

## Azithromycin for Oral Suspension

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 1 Expert Committee has revised the Azithromycin for Oral Suspension monograph. The purpose of this revision is to widen the *Organic Impurities* acceptance criterion for N-demethylazithromycin from NMT 0.50% to NMT 0.7% to accommodate FDA-approved drug products with different limits.

The Azithromycin for Oral Suspension Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Claire Chisolm, Senior Scientist II (301-230-3215 or [cnc@usp.org](mailto:cnc@usp.org)).

## Azithromycin for Oral Suspension

### DEFINITION

Azithromycin for Oral Suspension is a dry mixture of Azithromycin and one or more buffers, sweeteners, diluents, anticaking agents, and flavors. It contains 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 azithromycin peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B. SPECTROSCOPIC IDENTIFICATION TESTS** (197), *Infrared Spectroscopy*: 197A
  - Standard:** 25 mg/mL of [USP Azithromycin RS](#) in [acetonitrile](#). Pass the solution through a suitable filter, and remove the solvent by natural evaporation.
  - Sample:** Equivalent to 25 mg/mL of azithromycin from Azithromycin for Oral Suspension in [acetonitrile](#). Pass the solution through a suitable filter, and remove the solvent by natural evaporation.
  - Analysis:** Examine the spectra of the *Standard* and the *Sample* in the range between 3800 and 650  $cm^{-1}$ .
  - Acceptance criteria:** The *Sample* exhibits bands at about 900, 995, 1165, 1376, 1456, 1725, and 2936  $cm^{-1}$  similar to the spectrum from the *Standard* similarly obtained.

### ASSAY

#### • PROCEDURE

[NOTE—Solutions containing azithromycin are stable up to 12 h at 10°.]

**Solution A:** Dissolve 8.7 g of [dipotassium hydrogen phosphate anhydrous](#) in 1000 mL of [water](#) and adjust with [potassium hydroxide](#) or dilute [phosphoric acid](#) to a pH of 8.2.

**Solution B:** [Acetonitrile](#)

**Mobile phase:** *Solution A* and *Solution B* (30:70)

**Diluent:** [Acetonitrile](#), [methanol](#), and [water](#) (40:40:20)

**Standard solution:** 0.6 mg/mL of [USP Azithromycin RS](#) in *Diluent*. Sonicate in cool water to dissolve as needed.

**Sample solution:** Nominally 0.6 mg/mL of azithromycin in *Diluent* prepared as follows. Transfer an accurately measured portion of the constituted suspension to a suitable volumetric flask. Add *Diluent* equal to 50% of the volume of the flask, and sonicate for 20 min with shaking in cool water. Dilute with *Diluent* to volume. Pass a portion of this solution through a suitable filter of 0.45- $\mu m$  pore size.

#### Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm  $\times$  25-cm; 5- $\mu m$  packing [L1](#)

**Temperatures**

**Autosampler:** 10°

**Column:** 30°

**Flow rate:** 2 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 2 times the retention time of azithromycin

### 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 Azithromycin for Oral Suspension 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

• [DELIVERABLE VOLUME](#) (698): Meets the requirements

• [UNIFORMITY OF DOSAGE UNITS](#) (905).

**For single-unit containers:** Meets the requirements

• [DISSOLUTION](#) (711).

[NOTE—Solutions containing azithromycin are stable up to 12 h at 10°.]

**Medium:** Sodium phosphate buffer, pH 6.0 (14.2 g/L of [sodium phosphate, dibasic, anhydrous](#) in [water](#), adjusted with [dilute hydrochloric acid](#) to pH 6.0); 900 mL

**Apparatus 2:** 50 rpm

**Time:** 30 min

**Solution A:** Dissolve 8.7 g of [dipotassium hydrogen phosphate anhydrous](#) in 1000 mL of [water](#) and adjust with [potassium hydroxide](#) or dilute [phosphoric acid](#) to a pH of 8.2.

**Solution B:** [Acetonitrile](#)

**Mobile phase:** *Solution A* and *Solution B* (35:65)

**Standard stock solution:** 0.55 mg/mL of [USP Azithromycin RS](#) prepared as follows. Transfer an accurately weighed amount of [USP Azithromycin RS](#) to a suitable volumetric flask. Add [acetonitrile](#) to fill 5% of the volume of the flask and sonicate in cool water for 5 min to dissolve completely. Dilute with *Medium* to volume.

### Standard solution

**For Azithromycin for Oral Suspension labeled to contain 100 mg/5 mL:** 0.11 mg/mL of [USP Azithromycin RS](#) in *Medium* from *Standard stock solution*

**For Azithromycin for Oral Suspension labeled to contain 200 mg/5 mL:** 0.22 mg/mL of [USP Azithromycin RS](#) in *Medium* from *Standard stock solution*

**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 210 nm

**Column:** 4.6-mm × 15-cm; 5-μm packing [L1](#)

### Temperatures

**Autosampler:** 10°

**Column:** 50°

**Flow rate:** 2 mL/min

**Injection volume:** 100 μL

**Run time:** NLT 2 times the retention time of azithromycin

### 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 ( $Q$ ) of the labeled amount of azithromycin ( $C_{38}H_{72}N_2O_{12}$ ) dissolved:

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

$r_U$  = 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 of Azithromycin for Oral Suspension (mg/5 mL)

$D$  = dilution factor, necessary only if the *Sample solution* requires dilution (mL/mL)

$d$  = density of the *Sample solution* (g/mL)

$W$  = weight of Azithromycin for Oral Suspension taken (g)

$V$  = volume of *Medium*, 900 mL

**Tolerances:** NLT 75% ( $Q$ ) of the labeled amount of azithromycin ( $C_{38}H_{72}N_2O_{12}$ ) is dissolved.

## IMPURITIES

### Change to read:

#### • ORGANIC IMPURITIES

**Solution A:** Dissolve 1.8 g of [disodium hydrogen phosphate dihydrate](#) in 1000 mL of [water](#) and adjust with dilute [phosphoric acid](#) to a pH of 8.9.

