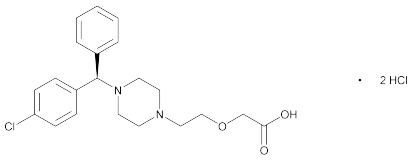
Levocetirizine Dihydrochloride



$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ 461.81
Acetic acid, [2-[4-[(*R*)-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-, dihydrochloride;
(2-{4-[(*R*)-(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy)acetic acid dihydrochloride [130018-87-0].
Levocetirizine free base

$C_{21}H_{25}ClN_2O_3$ 388.89
[130018-77-8].

DEFINITION

Levocetirizine Dihydrochloride contains NLT 98.0% and NMT 102.0% of levocetirizine dihydrochloride ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨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 ⟨191⟩,** *Chloride***:** Meets the requirements

ASSAY

Change to read:

- **PROCEDURE**

Mobile phase: Acetonitrile, water, and 1 M sulfuric acid •TS• (IRA 1-Jan-2018) (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 ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L3
Column temperature: 30°
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 ($C_{21}H_{25}ClN_2O_3 \cdot 2HCl$) in the portion of Levocetirizine Dihydrochloride taken:

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

r_U = peak response of levocetirizine 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* (mg/mL)
C_U = concentration of Levocetirizine Dihydrochloride in the *Sample solution* (mg/mL)

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

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%

Change to read:

- **ORGANIC IMPURITIES**

Mobile phase: Acetonitrile, water, and 1 M sulfuric acid •TS• (IRA 1-Jan-2018) (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 ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L3
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: •NLT• (IRA 1-Jan-2018) 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:

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

r_U = 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_S = concentration of USP Levocetirizine Amide RS or USP Chlorobenzhydryl Piperazine RS in the *Standard solution* (µg/mL)
C_U = concentration of Levocetirizine Dihydrochloride in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified impurity in the portion of Levocetirizine Dihydrochloride taken:

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

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

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Levocetirizine ●● (IRA 1-Jan-2018)	1.0	—
Chlorobenzhydryl piperazine	1.3	0.2
Levocetirizine amide	2.5	0.2
Any individual unspecified impurity	—	0.1
Total impurities	—	0.5

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 × 25-cm; 5-µm packing L90.
  [NOTE—A suitable guard column may be used.]
  Column temperature: 30°
  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:

$$\text{Result} = (r_U/r_T) \times 100$$

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*● (IRA 1-Jan-2018)

Acceptance criteria: NMT 2.0% of the *S*-enantiomer

SPECIFIC TESTS

- **LOSS ON DRYING** ⟨731⟩
  Analysis: Dry at 105° 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.
  $C_{17}H_{19}ClN_2$ 286.80
  USP Levocetirizine Amide RS
  (*R*)-2-(2-{4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl}ethoxy)acetamide.
  $C_{21}H_{26}ClN_3O_2$ 387.90
  USP Levocetirizine Dihydrochloride RS