Azithromycin Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	25–Jan–2019
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Expert Committee	Chemical Medicines Monographs 1

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 1 Expert Committee intends to revise the Azithromycin Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph.

- *Dissolution Test 2* was validated using the Xterra RP-18 brand of L1 column. The typical retention time for azithromycin is about 6.7 min.

Labeling information has been added to support the inclusion of *Dissolution Test 2*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Praveen Pabba, Scientific Liaison to the Chemical Medicines Monographs 1 Expert Committee (301-816-8540 or pkp@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Azithromycin Tablets

DEFINITION

Azithromycin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$).

IDENTIFICATION

• **A.** 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: Dissolve 4.6 g of monobasic potassium phosphate anhydrous in 900 mL of water. Adjust with 1 N sodium hydroxide to a pH of 7.5, and dilute with water to 1 L.

Mobile phase: Acetonitrile and *Buffer* (65:35)

Standard solution: 1 mg/mL of USP Azithromycin RS in *Mobile phase*. Sonicate and shake as needed to dissolve.

Sample solution: Nominally 1 mg/mL of azithromycin in *Mobile phase* from NLT 20 Tablets, finely powdered. Sonicate and shake as needed to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 100 µL

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 azithromycin ($C_{38}H_{72}N_2O_{12}$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F \times 100$$

r_U = peak response of azithromycin from the *Sample solution*

r_S = peak response of azithromycin from the *Standard solution*

C_S = concentration of USP Azithromycin RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of azithromycin in the *Sample solution* (mg/mL)

P = potency of USP Azithromycin RS (µg/mg)

F = conversion factor, 0.001 mg/µg

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

DISSOLUTION ⟨711⟩

▲**Test 1**▲ (TBD)

Medium: pH 6.0 phosphate buffer; 900 mL

Apparatus 2: 75 rpm

Time: 30 min

Solution A: 4.4 mg/mL of dibasic potassium phosphate and 0.5 mg/mL of sodium 1-octanesulfonate, adjusted with phosphoric acid to a pH of 8.20 ± 0.05

Mobile phase: Acetonitrile, methanol, and *Solution A* (9:3:8)

Diluent: 17.5 mg/mL of dibasic potassium phosphate. Adjust with phosphoric acid to a pH of 8.00 ± 0.05. Prepare a mixture of this solution and acetonitrile (80:20).

Standard stock solution: Dissolve USP Azithromycin RS in *Medium* to obtain a solution having a known concentration of about (*L*/1000) mg/mL, where *L* is the label claim in mg/Tablet.

Standard solution: Dilute the *Standard stock solution* with *Diluent* to obtain a solution having a known concentration of about (*L*/2000) mg/mL, where *L* is the label claim in mg/Tablet.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute a portion of the filtrate with *Diluent* to obtain a solution having a theoretical concentration of about (*L*/2000) mg/mL, where *L* is the label claim in mg/Tablet, assuming complete dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

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 azithromycin ($C_{38}H_{72}N_2O_{12}$) dissolved:

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

r_U = peak response of azithromycin from the *Sample solution*

r_S = peak response of azithromycin from the *Standard solution*

C_S = concentration of USP Azithromycin RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) 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 0.1 M phosphate buffer; 900 mL

Apparatus 1: 100 rpm

Time: 20 min

Mobile phase, Diluent, Standard solution, Sample solution, Chromatographic system, and **Analysis:** Proceed as directed in *Dissolution Test 1*.

Tolerances: NLT 80% (*Q*) of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) is dissolved.▲ (TBD)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

• **ORGANIC IMPURITIES**

Protect all solutions containing azithromycin from light. Refrigerate the *Standard solution* and the *Sample solution* after preparation and during analysis, using a refrigerated autosampler set at 4°. The solutions must be analyzed within 24 h of preparation.

Solution A: Water and ammonium hydroxide (2000: 1.2). The pH of this solution is about 10.5.
Solution B: Acetonitrile, methanol, and ammonium hydroxide (1800: 200: 1.2)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	54	46
20	54	46
35	10	90
35.1	54	46
50.1	54	46

