Guanfacine Extended-Release Tablets

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Revision Bulletin

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1-Jun-2022

**Expert Committee**  
Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Guanfacine Extended-Release Tablets monograph. The purpose of this revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*. The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

- *Dissolution Test 2* was validated using the Zorbax SB-C8 brand of column with L7 packing. The typical retention time for guanfacine is about 4 min.

The Guanfacine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Robyn Fales, Senior Scientist I (240-221-2047 or rnp@usp.org).
Guanfacine Extended-Release Tablets

**DEFINITION**
Guanfacine Extended-Release Tablets contain an amount of guanfacine hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of guanfacine (C9H9Cl2N3O).

**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:** 20 mM sodium bicarbonate and 10 mM tetrabutylammonium phosphate prepared as follows. For each liter, dissolve 1.68 g of sodium bicarbonate and 3.39 g of tetrabutylammonium phosphate in 970 mL of water. Adjust with 5 N sodium hydroxide to a pH of 10.0. Dilute with water to volume.
  - **Mobile phase:** Acetonitrile and Buffer (17:83)
  - **Standard solution:** 0.023 mg/mL of USP Guanfacine Hydrochloride RS in Mobile phase
  - **Sample solution:** Nominally 0.02 mg/mL of guanfacine prepared as follows. Transfer a portion of coarsely powdered Tablets (NLT 20) to an appropriate volumetric flask as directed in Table 1. Add 50% of the flask volume of Mobile phase, sonicate for 10 min, and shake mechanically for 1 h. [Note—The sonicator should be kept cold with ice to maintain a temperature below 25°.] Repeat the steps of the sonication/shaking sequence two additional times with an additional sonication of 10 min at the end. [Note—An additional 1 h of shaking and 10 min of sonication may be needed if the sample is not fully dissolved.] Dilute with Mobile phase to volume. Centrifuge a portion of this solution for 10 min and use the supernatant. [Note—The use of a centrifuge speed of NLT 2500 rpm may be suitable.]

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Quantity Equivalent to Guanfacine To Be Transferred (mg)</th>
<th>Volumetric Flask Size (mL)</th>
<th>Nominal Concentration of Guanfacine (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>50</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>100</td>
<td>0.02</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>200</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>200</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Chromatographic system
(See Chromatography (621), System Suitability.)

**Mode:** LC  
**Detector:** UV 220 nm. For Identification B, use a diode array detector in the range of 200–400 nm.  
**Column:** 4.6-mm × 15-cm; 5-µm packing L1  
**Temperatures**  
  - **Autosampler:** 4°  
  - **Column:** 27°  
**Flow rate:** 1 mL/min  
**Injection volume:** 100 µL  
**Run time:** NLT 1.8 times the retention time of guanfacine

**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 guanfacine (C9H9Cl2N3O) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

- \( r_U \) = peak response of guanfacine from the Sample solution  
- \( r_S \) = peak response of guanfacine from the Standard solution  
- \( C_S \) = concentration of USP Guanfacine Hydrochloride RS in the Standard solution (mg/mL)  
- \( C_U \) = nominal concentration of guanfacine in the Sample solution (mg/mL)  
- \( M_{r1} \) = molecular weight of guanfacine, 246.09  
- \( M_{r2} \) = molecular weight of guanfacine hydrochloride, 282.55

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution** (711)

  **Test 1** \(^{\uparrow}\) (RB 1-Jun-2022)  
  **Medium:** Hydrochloric acid buffer, pH 2.2; 900 mL prepared as follows. For each liter, mix 250 mL of 0.2 M potassium chloride with 39 mL of 0.2 N hydrochloric acid. Dilute with water to volume.  
  **Apparatus 2:** 75 rpm with suitable sinkers  
  **Times:** 1, 4, 8, and 20 h  
  **Buffer:** 20 mM sodium bicarbonate, prepared as follows. For each liter, dissolve 1.68 g of sodium bicarbonate in 970 mL of water, and adjust with 5 N sodium hydroxide to a pH of 10.0. Dilute with water to volume.  
  **Mobile phase:** Acetonitrile and Buffer (25:75)  
  **Standard stock solution:** 0.23 mg/mL of USP Guanfacine Hydrochloride RS in Mobile phase
**Standard solution:** 0.0023 mg/mL of USP Guanfacine Hydrochloride RS in Medium from Standard stock solution

