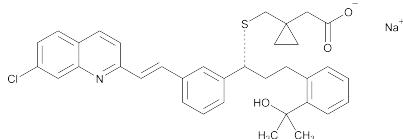


Montelukast Sodium



$C_{35}H_{35}ClNaO_3S$	608.17
Cyclopropaneacetic acid, 1-[[[1-[3-[2-(7-chloro-2-quinolyl)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 [151767-02-1].	
$C_{35}H_{36}ClNO_3S$	586.18
Montelukast [158966-92-8].	

DEFINITION

Montelukast Sodium contains NLT 98.0% and NMT 102.0% of $C_{35}H_{35}ClNaO_3S$, calculated on the anhydrous and solvent-free 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)**

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 the pyroantimonate precipitate test.

- **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 Di-cyclohexylamine 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 \times 5-cm; 1.8- μ m packing L11

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection size: 10 μ L

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 ($C_{35}H_{35}ClNaO_3S$) 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

- **HEAVY METALS**

Diluent: Acetone and water (4:1)

Sample solution: Dissolve 0.50 g of Montelukast Sodium in 20 mL of *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*

Analysis: To each solution, add 2 mL of *pH 3.5 Acetate Buffer*, prepared as directed under *Heavy Metals* (231). Mix, and add to 1.2 mL of thioacetamide–glycerin base TS. Mix immediately, and allow to stand for 2 min. Pass the solutions through a membrane filter of 0.45- μ m pore size. 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*.

Acceptance criteria: NMT 10 ppm

- **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 μ g/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
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-[[[(1R)-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-[[[(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.

^d 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.

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

^f 1-[[[(1R)-1-[3-[(E)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(1-methylethyl)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 μ g/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 \times 15-cm; 5- μ m packing L41

Column temperature: 30°

Flow rate: 0.9 mL/min

Injection size: 10 μ L

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 1a (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

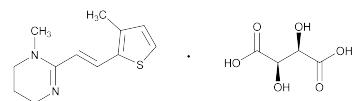
USP Montelukast Dicyclohexylamine RS

$C_{35}H_{36}ClNO_3 \cdot C_{12}H_{23}N \quad 767.50$

USP Montelukast Racemate RS

USP Montelukast for Peak Identification RS

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

Morantel Tartrate

$C_{12}H_{16}N_2S \cdot C_4H_6O_6 \quad 370.42$

Pyrimidine, 1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)ethenyl]-, (E) -,[*R*-(*R*^{*},*R*^{*})]-2,3-dihydroxybutane-1,4-dioate (1:1).

(*E*-1,4,5,6-tetrahydro-1-methyl-2-[2-(3-methyl-2-thienyl)vinyl]pyrimidine tartrate (1:1) [26155-31-7]. Morantel [20574-50-9].

» Morantel Tartrate contains not less than 96.4 percent and not more than 101.5 percent of $C_{12}H_{16}N_2S \cdot C_4H_6O_6$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate it is for veterinary use only.

USP Reference standards (11)—

USP Morantel Tartrate RS