Alprazolam Tablets

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$_3$H$_{13}$ClN$_4$).

**IDENTIFICATION**

**Add the following:**

**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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>2.5</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>9.0</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>9.1</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>11.0</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

| 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

**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.

**Tailing factor:** NMT 5.0, 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$_3$H$_{13}$ClN$_4$) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_S}{r_U} \right) \times \left( \frac{C_U}{C_S} \right) \times 100
\]

where:

- \( r_U \) = peak response from the **Sample solution**
- \( r_S \) = peak response from the **Standard solution**
- \( C_U \) = concentration of USP Alprazolam RS in the **Standard solution** (µg/mL)
- \( C_S \) = nominal concentration of alprazolam in the **Sample solution** (µg/mL)

**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 (35:35:60)

**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 × 30-cm; packing L7
Flow rate: 2 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 each degradation product in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{R_i}{R_0} \right) \times \left( \frac{C_i}{C_0} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \( R_0 \) = peak response of each degradation product from the Sample solution
- \( R_i \) = peak response of alprazolam from the Standard solution
- \( C_i \) = concentration of USP Alprazolam RS in the Standard solution (µg/mL)
- \( C_0 \) = 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%.

### IMPURITIES

**Add the following:**

<table>
<thead>
<tr>
<th>IMPURITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic Impurities</strong></td>
</tr>
<tr>
<td>Mobile phase, Diluent, System suitability solution, Sample solution, and Chromatographic system: Proceed as directed in the Assay.</td>
</tr>
<tr>
<td>Standard solution: 0.05 µg/mL of USP Alprazolam RS in Diluent</td>
</tr>
</tbody>
</table>

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

**Suitability requirements**
Resolution: NLT 1.5 between chlordiazepoxide related compound A and alprazolam related compound A.
System suitability solution
Relative standard deviation: NMT 3.0%, Standard solution

**Analysis**
Samples: Sample solution and Standard solution
Calculate the percentage of each degradation product in the portion of Tablets taken:

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide related compound A</td>
<td>0.7</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Alprazolam related compound A</td>
<td>0.8</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordazepam</td>
<td>1.2</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Alprazolam quinoline derivative</td>
<td>1.4</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>2-Amino-5-chlorobenzophenone</td>
<td>1.6</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td></td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Total degradation products</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

*If present, it is controlled as an unspecified degradation product.

**Notes:**
- 7-Chloro-3-phenyl-1H-benz[e]j1,4diazipin-2(3H)-one.
- 7-Chloro-1-methyl-5-phenyl-4,3′-oquinolin-4′-amine. (Proposed 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-3H-1,4-benzodiazepine.
C_{17}H_{15}ClN_{4}O$_{3}$ 326.78

USP Chlordiazepoxide Related Compound A RS
7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepine 4-oxide;
Also known as 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide.
C_{15}H_{11}ClN_{2}O$_{2}$ 286.71 ▲ 25 (USP41)