Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets

**DEFINITION**
Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of cetirizine hydrochloride (C₂₁H₂₅ClN₂O₃ · 2HCl) and pseudoephedrine hydrochloride (C₁₀H₁₅NO · HCl).

**IDENTIFICATION**
A. The retention times of the major peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

**ASSAY**

* Cetirizine Hydrochloride

<table>
<thead>
<tr>
<th>Buffer: 3.5 g/L of monobasic ammonium phosphate and 1.0 g/L of tetrabutylammonium bisulfate in water. Adjust with phosphoric acid to a pH of 2.5.</th>
<th>Solution A: Acetonitrile, methanol, and Buffer (2:3)</th>
<th>Solution B: Acetonitrile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent: Methanol and Buffer (2:3)</td>
<td>Mobile phase: See Table 1.</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>27.0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>30.0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>30.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>35.0</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

**Standard stock solution:** 0.5 mg/mL of USP Cetirizine Hydrochloride RS in Diluent. [NOTE—Sonicate to dissolve.]

**Standard solution:** 0.025 mg/mL of USP Cetirizine Hydrochloride RS in Diluent from the Standard stock solution

**Sample solution:** 0.025 mg/mL of cetirizine hydrochloride (from NMT 10 finely powdered Tablets) prepared as follows. Dissolve the Tablets first in methanol, using 22.5% of the final flask volume. Sonicate for NLT 20 min with vigorous swirling every 5 min. To the solution add a volume of Buffer equal to 26% of the final flask volume. Allow the solution to equilibrate to room temperature. Dilute with Diluent to volume. Pass a portion through a membrane filter of 0.45-µm pore size.

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

<mode: LC>
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L9
Flow rate: 1.5 mL/min
Injection volume: 25 µL
Run time: 2 times the retention time of pseudoephedrine

<mode: LC>
Detector: UV 254 nm
Column: 4.6-mm × 15-cm; 5-µm packing L9
Flow rate: 1 mL/min
Injection volume: 25 µL
Run time: 2 times the retention time of pseudoephedrine

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System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 1000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times 100 \]

\( r_0 \) = peak response of cetirizine from the Sample solution
\( r_s \) = peak response of cetirizine from the Standard solution
\( C_s \) = concentration of USP Pseudoephedrine Hydrochloride RS in the Standard solution (mg/mL)
\( C_0 \) = nominal concentration of pseudoephedrine hydrochloride in the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Dissolution (711)

Test 1: (88.1-Apr-2013)
Medium: 0.1 N hydrochloric acid; 500 mL, deaerated
Apparatus 1: 100 rpm
Time: 30 min for cetirizine hydrochloride and 30 min (used only for adjustments in the calculations); 1, 2, and 6 h for pseudoephedrine hydrochloride
Buffer: 0.77 g/L of ammonium acetate in water. To 1 L of the solution add 1.0 mL of triethylamine. Adjust with glacial acetic acid to a pH of 4.5 ± 0.05.
Mobile phase: Acetonitrile and Buffer (3:7)
Standard stock solution: 0.5 mg/mL of USP Cetirizine Hydrochloride RS in water
Standard solution: 0.24 mg/mL of USP Pseudoephedrine Hydrochloride RS and 0.01 mg/mL of USP Cetirizine Hydrochloride RS in Medium from the Standard stock solution
Sample solution: At the times specified, withdraw 5 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size, discarding the first few mL.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV, 230 nm for cetirizine hydrochloride, 254 nm for pseudoephedrine hydrochloride
Column: 4.6-mm × 15-cm; 5-µm packing L9
Flow rate: 1.5 mL/min
Injection volume: 25 µL
Run time: 2 times the retention time of pseudoephedrine

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0 for both cetirizine and pseudoephedrine
Relative standard deviation: NMT 2.0% for both cetirizine and pseudoephedrine

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
Medium: 0.1 N HCl; 500 mL
Apparatus 1: 100 rpm
Time: 30 min for cetirizine hydrochloride and 30 minutes (used only for adjustments in the calculations); 1, 2, 4 and 8 h for pseudoephedrine hydrochloride
Buffer: 6.8 g/L of sodium acetate and 16.2 g/L of sodium 1-octanesulfonate
Mobile phase: Methanol and Buffer (50:50). Adjust with glacial acetic acid to a pH of 5.5.
Standard solution: 0.01 mg/mL of USP Cetirizine Hydrochloride RS and 0.24 mg/mL of USP Pseudoephedrine Hydrochloride RS in Medium

Calculate the percentage of cetirizine hydrochloride dissolved:

\[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times 100 \]

