Guanfacine Extended-Release Tablets

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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).

Revision Bulletin
Official: June 1, 2022

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 ($C_9H_9Cl_2N_3O$).

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 1

Tablet Strength (mg)	Quantity Equivalent to Guanfacine To Be Transferred (mg)	Volumetric Flask Size (mL)	Nominal Concentration of Guanfacine (mg/mL)
1	1	50	0.02
2	2	100	0.02
3	4	200	0.02
4	4	200	0.02

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 ($C_9H_9Cl_2N_3O$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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▲ (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 ($C_9H_9Cl_2N_3O$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

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 ($C_9H_9Cl_2N_3O$) dissolved at each time point (*i*):

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

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

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

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

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 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	13–33
2	4	37–57
3	8	57–77
4	20	NLT 80

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 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 × 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 ($C_9H_9Cl_2N_3O$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result} = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

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 ($C_9H_9Cl_2N_3O$) dissolved at each time point (*i*):

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

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C1) \times V_S]) \times (1/L) \times 100$$

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

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

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 30
2	4	40–60
3	9	70–90
4	15	NLT 85

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

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 25

Time Point (*i*)	Time (h)	Amount Dissolved (%)
2	4	35–55
3	9	60–80
4	15	NLT 80

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*. ▲ (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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of 2,6-dichlorophenylacetic acid or any unspecified degradation product from the *Sample solution*

r_S = peak response of guanfacine from *Standard solution 1*

C_S = concentration of USP Guanfacine Hydrochloride RS in *Standard solution 1* (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

F = relative response factor (see ▲*Table 5*▲ (RB 1-Jun-2022))

Acceptance criteria: See ▲*Table 5*.

Table 5 ▲ (RB 1-Jun-2022)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
2,6-Dichlorophenylacetic acid	0.6	0.65	1.0
Guanfacine	1.0	—	—
Any unspecified degradation product	—	1.0	0.5
Total degradation products	—	—	1.5

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.▲ (RB 1-Jun-2022)

- **USP Reference Standards** ⟨11⟩

  USP Guanfacine Hydrochloride RS

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