**Solution B:** [Acetonitrile](#) and [methanol](#) (75:25)

**Mobile phase:** See [Table 1](#).

**Table 1**

<b>Time (min)</b>	<b>Solution A (%)</b>	<b>Solution B (%)</b>
0	50	50
25	45	55
30	40	60
80	25	75
81	50	50
90	50	50

**Buffer:** Dissolve 1.73 g of [ammonium dihydrogen phosphate](#) in 1000 mL of [water](#) and adjust with ammonia solution to a pH of 10.0 ± 0.05.

**Diluent:** *Buffer*, [methanol](#), and [acetonitrile](#) (35:35:30)

**System suitability solution:** 0.015 mg/mL of [USP Azithromycin Related Compound F RS](#) and 0.025 mg/mL of [USP Desosaminylazithromycin RS](#) in *Diluent*

**Standard solution:** 0.04 mg/mL of [USP Azithromycin RS](#) in *Diluent*. Sonicate in cool water to dissolve as needed.

**Sample solution:** Nominally 4.0 mg/mL solution of azithromycin in *Diluent* prepared as follows. Transfer a portion of the constituted suspension, equivalent to about 400.0 mg of azithromycin, to a 100-mL volumetric flask. Add 70 mL of *Diluent* and sonicate in cool water for about 15 min. Dilute with *Diluent* to volume. Pass a portion of this solution through a suitable filter of 0.45-µm pore size.

### Chromatographic system

(See [Chromatography](#) (621), [System Suitability](#).)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing [L1](#)

#### Temperatures

**Autosampler:** 10°

**Column:** 60°

**Flow rate:** 0.9 mL/min

**Injection volume:** 100 µL

**Run time:** NLT 2 times the retention time of azithromycin

### System suitability

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

#### Suitability requirements

**Resolution:** NLT 1.5 between desosaminylazithromycin and azithromycin related compound F, *System suitability solution*

**Relative standard deviation:** NMT 5.0%, *Standard solution*

### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Azithromycin for Oral Suspension 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](#). Disregard any peaks at relative retention times before 0.29 and after 1.31.

**Table 2**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Azithromycin <i>N</i> -oxide <sup>a</sup>	0.29	0.43	0.50
3'-( <i>N,N</i> -Didemethyl)-3'- <i>N</i> -formylazithromycin <sup>b</sup>	0.37	1.7	0.50
3'-( <i>N,N</i> -Didemethyl)azithromycin(aminoazithromycin) <sup>c</sup>	0.43	1.0	0.50
Azithromycin related compound F <sup>d</sup>	0.51	3.8	0.50
Desosaminylazithromycin <sup>e</sup>	0.54	1.0	0.30
<i>N</i> -Demethylazithromycin <sup>f</sup>	0.61	1.0	▲0.7▲ (RB 1-Jun-2022)
Azithromycin C (3''- <i>O</i> -demethylazithromycin) <sup>g,h</sup>	0.73	—	—
3'-De(dimethylamino)-3'-oxoazithromycin <sup>i</sup>	0.76	1.5	0.50
Azaerythromycin A <sup>h,j</sup>	0.83	—	—
Specified unidentified impurity <sup>h,k</sup>	0.92	—	—
Azithromycin	1.0	—	—
2-Desethyl-2-propylazithromycin <sup>h,l</sup>	1.23	—	—
3'- <i>N</i> -Demethyl-3'- <i>N</i> -[(4-methylphenyl)sulfonyl]azithromycin <sup>h,m</sup>	1.26	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
3-Deoxyazithromycin (azithromycin B) <sup>h,n</sup>	1.31	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total degradation products	—	—	3.5

<sup>a</sup> (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- $\alpha$ -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)- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>b</sup> (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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>c</sup> (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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>d</sup> 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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>e</sup> (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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>f</sup> (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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>g</sup> (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- $\alpha$ -L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-dimethylamino- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>h</sup> 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.

<sup>i</sup> (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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>j</sup> 9-Deoxy-9a-aza-9a-homoerythromycin A.

<sup>k</sup> Specified unidentified impurity.

<sup>l</sup> (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- $\alpha$ -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)- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one dihydrate.

<sup>m</sup> (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- $\alpha$ -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- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

<sup>n</sup> (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- $\alpha$ -L-*ribo*-hexopyranosyl)oxy]-2-ethyl-4,10-dihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

## SPECIFIC TESTS

- **pH** {791}

### For a solid packaged in single-unit containers

**Sample:** The suspension constituted as directed in the labeling

**Acceptance criteria:** 9.0–11.0

**For a solid packaged in multiple-unit containers**

**Sample:** The suspension constituted as directed in the labeling

**Acceptance criteria:** 8.5–11.0

**ADDITIONAL REQUIREMENTS**

● **PACKAGING AND STORAGE:** Preserve in tight containers.

● **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- $\alpha$ -*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- $\beta$ -*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- $\beta$ -*D*-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

$C_{30}H_{58}N_2O_9$                       590.79

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