Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets

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Expert Committee	Chemical Medicines Monographs 6
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 6 Expert Committee has revised the Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to widen the acceptance criteria for any unspecified impurity related both to naproxen sodium and pseudoephedrine hydrochloride from NMT 0.15% to NMT 0.2% in the test for *Organic Impurities* to accommodate the manufacturer's FDA-approved specification.

Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Richard Nguyen, Scientific Liaison (301-816-8170 or rbn@usp.org) or Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).

Add the following:

▲Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets

DEFINITION

Naproxen Sodium and Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$).

IDENTIFICATION

- **A.** The retention times of the naproxen and pseudoephedrine peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV absorption spectra of the naproxen and pseudoephedrine peaks of the *Sample solution* exhibit maxima and minima at the same wavelengths as those of the corresponding peaks of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: Dissolve 400 mg of sodium lauryl sulfate in 1 L of water. Add 5 mL of triethylamine and adjust with glacial acetic acid to a pH of 4.1.

Mobile phase: Acetonitrile, methanol, and *Buffer* (25:25:50)

Standard solution: 0.22 mg/mL of USP Naproxen Sodium RS and 0.12 mg/mL of USP Pseudoephedrine Hydrochloride RS in methanol

Sample stock solution: Nominally 2.2 mg/mL of naproxen sodium and 1.2 mg/mL of pseudoephedrine hydrochloride in methanol prepared as follows. Transfer NLT 5 whole Tablets to an appropriate volumetric flask, add 70% of the final volume of methanol, and shake to disintegrate the Tablets. Sonicate for 30 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with methanol to volume. Centrifuge 10 mL of the solution for 10 min, and use the clear supernatant to prepare the *Sample solution*.

Sample solution: Nominally 0.22 mg/mL of naproxen sodium and 0.12 mg/mL of pseudoephedrine hydrochloride in methanol from the *Sample stock solution*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 257 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 10 µL
Run time: NLT 6 times the retention time of pseudoephedrine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for the naproxen and pseudoephedrine peaks
Relative standard deviation: NMT 2.0% for the naproxen and pseudoephedrine peaks

Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) and pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response of naproxen or pseudoephedrine from the *Sample solution*
r_S = peak response of naproxen or pseudoephedrine from the *Standard solution*
C_S = concentration of USP Naproxen Sodium RS or USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of naproxen sodium or pseudoephedrine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Test 1
Medium: 0.01% sodium lauryl sulfate in water, degassed; 900 mL
Apparatus 1: 75 rpm
Times
Naproxen sodium: 1 h
Pseudoephedrine hydrochloride: 1, 3, and 8 h
Buffer: Add 5 mL of triethylamine to 1 L of 0.4 g/L of sodium lauryl sulfate in water. Adjust with glacial acetic acid to a pH of 4.1.
Mobile phase: Acetonitrile, methanol, and *Buffer* (25:25:50)
Standard stock solution: 1.22 mg/mL of USP Naproxen Sodium RS and 0.66 mg/mL of USP Pseudoephedrine Hydrochloride RS in methanol
Standard solution: 0.24 mg/mL of USP Naproxen Sodium RS and 0.13 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Medium* from the *Standard stock solution*
Sample solution: At the times specified, withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size. Replace the aliquots withdrawn for analysis with equal volumes of fresh portions of *Medium* maintained at 37°.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 257 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 40 µL
Run time: NLT 2.5 times the retention time of pseudoephedrine
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times for pseudoephedrine and naproxen are 0.5 and 1.0, respectively.]
Suitability requirements
Tailing factor: NMT 2.0 for the naproxen and pseudoephedrine peaks
Relative standard deviation: NMT 2.0% for the naproxen and pseudoephedrine peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage (*Q*) of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) dissolved:

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

r_U = peak response of naproxen from the *Sample solution*
r_S = peak response of naproxen from the *Standard solution*
C_S = concentration of USP Naproxen Sodium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of naproxen sodium (mg/Tablet)

Calculate the concentration (C_i), in mg/mL, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of pseudoephedrine from the *Sample solution*
r_S = peak response of pseudoephedrine from the *Standard solution*
C_S = concentration of USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of pseudoephedrine hydrochloride in *Medium* in the portion of the sample withdrawn at each time point (i) (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of pseudoephedrine hydrochloride (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances
Naproxen sodium: NLT 80% (Q) of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) is dissolved.
Pseudoephedrine hydrochloride: See *Table 1*.

