Buprenorphine and Naloxone Sublingual Tablets

Type of Posting	Revision Bulletin
Posting Date	31–Jul–2020
Official Date	01–Aug–2020
Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Buprenorphine and Naloxone Sublingual Tablets monograph. The purpose of the revision is to widen the acceptance criteria of the *Assay* from "94.0%–106.0% of the labeled amount of buprenorphine and naloxone" to "90.0%–110.0% of the labeled amount of buprenorphine and naloxone", to be consistent with FDA-approved specifications. The *Definition* is also revised accordingly to be consistent with the revised acceptance criteria of the *Assay*.

The Buprenorphine and Naloxone Sublingual Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Wei Yang, Scientific Liaison (301-816-8338 or wiy@usp.org).

Revision Bulletin
Official: August 1, 2020

Buprenorphine and Naloxone Sublingual Tablets

Change to read:

DEFINITION

Buprenorphine and Naloxone Sublingual Tablets contain amounts of buprenorphine hydrochloride and naloxone hydrochloride equivalent to ▲NLT 90.0% and NMT 110.0%▲ (RB 1-Aug-2020) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$).

IDENTIFICATION

● **A.** The retention times of the buprenorphine and naloxone peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

● **B.** The UV absorption spectra of the buprenorphine and naloxone peaks of the *Sample solution* and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.

ASSAY

Change to read:

● **Procedure**

[Note—It is suggested to protect all solutions containing buprenorphine and naloxone from light.]

Buffer: 9 mM of dibasic ammonium phosphate in water. Adjust with a solution of phosphoric acid and water (1:1) to a pH of 6.2.

Solution A: Acetonitrile, methanol, and *Buffer* (7:3:90)

Solution B: Acetonitrile, methanol, and *Buffer* (56:24:20)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	99	1
30	1	99
45	1	99
45.1	99	1
55	99	1

Solution C: Phosphoric acid and water (1:1000)

Diluent: Acetonitrile, methanol, and *Solution C* (7:3:90)

Standard solution: 0.57 mg/mL of USP Buprenorphine Hydrochloride RS and 0.13 mg/mL of USP Naloxone RS in *Diluent*

Sample solution: Nominally 0.52 mg/mL of buprenorphine and 0.13 mg/mL of naloxone prepared as follows. Transfer NLT 13 Tablets to a suitable volumetric flask, and add about 70% of the final volume of *Diluent*. Sonicate for 15 min with occasional swirling and shake for 15 min. Dilute with *Diluent* to volume. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. For *Identification B*, use a diode array detector in the range of 210–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L11

Column temperature: 60°

Flow rate: 0.8 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for both buprenorphine and naloxone

Relative standard deviation: NMT 2.0% for both buprenorphine and naloxone

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 = nominal concentration of buprenorphine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) in the portion of Tablets taken:

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

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

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

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

C_U = nominal concentration of naloxone in the *Sample solution* (mg/mL)

Acceptance criteria: ▲90.0%–110.0%▲ (RB 1-Aug-2020) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$)

PERFORMANCE TESTS

- **Dissolution** ⟨711⟩

Medium: Water (deaerated for 5 min); 500 mL

Apparatus 1: 100 rpm

Time: 10 min

Buffer: 0.018 M monobasic potassium phosphate in water prepared as follows. Dissolve 2.4 g of monobasic potassium phosphate and 0.5 g of sodium hydroxide in each liter of water. Adjust with phosphoric acid to a pH of 6.8.

Solution A: Acetonitrile, methanol, and *Buffer* (40:20:40)

Solution B: Acetonitrile and *Buffer* (78:22)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
2.0	100	0
3.0	0	100
6.0	0	100
6.1	100	0
8.0	100	0

Diluent: Methanol and water (50:50)
Standard solution: 0.01 mg/mL of USP Buprenorphine Hydrochloride RS and 0.0025 mg/mL of USP Naloxone RS in *Diluent*. Sonicate if necessary. Pass a portion through a suitable filter of 0.45-µm pore size. Discard the first 4 mL of filtrate.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 5-cm; 5-µm packing L7
Column temperature: 25°
Flow rate: 1.0 mL/min
Injection volume: 40 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for both buprenorphine and naloxone
Relative standard deviation: NMT 2.0% for both buprenorphine and naloxone
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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)

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

L = label claim of buprenorphine (mg/Tablet)

Calculate the percentage of the labeled amount of naloxone ($C_{19}H_{21}NO_4$) dissolved:

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

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

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

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

V = volume of *Medium*, 500 mL

L = label claim of naloxone (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of buprenorphine ($C_{29}H_{41}NO_4$) and naloxone ($C_{19}H_{21}NO_4$) is dissolved.

- **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

- **Organic Impurities**

[Note—It is suggested to protect all solutions containing buprenorphine and naloxone from light.]

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

Standard solution: 0.0015 mg/mL of USP Buprenorphine Hydrochloride RS and 0.0004 mg/mL of USP Naloxone RS in *Diluent*

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5% for buprenorphine and naloxone

Analysis

Samples: *Sample solution* and *Standard solution*

Identify the buprenorphine degradation products using the relative retention times given in *Table 3*.

Calculate the percentage of each buprenorphine related degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each individual buprenorphine related degradation product 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 = nominal concentration of buprenorphine in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of buprenorphine, 467.65

M_{r2} = molecular weight of buprenorphine hydrochloride, 504.11

Identify the naloxone degradation products using the relative retention times given in *Table 3*.

Calculate the percentage of each naloxone related degradation product and any other degradation product in the portion of Tablets taken:

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

r_U = peak response of each naloxone related degradation product or any other degradation product from the *Sample solution*

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

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

C_U = nominal concentration of naloxone in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 3*. Disregard any peaks below 0.05%.

Table 3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Naloxone degradation product 1[a]	0.30	0.5
Naloxone degradation product 2[a]	0.54	0.5
Dealkyl buprenorphine[b,c]	0.55	—
Naloxone	0.61	—
Naloxone degradation product 3[a]	0.67	0.5
Buprenorphine nitrile[c,d]	0.90	—
6-*O*-Desmethylbuprenorphine[c,e]	0.91	—
Buprenorphine degradation product 1[f]	0.95	0.3
Buprenorphine 7-(*S*)-epimer[c,g]	0.99	—
Buprenorphine	1.00	—
Buprenorphine butenyl analog[c,h]	1.03	—
3-*O*-Methylbuprenorphine[c,i]	1.16	—
Any unspecified degradation product[a]	—	0.3
Total degradation products	—	3.0

[a] Quantified relative to naloxone.

[b] (*S*)-2-(4,5α-Epoxy-3-hydroxy-6-methoxy-6α,14-ethanomorphinan-7α-yl)-3,3-dimethylbutan-2-ol.

[c] These are process impurities and are excluded from the total degradation products.

[d] 4,5α-Epoxy-7α-[(*S*)-2-hydroxy-3,3-dimethylbutan-2-yl]-3,6-dimethoxy-6α,14-ethanomorphinan-17-carbonitrile.

[e] (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,6-dihydroxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

[f] Quantified relative to buprenorphine.

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

[h] (*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.

[i] (*S*)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,6-dimethoxy-6α,14-ethanomorphinan-7α-yl]-3,3-dimethylbutan-2-ol.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

- **USP Reference Standards** ⟨11⟩
  USP Buprenorphine Hydrochloride RS
  USP Naloxone RS

Page Information:

Not Applicable

DocID: