Quetiapine Extended-Release Tablets

Type of Posting               Revision Bulletin
Posting Date                 27–Oct–2017
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Expert Committee             Chemical Medicines Monographs 4
Reason for Revision          Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Quetiapine Extended-Release Tablets monograph. The purpose for the revision is to:

- Add Dissolution Test 2, Test 3, and Test 4 to accommodate drug products which were approved by the FDA with different dissolution conditions and acceptance criteria. Add a Labeling section for the new tests.
- Revise the calculations in Dissolution Test 1 to reflect that the volume of Medium is kept constant throughout the test.
- Revise the definition of Ci in Dissolution Test 1.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Quetiapine Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement to USP 41–NF 36.

Should you have any questions, please contact K. Kalyana Seela, Ph.D., Senior Scientific Liaison (kks@usp.org).
Quetiapine Extended-Release Tablets

DEFINITION
Quetiapine Extended-Release Tablets contain quetiapine fumarate \([\text{C}_{21}\text{H}_{25}\text{N}_{3}\text{O}_{2}\text{S}]_2 \cdot \text{C}_4\text{H}_4\text{O}_4\) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of quetiapine \([\text{C}_{21}\text{H}_{25}\text{N}_{3}\text{O}_{2}\text{S}]\).

IDENTIFICATION

A. INFRARED ABSORPTION

B. • (197F)

Standard solution: Transfer 10 mg of USP Quetiapine Fumarate RS to a suitable vial. Add 10 mL of acetone and cap the vial. Sonicate for about 10 min. Allow the solution to equilibrate to room temperature. Evaporate the acetone completely. Add 2 mL of chloroform. Gently swirl for several minutes. Pass through a suitable filter of 0.45-µm pore size. Use the filtrate.

Sample solution: Grind NLT 10 Tablets. Transfer an amount of powder equivalent to NLT 10 mg of quetiapine fumarate to a suitable vial. Add 10 mL of acetone and cap the vial. Sonicate for about 10 min. Allow the solution to equilibrate to room temperature. Evaporate the acetone completely. Add 2 mL of chloroform. Gently swirl for several minutes. Pass through a suitable filter of 0.45-µm pore size. Use the filtrate.

Acceptance criteria:Meet the requirements

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

ASSAY

A. PROCEDURE

Buffer: Dissolve 2.6 g/L of dibasic ammonium phosphate in water.

Mobile phase: Methanol, acetonitrile, and Buffer (54:7:39)

Diluent: Acetonitrile and water (50:50)

System suitability stock solution: 0.05 mg/mL of USP Quetiapine Related Compound H RS in Mobile phase

System suitability solution: 0.005 mg/mL of USP Quetiapine Related Compound H RS and 0.5 mg/mL of USP Quetiapine System Suitability RS in Mobile phase prepared as follows. Transfer 5 mg of USP Quetiapine System Suitability RS to a 10-mL volumetric flask. Add 7 mL of Mobile phase and sonicate to dissolve. Transfer 1 mL of System suitability stock solution to the volumetric flask. Dilute with Mobile phase to volume.

Standard solution: 0.2 mg/mL of USP Quetiapine Fumarate RS in Mobile phase

Sample stock solution: Transfer NLT 5 Tablets to a homogenizer vessel. Add 50 mL of acetonitrile, swirl to wet, and allow to stand for approximately 10 min. Add an additional 160 mL of Diluent and extract for about 10 min. Transfer the contents of the homogenizer to a 500-mL volumetric flask. Dilute with Diluent to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size and use the filtrate.

Sample solution: Nominally 0.16–0.18 mg/mL of quetiapine from the Sample stock solution in Mobile phase

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.3 mL/min

Injection volume: 30 µL

Run time: NLT 2.5 times the retention time of quetiapine

System suitability

Samples: System suitability solution and Standard solution

[NOTE—See Table 5 for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between quetiapine related compound G and quetiapine related compound H; NLT 2.0 between the quetiapine desthoxy and quetiapine peaks; System suitability solution

Tailing factor: NMT 1.5; Standard solution

Relative standard deviation: NMT 2.0%; Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of quetiapine \([\text{C}_{21}\text{H}_{25}\text{N}_{3}\text{O}_{2}\text{S}]\) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_0}{r_S} \right) \times \left( \frac{C_S}{C_0} \right) \times \left( \frac{M_{12}}{M_{11}} \right) \times N \times 100 \]

where:

\[ r_0 = \text{peak response from the Sample solution} \]

\[ r_S = \text{peak response from the Standard solution} \]

\[ C_S = \text{concentration of USP Quetiapine Fumarate RS in the Standard solution (mg/mL)} \]

\[ C_0 = \text{nominal concentration of quetiapine in the Sample solution (mg/mL)} \]

\[ M_{11} = \text{molecular weight of quetiapine free base, 383.51} \]

\[ M_{12} = \text{molecular weight of quetiapine fumarate, 883.09} \]

\[ N = \text{number of moles of quetiapine free base per mole of quetiapine fumarate, 2} \]

