Nicardipine Hydrochloride Injection

Type of Posting	Notice of Intent to Revise
Posting Date	28-Apr-2023
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 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 revise the Nicardipine Hydrochloride Injection monograph to widen the *pH* test upper limit from “3.0–3.9” to “3.0–4.2”, add flexibility for the Sorbitol requirement in the *Definition*, and add “if present” to the *Content of Sorbitol* test to allow flexibility and to accommodate FDA-approved drug products with different formulation using different excipients.

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 V. Durga Prasad, Scientific Liaison (+91-40-4448-8723 or durgaprasad.v@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*.

Notice of Intent to Revise
Official: To Be Determined

Nicardipine Hydrochloride Injection

Change to read:

DEFINITION

Nicardipine Hydrochloride Injection is a sterile solution of Nicardipine Hydrochloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of nicardipine hydrochloride ($C_{26}H_{29}N_3O_6 \cdot HCl$). ▲If it contains sorbitol, NLT 90.0% and NMT 110.0% of the labeled amount of sorbitol ($C_6H_{14}O_6$) is present.▲ (TBD)

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*.

● **B.** The UV spectrum 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 monobasic potassium phosphate in *water*

Mobile phase: Methanol and *Buffer* (80:20)

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 the filtrate.

Sample solution: Nominally 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—The *Sample solution* is stable for about 26 h.]

Chromatographic system

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

Mode: LC

Detector: UV 254 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

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 response of nicardipine from the *Sample solution*

r_S = peak response 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 (50:50)

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 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

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1.5 mL/min

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 from the *Sample solution*

r_S = peak response of *N*-benzyl-*N*-methyl-ethanolamine from 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%

- **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 (70:30)

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.

Sensitivity solution: 0.002 mg/mL of USP Nicardipine Hydrochloride RS in methanol from *Standard solution*

Sample solution: Nominally 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—The *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

Temperatures

Autosampler: 10°

Column: 50°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified impurity and any unspecified degradation product 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 specified impurity or any unspecified degradation product from the *Sample solution*

r_S = peak response 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)

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 (nicardipine related compound A)[a]	0.72	1.00	0.2
Nicardipine pyridine analog (nicardipine related compound B)[b]	0.94	0.42	2.5
Nicardipine	1.00	1.00	—
Any unspecified degradation product	—	—	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

Change to read:

- **Content of Sorbitol** ▲(if present)▲ (TBD)

Buffer: 1 g/L of tetrabutylammonium hydrogen sulfate in water

Mobile phase: Acetonitrile and *Buffer* (70:30)

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 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

Temperatures

Column: 40°

Detector: 50°

Flow rate: 1 mL/min

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 ($C_6H_{14}O_6$) 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 USP Sorbitol RS 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⟩**:** Meets the requirements
- **Sterility Tests** ⟨71⟩**:** Meets the requirements

Change to read:

- **pH** ⟨791⟩**:** 3.0–▲4.2▲ (TBD)
- **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. Store at controlled room temperature.
- **Labeling:** Label it to indicate that it is to be diluted to the appropriate strength with a suitable intravenous fluid prior to administration.
- **USP Reference Standards** ⟨11⟩

USP *N*-Benzyl-*N*-methyl-ethanolamine RS

2-[Benzyl(methyl)amino]ethanol.

$C_{10}H_{15}NO$ 165.23

USP Nicardipine Hydrochloride RS

USP Sorbitol RS

D-Glucitol.

$C_6H_{14}O_6$ 182.17

Page Information:

Not Applicable

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