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Methylnaltrexone Bromide

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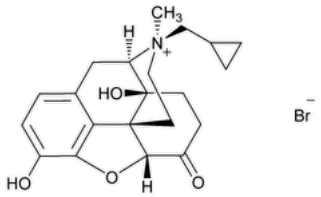

▲ (ERR 1-Mar-2024)

$C_{21}H_{26}BrNO_4$ 436.34

Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α,17*R*)-;

(17*R*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide CAS RN®: 916055-92-0.

DEFINITION

Methylnaltrexone Bromide contains NLT 98.0% and NMT 102.0% of methylnaltrexone bromide ($C_{21}H_{26}BrNO_4$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Bromide*:** Meets the requirements of the silver nitrate precipitation test

ASSAY

- **Procedure**

Protect solutions containing methylnaltrexone bromide from light.

Buffer: Dilute 3.0 mL of heptafluorobutyric acid with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 2.4.

Solution A: *Buffer* and methanol (85:15)

Solution B: *Buffer*, methanol, and tetrahydrofuran (85:5:10)

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the system for about 15 min.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
15	30	70
50	30	70

Diluent: *Solution A*

Standard solution: 3.0 mg/mL of USP Methylnaltrexone Bromide RS in *Diluent*

Sample solution: 3.0 mg/mL of Methylnaltrexone Bromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 25-cm; 3-µm packing L1

Column temperature: 50°

Flow rate: 1.0 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of methylnaltrexone bromide ($C_{21}H_{26}BrNO_4$) in the portion of Methylnaltrexone Bromide taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Methylnaltrexone Bromide RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Organic Impurities**

Protect solutions containing methylnaltrexone bromide from light.

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

System suitability solution: 3.0 mg/mL of USP Methylnaltrexone Bromide RS and 4.5 µg/mL of USP Naltrexone RS in *Diluent*

Sensitivity solution: 1.5 µg/mL of USP Methylnaltrexone Bromide RS in *Diluent*

Standard solution: 4.5 µg/mL of USP Methylnaltrexone Bromide RS in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between methylnaltrexone bromide and naltrexone, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each impurity in the portion of Methylnaltrexone Bromide taken:

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

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

r_S = peak response of methylnaltrexone from the *Standard solution*

C_S = concentration of USP Methylnaltrexone Bromide RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
S-Methylnaltrexone[a]	0.92	0.15
Methylnaltrexone	1.0	—
Naltrexone	1.15	0.15
N-Butenyl oxymorphone[b]	1.21	0.15

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acetylmethylnaltrexone[c]	1.32	0.15
Acetylnaltrexone[d]	1.48	0.15
O-Methyl methylnaltrexone[e]	1.59	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	1.0

[a] (17*S*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

[b] (17*RS*)-17-(But-3-en-1-yl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinanium bromide.

[c] 3-Acetyloxy-17-cyclopropylmethyl-4,5α-epoxy-14-hydroxy-17-methyl-6-oxomorphinanium bromide.

[d] 17-(Cyclopropylmethyl)-4,5α-epoxy-14-hydroxy-6-oxomorphinan-3-yl acetate.

[e] (17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-14-hydroxy-17-methyl-3-methoxy-6-oxomorphinanium bromide.

- **Limit of Methylnaltrexone Related Compound A**

Buffer: 1.1 g/L solution of 1-octanesulfonate sodium salt in water (5 mM). Adjust with phosphoric acid to a pH of 2.00 ± 0.05.

Solution A: Tetrahydrofuran and *Buffer* (50:950)

Solution B: Acetonitrile, tetrahydrofuran, and *Buffer* (600:50:350)

Mobile phase: See *Table 3*. Return to original conditions and re-equilibrate the system for about 8 min.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	95	5
36	86	14
40	50	50
50	50	50

Diluent: Acetonitrile, water, and phosphoric acid (100:900:1.2). [Note—This is v:v:v ratio equivalent to (100:900:2, v:v:w).]

Peak identification solution: 5 mg/mL of USP Methylnaltrexone Peak Identification Mixture RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Methylnaltrexone Bromide RS in *Diluent*

Sample solution: 5 mg/mL of Methylnaltrexone Bromide in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 3.0-mm × 15-cm; 3.5-µm packing L1

Column temperature: 15°

Flow rate: 0.4 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Peak identification solution*, *Standard solution*, and *Sample solution*

Identify the peak due to methylnaltrexone related compound A from the *Peak identification solution*. [Note—Typical relative retention times for methylnaltrexone and methylnaltrexone related compound A are 1.0 and 1.2, respectively.]

Calculate the amount, in ppm, of methylnaltrexone related compound A in the portion of Methylnaltrexone Bromide taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 1000$$

r_U = peak response of methylnaltrexone related compound A from the *Sample solution*

r_S = peak response of methylnaltrexone from the *Standard solution*

C_S = concentration of USP Methylnaltrexone Bromide RS in the *Standard solution* (µg/mL)

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

F = relative response factor for methylnaltrexone related compound A, 1.3

Acceptance criteria: NMT 100 ppm

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 75 mg/mL in water

Acceptance criteria: 4.3–5.3

• **Water Determination** ⟨921⟩, *Method I, Method Ia*: NMT 1.0%

• **Optical Rotation** ⟨781S⟩, *Procedures, Specific Rotation*

Sample solution: 10 mg/mL in water

Acceptance criteria: −160° to −166°

• **Microbial Enumeration Tests** ⟨61⟩ and **Tests for Specified Microorganisms** ⟨62⟩: The total aerobic microbial count is NMT 10^3 cfu/g, and the total combined yeasts and molds count is NMT 10^2 cfu/g.

• **Bacterial Endotoxins Test** ⟨85⟩: The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Methylnaltrexone Bromide is used can be met. Where the label states that Methylnaltrexone Bromide must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Methylnaltrexone Bromide is used can be met.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers and store at room temperature.

• **Labeling:** Where it must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, Methylnaltrexone Bromide is so labeled. Where it is sterile, it is so labeled.

• **USP Reference Standards** ⟨11⟩

USP Endotoxin RS

USP Methylnaltrexone Bromide RS

USP Methylnaltrexone Peak Identification Mixture RS

It contains Methylnaltrexone Bromide and a small amount of methylnaltrexone related compound A:
7,8-Didehydromethylnaltrexone bromide, or ABUK-Methylnaltrexone.
(17*RS*)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxy-17-methyl-6-oxomorphinan-7-enium bromide.

$C_{21}H_{24}BrNO_4$ 434.32

USP Naltrexone RS

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

Topic/Question	Contact	Expert Committee
METHYLNALTREXONE BROMIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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