Nicardipine Hydrochloride Injection

Type of Posting	Notice of Intent to Revise
Posting Date	26–Oct–2018
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Nicardipine Hydrochloride Injection monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to widen the acceptance criteria of the nicardipine pyridine analog in the *Organic Impurities* test from NMT 0.9% to NMT 2.5%.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Donald Min**,** Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Nicardipine Hydrochloride Injection

DEFINITION

Nicardipine Hydrochloride Injection is a sterile solution of Nicardipine Hydrochloride. It contains NTL 90.0% and NMT 110.0% each of the labeled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$) and sorbitol.

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**

Buffer: 1.36 g/L of potassium dihydrogen phosphate in water

Mobile phase: Methanol and *Buffer* (800:200)

Diluent: Acetonitrile and *Buffer* (50:50)

Standard solution: 0.1 mg/mL of USP Nicardipine Hydrochloride RS in *Diluent*. Sonication may be used to aid in dissolution. Pass through a suitable filter of 0.45-µm pore size. Discard the first 2–3 mL of filtrate.

Sample solution: Nominally equivalent to 0.1 mg/mL of nicardipine hydrochloride in *Diluent* from a suitable volume of Injection. Pass through a suitable filter of 0.45-µm pore size. Discard the first 2–3 mL of filtrate. [NOTE—*Sample solution* is stable for about 26 h.]

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 2 times the retention time of nicardipine

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 nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$) in the portion of Injection taken:

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

r_U = peak area of nicardipine from the *Sample solution*
r_S = peak area of nicardipine from the *Standard solution*
C_S = concentration of USP Nicardipine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **LIMIT OF *N*-BENZYL-*N*-METHYL-ETHANOLAMINE**

Solution A: Dissolve 2.80 g of sodium perchlorate monohydrate in 1 L of water. Adjust with perchloric acid to a pH of 2.5.

Solution B: Acetonitrile and methanol (500:500)

Diluent: Acetonitrile and water (20:80)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
10	82	18
12	20	80
22	20	80
24	95	5
32	95	5

Standard solution: 2.5 µg/mL of USP *N*-Benzyl-*N*-methyl-ethanolamine RS in *Diluent* prepared as follows. To a suitable amount of USP *N*-Benzyl-*N*-methyl-ethanolamine RS, add *Diluent* to 70% of the final volume. Sonicate to dissolve. Cool, and dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally equivalent to 0.5 mg/mL of nicardipine hydrochloride in *Diluent* from a suitable volume of Injection. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 205 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Temperatures
Column: 30°
Sample: 10°
Injection volume: 50 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 5.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of *N*-benzyl-*N*-methyl-ethanolamine in the portion of Injection taken:

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

r_U = peak response of *N*-benzyl-*N*-methyl-ethanolamine in the *Sample solution*
r_S = peak response of *N*-benzyl-*N*-methyl-ethanolamine in the *Standard solution*
C_S = concentration of USP *N*-Benzyl-*N*-methyl-ethanolamine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.7%

Change to read:

• **ORGANIC IMPURITIES**

Solution A: 3.5 g/L of sodium perchlorate monohydrate in water. Add 1 mL/L of triethylamine, and adjust with perchloric acid to a pH of 2.0.

Solution B: Acetonitrile and methanol (700:300)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	70	30
15	70	30
55	35	65
60	35	65
62	70	30
70	70	30

Standard solution: 0.02 mg/mL of USP Nicardipine Hydrochloride RS in methanol prepared as follows. To a suitable amount of USP Nicardipine Hydrochloride RS add methanol to 60% of the final volume. Sonicate to dissolve. Cool, and dilute with methanol to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally equivalent to 2 mg/mL of nicardipine hydrochloride in methanol from a suitable volume of Injection. Pass the solution through a suitable filter of 0.45-µm pore size. [NOTE—*Sample solution* is stable for about 42 h at 10°.]

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 239 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Temperatures
Column: 50°
Sample: 10°
Injection volume: 10 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 5.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Injection taken:

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

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of nicardipine from the *Standard solution*
C_S = concentration of nicardipine hydrochloride in the *Standard solution* (mg/mL)
C_U = nominal concentration of nicardipine hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Nicardipine monoacid[a]	0.72	1.00	0.2
Nicardipinepyridine analog[b]	0.94	0.42	▲2.5▲ (TBD)
Nicardipine	1.00	1.00	—
Any unspecified degradation impurity	—	—	0.2
Total impurities[c]	—	—	3.5

[a] 5-(Methoxycarbonyl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid.
[b] 3-{2-[Benzyl(methyl)amino]ethyl} 5-methyl 2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylate.
[c] Total impurities include the sum of all organic impurities and *N*-benzyl-*N*-methyl-ethanolamine.

OTHER COMPONENTS

- **CONTENT OF SORBITOL**

Buffer: 1 g/L of tetrabutylammonium hydrogen sulfate in water
Mobile phase: Acetonitrile and *Buffer* (700:300)
Standard solution: 4.8 mg/mL of USP Sorbitol RS in *Mobile phase*. Pass the solution through a suitable filter of 0.45-µm pore size. Sonication may be necessary to aid in dissolution.
Sample solution: Nominally equivalent to 4.8 mg/mL of sorbitol in *Mobile phase* from the contents of NLT 3 injection vials. Pass the solution through a suitable filter of 0.45-µm pore size. [NOTE—*Sample solution* is stable for about 24 h.]

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: Refractive index
Column: 4.6-mm × 25-cm; 5-µm packing L8
Flow rate: 1 mL/min
Temperatures
Column: 40°
Detector: 50°
Injection volume: 25 µL
Run time: NLT 2 times the retention time of sorbitol

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 sorbitol in the portion of Injection taken:

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

r_U = peak response of sorbitol from the *Sample solution*
r_S = peak response of sorbitol from the *Standard solution*
C_S = concentration of sorbitol in the *Standard solution* (mg/mL)
C_U = nominal concentration of sorbitol in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

SPECIFIC TESTS

- **BACTERIAL ENDOTOXINS TEST** ⟨85⟩**:** NMT 8.33 USP Endotoxin Units/mg of nicardipine hydrochloride
- **STERILITY TESTS** ⟨71⟩**:** Meets the requirements
- **PH** ⟨791⟩**:** 3.0–3.9
- **PARTICULATE MATTER IN INJECTIONS** ⟨788⟩**:** Meets the requirements for small-volume injections
- **OTHER REQUIREMENTS:** Meets the requirements for *Injections and Implanted Drug Products* ⟨1⟩

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in single-dose amber glass vials.
- **LABELING:** Label it to indicate that it is to be diluted to the appropriate strength with a suitable intravenous fluid prior to administration.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩

USP *N*-Benzyl-*N*-methyl-ethanolamine RS
2-[Benzyl(methyl)amino]ethanol.
$C_{10}H_{15}NO$ 165.23

▲▲ (CN 1-May-2018)
USP Nicardipine Hydrochloride RS
USP Sorbitol RS
D-Glucitol;
(2*S*,3*R*,4*R*,5*R*)-Hexane-1,2,3,4,5,6-hexol.
$C_6H_{14}O_6$ 182.17