Nicardipine Hydrochloride Injection

Type of Posting: Notice of Intent to Revise
Posting Date: 23-Feb-2024
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 impurity limit for "N-Benzyl-N-methyl-ethanolamine" from NMT 0.7% to NMT 2.0%.

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, Senior Scientist II (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.
Nicardipine Hydrochloride Injection

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 \(\text{C}_{26}\text{H}_{29}\text{N}_{3}\text{O}_{6} \cdot \text{HCl}\).

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.
  \[\text{Note—The Sample solution is stable for about 26 h.}\]

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 \(\text{C}_{26}\text{H}_{29}\text{N}_{3}\text{O}_{6} \cdot \text{HCl}\) in the portion of Injection taken:
Result = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100

- \quad r_U = \text{peak response of nicardipine from the Sample solution}
- \quad r_S = \text{peak response of nicardipine from the Standard solution}
- \quad C_S = \text{concentration of USP Nicardipine Hydrochloride RS in the Standard solution (mg/mL)}
- \quad C_U = \text{nominal concentration of nicardipine hydrochloride in the Sample solution (mg/mL)}

Acceptance criteria: 90.0%–110.0%

IMPURITIES

Change to read:

- **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>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>22</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>32</td>
</tr>
</tbody>
</table>

- **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:

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

- \(r_U\) = 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 2.0%▲(TBD)

- **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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>15</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>55</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>60</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>62</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>70</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

**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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \(r_U\) = 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**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine monoacid (nicardipine related compound A)(^a)</td>
<td>0.72</td>
<td>1.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
<td>Relative Response Factor</td>
<td>Acceptance Criteria, NMT (%)</td>
</tr>
<tr>
<td>---------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Nicardipine pyridine analog (nicardipine related compound B) b</td>
<td>0.94</td>
<td>0.42</td>
<td>2.5</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>1.00</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities c</td>
<td>—</td>
<td>—</td>
<td>3.5</td>
</tr>
</tbody>
</table>

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** (if present)

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 (C₆H₁₄O₆) in the portion of Injection taken:

\[
\text{Result} = \left( \frac{r_f}{r_s} \right) \times \left( \frac{C_s}{C_U} \right) \times 100
\]
\[ r_U = \text{peak response of sorbitol from the Sample solution} \]
\[ r_S = \text{peak response of sorbitol from the Standard solution} \]
\[ C_S = \text{concentration of USP Sorbitol RS in the Standard solution (mg/mL)} \]
\[ C_U = \text{nominal concentration of sorbitol in the Sample solution (mg/mL)} \]

\textbf{Acceptance criteria:} 90.0\%–110.0\%

\section*{SPECIFIC TESTS}
\begin{itemize}
  \item \textbf{Bacterial Endotoxins Test} (85): Meets the requirements
  \item \textbf{Sterility Tests} (71): Meets the requirements
  \item \textbf{pH} (791): 3.0–4.2
  \item \textbf{Particulate Matter in Injections} (788): Meets the requirements for small-volume injections
  \item \textbf{Other Requirements:} Meets the requirements for \textit{Injections and Implanted Drug Products} (1).
\end{itemize}

\section*{ADDITIONAL REQUIREMENTS}
\begin{itemize}
  \item \textbf{Packaging and Storage:} Preserve in single-dose amber glass vials. Store at controlled room temperature.
  \item \textbf{Labeling:} Label it to indicate that it is to be diluted to the appropriate strength with a suitable intravenous fluid prior to administration.
  \item \textbf{USP Reference Standards} (11)
    \begin{itemize}
      \item \textbf{USP N-Benzyl-N-methyl-ethanolamine RS}
        \begin{itemize}
          \item \( \text{C}_{10}\text{H}_{15}\text{NO} \quad 165.23 \)
        \end{itemize}
      \item \textbf{USP Nicardipine Hydrochloride RS}
      \item \textbf{USP Sorbitol RS}
        \begin{itemize}
          \item \( \text{d-Glucitol}. \quad \text{C}_{6}\text{H}_{14}\text{O}_{6} \quad 182.17 \)
        \end{itemize}
    \end{itemize}
\end{itemize}

\textbf{Page Information:}
Not Applicable

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