Buffer: 1.7 g/L of monobasic ammonium phosphate in water. Adjust with ammonium hydroxide to a pH of 10.
Diluent A: Methanol, acetonitrile, and *Buffer* (350:300:350)
Diluent B: Methanol and *Buffer* (1:1)
System suitability stock solution: 0.1 mg/mL each of USP Desosaminylazithromycin RS and USP Azithromycin Related Compound F RS in acetonitrile
System suitability solution: 0.028 mg/mL each of USP Desosaminylazithromycin RS and USP Azithromycin Related Compound F RS from *System suitability stock solution* in *Diluent A*
Standard stock solution: 0.4 mg/mL of USP Azithromycin RS in acetonitrile. Sonicate and shake as needed to dissolve.
Standard solution: 0.02 mg/mL of azithromycin from the *Standard stock solution* in *Diluent A*
Sensitivity solution: 0.004 mg/mL of azithromycin from the *Standard solution* in *Diluent A*
Sample stock solution: Nominally 14.3 mg/mL of azithromycin prepared as follows. Weigh and finely powder NLT 20 Tablets. Transfer nominally 1430 mg of azithromycin to a 100-mL volumetric flask. Add 75 mL of acetonitrile, and sonicate for NLT 15 min. Shake by mechanical means for NLT 15 min. Allow the solution to equilibrate to room temperature, dilute with acetonitrile to volume, and mix.
Sample solution: Nominally 4 mg/mL of azithromycin prepared as follows. Centrifuge an aliquot of the *Sample stock solution* for NLT 15 min. Transfer 7.0 mL of the supernatant to a 25-mL volumetric flask, and dilute with *Diluent B* to volume.
Blank: *Diluent A*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 3.5-µm packing L1
Temperatures
Autosampler: 4°
Column: 50°
Flow rate: 1.2 mL/min
Injection volume: 100 µL
System suitability
Samples: *System suitability solution*, *Standard solution*, and *Sensitivity solution*
Suitability requirements
Resolution: NLT 1.0 between desosaminylazithromycin and azithromycin related compound F, *System suitability solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution*, *Sample solution*, and *Blank*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times F_1 \times (1/F_2) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of azithromycin from the *Standard solution*
C_S = concentration of USP Azithromycin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of azithromycin in the *Sample solution* (mg/mL)
P = potency of USP Azithromycin RS (µg/mg)
F_1 = conversion factor, 0.001 mg/µg
F_2 = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. The reporting level for impurities is 0.1%. Disregard any peaks in the *Sample solution* that correspond to peaks in the *Blank*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Azithromycin *N*-oxide[a]	0.20	0.42	1.0
3′-(*N*,*N*-Didemethyl)-3′-*N*-formylazithromycin[b, c]	0.29 0.30	1.7	1.0
3′-(*N*,*N*-Didemethyl)azithromycin (aminoazithromycin)[d]	0.34	0.49	0.5
Azithromycin related compound F[c, e]	0.40 0.46	5.5	1.0
Desosaminylazithromycin[f]	0.47	1.1	0.5
N-Demethylazithromycin[g]	0.50	0.47	0.7
3′-De(dimethylamino)-3′-oxoazithromycin[h]	0.87	1.7	1.0
Azaerythromycin A[i, j]	0.94	—	—
Azithromycin	1.0	—	—
2-Desethyl-2-propylazithromycin[i, k]	1.10	—	—
3′-*N*-Demethyl-3′-*N*-[(4-methylphenyl)sulfonyl] azithromycin[i, l]	1.11	—	—
3-Deoxyazithromycin (azithromycin B)[i, m]	1.14	—	—
Any individual unspecified impurity[i]	—	1.0	0.2

Table 2 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities[i]	—	—	5.0

[a] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylazinoyl)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[b] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[c] The system may resolve two rotamers. The limit is for the sum of the two rotamers.

[d] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-amino-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[e] 3′-(*N*-Demethyl)-3′-*N*-formylazithromycin; (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-(*N*-methyl)formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[f] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-Ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[g] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-methylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[h] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3,3-dimethyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-oxo-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[i] Process impurities that are controlled in the drug substance are not to be reported. They are listed here for information only. The unspecified impurities and total impurities limits do not include these impurities.

[j] 9-Deoxo-9a-aza-9a-homoerythromycin A.

[k] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-propyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one dihydrate.

[l] (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-[*N*-(4-methylphenylsulfonyl)-*N*-methylamino]-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[m] (2*R*,3*R*,4*S*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-4,10-dihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

Add the following:

▲• **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.▲ (TBD)

- **USP REFERENCE STANDARDS** ⟨11⟩

USP Azithromycin RS

USP Azithromycin Related Compound F RS
3′-(*N*-Demethyl)-3′-*N*-formylazithromycin;
(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3-(*N*-methyl)formamido-3,4,6-trideoxy-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.
$C_{38}H_{70}N_2O_{13}$ 762.97

USP Desosaminylazithromycin RS
(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-2-Ethyl-3,4,10,13-tetrahydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.
$C_{30}H_{58}N_2O_9$ 590.79