**Sample solution:** Pass a portion of the solution under test through a suitable filter at the time points specified.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

**Mode:** LC
**Detector:** UV 220 nm
**Column:** 4.6-mm × 15-cm; 5-µm packing L1
**Flow rate:** 1.2 mL/min
**Injection volume:** 20 µL
**Run time:** NLT 1.4 times the retention time of guanfacine

**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 of guanfacine (C₉H₉Cl₂N₃O) in the sample withdrawn from the vessel at each time point (i):

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times \left( \frac{M_{r1}}{M_{r2}} \right)
\]

- \(r_U\) = peak response of guanfacine from the Sample solution
- \(r_S\) = peak response of guanfacine from the Standard solution
- \(C_S\) = concentration of USP Guanfacine Hydrochloride RS in the Standard solution (mg/mL)
- \(M_{r1}\) = molecular weight of guanfacine, 246.09
- \(M_{r2}\) = molecular weight of guanfacine hydrochloride, 282.55

Calculate the percentage of the labeled amount of guanfacine (C₉H₉Cl₂N₃O) dissolved at each time point (i):

\[
\text{Result}_1 = C_I \times V \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_2 = \left\{ \left[ C_2 \times (V - V_S) \right] + (C_I \times V_S) \right\} \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_3 = \left\{ \left[ C_3 \times (V - (2 \times V_S)) \right] \right\} + \left[ \left[ C_2 + C_I \times V_S \right] \right] \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_4 = \left\{ \left[ C_4 \times (V - (3 \times V_S)) \right] \right\} + \left[ \left[ C_3 + C_2 + C_I \times V_S \right] \right] \times \left( \frac{1}{L} \right) \times 100
\]

- \(C_I\) = concentration of guanfacine in the portion of the sample withdrawn at the specified time point (i) (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Tablet)
- \(V_S\) = volume of the Sample solution withdrawn at each time point (i) (mL)

**Tolerances:** See Table 2.
Table 2

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>13–33</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>37–57</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>57–77</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of guanfacine \((C_9H_9Cl_2N_3O)\) 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:** Hydrochloric acid buffer, pH 2.2 \((3.73 \text{ g/L of potassium chloride in water})\). Adjust with hydrochloric acid to a pH of 2.2.; 900 mL, deaerated

**Apparatus 2:** 75 rpm with wire helix sinker

**Times:** 1, 4, 9, and 15 h

**Solution A:** 1 g/L of sodium dodecyl sulfate and 0.1% of phosphoric acid in water prepared as follows. Dissolve 1 g of sodium dodecyl sulfate in 1000 mL of water. Add 1 mL of phosphoric acid to the resulting solution.

**Mobile phase:** Acetonitrile and Solution A (50:50)

**Standard stock solution:** 0.2525 mg/mL of USP Guanfacine Hydrochloride RS in methanol

**Standard solution:** \((L/900 \times 1.15)\) mg/mL of USP Guanfacine Hydrochloride RS prepared by diluting Standard stock solution with Medium, where \(L\) is the label claim in mg/Tablet.