Table 1

Time Point (i)	Time (h)	Amount of Pseudoephedrine Hydrochloride Dissolved (%)
1	1	35–55
2	3	75–95
3	8	NLT 85

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.01% sodium lauryl sulfate in water; 900 mL
Apparatus 1: 75 rpm
Times
Naproxen sodium: 1 h
Pseudoephedrine hydrochloride: 1, 3, and 8 h
Solution A: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 4.0.
Solution B: Acetonitrile
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0.0	90	10
10.0	45	55
11.0	90	10
14.0	90	10

Standard solution: 0.24 mg/mL of USP Naproxen Sodium RS and 0.13 mg/mL of USP Pseudoephedrine Hydrochloride RS prepared as follows. Dissolve suitable quantities of USP Naproxen Sodium RS and USP Pseudoephedrine Hydrochloride RS with 2% of the final volume of methanol and sonicate if necessary. Dilute with *Medium* to volume.
Sample solution: At the times specified, withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm for the pseudoephedrine peak (before relative retention time of 0.5 in relation to the naproxen peak); UV 290 nm for the naproxen peak (at relative retention time of 0.5 and after relative retention time of 0.5 in relation to the naproxen peak)
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.6 mL/min
Injection volume: 30 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for the naproxen and pseudoephedrine peaks
Relative standard deviation: NMT 2.0% for the naproxen and pseudoephedrine peaks
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage (Q) of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) dissolved:

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

r_U = peak response of naproxen from the *Sample solution*
r_S = peak response of naproxen from the *Standard solution*
C_S = concentration of USP Naproxen Sodium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of naproxen sodium (mg/Tablet)

Calculate the concentration (C_i), in mg/mL, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

$$Result_i = (r_U/r_S) \times C_S$$

r_U = peak response of pseudoephedrine from the *Sample solution*
r_S = peak response of pseudoephedrine from the *Standard solution*
C_S = concentration of USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at each time point (*i*):

$$Result_1 = C_1 \times V \times (1/L) \times 100$$
$$Result_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$Result_3 = \{C_3 \times [V - (2 \times V_S)] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of pseudoephedrine hydrochloride in *Medium* in the portion of the sample withdrawn at each time point (*i*) (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of pseudoephedrine hydrochloride (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn from the vessel, 10 mL

Tolerances
Naproxen sodium: NLT 80% (*Q*) of the labeled amount of naproxen sodium ($C_{14}H_{13}NaO_3$) is dissolved.
Pseudoephedrine hydrochloride: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount of Pseudoephedrine Hydrochloride Dissolved (%)
1	1	40–65
2	3	75–100
3	8	NLT 85

The percentages of the labeled amount of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

IMPURITIES

Change to read:

• **Organic Impurities**
Naproxen sodium related impurities
Mobile phase: Acetonitrile, water, and glacial acetic acid (50:50:1)
Diluent: Acetonitrile and water (90:10)
System suitability solution: 3.1 mg/mL of USP Naproxen Sodium RS and 8 µg/mL each of USP Naproxen Related Compound K RS and USP Naproxen Related Compound L RS in *Diluent*
Standard solution: 0.006 mg/mL of USP Naproxen Sodium RS in *Diluent*
Sample solution: Nominally 3.1 mg/mL of naproxen sodium in *Diluent* prepared as follows. Transfer a suitable amount of naproxen sodium from NLT 20 finely powdered Tablets to an appropriate volumetric flask, add 70% of the final volume of *Diluent*, and sonicate for 20 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 10 µL
Run time: NLT 5.6 times the retention time of naproxen
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2 between naproxen related compound K and naproxen; NLT 2 between naproxen and naproxen related compound L, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each naproxen sodium related impurity in the portion of Tablets taken:

