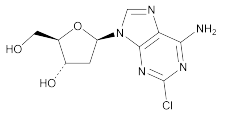
Table 1

Name	Relative Retention Time	Limit (%)
2,6-Diaminopurine-2′-deoxyriboside	about 0.41	0.20
2′-Deoxyadenosine	about 0.47	0.20
2-Chloroadenine	about 0.60	0.20
2-Methoxy-2′-deoxyadenosine (cladribine related compound A)	about 0.91	0.20
Any individual unspecified impurity	—	0.10
Total impurities	—	1.0

Cladribine



$C_{10}H_{12}ClN_5O_3$ 285.69
Adenosine, 2-chloro-2′-deoxy-.
2-Chloro-2′-deoxyadenosine [4291-63-8].

» Cladribine contains not less than 98.0 per cent and not more than 102.0 per cent of $C_{10}H_{12}ClN_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and protect from light. Store between 2 ° and 8 °.

USP Reference standards ⟨11⟩**—**
USP Cladribine RS
USP Cladribine Related Compound A RS

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.

Specific rotation ⟨781S⟩**:** between −17.0° and −21.0°.

Test solution: 10 mg per mL, in dimethylformamide.

Water, *Method I* ⟨921⟩**:** not more than 4.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Buffer, Diluent, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay*.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; and the tailing factor is not more than 2.0.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the per centage of each impurity in the portion of Cladribine taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of each individual impurity, and r_s is the sum of the responses of all the peaks. Refer to *Table 1* for the impurity limits.

Assay—

Buffer—Dissolve 9.96 g of triethylamine phosphate, accurately weighed, in 500 mL of water, and add another 500 mL of water. Adjust with potassium hydroxide to a pH of 6.1.

Diluent—Prepare a mixture of water and methanol (90:10).

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and methanol (78:22). Make adjustments if necessar y (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Cladribine RS and USP Cladribine Related Compound A RS in *Diluent* to obtain known concentrations of about 0.02 mg per mL each.

Standard preparation—Dissolve an accurately weighed quantity of USP Cladribine RS in *Diluent* to obtain a concentration of 0.5 mg per mL.

Assay preparation—Transfer about 25 mg of Cladribine, accurately weighed, to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

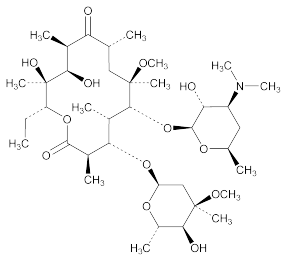
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; the tailing factor for the cladribine peak in the *System suitability solution* is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{10}H_{12}ClN_5O_3$ in the portion of Cladribine taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cladribine RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Clarithromycin



$C_{38}H_{69}NO_{13}$ 747.95
Erythromycin, 6-*O*-methyl-.
6-*O*-Methylerythromycin [81103-11-9].

» Clarithromycin contains not less than 96.0 percent and not more than 102.0 per cent of $C_{38}H_{69}NO_{13}$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Clarithromycin RS
USP Clarithromycin Identity RS

Identification, *Infrared Absorption* ⟨197K⟩**.**

Specific rotation ⟨781S⟩**:** between −94° and −102° (*t* = 20°).

Test solution: 10 mg per mL, in methylene chloride.

Crystallinity ⟨695⟩**:** meets the requirements.

pH ⟨791⟩**:** between 8.0 and 10.0, determined in a 1 in 500 suspension of it in a mixture of water and methanol (19:1).

Water, *Method I* ⟨921⟩: not more than 2.0%.

Residue on ignition ⟨281⟩**:** not more than 0.2%, 0.5 g of it being taken, the charred residue being moistened with 1 mL of sulfuric acid.

Heavy metals: not more than 0.002%.

Test solution—Dissolve 1.0 g of it in an 85% (v/v) solution of dioxane in water, and dilute with the same diluent to 20 mL. Transfer 12 mL of this solution to a color-comparison tube.

Blank—Add 10 mL of an 85% (v/v) solution of dioxane in water and 2 mL of the *Test solution* to a color-comparison tube.

Standard solution—Prepare using standard lead solution (1 ppm Pb) obtained by diluting standard lead solution (100 ppm Pb) with an 85% (v/v) solution of dioxane in water. Add 10 mL of this solution (1 ppm Pb) and 2 mL of the *Test solution* to a color-comparison tube. To each of the three tubes containing the *Test solution,* the *Blank,* and the *Standard solution* add 2 mL of pH 3.5 acetate buffer, mix, add 1.2 mL of thioacetamide–glycerin base TS, and mix. Compared to the *Blank,* the *Standard solution* shows a slight brown color. After 2 minutes, any brown color in the *Test solution* is not more intense than that in the *Standard solution*.