\( r_0 \) = peak response of cetirizine from the Sample solution
\( r_s \) = peak response of cetirizine from the Standard solution
\( C_s \) = concentration of cetirizine hydrochloride in the Standard solution (mg/mL)
\( C_0 \) = concentration of cetirizine hydrochloride (mg/Tablet)
\( V \) = volume of Medium, 500 mL

Tolerances
Cetirizine hydrochloride: NLT 80% (Q) of the labeled amount of cetirizine hydrochloride is dissolved in 30 min
Pseudoephedrine hydrochloride (C₁₀H₁₅NO·HCl): See Table 2.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30%–50%</td>
</tr>
<tr>
<td>2</td>
<td>50%–70%</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of pseudoephedrine hydrochloride dissolved at the times specified conform to Acceptance Table 2 in (711).

Table 2

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30%–50%</td>
</tr>
<tr>
<td>2</td>
<td>50%–70%</td>
</tr>
<tr>
<td>6</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>
Sample solution: Pass a 5-mL portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatography system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 242 nm
Column: 4.6-mm × 10-cm; 5-µm packing 1
Column temperature: 35°C
Flow rate: 2 mL/min
Injection volume: 100 µL
System suitability
[NOTE—The relative retention times for pseudoephedrine and cetirizine are 1.0 and 2.9, respectively.]
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 2000 theoretical plates for both pseudoephedrine and cetirizine
Tailing factor: NMT 2.0 for both pseudoephedrine and cetirizine
Relative standard deviation: NMT 2.0% for both pseudoephedrine and cetirizine
Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of cetirizine hydrochloride (C21H25ClN2O3 · 2HCl) dissolved:

\[
\text{Result} = \left(\frac{r_0}{r_s}\right) \times \left(\frac{C_3}{L}\right) \times V \times 100
\]

\( r_0 \) = peak response of cetirizine from the Sample solution
\( r_s \) = peak response of cetirizine from the Standard solution
\( C_3 \) = concentration of USP Cetirizine Hydrochloride RS in the Standard solution (mg/mL)
\( L \) = label claim (mg/Tablet)
\( V \) = volume of Medium, 500 mL

Calculate the concentration (C) of pseudoephedrine hydrochloride (C10H15NO · HCl) in the sample withdrawn from the vessel at each time point (i) shown in Table 3:

\[
\text{Result}_i = \left(\frac{r_0}{r_s}\right) \times C_i
\]

\( r_0 \) = peak response of pseudoephedrine from the Sample solution
\( r_s \) = peak response of pseudoephedrine from the Standard solution
\( C_i \) = concentration of USP Pseudoephedrine Hydrochloride RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amounts (Q) of pseudoephedrine hydrochloride (C10H15NO · HCl) dissolved at each time point (i) shown in Table 3:

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

\[
\text{Result}_2 = [(C_2 \times (V - V_0) + (C_1 \times V_0)) \times (1/L) \times 100
\]

\[
\text{Result}_3 = [(C_2 \times (2 \times V_0)) + (C_2 + C_3) \times V_0] \times (1/L) \times 100
\]

\[
\text{Result}_4 = [(C_2 \times (3 \times V_0)) + (C_2 + C_3 + C_4) \times V_0] \times (1/L) \times 100
\]

\[
\text{Result}_5 = [(C_3 \times (4 \times V_0)) + (C_3 + C_2 + C_4) \times V_0] \times (1/L) \times 100
\]

The percentages of the labeled amount of pseudoephedrine hydrochloride dissolved at the times specified conform to Acceptance Table 2 in (711). [81 1-Apr-2013]

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

**Impurities**
- **Cetirizine Hydrochloride Related Compounds**
 Buffer, Diluent, Solution A, and Solution B: Proceed as directed in the Assay for Cetirizine Hydrochloride.
 Mobile phase: See Table 4.

<table>
<thead>
<tr>
<th>Time point</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>30%–50%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>50%–70%</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>70%–90%</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The standard stock solution: 0.5 mg/mL of USP Cetirizine Hydrochloride RS in Diluent. [Note—Sonicate to dissolve.]

The standard solution: 1 µg/mL of USP Cetirizine Hydrochloride (from NMT 10 finely powdered Tablets) prepared as follows. Dissolve the Tablets first in methanol, using 70% of the final flask volume. Sonicate for 15 min, and then shake for 15 min. Allow the solution to cool to room temperature, and dilute with methanol to volume. Centrifuge a portion for 10 min.

The sample stock solution: 0.2 mg/mL of cetirizine hydrochloride in Buffer from the Sample stock solution. Pass a portion through a suitable membrane filter of 0.45-µm pore size.