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

r_U = peak response of each naproxen related impurity from the *Sample solution*
r_S = peak response of naproxen from the *Standard solution*
C_S = concentration of USP Naproxen Sodium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of naproxen sodium in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 4*)

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Naproxen related compound K	0.84	1.2	0.2
Naproxen	1.00	—	—
Naproxen related compound L	1.33	6.8	0.2
Naproxen methyl ester[a]	2.23	0.95	0.2
Naproxen isopropyl ester[b]	4.61	0.83	0.2
Any unspecified impurity	—	1.0	▲0.2▲ (RB 1-Mar-2019)
Total impurities[c]	—	—	1.0

[a] Methyl 2-(6-methoxynaphthalen-2-yl)propionate.
[b] Isopropyl 2-(6-methoxynaphthalen-2-yl)propionate.
[c] Exclude pseudoephedrine related peaks before the relative retention time of 0.4.

Pseudoephedrine hydrochloride related impurities
Solution A: 5 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile and water (90:10)
Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	100	0
30	100	0
40	0	100
50	0	100
55	100	0
90	100	0

Diluent: 5 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 6.8.
System suitability solution: 0.5 mg/mL of USP Pseudoephedrine Hydrochloride RS and 1.5 µg/mL of USP Ephedrine Hydrochloride RS in *Diluent*
Standard solution: 0.001 mg/mL of USP Pseudoephedrine Hydrochloride RS in *Diluent*
Sample solution: Nominally 0.5 mg/mL of pseudoephedrine hydrochloride in *Diluent* prepared as follows. Transfer a suitable amount of pseudoephedrine hydrochloride from NLT 20 finely powdered Tablets to an appropriate volumetric flask, add 70% of the total volume of *Diluent*, and sonicate for 30 min with intermittent shaking. Allow the solution to cool to room temperature and dilute with *Diluent* to volume. Centrifuge a portion of the solution for 10 min. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between ephedrine and pseudoephedrine, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each pseudoephedrine hydrochloride related impurity in the portion of Tablets taken:

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

r_U = peak response of each pseudoephedrine hydrochloride related impurity from the *Sample solution*
r_S = peak response of pseudoephedrine from the *Standard solution*
C_S = concentration of USP Pseudoephedrine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of pseudoephedrine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 6*)

Acceptance criteria: See *Table 6*.

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Norephedrine hydrochloride[a]	0.62	1.0	0.2
Norpseudoephedrine hydrochloride[b]	0.72	1.3	0.2
Ephedrine hydrochloride	0.90	0.94	0.2
Pseudoephedrine hydrochloride	1.00	—	—
Any unspecified impurity	—	1.0	▲0.2▲ (RB 1-Mar-2019)
Total impurities[c]	—	—	1.0

[a] (1*R*,2*S*)-2-Amino-1-phenylpropan-1-ol hydrochloride.
[b] (1*S*,2*S*)-2-Amino-1-phenylpropan-1-ol hydrochloride.
[c] Exclude naproxen related peaks after a relative retention time of 1.8 and blank peaks before a relative retention time of 0.2.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in a dry place. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Ephedrine Hydrochloride RS
  (1*R*,2*S*)-2-(Methylamino)-1-phenylpropan-1-ol hydrochloride.
  $C_{10}H_{15}NO \cdot HCl$ 201.69
  USP Naproxen Sodium RS
  USP Naproxen Related Compound K RS
  1-(6-Methoxynaphthalen-2-yl)ethanol.
  $C_{13}H_{14}O_2$ 202.25
  USP Naproxen Related Compound L RS
  1-(6-Methoxynaphthalen-2-yl)ethanone.
  $C_{13}H_{12}O_2$ 200.23
  USP Pseudoephedrine Hydrochloride RS
  ▲ 2S (USP41)