r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of travoprost in the *Standard solution* (mg/mL)
C_U = nominal concentration of travoprost in the *Sample solution* (mg/mL)
Acceptance criteria: 90.0%–110.0%

IMPURITIES

- **LIMIT OF TRAVOPROST RELATED COMPOUND A**

Buffer: Add 1.0 mL of phosphoric acid to 1.0 L of water, and adjust with sodium hydroxide to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (6:19)
Standard solution: 0.3 µg/mL of USP Travoprost Related Compound A RS in a mixture of acetonitrile and water (1:4)
Sample solution: Use Ophthalmic Solution without dilution.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 5-cm; packing L1
Flow rate: 3.0 mL/min
Injection volume: 100 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Relative standard deviation: NMT 10.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of travoprost related compound A in the portion of Ophthalmic Solution taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Travoprost Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of travoprost in the *Sample solution* (mg/mL)
Acceptance criteria: NMT 1.0%

- **LIMIT OF DEGRADATION PRODUCTS**

Buffer, Mobile phase, Standard solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each degradation product in the portion of Ophthalmic Solution taken:

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

r_U = peak response of each degradation product from the *Sample solution*
r_S = peak response of travoprost from the *Standard solution*
C_S = concentration of USP Travoprost RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of travoprost in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 1*)
Acceptance criteria: See *Table 1*.
Total impurities: NMT 5.5%. It is the sum of all degradation products, including travoprost related compound A, obtained in *Limit of Travoprost Related Compound A*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
5,6-*trans* Isomer[a]	1.1	1.0	5.0
15-keto Derivative[b]	1.4	1.7	1.0

[a] (5*E*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester.
[b] (5*Z*,13*E*)-(9*S*,11*R*)-9,11,-Dihydroxy-15-oxo-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester.

SPECIFIC TESTS

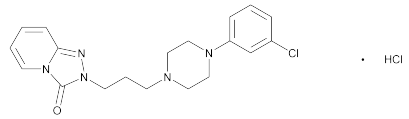
- **STERILITY TESTS** ⟨**71**⟩**:** Meets the requirements when tested as directed in *Test for Sterility of the Product to Be Examined, Membrane Filtration*
- **pH** ⟨**791**⟩**:** 5.5–6.5

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store between 2° and 25°.
- **USP REFERENCE STANDARDS** ⟨**11**⟩

USP Travoprost RS
USP Travoprost Related Compound A RS
(5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid.
$C_{23}H_{29}F_3O_6$ 458.52

Trazodone Hydrochloride



$C_{19}H_{22}ClN_5O \cdot HCl$ 408.32
1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-, monohydrochloride;
2-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-*s*-triazolo[4,3-*a*]-pyridin-3(2*H*)-one monohydrochloride [25332-39-2].

DEFINITION
Trazodone Hydrochloride contains NLT 98.0% and NMT 102.0% of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$), 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 *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Solution A: 0.01% (v/v) of triethylamine in water
Solution B: 0.01% (v/v) of triethylamine in acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
12	32	68
12.01	80	20
15	80	20

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Diluent: *Solution A* and *Solution B* (80:20)
System suitability solution: 1 µg/mL each of USP Trazodone Related Compound C RS and USP Trazodone Related Compound D RS, and 0.1 mg/mL of USP Trazodone Hydrochloride RS in *Diluent*
Standard solution: 1 mg/mL of USP Trazodone Hydrochloride RS in *Diluent*
Sample solution: 1 mg/mL of Trazodone Hydrochloride in *Diluent*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 7.5-cm; 3.5-µm packing L1
Flow rate: 2 mL/min
Injection volume: 10 µL
[NOTE—A mixture of acetonitrile, 2-propanol, acetone, and formic acid (400:300:300:2) is recommended for injector wash to minimize the sample carry-over.]
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.5 between trazodone related compound C and trazodone; NLT 2.8 between trazodone and trazodone related compound D, *System suitability solution*
Relative standard deviation: NMT 1.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$) in the portion of Trazodone Hydrochloride taken:

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

r_U = peak response of trazodone from the *Sample solution*
r_S = peak response of trazodone from the *Standard solution*
C_S = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Trazodone Hydrochloride in the *Sample solution* (mg/mL)
Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

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

Solution A, Solution B, Mobile phase, Diluent, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: 1 µg/mL each of USP Trazodone Related Compound C RS and USP Trazodone Related Compound D RS in the *Standard solution*
Standard solution: 1 µg/mL of USP Trazodone Hydrochloride RS in *Diluent*
Sample solution: 1 mg/mL of Trazodone Hydrochloride in *Diluent*
System suitability
Sample: *System suitability solution*
[NOTE—Refer to *Table 2* for the relative retention times.]
Suitability requirements
Relative standard deviation: NMT 5.0% for the trazodone peak
Resolution: NLT 1.5 between trazodone related compound C and trazodone; NLT 2.8 between trazodone and trazodone related compound D
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each individual impurity in the portion of Trazodone Hydrochloride taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of trazodone from the *Standard solution*
C_S = concentration of USP Trazodone Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = concentration of Trazodone Hydrochloride in the *Sample solution* (mg/mL)
F = relative response factor (see *Table 2*)
Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Triazolopyridinone[a]	0.1	0.48	0.10
Trazodone *N*-oxide[b]	0.40	1.0	0.1
Deschloro trazodone[c]	0.65	0.71	0.1
Trazodone related compound C	0.96	1.0	0.1
Trazodone	1.0	—	—
Trazodone related compound D	1.1	1.0	0.1
4-Ethyl trazodone[d]	1.4	1.0	0.1
Trazodone isobutyl ether analog[e]	2.0	1.0	0.1
Bispiperazine analog[f]	2.1	1.3	0.1
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] [1,2,4]Triazolo[4,3-*a*]pyridin-3(2*H*)-one.
[b] 4-(3-Chlorophenyl)-1-[3-(3-oxo-[1,2,4]triazolo[4,3-*a*]pyridin-2(3*H*)-yl)propyl]piperazine 1-oxide.
[c] 2-[3-(4-Phenylpiperazin-1-yl)propyl]-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one.
[d] 2-{3-[4-(3-Chloro-4-ethylphenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one.
[e] 1-(3-Chlorophenyl)-4-(3-isobutoxypropyl)piperazine.
[f] 1,3-Bis(4-(3-chlorophenyl)piperazin-1-yl)propane.

- **LIMIT OF TRAZODONE RELATED COMPOUND F AND CYCLOPHOSPHAMIDE RELATED COMPOUND A**

[NOTE—Perform this test only if trazodone related compound F and cyclophosphamide related compound A are known process impurities.]
Solution A: 5 mM ammonium bicarbonate solution
Solution B: Acetonitrile
Diluent: Acetonitrile, water, and formic acid (100:900:1)
Standard solution: 0.025 µg/mL each of USP Trazodone Related Compound F RS and USP Cyclophosphamide Related Compound A RS, in *Diluent*
Sample solution: 0.01 g/mL of Trazodone Hydrochloride in *Diluent*
Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	90	10
6.5	20	80
6.51	90	10

