Olanzapine Tablets

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Expert Committee	Chemical Medicines 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines 4 Expert Committee has revised the Olanzapine Tablets monograph. The purpose for the revision is to add two specified degradation products and the acceptance criteria to Table 2 of the *Organic Impurities* section based on a sponsor's approved new specifications. The limit of total impurities remains unchanged.

The Olanzapine Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Gerald Hsu, Senior Scientific Liaison, (240-221-2097 or gdh@usp.org).

Olanzapine Tablets

DEFINITION

Olanzapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$).

IDENTIFICATION

Change to read:

• **▲SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩**,** *Infrared Spectroscopy***:** 197K▲ (CN 1-May-2020)

Standard: Dissolve 10 mg of USP Olanzapine RS in 10 mL of chloroform. Evaporate to dryness on a water bath maintained at 55°. Use about 2 mg of the residue to prepare a potassium bromide pellet.

Sample: Crush NLT 5 Tablets, and transfer the powder equivalent to 30 mg of olanzapine to a suitable container. Add 30 mL of chloroform, and sonicate for 15 min to dissolve. Pass through a suitable filter, and evaporate the filtrate to dryness on a water bath maintained at 55°. Use about 2 mg of the residue to prepare a potassium bromide pellet.

Acceptance criteria: Meet the requirements

ASSAY

• **PROCEDURE**

[NOTE—A few drops of acetonitrile, not to exceed 5% of the final volume, may be added to the *Standard solution* and *Sample solution* before final dilution to reduce foaming.]

Buffer 1: 6.9 g/L of monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 2.5.

Buffer 2: 12 g/L of sodium dodecyl sulfate in *Buffer 1*

Mobile phase: Acetonitrile and *Buffer 2* (1:1)

System suitability solution: 0.1 mg/mL of USP Olanzapine RS and 0.01 mg/mL of USP Olanzapine Related Compound A RS in *Mobile phase*

Standard solution: 0.1 mg/mL of USP Olanzapine RS in *Mobile phase*

Sample solution: Transfer a known quantity of Tablets (NLT 5), equivalent to NLT 25 mg of olanzapine, to a suitable volumetric flask. Dilute with *Mobile phase* to volume, mix, and sonicate for 10 min. Centrifuge a portion of this solution, and dilute the clear supernatant with *Mobile phase* to obtain a solution containing about 0.1 mg/mL of olanzapine. [NOTE—Agitation of the flask may be necessary before sonication to prevent Tablets from adhering to the flask, making disintegration and dissolution difficult.]

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.5 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for olanzapine related compound A and olanzapine are 0.89 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between olanzapine and olanzapine related compound A, *System suitability solution*
Tailing factor: NMT 1.8, *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 olanzapine ($C_{17}H_{20}N_4S$) 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 Olanzapine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of olanzapine in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **DISSOLUTION** ⟨711⟩

Test 1
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Mobile phase: 10 g/L of ammonium acetate in a mixture of methanol and water (2:3). Adjust with hydrochloric acid to a pH of 4.0.
Standard solution: (*L*/1000) mg/mL of USP Olanzapine RS in *Medium*, where *L* is the label claim in mg/Tablet. Transfer 5.0 mL of this solution to a tube, and add 2.0 mL of *Mobile phase*.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a tube, and add 2.0 mL of *Mobile phase*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 15-cm; 5-µm packing L10
Flow rate: 1.5 mL/min
Injection volume: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Olanzapine 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 olanzapine ($C_{17}H_{20}N_4S$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 20 min
Mobile phase: 10 g/L of ammonium acetate in a mixture of methanol and water (2:3). Adjust with hydrochloric acid to a pH of 4.0. Pass through a suitable filter of 0.45-µm pore size.
Standard stock solution: 0.28 mg/mL of USP Olanzapine RS prepared as follows. Transfer a suitable amount of USP

Olanzapine RS to a suitable volumetric flask. Add about 8% of the final flask volume of acetonitrile. Sonicate to dissolve the Reference Standard. Dilute with *Medium* to volume.

