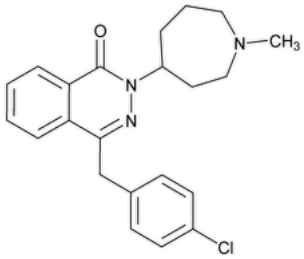
Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Dec-2021
Document Type: USP Monographs
DocId: GUID-DC918A3A-EE9A-4EEA-BF52-0D39CDA70546_5_en-US
DOI: https://doi.org/10.31003/USPNF_M6738_05_01
DOI Ref: bcn2j

Azelastine Hydrochloride



• HCl

$C_{22}H_{24}ClN_3O \cdot HCl$ 418.36

1(2*H*)-Phthalazinone, 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1*H*-azepin-4-yl), monohydrochloride;

4-(*p*-Chlorobenzyl)-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone monohydrochloride CAS RN®: 79307-93-0.

UNII: 0L591QR10I

DEFINITION

Azelastine Hydrochloride contains NLT 99.0% and NMT 101.0% of azelastine hydrochloride ($C_{22}H_{24}ClN_3O \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Identification solution*, as obtained in the test for *Organic Impurities*.

• **C. Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride*:** Meets the requirements

ASSAY

Change to read:

• **Procedure**

Sample: 300 mg

Blank: 5 mL of anhydrous formic acid and 30 mL of acetic anhydride

Titrimetric system

(See *Titrimetry ⟨541⟩*.)

Mode: Direct titration

Titrant: ▲0.1 N perchloric acid in glacial acetic acid VS▲ (USP 1-Dec-2021)

Endpoint detection: Potentiometric

Analysis: In order to avoid overheating in the reaction medium, mix thoroughly throughout and stop the titration immediately after the endpoint has been reached.

Dissolve the *Sample* in 5 mL of anhydrous formic acid, and add 30 mL of acetic anhydride. Titrate with *Titrant*.

Calculate the percentage of azelastine hydrochloride ($C_{22}H_{24}ClN_3O \cdot HCl$) in the portion of Azelastine Hydrochloride taken:

$$\text{Result} = \{[(V_S - V_B) \times N \times F]/W\} \times 100$$

V_S = *Titrant* volume consumed by the *Sample* (mL)

V_B = *Titrant* volume consumed by the *Blank* (mL)

N = actual normality of the *Titrant* (mEq/mL)

F = equivalency factor, ▲418.4▲ (USP 1-Dec-2021) mg/mEq

W = weight of the *Sample* (mg)

Acceptance criteria: 99.0%–101.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.2%

Change to read:

• **Organic Impurities**

▲**Solution A:** 127 mL/L of phosphoric acid in water▲ (USP 1-Dec-2021)

Buffer: ▲2.9 g/L of octanesulfonic acid sodium salt and 0.9 g/L of monobasic potassium phosphate in water. Adjust with *Solution A* to a pH of 3.0.▲ (USP 1-Dec-2021)

Mobile phase: Acetonitrile and *Buffer*▲(23:77)▲ (USP 1-Dec-2021)

Diluent: Acetonitrile and water (45:55)

Identification solution: 2.5 mg/mL of USP Azelastine Hydrochloride RS in *Diluent*. [Note—This solution is used for *Identification B*.]

System suitability stock solution: 0.5 mg/mL each of ▲benzoyl hydrazide,▲ (USP 1-Dec-2021) USP Azelastine Related Compound B RS, ▲chlorophenylacetylbenzoic acid,▲ (USP 1-Dec-2021) USP Azelastine Related Compound D RS, and USP Azelastine Related Compound E RS in acetonitrile. ▲[Note—The concentration of each related compound is in terms of the free form.]▲ (USP 1-Dec-2021)

System suitability solution: ▲0.05 mg/mL▲ (USP 1-Dec-2021) each of ▲benzoyl hydrazide,▲ (USP 1-Dec-2021) USP Azelastine Related Compound B RS, ▲chlorophenylacetylbenzoic acid,▲ (USP 1-Dec-2021) USP Azelastine Related Compound D RS, and USP Azelastine Related Compound E RS from the *System suitability stock solution* and 2.5 mg/mL of USP Azelastine Hydrochloride RS in *Diluent*. ▲[Note—The concentration of each related compound is in terms of the free form.]▲ (USP 1-Dec-2021)