USP Monographs

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Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: MS/MS (tandem mass spectrometer)
MS conditions
Ionization: Triple quadrupole ionization in positive ion mode
Acquisition mode: Multiple reaction monitoring (MRM) of the following mass transitions:
Cyclophosphamide related compound A 142 → 63
Trazodone related compound F 273 → 120
Column: 4.6-mm × 7.5-cm; 3.5-µm packing L1
Column temperature: 40°
Flow rate: 1.5 mL/min
Flow rate to ion source: 0.5 mL/min
Injection volume: Adjust to between 5 and 50 µL, depending on the mass spectrometer. [NOTE—A mixture of 2-propanol, water, and formic acid (800:200:1) is recommended for the injector wash to minimize the sample carry-over.]
System suitability
Sample: *Standard solution*
[NOTE—The relative retention times of cyclophosphamide related compound A and trazodone related compound F are 0.4 and 1.0, respectively.]
Suitability requirements
Signal-to-noise ratio: NLT 100 for the trazodone related compound F peak and NLT 50 for the cyclophosphamide related compound A peak
Relative standard deviation: NMT 15.0% each for trazodone related compound F and cyclophosphamide related compound A
Analysis
Samples: *Standard solution* and *Sample solution*
[NOTE—Under the chromatographic conditions, the elution order is cyclophosphamide related compound A, trazodone, and trazodone related compound F. Use of an appropriate switching valve program in order to completely divert the trazodone peak to waste between the elution times of the two impurities is recommended.]
Calculate, in µg/g, the amount of trazodone related compound F and cyclophosphamide related compound A in the portion of Trazodone Hydrochloride taken:

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

r_U = peak response of trazodone related compound F or cyclophosphamide related compound A from the *Sample solution*
r_S = peak response of trazodone related compound F or cyclophosphamide related compound A from the *Standard solution*
C_S = concentration of USP Trazodone Related Compound F RS or USP Cyclophosphamide Related Compound A RS in the *Standard solution* (µg/mL)
C_U = concentration of Trazodone Hydrochloride in the *Sample solution* (g/mL)
Acceptance criteria: NMT 2.5 µg/g each of trazodone related compound F and cyclophosphamide related compound A

SPECIFIC TESTS

• **LOSS ON DRYING** ⟨**731**⟩
Analysis: Dry at a pressure of 50 mm of mercury at 105° for 3 h.
Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers.

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Cyclophosphamide Related Compound A RS
Bis(2-chloroethyl)amine hydrochloride.
$C_4H_{10}Cl_3N$ 178.48
USP Trazodone Hydrochloride RS
USP Trazodone Related Compound C RS
2-{3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.
$C_{19}H_{22}ClN_5O \cdot HCl$ 408.32
USP Trazodone Related Compound D RS
2-{3-[4-(3-Bromophenyl)piperazin-1-yl]propyl}-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one hydrochloride.
$C_{19}H_{22}BrN_5O \cdot HCl$ 452.78
USP Trazodone Related Compound F RS
1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride.
$C_{13}H_{18}Cl_2N_2 \cdot HCl$ 309.66

Trazodone Hydrochloride Tablets

DEFINITION

Trazodone Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of trazodone hydrochloride ($C_{19}H_{22}ClN_5O \cdot HCl$).

IDENTIFICATION

• **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** ⟨**201**⟩
Standard solution: 20 mg/mL of USP Trazodone Hydrochloride RS in methanol
Sample solution: Nominally 20 mg/mL of trazodone hydrochloride in methanol from a suitable number of Tablets (equivalent to NLT 150 mg) prepared as follows. Place the Tablets in a tube. Add the required amount of methanol, and sonicate until the Tablets have disintegrated. Shake the tube, by hand, for a few seconds to mix, and then filter.
Application volume: 1 µL
Developing solvent system: Cyclohexane, alcohol, toluene, and diethylamine (80:30:20:20)
Analysis
Samples: *Standard solution* and *Sample solution*
Proceed as directed in the chapter, except locate the spots on the plate by examination under long-wavelength UV light.
• **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

• **PROCEDURE**
Buffer: 1.15 g/L of monobasic ammonium phosphate, adjusted with sodium hydroxide to a pH of 6.0
Mobile phase: Methanol and *Buffer* (75:25)
Standard solution: 0.1 mg/mL of USP Trazodone Hydrochloride RS in 0.01 N hydrochloric acid
Sample solution: Nominally 0.1 mg/mL of trazodone hydrochloride from NLT 20 finely powdered Tablets. Transfer a suitable quantity of the powder to a suitable volumetric flask. Dissolve in 0.01 N hydrochloric acid, and dilute with 0.01 N hydrochloric acid to volume. Sonicate for about 30 min, and pass through a nylon filter of 0.45-µm pore size.

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