Standard solution: (*L*/900) mg/mL of USP Olanzapine RS in *Medium* from *Standard stock solution*, where *L* is the label claim in mg/Tablet. Transfer 5.0 mL of this solution to a tube, and add 2.0 mL of *Mobile phase*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a tube, and add 2.0 mL of *Mobile phase*.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 260 nm
Column: 4.6-mm × 15-cm; 5-µm packing L11
Column temperature: 40°
Flow rate: 1.5 mL/min
Injection volume: 50 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Olanzapine 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 olanzapine ($C_{17}H_{20}N_4S$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**
[Note—A few drops of acetonitrile, not to exceed 5% of the final volume, may be added to the *Standard solution* and *Sample solution* before final dilution to reduce foaming.]

Buffer 1: 3.3 mL/L of phosphoric acid. Adjust with 50% sodium hydroxide to a pH of 2.5.
Buffer 2: 8.7 g/L of sodium dodecyl sulfate in *Buffer 1*
Buffer 3: 18.6 mg/L of edetate disodium (EDTA) in *Buffer 2*
Solution A: Acetonitrile and *Buffer 2* (12:13)
Solution B: Acetonitrile and *Buffer 2* (7:3)
Diluent: Acetonitrile and *Buffer 3* (2:3)
System suitability solution: 20 µg/mL of USP Olanzapine RS and 2 µg/mL each of USP Olanzapine Related Compound B RS and USP Olanzapine Related Compound C RS in *Diluent*
Standard solution: 0.002 mg/mL of USP Olanzapine RS in *Diluent*
Sensitivity solution: 0.4 µg/mL of USP Olanzapine RS in *Diluent* from the *Standard solution*
Sample solution: Nominally 0.375–0.500 mg/mL of olanzapine from a suitable number of Tablets prepared as follows. Transfer a known quantity of Tablets to a suitable volumetric flask, and dilute with *Diluent* to volume. Centrifuge a portion of this solution, and use the supernatant. [Note—Immediate agitation of the flask may be necessary to prevent Tablets from adhering to the flask, making dissolution and disintegration difficult. [**Caution**—Do not sonicate.] The *Sample solution* is stable for 12 h at room temperature and 48 h if refrigerated.]
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	100	0
20	0	100
25	0	100
27	100	0
35	100	0

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 5-µm packing L7
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 20 µL

System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 3.0 between olanzapine and olanzapine related compound C, *System suitability solution*
Tailing factor: NMT 1.5 for the olanzapine peak, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity 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 impurity from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Olanzapine RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of olanzapine in the *Sample solution* (mg/mL)
F = relative response factor for each impurity listed in *Table 2*

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
▲Olanzapine open ring analog [a] (if present)	0.18	1.0	0.50▲ (RB 1-May-2020)
Olanzapine lactam[b]	0.26	1.0	0.50

Table 2 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Olanzapine related compound B	0.30	2.3	0.50
Olanzapine thiolactam[c]	0.34	1.0	0.50
▲Olanzapine acetyl open ring analog[d] (if present)	0.37	1.0	0.50▲ (RB 1-May-2020)
Olanzapine related compound C	0.83	0.76	0.50
Olanzapine	1.0	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total impurities	—	—	1.5

[a] (*Z*)-3-(Hydroxymethylene)-4-(4-methylpiperazin-1-yl)-1,3-dihydro-2*H*-benzo[*b*][1,4]diazepine-2-thione.
[b] (*Z*)-4-(4-Methylpiperazin-1-yl)-3-(2-oxopropylidene)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one.
[c] (*Z*)-1-{4-(4-Methylpiperazin-1-yl)-2-thioxo-1*H*-benzo[*b*][1,4]diazepin-3(2*H*)-ylidene}propan-2-one.
[d] (*Z*)-(4-(4-Methylpiperazin-1-yl)-2-thioxo-1,2-dihydro-3*H*-benzo[*b*][1,4]diazepin-3-ylidene)methyl acetate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩
  USP Olanzapine RS
  USP Olanzapine Related Compound A RS
  5-Methyl-2-((2-nitrophenyl)amino)-3-thiophenecarbonitrile.
  $C_{12}H_9N_3O_2S$ 259.28
  USP Olanzapine Related Compound B RS
  2-Methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepin-4[5*H*]-one.
  $C_{12}H_{10}N_2OS$ 230.29
  USP Olanzapine Related Compound C RS
  2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepine 4′-*N*-oxide.
  $C_{17}H_{20}N_4OS$ 328.43