Standard stock solution: ▲0.05 mg/mL▲ (USP 1-Dec-2021) of USP Azelastine Hydrochloride RS in acetonitrile

Standard solution: ▲0.0025 mg/mL▲ (USP 1-Dec-2021) of USP Azelastine Hydrochloride RS in *Diluent*

▲**Sensitivity solution:** 0.0013 mg/mL of USP Azelastine Hydrochloride RS in *Diluent* from the *Standard solution*▲ (USP 1-Dec-2021)

Sample solution: 2.5 mg/mL of Azelastine Hydrochloride in *Diluent*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; ▲5-µm packing▲ (USP 1-Dec-2021) L10

Column temperature: 30°

Flow rate: 2 mL/min

Injection volume: 10 µL

Run time: ▲NLT▲ (USP 1-Dec-2021) 2.4 times the retention time of azelastine

System suitability

Samples: *System suitability solution* and *Standard solution*

▲[Note—See *Table 1* for the relative retention times.]▲ (USP 1-Dec-2021)

Suitability requirements

Resolution: ▲NLT 1.5 between benzoyl hydrazide and azelastine related compound B; NLT 1.5 between chlorophenylacetylbenzoic acid and azelastine related compound D;▲ (USP 1-Dec-2021) NLT 1.5 between azelastine related compound D and azelastine; NLT 1.5 between azelastine and azelastine related compound E, *System suitability solution*

▲**Tailing factor:** 0.9–2.0, *Standard solution*▲ (USP 1-Dec-2021)

Relative standard deviation: NMT 5.0%, *Standard solution*

▲**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*▲ (USP 1-Dec-2021)

Analysis

Samples: ▲▲ (USP 1-Dec-2021) *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Azelastine Hydrochloride taken:

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

r_U = peak area of each impurity from the *Sample solution*

r_S = peak area of azelastine from the *Standard solution*

C_S = concentration of USP Azelastine Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Azelastine Hydrochloride in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. ▲The reporting threshold is 0.05%.▲ (USP 1-Dec-2021)

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
▲Benzoyl hydrazide [a]	0.15▲ (USP 1-Dec-2021)	0.38	0.1
Azelastine related compound B▲▲ (USP 1-Dec-2021)	▲0.20▲ (USP 1-Dec-2021)	0.22	0.1
Chlorophenylacetylbenzoic acid[b]	▲0.48	0.56▲ (USP 1-Dec-2021)	0.1
Azelastine related compound D▲▲ (USP 1-Dec-2021)	▲0.54▲ (USP 1-Dec-2021)	1.2	0.1
Azelastine	1.0	1.0	—
Azelastine related compound E▲▲ (USP 1-Dec-2021)	1.4	0.48	0.1
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.2

[a] Benzohydrazide.

[b] 2-[2-(4-Chlorophenyl)acetyl]benzoic acid.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry at 105° to constant weight.

Acceptance criteria: NMT 1.0%

Delete the following:

▲• **Acidity or Alkalinity**

Sample solution: 10 mg/mL of Azelastine Hydrochloride in water

Analysis: Add 0.2 mL of bromothymol blue TS to 10 mL of the *Sample solution*.

Acceptance criteria: NMT 0.1 mL of 0.01 M hydrochloric acid or 0.01 M sodium hydroxide is required to produce a color change.▲ (USP 1-Dec-2021)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers. Protect from light and moisture. Store at controlled room temperature.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Azelastine Hydrochloride RS

USP Azelastine Related Compound B RS

▲*N*'-(1-Methylazepan-4-yl)benzohydrazide hydrochloride.

$C_{14}H_{21}N_3O \cdot HCl$ 283.80▲ (USP 1-Dec-2021)

USP Azelastine Related Compound D RS

4-(4-Chlorobenzyl)phthalazin-1(2*H*)-one.

$C_{15}H_{11}ClN_2O$ 270.71

USP Azelastine Related Compound E RS

3-(4-Chlorobenzylidene)isobenzofuran-1(3*H*)-one.

$C_{15}H_9ClO_2$ 256.68

Topic/Question	Contact	Expert Committee
AZELASTINE HYDROCHLORIDE	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(2)

Current DocID: GUID-DC918A3A-EE9A-4EEA-BF52-0D39CDA70546_5_en-US

DOI: https://doi.org/10.31003/USPNF_M6738_05_01

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