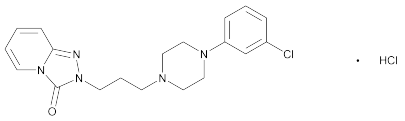
Trazodone Hydrochloride



$C_{19}H_{22}ClN_5O \cdot HCl$ 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

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.

Change to read:

- **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, ●● (RB 1-Feb-2015) 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

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● (ERR 1-Dec-2014) → 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.● (RB 1-Feb-2015)]

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.]● (RB 1-Feb-2015)

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.

Change to read:

- **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-α]pyridin-3(2*H*)-one hydrochloride. ● (ERR 1-Dec-2014)
  $C_{19}H_{22}BrN_5O \cdot HCl$ 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