Related substances—

Solution A—Prepare a solution containing 4.76 g of monobasic potassium phosphate per L. Adjust with dilute phosphoric acid (l in 10) or potassium hydroxide (45% w/v) to a pH of 4.4. Pass this solution through a C18 filtration kit.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed under *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solution—Prepare a mixture of acetonitrile and water (50:50).

Standard solution A—Transfer about 75 mg of USP Clarithromycin RS, accurately weighed, to a 50-mL volumetric flask, and dissolve in 25 mL of acetonitrile. Dilute with water to volume, and mix.

Standard solution B—Transfer 5.0 mL of *Standard solution A* to a 100-mL volumetric flask, dilute with *Diluting solution* to volume, and mix.

Standard solution C—Transfer 1.0 mL of *Standard solution B* to a 10-mL volumetric flask, dilute with *Diluting solution* to volume, and mix. This solution contains about 0.0075 mg of USP Clarithromycin RS per mL.

Standard solution D—Transfer about 15 mg of USP Clarithromycin Identity RS, accurately weighed, to a 10-mL volumetric flask, dissolve in 5.0 mL of acetonitrile, dilute with water to volume, and mix.

Test solution—Transfer about 75 mg of Clarithromycin, accurately weighed, to a 50-mL volumetric flask, dissolve in 25 mL of acetonitrile, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 10-cm column that contains packing L1 and is maintained at a constant temperature of about 40 °. The flow rate is about 1.1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0→32	75→40	25→60	linear gradient
32→34	40	60	isocratic
34→36	40→75	60→25	linear gradient
36→42	75	25	isocratic

Relative retention times with reference to clarithromycin (retention time = about 11 minutes) include the following: impurity I = about 0.38; impurity C = about 0.89; impurity F = about 1.33; impurity A = about 0.42; impurity D = about 0.96; impurity P = about 1.35; impurity J = about 0.63; impurity N = about 1.15; impurity K = about 1.59; impurity L = about 0.74; impurity E = about 1.27; impurity G = about 1.72; impurity B = about 0.79; impurity 0 = about 1.38; impurity H = about 1.82; and impurity M = about 0.81.

System suitability—Chromatograph *Standard solution B,* and record the responses as directed for *Procedure:* the tailing factor for the main clarithromycin peak is not more than 1.7. Chromatograph *Standard solution D,* and record the responses as directed for *Procedure:* the peak-to-valley ratio (H_P / H_V) of impurity D and clarithromycin is not less than 3.0, where H_P is the height above the baseline of the peak due to impurity D; and H_V is the height above the baseline of the lowest point of the curve separating this peak from the peak due to clarithromycin.

Procedure—Separately inject equal volumes (about 10 µL) of the *Diluting solution, Standard solution B, Standard solution D, Standard solution C,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of each impurity in the Clarithromycin taken by the formula:

$$50(C_C / W)(r_i F / r_C)P$$

in which C_C is the concentration, in mg per mL, of USP Clarithromycin RS in *Standard solution C; W* is the weight, in mg, of Clarithromycin taken to prepare the *Test solution;* r_i is the peak area response for any individual impurity observed in the chromatogram obtained from the *Test solution; F* is 1.0, or the correction factor of 0.27, and 0.15 applied to the responses for peaks at relative retention times in relation to that of clarithromycin of about 1.72, and 1.82, corresponding to related compound G and related compound H, respectively; r_C is the peak area response of the main clarithromycin peak in the chromatogram obtained from *Standard solution C;* and *P* is the purity of USP Clarithromycin RS taken to prepare *Standard solution A*. Not more than 1.0% of any single related compound is found, not more than four related compounds exceed the limit of 0.4%, and the total of all related compounds is not more than 3.5%.

Assay—

Solution A, Solution B, Diluting solution, and *Standard solution D*—Proceed as directed in the test for *Related substances*.

Standard preparation—Use *Standard solution A,* prepared as directed in the test for *Related substances*.

Assay preparation—Use the *Test solution,* prepared as directed in the test for *Related substances*.