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

Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Temperatures
Column: 30°
Autosampler: 5°
Flow rate: 1 mL/min
Injection volume: 25 µL
System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 1300 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 5.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_i}{r_0} \times \frac{C_i}{C_0} \times \frac{1}{F} \right) \times 100 \]

- \( r_i \) = peak response of the individual impurity from the Sample solution
- \( r_0 \) = peak response of cetirizine from the Standard solution
- \( C_i \) = concentration of USP Cetirizine Hydrochloride RS in the Standard solution (mg/mL)
- \( C_0 \) = nominal concentration of cetirizine hydrochloride in the Sample solution (mg/mL)
- \( F \) = relative response factor (see Table 5)

Acceptance criteria: See Table 5.

[NOTE—Disregard any peak less than 0.05% of the main peak.]

### 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>Cetirizine methanol*</td>
<td>0.54</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Chlorobenzhydryl piperazine (CBHP)*</td>
<td>0.57</td>
<td>1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cetirizine acetic acid*</td>
<td>1.30</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Cetirizine N-Oxide*</td>
<td>1.47</td>
<td>1.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### PSEUDOEPHEDRINE HYDROCHLORIDE RELATED COMPOUNDS

- Buffer: 11.2 g/L of sodium perchlorate monohydrate in water. Adjust with hydrochloric acid to a pH of 2.7.
- Solution A: Methanol and Buffer (3:17)
- Solution B: Methanol and Buffer (1:1)
- Diluent: Solution A
- Mobile phase: See Table 6.

### Table 6

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>28</td>
<td>72</td>
</tr>
</tbody>
</table>

### Standard stock solution
- 0.48 mg/mL of USP Pseudoephedrine Hydrochloride RS in Diluent

### Standard solution
- 4.8 µg/mL of USP Pseudoephedrine Hydrochloride RS in Diluent from the Standard stock solution

### System suitability stock solution
- 49 µg/mL of ephe-drine in Diluent from USP Ephedrine Sulfate RS

### System suitability solution
- 1.96 µg/mL of ephe-drine and 0.46 mg/mL of USP Pseudoephedrine Hydrochloride RS in Standard stock solution from the System suitability stock solution, respectively

### Sample stock solution
- 2.4 mg/mL of pseudoephedrine hydrochloride from NMT 25 finely powdered Tablets prepared as follows. Dissolve the Tablets first in methanol, using 75% of the final flask volume. Sonicate for NLT 15 min, and then shake for 15 min. Allow the solution to cool to room temperature, and dilute with methanol to volume. Centrifuge a portion for 10 min.

### Sample solution
- 0.48 mg/mL of pseudoephedrine hydrochloride from the Sample stock solution. Pass a portion through a suitable membrane filter of 0.45-µm pore size.

### Chromatographic system

- Mode: LC
- Detector: UV 212 nm
- Column: 4.6-mm × 25-cm; 4-µm packing L1
- Column temperature: 40°
- Flow rate: 1 mL/min
- Injection volume: 30 µL

### System suitability

Samples: Standard solution and System suitability solution

Suitability requirements
- Resolution: NLT 1.3 between ephe-drine and pseudoephedrine, System suitability solution
- Tailing factor: NMT 1.5, Standard solution
- Relative standard deviation: NMT 3.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_i}{r_0} \times \frac{C_i}{C_0} \times \frac{1}{F} \right) \times 100 \]

- \( r_i \) = peak response of the individual impurity from the Sample solution
- \( r_0 \) = peak response of pseudoephedrine from the Standard solution
- \( C_i \) = concentration of USP Pseudoephedrine Hydrochloride RS in the Standard solution (mg/mL)
- \( C_0 \) = nominal concentration of pseudoephedrine hydrochloride in the Sample solution (mg/mL)
- \( F \) = relative response factor (see Table 7)

Acceptance criteria: See Table 7.

[NOTE—Disregard any peak less than 0.05% of the main peak.]
### ADDITIONAL REQUIREMENTS

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

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.

- **USP REFERENCE STANDARDS (11)**
  - USP Cetirizine Hydrochloride RS
  - USP Ephedrine Sulfate RS
  - USP Pseudoephedrine Hydrochloride RS

---

### Table 7

<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>Ephedrine&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.95</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Methcathinone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.1</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total pseudoephedrine related impurities</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*<sup>a</sup> [(R<sup>*</sup>,S<sup>*</sup>)]-α-[(Methylamino)ethyl]-benzenemethanol.

*<sup>b</sup> For system suitability and identification purposes only.

*<sup>c</sup> 2-Methylamino-1-phenylpropan-1-one.

**Sum of cetirizine and pseudoephedrine related impurities: NMT 1.0%**