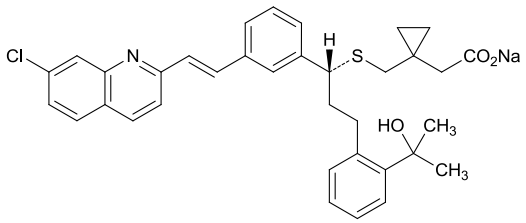
Montelukast Sodium

モンテルカストナトリウム



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

Sodium (1-{[((1*R*)-1-{3-[(1*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl}-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfanyl]methyl}cyclopropyl)acetate

[*151767-02-1*]

Montelukast Sodium contains not less than 98.0% and not more than 102.0% of $C_{35}H_{35}ClNNaO_3S$, calculated on the anhydrous basis and corrected on the amount of the residual solvent.

Description Montelukast Sodium occurs as a white to pale yellowish white powder.

It is very soluble in methanol and in ethanol (99.5), and freely soluble in water.

It is hygroscopic.

It turns yellow on exposure to light.

Identification **(1)** Place 0.1 g of Montelukast Sodium in a crucible, and heat until a white residue is formed. To the residue add 2 mL of water, and then filter. To the filtrate add 2 mL of potassium carbonate solution (3 in 20), and heat to boiling: no precipitate is observed. To this solution add 4 mL of potassium hexahydroxoantimonate (V) TS, heat to boiling, and cool immediately in ice water: a white precipitate is formed. Rub the inside wall of the test tube with a glass rod, if necessary.

(2) Determine the absorption spectrum of a solution of Montelukast Sodium in a mixture of methanol and water (3:1) (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Montelukast Sodium RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(3) Determine the infrared absorption spectrum of Montelukast Sodium as directed in the paste method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of Montelukast Sodium RS: both spectra exhibit similar intensities of absorption at the same wave numbers. Or, perform the test by the potassium bromide disk method or ATR method, and compare the spectrum with the spectrum of Montelukast Sodium RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity **(1)** Heavy metals－Dissolve 0.5 g of Montelukast Sodium in 20 mL of a mixture of acetone and water (4:1), and use this solution as the sample solution. Separately, take 0.5 mL of Standard Lead Solution, add 20 mL of the mixture of acetone and water (4:1), and use this solution as the standard solution. To the sample solution and the standard solution add 2 mL of acetate buffer solution, pH 3.5, and shake. To these solutions add 1.2 mL of thioacetamide-alkaline glycerin TS, shake immediately, then allow to stand for 2 minutes, and filter through a membrane filter with pore size 0.45 μm (about 13 mm in diameter). Compare the color on the membrane filters through which each solution is filtered: the color obtained from the sample solution is not darker than that obtained from the standard solution (not more than 10 ppm).

(2) Related substances－Conduct this procedure using light-resistant vessels. Dissolve 50 mg of Montelukast Sodium in 50 mL of a mixture of methanol and water (9:1), and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of them by the area percentage method: the amount of the peak having the relative retention time of about 1.9 to montelukast (related substance F) is not more than 0.3%, the amount of the peak having the relative retention time of about 0.4 (related substance A) is not more than 0.2%, the amounts of the peaks having the relative retention times of about 0.8 (related substance B) and about 1.2 (related substance E) are not more than 0.15%, respectively, the total amount of the two peaks having the relative retention time about 0.9 (related substances C and D) is not more than 0.15%, and the amounts of the peaks other than montelukast and the peaks mentioned above are not more than 0.10%, respectively. The total amount of the peaks other than montelukast is not more than 0.6%.

Operating conditions－

Detector, column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay.

Time span of measurement: For 16 minutes after injection, beginning after the solvent peak.

System suitability－

System performance: Proceed as directed in the system suitability in the Assay.

Test for required detectability: Pipet 1 mL of the sample solution, add the mixture of methanol and water (9:1) to make exactly 100 mL. Pipet 1 mL of this solution, add the mixture of methanol and water (9:1) to make exactly 20 mL, and use this solution as the solution for system suitability test.

When the procedure is run with 10 μL of the solution for system suitability test under the above operating conditions, the SN ratio of the peak of montelukast is not less than 10.

For the calculations mentioned above, the peak areas smaller than that of montelukast, founded in the chromatogram obtained with 10 μL of the solution for system suitability test, are excluded.

