Levocetirizine Dihydrochloride

C₃₁H₂₅ClN₂O₃·2HCl 461.81
Acetic acid, [2-[(4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl)ethoxy]-(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy)acetic acid dihydrochloride \([130018-87-0]\).

Levocetirizine free base

C₃₁H₂₅ClN₂O₃ 388.89

DEFINITION

Levocetirizine Dihydrochloride contains NLT 98.0% and NMT 102.0% of levocetirizine dihydrochloride \((C₃₁H₂₅ClN₂O₃·2HCl)\), calculated on the dried basis.

IDENTIFICATION

A. INFRARED ABSORPTION \((\text{197K})\)

B. THE RETENTION TIME OF THE MAJOR PEAK OF THE Sample solution corresponds to that of the levocetirizine peak of the System suitability solution, as obtained in the test for enantiomeric purity.

C. IDENTIFICATION TESTS—GENERAL \((\text{191})\), Chloride

Meets the requirements

ASSAY

Change to read:

PROCEDURE

Mobile phase: Acetonitrile, water, and 1 M sulfuric acid \((93: 6.6: 0.4)\)

Standard solution: 0.05 mg/mL of USP Levocetirizine Dihydrochloride RS in Mobile phase

Sample solution: 0.05 mg/mL of Levocetirizine Dihydrochloride in Mobile phase

Chromatographic system

(See Chromatography \((\text{621})\), System Suitability.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm \(\times\) 25-cm; 5-µm packing L3

Column temperature: 30°C

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of levocetirizine dihydrochloride \((C₃₁H₂₅ClN₂O₃·2HCl)\) in the portion of Levocetirizine Dihydrochloride taken:

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

Where:

- \(r_0\) = peak response of levocetirizine from the Sample solution
- \(r_s\) = peak response of levocetirizine from the Standard solution
- \(C_0\) = concentration of Levocetirizine Dihydrochloride in the Sample solution (mg/mL)
- \(C_s\) = concentration of Levocetirizine Dihydrochloride in the Standard solution (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- RESIDUE ON IGNITION \((\text{281})\): NMT 0.2%

- ORGANIC IMPURITIES

Mobile phase: Acetonitrile, water, and 1 M sulfuric acid \((93: 6.6: 0.4)\)

System suitability solution: 0.2 mg/mL of USP Levocetirizine Dihydrochloride RS and 0.2 µg/mL each of USP Levocetirizine Amide RS and USP Chlorobenzhydryl Piperazine RS in Mobile phase. Use the solution within 16 h.

Standard solution: 0.2 µg/mL each of USP Levocetirizine Dihydrochloride RS, USP Levocetirizine Amide RS, and USP Chlorobenzhydryl Piperazine RS in Mobile phase. Use the solution within 16 h.

Sample solution: 200 µg/mL of Levocetirizine Dihydrochloride in Mobile phase. Use the solution within 16 h.

Chromatographic system

(See Chromatography \((\text{621})\), System Suitability.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm \(\times\) 25-cm; 5-µm packing L3

Column temperature: 30°C

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 3 times the retention time of levocetirizine

System suitability

Samples: System suitability solution and Standard solution

([Note—See Table 1 for the relative retention times.])

Suitability requirements

Resolution: NLT 3.0 between levocetirizine and chlorobenzhydryl piperazine, System suitability solution

Tailing factor: NMT 2.0 for levocetirizine, System suitability solution

Relative standard deviation: NMT 5.0% for levocetirizine, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of levocetirizine amide or chlorobenzhydryl piperazine in the portion of Levocetirizine Dihydrochloride taken:

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

Where:

- \(r_0\) = peak response of levocetirizine amide or chlorobenzhydryl piperazine from the Sample solution
- \(r_s\) = peak response of levocetirizine amide or chlorobenzhydryl piperazine from the Standard solution
- \(C_0\) = concentration of USP Levocetirizine Amide RS or USP Chlorobenzhydryl Piperazine RS in the Standard solution (µg/mL)
- \(C_s\) = concentration of Levocetirizine Dihydrochloride in the Sample solution (µg/mL)
Interim Revision Announcement
Official January 1, 2018

Levocetirizine

Calculate the percentage of any unspecified impurity in the portion of Levocetirizine Dihydrochloride 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 any unspecified impurity from the Sample solution
- \( r_S \) = peak response of levocetirizine from the Standard solution
- \( C_S \) = concentration of USP Levocetirizine Dihydrochloride RS in the Standard solution (µg/mL)
- \( C_U \) = concentration of Levocetirizine Dihydrochloride in the Sample solution (µg/mL)

Acceptance criteria: See Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levocetirizine</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Chlorobenzhydryl piperazine</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Levocetirizine amide</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Change to read:**

- **Enantiomeric Purity**
  - Protect solutions containing levocetirizine from direct exposure to light.
  - **Buffer:** 1.5 g/L of ammonium acetate in water. Adjust with glacial acetic acid to a pH of 4.8.
  - **Mobile phase:** Acetonitrile and Buffer (30:70)
  - **System suitability solution:** 0.5 mg/mL of USP Cetirizine Hydrochloride RS in water
  - **Sample solution:** 0.5 mg/mL of Levocetirizine Dihydrochloride in water

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm x 25-cm; 5-µm packing L90.

**Column temperature:** 30°C

**Flow rate:** 0.5 mL/min

**Injection volume:** 20 µL

**Run time:** NLT 1.8 times the retention time of levocetirizine

**System suitability**

**Sample:** System suitability solution

[Note—The relative retention times for the S-enantiomer (of cetirizine) and levocetirizine, which is the R-enantiomer (of cetirizine), are about 0.83 and 1.0, respectively.]

**Suitability requirements**

- **Resolution:** NLT 1.4 between the S-enantiomer and levocetirizine
- **Tailing factor:** NMT 2.0 for levocetirizine
- **Relative standard deviation:** NMT 1.5% each for levocetirizine and the S-enantiomer

**Analysis**

**Sample:** Sample solution

Calculate the percentage of the S-enantiomer in the portion of Levocetirizine Dihydrochloride taken:

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

- \( r_U \) = peak response of the S-enantiomer from the Sample solution
- \( r_T \) = sum of the peak responses of the S-enantiomer and levocetirizine from the Sample solution

Acceptance criteria: NMT 2.0% of the S-enantiomer

**SPECIFIC TESTS**

- **Loss on Drying (731)**
  - Analysis: Dry at 105°C to constant weight.
  - Acceptance criteria: NMT 1.0%

- **pH (791)**
  - Sample solution: 50 mg/mL of Levocetirizine Dihydrochloride in water
  - Acceptance criteria: 1.2–1.8

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed containers, protected from light at controlled room temperature.

- **USP Reference Standards (11)**
  - USP Cetirizine Hydrochloride RS
  - USP Chlorobenzhydryl Piperazine RS
  - (R)-1-[(4-Chlorophenyl)phenylmethyl]piperazine. C₁₇H₁₉ClN₂ 286.80
  - USP Levocetirizine Amide RS
  - (R)-2-(2-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl)ethoxy)acetamide. C₉H₁₃ClN₂O₂ 387.90
  - USP Levocetirizine Dihydrochloride RS

©2017 The United States Pharmacopeial Convention  All Rights Reserved.