Alprazolam Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Alprazolam Tablets monograph. The purpose for the revision is to postpone the implementation of the test for *Organic Impurities*.

The Alprazolam Tablets Revision Bulletin supersedes the monograph becoming official on March 1, 2019.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison (301-998-6792 or hrj@usp.org).

Alprazolam Tablets

DEFINITION

Alprazolam Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$).

IDENTIFICATION

Delete the following:

▲• **A. Infrared Absorption**

Sample: An amount of finely powdered Tablets, equivalent to 15 mg of alprazolam, prepared as follows. Dissolve the *Sample* in 10 mL of 10 mg/mL of sodium carbonate solution. Add 15 mL of chloroform, and shake vigorously for 30 min. Centrifuge, withdraw the aqueous layer, and transfer the chloroform to a clean container. Add 200 mg of potassium bromide. Evaporate the chloroform from this mixture to dryness, and dry the dispersion in vacuum at 60° for 24 h. Grind this dispersion into a fine powder. Prepare a suitable pellet for testing by placing 100 mg of dried potassium bromide into a die. Sprinkle 20 mg of the finely ground alprazolam–potassium bromide dispersion onto the dried potassium bromide layer, and cover with another specimen of 100 mg of dried potassium bromide.

Acceptance criteria: The IR absorption spectrum of the potassium bromide dispersion so obtained exhibits maxima characteristic of alprazolam, as compared to that of a similar preparation of USP Alprazolam RS, at the following wavenumbers: at 1609, 1578, 1566, 1539, 1487, and 1379 wavenumbers in the region of 1650–1300 cm^{-1}; at 932, 891, 826, 779, 746, 696, and 658 wavenumbers in the region of 975–600 cm^{-1}.▲ 2S (USP41)

Add the following:

▲• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ 2S (USP41)

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ 2S (USP41)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** 0.77 g/L of ammonium acetate prepared as follows. Dissolve 0.77 g of ammonium acetate in each liter of water and adjust with acetic acid to a pH of 4.7.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
2.5	60	40
9.0	5	95
9.1	60	40
11.0	60	40

Diluent: Acetonitrile and water (40:60)

System suitability solution: 50 µg/mL of USP Alprazolam RS, 1 µg/mL of USP Alprazolam Related Compound A RS, and 1 µg/mL of USP Chlordiazepoxide Related Compound A RS in *Diluent*

Standard solution: 50 µg/mL of USP Alprazolam RS in *Diluent*

Sample solution: Nominally 50 µg/mL of alprazolam from Tablets prepared as follows. Transfer a suitable portion of powder from NLT 10 Tablets to an appropriate volumetric flask. Add 80% of the total flask volume of *Diluent*. Sonicate for NLT 10 min. Dilute with *Diluent* to volume. Centrifuge a portion and use the clear supernatant. [Note—The use of a centrifuge speed of 3500 rpm for 10 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 260 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 3-µm packing L7

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

Samples: *System suitability solution* and *Standard solution* [Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between chlordiazepoxide related compound A and alprazolam related compound A, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) in the portion of Tablets 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 Alprazolam RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of alprazolam in the *Sample solution* (µg/mL)▲ 2S (USP41)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩**,** *Procedure, Apparatus 1 and Apparatus 2, Immediate-release dosage forms, Procedure for a pooled sample for immediate-release dosage forms*

Buffer stock solution: Dissolve 80 g of monobasic potassium phosphate and 20 g of dibasic potassium phosphate in 1 L of water. Add, with mixing, phosphoric acid or potassium hydroxide solution (45 in 100), as necessary to adjust the solution, such that the resulting solution has a pH of 6.0 ± 0.1.

Buffer: Prepare a 1-in-10 dilution of the *Buffer stock solution* to obtain a solution that has a pH of 6.0 ± 0.1.

Medium: *Buffer*, 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Mobile phase: Acetonitrile, tetrahydrofuran, and *Buffer* (35:5:60)

Standard stock solution: 0.05 mg/mL of USP Alprazolam RS in methanol

Standard solution: Add 50 mL of *Buffer stock solution* and 250 mL of water to a 500-mL flask. Add to the flask 5.0 mL of *Standard stock solution* for every 0.25 mg of

alprazolam contained in the Tablet being assayed. Dilute with water to volume.
Sample solution: Pass a portion of the solution under test through a suitable filter.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 10-cm; packing L7
Flow rate: 1 mL/min
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 500 theoretical plates
Relative standard deviation: NMT 3.0% for replicate injections
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved.
Tolerances: NLT 80% (*Q*) of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) is dissolved.

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩
▲**Mobile phase:** Acetonitrile, chloroform, butyl alcohol, glacial acetic acid, and water (850: 80: 50: 0.5: 20)▲ 2S (USP41)
Internal standard solution: 0.032 mg/mL of triazolam in acetonitrile
Standard solution: 0.025 mg/mL of USP Alprazolam RS in *Internal standard solution*
Sample solution: Transfer 1 Tablet to a container. Add 0.4 mL of water directly onto the Tablet, allow the Tablet to stand for 2 min, and then swirl the container to disperse the Tablet. For every 0.25 mg of alprazolam contained in the Tablet, add 10.0 mL of *Internal standard solution* to the container. Shake, and centrifuge if necessary.
▲**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 30-cm; packing L3
Flow rate: 2 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between triazolam and alprazolam
Relative standard deviation: NMT 2.0% for replicate injections▲ 2S (USP41)
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) in the Tablet taken:

$$\text{Result} = (R_U/R_S) \times C \times V \times (100/L)$$

R_U = peak area response ratio of alprazolam relative to the internal standard from the *Sample solution*
R_S = peak area response ratio of alprazolam relative to the internal standard from the *Standard solution*
C = concentration of USP Alprazolam RS in the *Standard solution* (mg/mL)
V = volume of the *Internal standard solution* used to prepare the *Sample solution* (mL)
L = label claim (mg/Tablet)

Acceptance criteria: Meet the requirements

IMPURITIES

Add the following:

▲• **Organic Impurities**
Mobile phase, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
Standard solution: 0.05 µg/mL of USP Alprazolam RS in *Diluent*
System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—See *Table 2* for the relative retention times.]
Suitability requirements
Resolution: NLT 1.5 between chlordiazepoxide related compound A and alprazolam related compound A, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of each degradation product in the portion of Tablets 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 alprazolam from the *Standard solution*
C_S = concentration of USP Alprazolam RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of alprazolam in the *Sample solution* (µg/mL)
F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlordiazepoxide related compound A[a]	0.7	1.1	0.5
Alprazolam related compound A[a]	0.8	1.7	0.5
Alprazolam	1.0	—	—
Nordazepam[a, b]	1.2	1.3	0.5
Alprazolam quinoline derivative[a, c]	1.4	1.1	0.5
2-Amino-5-chlorobenzophenone[a]	1.6	1.4	0.5
Any individual unspecified degradation product	—	1.0	0.5
Total degradation products	—	—	1.0

[a] If present, it is controlled as an unspecified degradation product.
[b] 7-Chloro-5-phenyl-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one.
[c] 7-Chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-*a*]quinolin-4-amine.▲ (Postponed on 1-Mar-2019)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

Change to read:

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Alprazolam RS
  ▲

USP Alprazolam Related Compound A RS
2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.
$C_{17}H_{15}ClN_4O$ 326.78

USP Chlordiazepoxide Related Compound A RS
7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepine 4-oxide;
Also known as 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide.
$C_{15}H_{11}ClN_2O_2$ 286.71 ▲ 2S (USP41)