Analysis
Sample: *Sample solution*
Calculate the percentage of each impurity in the portion of Modafinil taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each individual impurity
r_T = sum of the responses of all the peaks
F = relative response factor (see *Table 1*)
Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Modafinil	1.0	—	—
Salicylic acid[a]	1.1	—	—
Modafinil acid[b]	1.4	1.0	0.5
Modafinil sulfone[c]	1.7	0.9	0.5
Modafinil ester[d]	3.0	1.0	0.5
Any other individual unspecified impurity	—	1.0	0.05
Total impurities	—	—	1.0

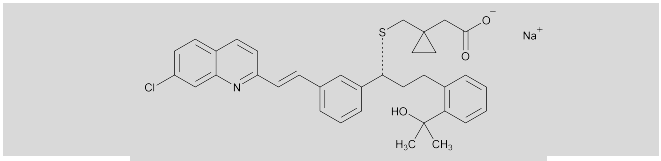
[a] Salicylic acid is used for calculating resolution and is not a potential impurity.
[b] 2-[(Diphenylmethyl)sulfinyl]acetic acid.
[c] 2-[(Diphenylmethyl)sulfonyl]acetamide.
[d] 2-[(Diphenylmethyl)sulfinyl]acetic acid methyl ester.

SPECIFIC TESTS
- **WATER DETERMINATION,** *Method I* ⟨**921**⟩**:** NMT 0.2%

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Modafinil RS
  USP Salicylic Acid RS

Add the following:

▪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 [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 $C_{35}H_{35}ClNNaO_3S$, 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 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

• **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-µm 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 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
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)■1S (*USP35*)

Add the following:

■Omega-3-Acid Ethyl Esters Capsules

DEFINITION

Omega-3-Acid Ethyl Esters Capsules contain Omega-3-Acid Ethyl Esters, which are obtained by transesterification of the body oil obtained from fish of families such as *Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae,* and *Scombridae* and subsequent purification processes including urea fractionation followed by molecular distillation with NLT 95.0% and NMT 105.0% of the labeled sum of eicosapentaenoic acid ethyl ester (EPAee) and docosahexaenoic acid ethyl ester (DHAee). The content of EPAee plus the content of DHAee is NLT 800 mg/g and NMT 880 mg/g, with NLT 430 mg/g and NMT 495 mg/g of EPAee and NLT 347 mg/g and NMT 403 mg/g of DHAee. Tocopherol may be added as an antioxidant.

IDENTIFICATION

• **A.** The retention times of the peaks for eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay* for *Content of EPAee and DHAee*.

ASSAY

• **CONTENT OF EPAEE AND DHAEE**

[NOTE—Carry out the procedure as rapidly as possible, avoiding exposure to actinic light, oxidizing agents, oxidation catalysts (i.e., copper and iron), and air.]

Antioxidant solution: 50 mg/L of butylated hydroxytoluene in isooctane

Internal standard solution: 7.0 mg/mL of USP Methyl Tricosanate RS in *Antioxidant solution*

System suitability solution: 5.5 mg/mL of docosahexaenoic acid methyl ester and 0.5 mg/mL of tetracos-15-enoic acid methyl ester in *Antioxidant solution*

Standard solution: Dissolve 60.0 mg of USP Docosahexaenoic Acid Ethyl Ester RS and 90.0 mg of USP Eicosapentaenoic Acid Ethyl Ester RS in 10.0 mL of *Internal standard solution*.

Sample solution: Weigh NLT 10 Capsules in a tared weighing bottle. With a sharp blade, carefully open the Capsules, without loss of shell material, and transfer the combined Capsule contents to a 100-mL beaker. Remove any adhering substance from the emptied Capsules by washing with several small portions of diethyl ether. Discard the washings, and allow the empty Capsules to air-dry over a period of NMT 30 min, taking precautions to avoid uptake or loss of moisture. Weigh the empty Capsules in the original tared weighing bottle, and calculate the average fill weight per Capsule (AFW). Transfer 250 mg of the combined Capsule contents to a suitable flask, and dissolve with 10.0 mL of *Internal standard solution*.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.25-mm × 25–50-m fused silica capillary column coated with a 0.25-µm film of G16

Temperature

Injector: 250°

Detector: 270°

Column: See *Table 1*.

Table 1

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
170	0	170	2
170	3.5	255	9

Carrier gas: Hydrogen or helium

Linear velocity: Adjust to obtain a retention time for docosahexaenoic acid ethyl ester of 26 ± 3 min.

Split flow ratio: 1:220

Injection size: 1 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.2 between the peaks in the *System suitability solution* due to docosahexaenoic acid methyl ester and tetracos-15-enoic acid methyl ester

Relative standard deviation: NMT 2.0% for the ratios of the peak responses of DHAee and EPAee relative to the internal standard, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the content, in mg/g, of EPAee and DHAee in the content of the Capsules taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U)$$

R_U = peak area ratio of the EPAee or DHAee peak to the internal standard peak in the *Sample solution*

R_S = peak area ratio of the EPAee or DHAee peak to the internal standard peak in the *Standard solution*

C_S = concentration of USP Eicosapentaenoic Acid Ethyl Ester RS or USP Docosahexaenoic Acid Ethyl Ester RS in the *Standard solution* (mg/mL)

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