.7 for the *S*-enantiomer.]

Suitability requirements

Resolution: NLT 2.9 between the *S*-enantiomer and montelukast, *System suitability solution*

Signal-to-noise ratio: NLT 10 for the montelukast peak, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of *S*-enantiomer in the portion of Montelukast Sodium taken:

$$\text{Result} = (r_U/r_T) \times 100$$

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

SPECIFIC TESTS

• **Water Determination, *Method Ia*⟨921⟩:** NMT 4.0%

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 RS	$C_{35}H_{36}ClNO_3S \cdot C_{12}H_{23}N$	767.50
USP Montelukast Racemate RS		
USP Montelukast for Peak Identification RS		

(montelukast containing sulfoxide impurity, michael adducts 1 and 2, methylketone impurity, and methylstyrene impurity)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
MONTELUKAST SODIUM	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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