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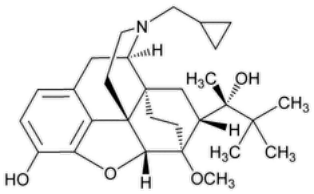
Buprenorphine Hydrochloride

Change to read:



• HCl

$C_{29}H_{41}NO_4 \cdot HCl$ 504.11

6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-, hydrochloride, [5α,7α(*S*)]-;

21-Cyclopropyl-7α-[(*S*)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethano-6,7,8,14-tetrahydrooripavine hydrochloride;

▲(*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7α-yl]- 3,3-dimethylbutan-2-ol hydrochloride▲ (USP 1-Aug-2022) CAS RN®: 53152-21-9; UNII: 56W8MW3EN1.

Change to read:

DEFINITION

Buprenorphine Hydrochloride contains NLT 98.0% and NMT 102.0% of buprenorphine hydrochloride ($C_{29}H_{41}NO_4 \cdot HCl$), calculated on the anhydrous ▲and solvent-free▲ (USP 1-Aug-2022) basis.

IDENTIFICATION

Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-Aug-2022)

• **B.** The retention time of the buprenorphine 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, Chloride***

Sample stock solution: 50 mg/mL of Buprenorphine Hydrochloride in methanol

Sample solution: 10 mg/mL of Buprenorphine Hydrochloride in carbon dioxide-free water from the *Sample stock solution*

Analysis: Use 3 mL of the *Sample solution*.

Acceptance criteria: Meets the requirements

ASSAY

Change to read:

• **Procedure**

Buffer: 5.44 g/L of monobasic potassium phosphate prepared as follows. Initially dissolve in 90% volume of water, and adjust with 5% (v/v) phosphoric acid to a pH of 4.5. Dilute with water to volume.

Solution A: Acetonitrile and *Buffer* (10:90)

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to the initial conditions and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	89	11
2	89	11
12	64	36
15	41	59

Time (min)	Solution A (%)	Solution B (%)
20	39	61

Diluent: Methanol and water (80:20)

Standard solution: 2.0 mg/mL of USP Buprenorphine Hydrochloride RS in *Diluent*

Sample solution: 2.0 mg/mL of Buprenorphine Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1.3 mL/min

Injection volume: 5 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 buprenorphine hydrochloride ($C_{29}H_{41}NO_4 \cdot HCl$) in the portion of Buprenorphine Hydrochloride taken:

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

r_U = peak response of buprenorphine from the *Sample solution*

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous ▲and solvent-free▲ (USP 1-Aug-2022) basis

IMPURITIES

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

Change to read:

• **Organic Impurities**

Buffer, Solution A, Solution B, and **Mobile phase:** Prepare as directed in the *Assay*.

System suitability solution: 5.0 mg/mL of USP Buprenorphine System Suitability Mixture RS in methanol

▲**Sensitivity solution:** 2.5 µg/mL of USP Buprenorphine Hydrochloride RS in methanol▲ (USP 1-Aug-2022)

Standard solution: 0.005 mg/mL of USP Buprenorphine Hydrochloride RS and 0.01 mg/mL of USP Buprenorphine Related Compound A RS in methanol

Sample solution: 5.0 mg/mL of Buprenorphine Hydrochloride in methanol

Chromatographic system: Proceed as directed in the *Assay* except for the *Column*.

Column: 4.6-mm × 5.0-cm; 3.5-µm packing L1

System suitability

Samples: *System suitability solution*, ▲*Sensitivity solution*,▲ (USP 1-Aug-2022) and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between buprenorphine and ethenobuprenorphine, *System suitability solution*

Relative standard deviation: NMT 5% for buprenorphine and buprenorphine related compound A, *Standard solution*

▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (USP 1-Aug-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of buprenorphine related compound A in the portion of Buprenorphine Hydrochloride taken:

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

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

r_S = peak response of buprenorphine related compound A from the *Standard solution*

C_S = concentration of USP Buprenorphine Related Compound A RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of each other individual impurity in the portion of Buprenorphine Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor (see *Table 2*)

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Buprenorphine	1.0	—	—
Ethenobuprenorphine▲▲ (USP 1-Aug-2022)	1.1	1.0	0.10
Buprenorphine related compound A	1.4	—	0.20
Buprenorphine 2,2′-dimer[a]	1.8	3.3	0.10
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.65

[a] 2,2′-Bi{17-(cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-7α-[(*S*)-2-hydroxy-3,3-dimethylbutan-2-yl]-6-methoxy-6α,14-ethanomorphinan}.

SPECIFIC TESTS

Change to read:

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

  Sample solution: 20 mg/mL in methanol

  Acceptance criteria: −92° to −98°,▲calculated on the anhydrous and solvent-free basis▲ (USP 1-Aug-2022)

- **Acidity or Alkalinity**

  Sample stock solution: 50 mg/mL of Buprenorphine Hydrochloride in methanol

  Sample solution: 10 mg/mL of Buprenorphine Hydrochloride in carbon dioxide-free water from *Sample stock solution*

  Analysis: Add 0.05 mL of methyl red TS 2 to 10 mL of *Sample solution* and titrate with 0.02 N sodium hydroxide or 0.02 N hydrochloric acid.

  Acceptance criteria: NMT 0.2 mL of 0.02 N sodium hydroxide or 0.02 N hydrochloric acid is required to change the color of the indicator

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

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers.
- **USP Reference Standards** ⟨11⟩

  USP Buprenorphine Hydrochloride RS

  USP Buprenorphine Related Compound A RS

  (*S*)-2-[17-(But-3-en-1-yl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

  $C_{29}H_{41}NO_4$ 467.65

  USP Buprenorphine System Suitability Mixture RS

  Contains a mixture of the following two compounds:

Buprenorphine.

Ethenobuprenorphine (about 0.5%): (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethenomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

$C_{29}H_{39}NO_4$ 465.63

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

Topic/Question	Contact	Expert Committee
BUPRENORPHINE HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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