Nevirapine Extended-Release Tablets

Type of Posting	Revision Bulletin
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Expert Committee	Chemical Medicines Monographs 1
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 1 Expert Committee has revised the Nevirapine Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate the FDA-approved drug product. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using a Waters Symmetry C18 brand of L1 column. The typical retention time for nevirapine is about 3 min.

The Nevirapine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Shankari Shivaprasad, Ph.D., Senior Scientific Liaison (301-230-7426 or sns@usp.org).

Nevirapine Extended-Release Tablets

DEFINITION

Nevirapine Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$).

IDENTIFICATION

- **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The retention time of the nevirapine peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Solution A: Acetonitrile and water (15:85)
Solution B: Acetonitrile and water (40:60)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
7	100	0
23	0	100
33	0	100
33.1	100	0
48	100	0

[NOTE—These gradient elution times are established on an HPLC system with a hold time of approximately 7 min based on the dwell volume of 0.7 mL. Adjust the start of the gradient to be approximately 2 min after the retention time of nevirapine and adjust the remaining gradient accordingly. The hold time (*X*) can be calculated using the formula: *X* = (11.2 mL – dwell volume)/flow rate.]

Diluent: Acetonitrile and water (30:70)
Standard solution: 0.5 mg/mL of USP Nevirapine Anhydrous RS in *Solution B*. Sonicate if necessary to dissolve, before final dilution.
Sample stock solution: Nominally 2 mg/mL of nevirapine prepared as follows. Transfer an appropriate number of Tablets to a suitable volumetric flask. Add 50% of the flask volume of acetonitrile and shake for 30 min. Add 30% of the flask volume of water and continue shaking for another 30 min. Allow it to stand for at least 1 h and dilute with water to volume. Centrifuge a portion and use the supernatant.
Sample solution: Nominally 0.5 mg/mL of nevirapine in *Diluent* from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 282 nm. For *Identification A*, use a diode array detector in the range of 210–400 nm.
Column: 3.9-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 25 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) in the portion of Tablets taken:

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

r_U = peak response of nevirapine from the *Sample solution*
r_S = peak response of nevirapine from the *Standard solution*
C_S = concentration of USP Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of nevirapine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

▲Test 1▲ (RB 1-May-2018)
Medium: 0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium dodecyl sulfate prepared as follows. Dissolve 6.0 g of monobasic sodium phosphate in 800 mL of water and adjust with a 50% sodium hydroxide solution to a pH of 6.8. Add 20 g of sodium dodecyl sulfate and dilute with water to 1000 mL; 900 mL.
Apparatus 1: 75 rpm
Times
For Tablets labeled to contain 100 mg: 1, 5, and 12 h
For Tablets labeled to contain 400 mg: 2, 8, and 20 h
Mobile phase: Acetonitrile and water (18:82)
Standard solution: (*L*/900) mg/mL of USP Nevirapine Anhydrous RS in *Medium*, where *L* is the label claim in mg/Tablet prepared as follows. Transfer a weighed quantity of USP Nevirapine Anhydrous RS to a suitable volumetric flask and add ethyl alcohol to fill 12% of the flask volume. Sonicate for 15 min or until dissolved. Allow to cool to room temperature and dilute with *Medium* to volume.
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 282 nm
Column: 3.9-mm × 15-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
Run time: About 1.6 times the retention time of nevirapine
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of nevirapine ($C_{15}H_{14}N_4O$) dissolved in the portion of the sample withdrawn at each time point (i) (mg/mL):

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

r_U = peak response of nevirapine from the *Sample solution*
r_S = peak response of nevirapine from the *Standard solution*
C_S = concentration of USP Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = \{C_3 \times [V - (2 \times V_S)] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

Tolerances

For Tablets labeled to contain 100 mg: See *Table 2*.

Table 2

Time Point	Time	Amount Dissolved (%)
1	1	4–24
2	5	53–73
3	12	NLT 80

The percentages of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

For Tablets labeled to contain 400 mg: See *Table 3*.