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

Dissolution (711)

Test 1. (88.1-Nov-2017)

Medium 1: Citrate buffer, pH 4.8. Dissolve 9.6 g of anhydrous citric acid in 600 mL of water. Add 90 mL of 1 N sodium hydroxide. Dilute with water to 1 L; 900 mL

Medium 2: Dissolve 17.9 g of dibasic sodium phosphate dodecahydrate in 400 mL of water. Add 460 mL of 1 N sodium hydroxide and dilute with water to 1 L; 100 mL

[NOTE—It is recommended to check the pH of the mixture of 90 mL of Medium 1 and 10 mL of Medium 2, which should be between 6.4 and 6.8. If the pH of the mixture is less than 6.4, 10 mL/L of 1 N sodium hydroxide may be added to Medium 2. If the pH of the mixture is greater than 6.8, 10 mL/L of 1 N hydrochloric acid may be added to Medium 2.]

Start the test with 900 mL of Medium 1. Add 100 mL of Medium 2 to the vessel after 5 h of the test and continue the test.

Apparatus 1: 200 rpm

Times: 1, 6, 12, and 20 h

Diluent: Medium 1 and Medium 2 (90:10)

Standard solution: (L/1000) mg/mL of USP Quetiapine Fumarate RS in Diluent, where L is the label claim in mg/Tablet

Sample solution: Pass a suitable portion of the solution under test through a suitable filter.
Quetiapine

Instrumental conditions
Mode: UV
Analytical wavelength: About 290 nm
Blank: Diluent

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration, \( C_i \), of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) in Medium (mg/mL) after each time point (\( t \)):

\[
C_i = \left( \frac{A_i}{A_1} \right) \times \left( \frac{M_1}{M_2} \right) \times N
\]

\( A_i \) = absorbance of the Sample solution
\( A_1 \) = absorbance of the Standard solution
\( M_1 \) = molecular weight of quetiapine free base, 383.51
\( M_2 \) = molecular weight of quetiapine fumarate, 883.09
\( N \) = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Calculate the percentage of the labeled amount of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) dissolved at each time point (\( t \)):

\[
Result_1 = C_i \times V \times (1/L) \times 100
\]

\[
Result_2 = [(C_2 \times V) + ([C_1 + C_2] \times V_3)] \times (1/L) \times 100
\]

\[
Result_3 = ([C_1 \times V] + ([C_2 + C_1] \times V_3)] \times (1/L) \times 100
\]

\[
Result_4 = (C_i \times V) + ([C_1 + C_2 + C_1] \times V_3)] \times (1/L) \times 100
\]

\( C_i \) = concentration of quetiapine in Medium in the portion of sample withdrawn at each time point (mg/mL)
\( V \) = volume of Medium, 900 mL for 1 h; 1000 mL for 6-, 12-, and 20-h time points
\( L \) = label claim (mg/Tablet)
\( V_3 \) = volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time Point (( t ))</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>47-49</td>
</tr>
<tr>
<td>3</td>
<td>65-95</td>
</tr>
<tr>
<td>4</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) 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: Water; 900 mL
Apparatus 1: 100 rpm
Times: 2, 4, 8, and 24 h
Standard solution: 0.03 mg/mL of USP Quetiapine Fumarate RS in water

Sample solution: Pass a suitable portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of filtrate. Replace the volume withdrawn with an equal volume of Medium. Dilute with Medium to a concentration that is similar to that of the Standard solution.

Instrumental conditions
Mode: UV
Analytical wavelength: 290 nm
Blank: Water

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration, \( C_i \), of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) in Medium (mg/mL) after each time point (\( t \)):

\[
C_i = \left( \frac{A_i}{A_1} \right) \times \left( \frac{M_1}{M_2} \right) \times N
\]

\( A_i \) = absorbance of the Sample solution
\( A_1 \) = absorbance of the Standard solution
\( M_1 \) = molecular weight of quetiapine fumarate in the Standard solution (mg/mL)
\( M_2 \) = molecular weight of quetiapine free base, 383.51
\( N \) = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Calculate the percentage of the labeled amount of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) dissolved at each time point (\( t \)):

\[
Result_1 = C_i \times V \times (1/L) \times 100
\]

\[
Result_2 = [(C_2 \times V) + ([C_1 + C_2] \times V_3)] \times (1/L) \times 100
\]

\[
Result_3 = ([C_1 \times V] + ([C_2 + C_1] \times V_3)] \times (1/L) \times 100
\]

\[
Result_4 = (C_i \times V) + ([C_1 + C_2 + C_1] \times V_3)] \times (1/L) \times 100
\]

