Buprenorphine and Naloxone Sublingual Tablets

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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).
Buprenorphine and Naloxone Sublingual Tablets

**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_{5}) 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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>45</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>45.1</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>55</td>
<td>99</td>
<td>1</td>
</tr>
</tbody>
</table>

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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

\(r_U\) = 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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\(r_U\) = 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% 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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>2.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>6.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>8.0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[r_U\] = 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
Calculate the percentage of the labeled amount of naloxone (C_{19}H_{21}NO_{4}) dissolved:

\[
\text{Result} = \left( \frac{r_J}{r_S} \right) \times C_S \times V \times \left( \frac{1}{L} \right) \times 100
\]

\( r_U \) = 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:

\[
\text{Result} = \left( \frac{r_J}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

\( r_U \) = 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:

\[
\text{Result} = \left( \frac{r_J}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]
\[ r_U = \text{peak response of each naloxone related degradation product or any other degradation product from the Sample solution} \]

\[ r_S = \text{peak response of naloxone from the Standard solution} \]

\[ C_S = \text{concentration of USP Naloxone RS in the Standard solution (mg/mL)} \]

\[ C_U = \text{nominal concentration of naloxone in the Sample solution (mg/mL)} \]

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

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

\(^a\) Quantified relative to naloxone.

\(^b\) \((S)-2-(4,5\alpha\text{-Epoxy}-3-hydroxy-6-methoxy-6\alpha,14\text{-ethanomorphinan-7\alpha-yl})\)-3,3-dimethylbutan-2-ol.

\(^c\) These are process impurities and are excluded from the total degradation products.

\(^d\) 4,5\alpha\text{-Epoxy-7\alpha-[(S)-2-hydroxy-3,3-dimethylbutan-2-yl]-3,6-dimethoxy-6\alpha,14\text{-ethanomorphinan-17-carbonitrile.}}\)

\(^e\) \((S)-2-[(17-(Cyclopropylmethyl)-4,5\alpha\text{-epoxy-3,6-dihydroxy-6\alpha,14\text{-ethanomorphinan-7\alpha-yl})]-3,3-dimethylbutan-2-ol.}\)

\(^f\) Quantified relative to buprenorphine.

\(^g\) \((S)-2-[(17-(Cyclopropylmethyl)-4,5\alpha\text{-epoxy-3-hydroxy-6-methoxy-6\alpha,14\text{-ethanomorphinan-7\beta-yl})]-3,3-dimethylbutan-2-ol.}\)

\(^h\) \((S)-2-[(3-But-3-en-1-yl)-4,5\alpha\text{-epoxy-3-hydroxy-6-methoxy-6\alpha,14\text{-ethanomorphinan-7\alpha-yl}}]-3,3-dimethylbutan-2-ol.}\)

\(^i\) \((S)-2-[(17-(Cyclopropylmethyl)-4,5\alpha\text{-epoxy-3,6-dimethoxy-6\alpha,14\text{-ethanomorphinan-7\alpha-yl}}]-3,3-dimethylbutan-2-ol.}\)

**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

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**Page Information:**

Not Applicable

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