Table 3

Time Point	Time	Amount Dissolved (%)
1	2	NMT 30
2	8	40–70
3	20	NLT 80

The percentages of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) 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: 0.04 M sodium phosphate buffer pH 6.8 containing 2% sodium dodecyl sulfate prepared as follows. Dissolve 6.24 g of sodium dihydrogen phosphate dihydrate and 0.89 g of sodium hydroxide in 1000 mL of water. Adjust with 0.2 N hydrochloric acid or with 0.2 N sodium hydroxide solution to a pH of 6.8. Add 20 g of sodium dodecyl sulfate and sonicate for about 30 min to dissolve; 900 mL.

Apparatus 1: 75 rpm

Times

For Tablets labeled to contain 100 mg: 1, 4, and 8 h

For Tablets labeled to contain 400 mg: 1, 6, and 20 h

Solution A: 0.2% (v/v) of triethylamine in water. Adjust with phosphoric acid to a pH of 5.0.

Mobile phase: Acetonitrile and *Solution A* (30:70)

Standard stock solution: 0.9 mg/mL of USP Nevirapine Anhydrous RS in methanol prepared as follows. Transfer a weighed quantity of USP Nevirapine Anhydrous RS to a suitable volumetric flask, add methanol to fill 60% of the flask volume, and sonicate to dissolve. Dilute with methanol to volume.

Standard solution: 0.036 mg/mL of USP Nevirapine Anhydrous RS in *Medium* from *Standard stock solution*. Pass through a suitable filter of 0.45-µm pore size.

Sample solution: Dilute a filtered portion of the solution under test with *Medium* to a concentration similar to that of the *Standard solution*.

Chromatographic system

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

Mode: LC

Detector: UV 285 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 25°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of nevirapine ($C_{15}H_{14}N_4O$) dissolved in the portion of the sample withdrawn at each time point (i) (mg/mL):

$$C_i = (r_U/r_S) \times C_S \times D$$

r_U = peak response of nevirapine from the *Sample solution*
r_S = peak response of nevirapine from the *Standard solution*
C_S = concentration of USP Nevirapine Anhydrous RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*

Calculate the percentage of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) 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 nevirapine in the portion of sample withdrawn at the time point (i)
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances

For Tablets labeled to contain 100 mg: See *Table 4*.

Table 4

Time Point	Time	Amount Dissolved (%)
1	1	NMT 20
2	4	43–63
3	8	NLT 80

The percentages of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

For Tablets labeled to contain 400 mg: See *Table 5*.

Table 5

Time Point	Time	Amount Dissolved (%)
1	1	NMT 15
2	6	33–53
3	20	NLT 85

The percentages of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-May-2018)

• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirement

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**

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

System suitability solution: 0.5 mg/mL of USP Nevirapine Anhydrous RS and 0.005 mg/mL of USP Nevirapine Related Compound A RS in *Solution B*. Sonicate if necessary to dissolve, before final dilution.

Standard stock solution: Use the *Standard solution* from the *Assay*.

Standard solution: 0.0005 mg/mL of USP Nevirapine Anhydrous RS in *Solution B* from the *Standard stock solution*

System suitability

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

Suitability requirements

Resolution: NLT 4.0 between the nevirapine and nevirapine related compound A peaks, *System suitability solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of any individual impurity in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: See *Table* ▲*6*.▲ (RB 1-May-2018)

Disregard any impurity peak less than 0.1%.

Table ▲**6**▲ (RB 1-May-2018)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Nevirapine related compound B[a, b]	0.64	—
Nevirapine	1.00	—
Nevirapine related compound A[b]	1.34	—
Nevirapine related compound C[b, c]	1.73	—
Any individual unspecified impurity	—	0.2
Total impurities	—	0.4

[a] 5,11-Dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one.
[b] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.
[c] 5,11-Dihydro-6*H*-11-propyl-4-methyl-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one.

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

▲• **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-May-2018)

• **USP REFERENCE STANDARDS ⟨11⟩**

USP Nevirapine Anhydrous RS

USP Nevirapine Related Compound A RS

5,11-Dihydro-6*H*-11-ethyl-4-methyl-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one.

$C_{14}H_{14}N_4O$ 254.29