\( C_i \) = concentration of quetiapine in Medium in the portion of sample withdrawn at each time point (mg/mL)
\( V \) = volume of Medium, 900 mL
\( L \) = label claim (mg/Tablet)
\( V_3 \) = volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Time Point (( t ))</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-25</td>
</tr>
<tr>
<td>2</td>
<td>20-45</td>
</tr>
<tr>
<td>3</td>
<td>45-75</td>
</tr>
<tr>
<td>4</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of quetiapine (C\(_{21}\)H\(_{25}\)N\(_3\)O\(_2\)S) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Times: 1, 4, and 8 h
Standard solution: USP Quetiapine Fumarate RS equivalent to (1/900) mg/mL of quetiapine in Medium, where \( L \) is the label claim in mg/Tablet

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Sample solution: Pass a suitable portion of the solution under test through a suitable full flow filter of 10-μm pore size.

Instrumental conditions

Mode: UV
Analytical wavelength: 295 nm

Cell
For 50-mg Tablets: 10 mm
For 150-, 200-, 300-, and 400-mg Tablets: 1 mm

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of quetiapine (C21H25N3O2S) dissolved at each time point (i):

\[
\text{Result} = \left( \frac{A_i}{A_j} \right) \times C_i \times V \times (1/L) \times (M_{r1}/M_{r2}) \times N \times 100
\]

- \( A_j \) = absorbance of the Sample solution
- \( A_i \) = absorbance of the Standard solution
- \( C_i \) = concentration of quetiapine fumarate in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( M_{r1} \) = molecular weight of quetiapine free base, 383.51
- \( M_{r2} \) = molecular weight of quetiapine fumarate, 883.09
- \( N \) = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Tolerances: See Table 3.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (for 50-, 150-, and 200-mg Tablets) (%)</th>
<th>Amount Dissolved (for 300- and 400-mg Tablets) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 40</td>
<td>NMT 35</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>55–75</td>
<td>45–65</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NLT 85</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of quetiapine (C21H25N3O2S) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 4: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 4.

Medium: Water; 900 mL
Apparatus 2: 100 rpm

Analysis

Sample solution: Pass a suitable portion of the solution under test through a suitable filter.

Instrumental conditions

Mode: UV
Analytical wavelength: 250 nm
Blank: Medium

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of quetiapine (C21H25N3O2S) dissolved at each time point (i):

\[
\text{Result} = \left( \frac{A_i}{A_j} \right) \times C_i \times V \times (1/L) \times (M_{r1}/M_{r2}) \times N \times 100
\]

- \( A_j \) = absorbance of the Sample solution
- \( A_i \) = absorbance of the Standard solution
- \( C_i \) = concentration of quetiapine fumarate in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( M_{r1} \) = molecular weight of quetiapine free base, 383.51
- \( M_{r2} \) = molecular weight of quetiapine fumarate, 883.09
- \( N \) = number of moles of quetiapine free base per mole of quetiapine fumarate, 2

Tolerances: See Table 4. The percentages of the labeled amount of quetiapine (C21H25N3O2S) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (for 50-mg Tablets) (%)</th>
<th>Amount Dissolved (for 150-mg Tablets) (%)</th>
<th>Amount Dissolved (for 200-mg Tablets) (%)</th>
<th>Amount Dissolved (for 300-mg Tablets) (%)</th>
<th>Amount Dissolved (for 400-mg Tablets) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 20</td>
<td>NMT 20</td>
<td>NMT 20</td>
<td>NMT 15</td>
<td>NMT 15</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>60–85</td>
<td>65–90</td>
<td>60–85</td>
<td>52–76</td>
<td>50–75</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>NLT 85</td>
<td>NLT 85</td>
<td>NLT 85</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>
Acceptance criteria: See Table 5. Disregard peaks less than 0.05%.

<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>Fumaric acid</td>
<td>0.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quetiapine related compound G</td>
<td>0.48</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Quetiapine related compound H</td>
<td>0.57</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Quetiapine desethoxy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.87</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Quetiapine related compound B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Counter ion peak, not to be included in the total impurities.

<sup>b</sup>Process impurity controlled in the drug substance. Included for identification purposes only. Not reported for the drug product and not included in the total impurities.

**Add the following:**

* **LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. (RB 1-Nov-2017)

* **USP REFERENCE STANDARDS (11):**
  - USP Quetiapine Fumarate RS
  - USP Quetiapine Related Compound H RS
  - USP Quetiapine System Suitability RS

Quetiapine contains quetiapine fumarate and at least 0.1% of each of the following impurities: Quetiapine related compound B: 11-(Piperazin-1-yl)dibenzo[b,f][1,4]thiazepine; Quetiapine related compound G: Dibenzo[b,f][1,4]thiazepin-11(10H)-one; and Quetiapine desethoxy: 2-[4-(Dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl]ethanol.

**ADDITIONAL REQUIREMENTS**

* **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.