(3) Optical isomer－Conduct this procedure using light-resistant vessels. Dissolve 50 mg of Montelukast Sodium in 50 mL of a mixture of water and acetonitrile (1:1), and use this solution as the sample solution. Perform the test with 10 μL of the sample solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amounts of them by the area percentage method: the amount of the peak having the relative retention time of about 0.7 to montelukast is not more than 0.2%.

Operating conditions－

Detector: An ultraviolet absorption photometer (wavelength: 280 nm).

Column: A stainless steel column 4.0 mm in inside diameter and 15 cm in length, packed with α_1-acid glycoprotein binding silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 30℃.

Mobile phase A: Dissolve 2.3 g of ammonium acetate in 1000 mL of water, and adjust to pH 5.7 with acetic acid (100).

Mobile phase B: A mixture of methanol and acetonitrile (3:2).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 30	70 → 60	30 → 40
30 － 35	60	40

Flow rate: 0.9 mL per minute (the retention time of montelukast is about 25 minutes).

System suitability－

Test for required detectability: Pipet 1 mL of the sample solution, add the mixture of water and acetonitrile (1:1) to make exactly 100 mL. Pipet 1 mL of this solution, add the mixture of water and acetonitrile (1:1) to make exactly 10 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the SN ratio of the peak of montelukast is not less than 10.

System performance: Dissolve about 5 mg of Montelukast Racemate RS in the mixture of water and acetonitrile (1:1) to make 50 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the resolution between the peak of montelukast and the peak having the relative retention time of about 0.7 to montelukast is not less than 2.9.

(4) Residual solvent－Being specified separately when the drug is granted approval based on the Pharmaceutical Affairs Law.

Water *<2.48>* Not more than 4.0% (0.3 g, volumetric titration, direct titration).

Assay Conduct this procedure using light-resistant vessels. Weigh accurately about 50 mg of Montelukast Sodium, and dissolve in a mixture of methanol and water (9:1) to make exactly 50 mL. Pipet 10 mL of this solution, add the mixture of methanol and water (9:1) to make exactly 100 mL, and use this solution as the sample solution. Separately, weigh accurately about 26 mg of Montelukast Dicyclohexylamine RS, dissolve in the mixture of methanol and water (9:1) to make exactly 50 mL. Pipet 5 mL of this solution, add the mixture of methanol and water (9:1) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions. Determine the peak areas, A_T and A_S, of montelukast in each solution.

Amount (mg) of $C_{35}H_{35}ClNNaO_3S$
$= M_S \times A_T / A_S \times 5/2 \times 0.792$

M_S: Amount (mg) of Montelukast Dicyclohexylamine RS

Operating conditions－

Detector: An ultraviolet absorption photometer (wavelength: 238 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 5 cm in length, packed with phenylsilanized silica gel for liquid chromatography (1.8 μm in particle diameter).

Column temperature: A constant temperature of about 30℃.

Mobile phase A: A mixture of water and trifluoroacetic acid (2000:3).

Mobile phase B: A mixture of acetonitrile and trifluoroacetic acid (2000:3).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 － 3	60	40
3 － 16	60 → 49	40 → 51

Flow rate: 1.2 mL per minute (the retention time of montelukast is about 7 minutes).

System suitability－

System performance: Dissolve 10 mg of Montelukast for Peak Identification RS in the mixture of methanol and water (9:1) to make 10 mL, and use this solution as the solution A for peak identification. Perform the test with 10 μL of the solution A for peak identification under the above operating conditions, and identify the peaks having the relative retention times to montelukast of about 0.4 (related substance A), about 0.9 (related substances C and D), about 1.2 (related substance E), and about 1.9 (related substance F). Place 1 mL of the solution A for peak identification in a clear glass container, allow to stand for about 20 minutes, and use this solution as the solution B for peak identification. When the procedure is run with 10 μL of the solution B for peak identification under the above operating conditions, and identify the peak having the relative retention time of about 0.8 to montelukast (related substance B), the resolution between the peaks of related substance B and montelukast is not less than 2.5, and between the peaks of montelukast and related substance E is not less than 1.5.

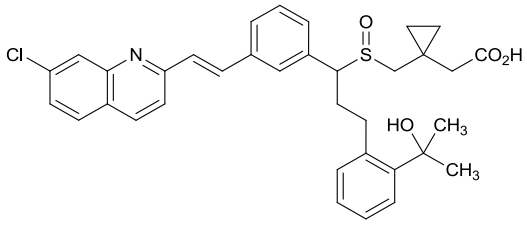
System repeatability: When the test is repeated 5 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of montelukast is not more than 0.73%.

Containers and storage Containers－Tight containers

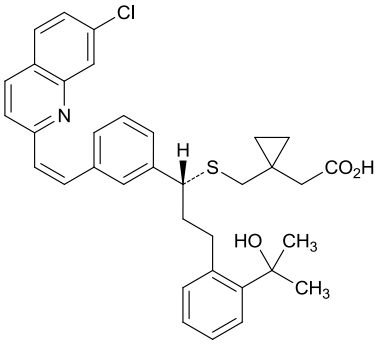
Storage－Light-resistant.

Related substances

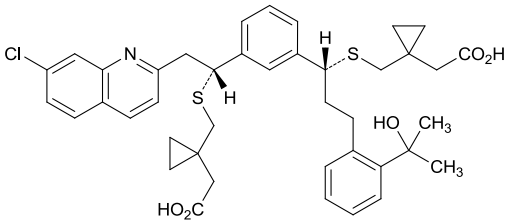
Related substance A:
(1-{[(1-{3-[(1*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl}-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfinyl]methyl}cyclopropyl)acetic acid



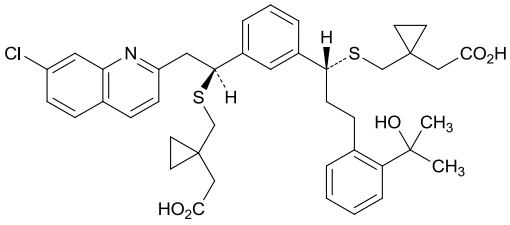
Related substance B:
(1-{[((1*R*)-1-{3-[(1*Z*)-2-(7-Chloroquinolin-2-yl)ethenyl]phenyl}-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfanyl]methyl}cyclopropyl)acetic acid



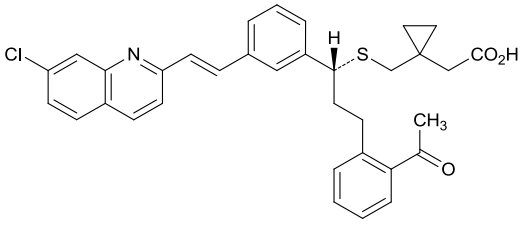
Related substance C:
(1-{[((1*R*)-1-{3-[(1*R*)-1-({[1-(Carboxymethyl)cyclopropyl]methyl}sulfanyl)-2-(7-chloroquinolin-2-yl)ethyl]phenyl}-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfanyl]methyl}cyclopropyl)acetic acid



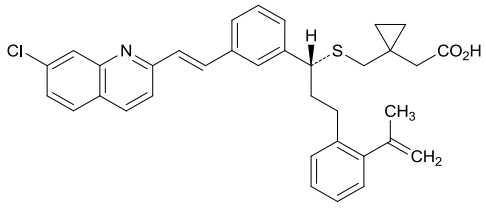
Related substance D:
(1-{[((1*R*)-1-{3-[(1*S*)-1-({[1-(Carboxymethyl)cyclopropyl]methyl}sulfanyl)-2-(7-chloroquinolin-2-yl)ethyl]phenyl}-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl)sulfanyl]methyl}cyclopropyl)acetic acid



Related substance E:
(1-{[((1*R*)-3-(2-Acetylphenyl)-1-{3-[(1*E*)-2-(7-chloroquinolin-2-yl)ethenyl]phenyl}propyl)sulfanyl]methyl}cyclopropyl)acetic acid



Related substance F:
(1-{[((1*R*)-1-{3-[(1*E*)-2-(7-Chloroquinolin-2-yl)ethenyl]
phenyl}-3-[2-(1-methylethenyl)phenyl]propyl)sulfanyl]
methyl}cyclopropyl)acetic acid



Add the following to 9.01 Reference Standards (1):

Montelukast Sodium RS

Montelukast Dicyclohexylamine RS

Montelukast Racemate RS

Montelukast for Peak Identification RS