Add the following:

▲Alprazolam Orally Disintegrating Tablets■

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

IDENTIFICATION
- 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: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
  Diluent: Acetonitrile and water (60:40)
  Mobile phase: Acetonitrile, methanol, and *Buffer* (35:10:55)
  Standard solution: 10 µg/mL of USP Alprazolam RS in *Diluent*
  Sample solution: 10 µg/mL of alprazolam in *Diluent*. Prepare using 10 Tablets, and pass through a suitable filter. [NOTE—Sonicate with intermittent shaking to help dissolve, if necessary.]
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 221 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L7
  Column temperature: 30°
  Flow rate: 1.5 mL/min
  Injection volume: 30 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 1.5
  Relative standard deviation: NMT 2.0%
  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:

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

  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)
  Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISINTEGRATION** ⟨701⟩
  •**Test 1**• (RB 1-May-2012)
  Time: NMT 60 s
  •**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Disintegration Test 2*.
  Time: NMT 30 s• (RB 1-May-2012)

Change to read:

- **DISSOLUTION** ⟨711⟩
  •**Test 1**• (RB 1-May-2012)
  Medium: pH 6.0 phosphate buffer (•8 g/L of monobasic potassium phosphate and 2 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or diluted potassium hydroxide to a pH of 6.0 ± 0.1• (RB 1-May-2012)); 900 mL
  Apparatus 2: 50 rpm
  Time: 10 min
  Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*, except use an injection size of 100 µL.
  Standard stock solution: 50 µg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]
  Standard solution: (*L*/1000) µg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in µg/Tablet
  Sample solution: Pass a portion of the solution under test through a nylon membrane filter of 0.45-µm pore size, discarding the first few mL.
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved:

$$Result = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

  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* (mg/mL)
  V = volume of *Medium*, 900 mL
  L = label claim (mg/Tablet)
  Tolerances: NLT 80% (*Q*) of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) is dissolved.
  •**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
  Medium: pH 6.0 phosphate buffer (8 g/L of monobasic potassium phosphate and 2 g/L of dibasic potassium phosphate in water, adjusted with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL
  Apparatus 2: 50 rpm
  Time: 10 min
  Buffer: 1.36 g/L of monobasic potassium phosphate adjusted with dilute sodium hydroxide to a pH of 6.0
  Mobile phase: Acetonitrile and *Buffer* (35:65)
  Standard stock solution: 50 µg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]
  Standard solution: (*L*/500) µg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in µg/Tablet
  Sample solution: Pass a 5-mL aliquot of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 230 nm
  Column: 4.6-mm × 7.5-cm; 5-µm packing L7
  Flow rate: 1.5 mL/min
  Injection volume: 40 µL
  Run time: 3 times the retention time of alprazolam

System Suitability
  Sample: *Standard solution*
  Suitability requirements
    Tailing factor: NMT 2.0
    Relative standard deviation: NMT 2.0%
Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of
  alprazolam ($C_{17}H_{13}ClN_4$) dissolved:

$$Result = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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 (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)
Tolerances: NLT 70% (*Q*) of the labeled amount of
alprazolam ($C_{17}H_{13}ClN_4$) is dissolved.● (RB 1-May-2012)
• **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the
requirements

IMPURITIES
• **ORGANIC IMPURITIES**
  Buffer and **Diluent:** Prepare as directed in the *Assay*.
  Solution A: Acetonitrile, methanol, and *Buffer*
  (25:20:55)
  Solution B: Acetonitrile, methanol, and *Buffer* (40:5:55)
  Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
12	100	0
15	0	100
60	0	100
65	100	0
70	100	0

Standard solution: 0.6 µg/mL of USP Alprazolam RS in
Diluent
Sample solution: 200 µg/mL of alprazolam in *Diluent*.
Prepare using 10 Tablets, and pass through a suitable
filter.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 240 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L7
  Column temperature: 30°
  Flow rate: 1.2 mL/min
  Injection volume: 25 µL
System suitability
  Sample: *Standard solution*
  Suitability requirements
    Theoretical plates: NLT 2000
    Tailing factor: NMT 1.5
    Relative standard deviation: NMT 6.0%
Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of each impurity in the portion
  of Tablets taken:

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

r_U = peak response of each impurity 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*. Disregard any peaks
less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Alprazolam related compound A[a,b]	0.8	—	—
Alprazolam	1.0	—	—
2-Amino-5-chlorobenzophenone	2.9	1.9	0.5
Any other unknown impurity	—	1.0	0.5
Total impurities	—	—	2.0

[a] 2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.
[b] Disregard the peak due to alprazolam related compound A, because it
is a process impurity in alprazolam.

ADDITIONAL REQUIREMENTS
• **PACKAGING AND STORAGE:** Preserve in tight containers,
and store at controlled room temperature.

Add the following:

•• **LABELING:** When more than one *Disintegration* test is
given, the labeling states the *Disintegration* test used only if
Test 1 is not used. When more than one *Dissolution* test is
given, the labeling states the *Dissolution* test used only if
Test 1 is not used.● (RB 1-May-2012)
• **USP REFERENCE STANDARDS ⟨11⟩**
  USP Alprazolam RS▲USP35