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# Azithromycin for Oral Suspension

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click https://www.uspnf.com/rb-azithromycin-for-os-20240426.

## 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-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:** 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

***Change to read:***

• **Dissolution ⟨711⟩**

▲**Test 1**▲ (RB 1-May-2024)

[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.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

[NOTE—Solutions containing azithromycin may be stable for 72 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 a pH of 6.0); 900 mL

**Apparatus 2:** 25 rpm

**Time:** 45 min

**Buffer:** Dissolve 8.7 g of dipotassium hydrogen phosphate anhydrous in 1000 mL of water. Adjust with potassium hydroxide or dilute phosphoric acid to a pH of 8.2.

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

**Standard stock solution:** 0.55 mg/mL of USP Azithromycin RS prepared as follows. Transfer a quantity of USP Azithromycin RS to an appropriate volumetric flask and dissolve in 5% of the flask volume of acetonitrile. Sonicate in cool water for about 5 min. Dilute with *Medium* to volume.

**Standard solution**

**For Azithromycin for Oral Suspension constituted to 100 mg/5 mL:** 0.11 mg/mL of USP Azithromycin RS from *Standard stock solution* in *Medium*

**For Azithromycin for Oral Suspension constituted to 200 mg/5 mL:** 0.22 mg/mL of USP Azithromycin RS from *Standard stock solution* in *Medium*

**Sample solution:** Proceed constitution as directed in the *Labeling*. Determine the density, $d$ (g/mL), of the constituted suspension using appropriate means. Using a suitable syringe, collect approximately 5 mL of suspension, and record the weight. With the paddles lowered, gently add the collected suspension into each vessel containing the *Medium*. Start rotating the paddles. Reweigh the syringe, and determine the weight, $W$ (g), of suspension delivered into each vessel. At the end of 45 min, withdraw a suitable volume of the solution under test. Pass through a suitable filter, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

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

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (d/W) \times (1/L) \times 100$$

$r_U$ = 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)

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

$d$ = density of the constituted suspension (g/mL)

$W$ = weight of the constituted suspension taken (g)

$L$ = label claim of constituted suspension (100 mg/5 mL, or 200 mg/5 mL)

**Tolerances:** NLT 80% ($Q$) of the labeled amount of azithromycin ($C_{38}H_{72}N_2O_{12}$) is dissolved. ▲ (RB 1-May-2024)

## IMPURITIES

• **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**

| Time (min) | Solution A (%) | Solution 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 *N*-oxide[a] | 0.29 | 0.43 | 0.50 |
| 3'-(*N*,*N*-Didemethyl)-3'-*N*-formylazithromycin[b] | 0.37 | 1.7 | 0.50 |
| 3'-(*N*,*N*-Didemethyl)azithromycin(aminoazithromycin)[c] | 0.43 | 1.0 | 0.50 |
| Azithromycin related compound F[d] | 0.51 | 3.8 | 0.50 |
| Desosaminylazithromycin[e] | 0.54 | 1.0 | 0.30 |
| *N*-Demethylazithromycin[f] | 0.61 | 1.0 | 0.7 |
| Azithromycin C (3"-*O*-demethylazithromycin)[g,h] | 0.73 | — | — |
| 3'-De(dimethylamino)-3'-oxoazithromycin[i] | 0.76 | 1.5 | 0.50 |
| Azaerythromycin A[h,j] | 0.83 | — | — |
| Specified unidentified impurity[h,k] | 0.92 | — | — |
| Azithromycin | 1.0 | — | — |
| 2-Desethyl-2-propylazithromycin[h,l] | 1.23 | — | — |
| 3'-*N*-Demethyl-3'-*N*-[(4-methylphenyl)sulfonyl]azithromycin[h,m] | 1.26 | — | — |
| 3-Deoxyazithromycin (azithromycin B)[h,n] | 1.31 | — | — |
| Any individual unspecified degradation product | — | 1.0 | 0.20 |
| Total degradation products | — | — | 3.5 |

[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] (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.

[d] 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.

[e] (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.

[f] (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.

[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-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-dimethylamino-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

[h] 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.

[i] (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.

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

[k] Specified unidentified impurity.

[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-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.

[m] (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.

[n] (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.

## 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.

***Add the following:***

▲• **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-May-2024)

• **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.
$C_{38}H_{70}N_2O_{13}$ 762.98

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.
$C_{30}H_{58}N_2O_9$ 590.80

**Chromatographic Database Information:** Chromatographic Database

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