**Sample solution:** At the times specified, withdraw a known volume of the solution under test. Pass through a suitable filter.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm × 15-cm; 5 μm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** 50 μL

**Run time:** NLT 1.5 times the retention time of guanfacine

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Tailing factor:** NMT 1.5

**Relative standard deviation:** NMT 2.0%

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

Calculate the concentration of guanfacine (C₉H₉Cl₂N₃O) in the sample withdrawn from the vessel at each time point (i):

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times \left( \frac{M_{r1}}{M_{r2}} \right)
\]

- \(r_U\) = peak response of guanfacine from the Sample solution
- \(r_S\) = peak response of guanfacine from the Standard solution
- \(C_S\) = concentration of USP Guanfacine Hydrochloride RS in the Standard solution (mg/mL)
- \(M_{r1}\) = molecular weight of guanfacine, 246.09
- \(M_{r2}\) = molecular weight of guanfacine hydrochloride, 282.55

Calculate the percentage of the labeled amount of guanfacine (C₉H₉Cl₂N₃O) dissolved at each time point (i):

\[
\text{Result}_1 = C_1 \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = \left\{ [C_2 \times (V - V_S)] + (C_1 \times V_S) \right\} \times (1/L) \times 100
\]

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

\[
\text{Result}_4 = \left\{ [C_4 \times (V - (3 \times V_S))] + [(C_3 + C_2 + C_1) \times V_S] \right\} \times (1/L) \times 100
\]

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

**Tolerances:** See *Table 3* and *Table 4*.

### Table 3. For Tablets Labeled to Contain 1 mg

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>70–90</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

### Table 4. For Tablets Labeled to Contain 2, 3, and 4 mg

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 25</td>
</tr>
<tr>
<td>Time Point ((i))</td>
<td>Time ((h))</td>
<td>Amount Dissolved ((%))</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>------------------</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>35–55</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>60–80</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of guanfacine \((C_{9}H_{9}Cl_{2}N_{3}O)\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2•▲ (RB 1-Jun-2022)

**Uniformity of Dosage Units** (905): Meet the requirements

**Impurities**

*Change to read:*

**Organic Impurities**

Buffer, Mobile phase, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

**Standard solution 1:** Prepare as directed for the Standard solution in the Assay.

**Standard solution 2:** 0.023 mg/mL of 2,6-dichlorophenylacetic acid in Mobile phase

**System suitability solution:** 0.046 µg/mL each of USP Guanfacine Hydrochloride RS and 2,6-dichlorophenylacetic acid in Mobile phase from Standard solution 1 and Standard solution 2

**System suitability**

**Samples:** Standard solution 1 and System suitability solution

[NOTE—See ▲Table 5▲ (RB 1-Jun-2022) for the relative retention times.]

**Suitability requirements**

Resolution: NLT 4.0 between 2,6-dichlorophenylacetic acid and guanfacine, System suitability solution

Relative standard deviation: NMT 2.0%, Standard solution 1

**Analysis**

**Samples:** Standard solution 1 and Sample solution

Calculate the percentage of 2,6-dichlorophenylacetic acid or any unspecified degradation product in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{F} \right) \times 100
\]

\[
r_U = \text{peak response of 2,6-dichlorophenylacetic acid or any unspecified degradation product from the Sample solution}
\]

\[
r_S = \text{peak response of guanfacine from Standard solution 1}
\]

\[
C_S = \text{concentration of USP Guanfacine Hydrochloride RS in Standard solution 1 (mg/mL)}
\]

\[
C_U = \text{nominal concentration of guanfacine in the Sample solution (mg/mL)}
\]

\[
M_{r1} = \text{molecular weight of guanfacine, 246.09}
\]

\[
M_{r2} = \text{molecular weight of guanfacine hydrochloride, 282.55}
\]

\[
F = \text{relative response factor (see ▲Table 5▲ (RB 1-Jun-2022))}
\]

**Acceptance criteria:** See ▲Table 5▲.
**Table 5**

<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>2,6-Dichlorophenylacetic acid</td>
<td>0.6</td>
<td>0.65</td>
<td>1.0</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight containers and store at controlled room temperature.

*Add the following:*

- **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

- **USP Reference Standards (11).**
  - USP Guanfacine Hydrochloride RS

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**Page Information:**

Not Applicable

**Current DocID:**

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