Chromatographic system—Proceed as directed in the test for *Related substances*. In addition, the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area responses for the major peaks. Calculate the per cent-

age of $C_{38}H_{69}NO_{13}$ in the portion of Clarithromycin taken by the formula:

$$50(C_S / W)(r_U / r_S)P$$

in which C_S is the concentration, in mg per mL, of USP Clarithromycin RS in the *Standard preparation; W* is the weight, in mg, of Clarithromycin taken to prepare the *Assay preparation;* r_U and r_S are the clarithromycin peak area responses obtained from the chromatograms of the *Assay preparation* and the *Standard preparation,* respectively; and *P* is the purity of USP Clarithromycin RS taken to prepare the *Standard preparation.*

Clarithromycin for Oral Suspension

» Clarithromycin for Oral Suspension is a dry mixture of Clarithromycin, dispersing agents, diluents, preservatives, and flavorings. It contains not less than 90.0 per cent and not more than 115.0 percent of the labeled amount of $C_{38}H_{69}NO_{13}$, the labeled amount being 25 mg or 50 mg per mL when constituted as directed in the labeling.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩**—**
USP Clarithromycin RS

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Uniformity of dosage units ⟨905⟩**—**

FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.

Deliverable volume ⟨698⟩**—**

FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.

pH ⟨791⟩**:** between 4.0 and 5.4, in the suspension constituted as directed in the labeling.

Loss on drying ⟨731⟩**—**Dry about 1 g of it in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours: it loses not more than 2.0% of its weight.

Assay—

Mobile phase—Prepare a mixture of methanol and 0.067 M monobasic potassium phosphate (600:400), adjust with phosphoric acid to a pH of 3.5, pass through a filter having a 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Clarithromycin RS in methanol, shaking and sonicating if necessary to effect dissolution, to obtain a solution having a known concentration of about 2100 µg of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL, taking into account the stated potency, in µg per mg, of USP Clarithromycin RS. Transfer 10.0 mL of this stock solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Standard preparation.* This solution contains about 415 µg of clarithromycin per mL.

Assay preparation—Constitute Clarithromycin for Oral Suspension as directed in the labeling. Transfer an accurately measured volume of the constituted Oral Suspension, equivalent to about 1 to 2 g of clarithromycin, with the aid of about 330 mL of 0.067 M dibasic potassium phosphate, to a 1000-mL volumetric flask containing about 50 mL of 0.067 M dibasic potassium phosphate. Shake by mechanical means for 30 minutes, dilute with methanol to volume, and mix. Sonicate for about 30 minutes, and allow to cool. Dilute with methanol to volume, add a magnetic stirring bar, and stir for 60 minutes. Allow to settle, and transfer an accurately measured volume of the clear supernatant, equivalent to about 20 mg of clarithromycin, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, mix, and pass through a filter having a 0.5-µm or finer porosity. Use the filtrate as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector, an optional guard column that contains packing L1, and a 4.6-mm × 15-cm analytical column that contains packing L1 and is maintained at a constant temperature of about 50 °. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency, determined from the clarithromycin peak, is not less than 2100 theoretical plates when calculated by the formula:

$$5.545(t/W_{h/2})^2$$

the tailing factor is not less than 1.0 and not more than 1.7; the capacity factor, k', is not less than 2.5 and not more than 6; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{38}H_{69}NO_{13}$ in each mL of the constituted Oral Suspension taken by the formula:

$$50(C/Vv)(r_U / r_S)$$

in which *C* is the concentration, in µg per mL, of clarithromycin ($C_{38}H_{69}NO_{13}$) in the *Standard preparation; V* is the volume, in mL, of constituted Oral Suspension taken to prepare the *Assay preparation; v* is the volume, in mL, of clear supernatant taken to prepare the *Assay preparation;* and r_U and r_S are the clarithromycin peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Clarithromycin Tablets

DEFINITION

Clarithromycin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of $C_{38}H_{69}NO_{13}$.

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**

Mobile phase: Methanol and 0.067 M monobasic potassium phosphate (13:7). Adjust with phosphoric acid to a pH of 4.0, and pass through a suitable filter.

Standard stock solution: 625 µg/mL of clarithromycin from USP Clarithromycin RS dissolved in methanol. [NOTE—Shake and sonicate to facilitate dissolution.]

Standard solution: 125 µg/mL of clarithromycin from *Standard stock solution* in *Mobile phase*. Pass through a suitable filter.

System suitability stock solution: 625 µg/mL of USP Clarithromycin Related Compound A RS in methanol.

System suitability solution: 125 µg/mL of USP Clarithromycin RS from *Standard stock solution* and 125 µg/mL of USP Clarithromycin Related Compound A RS from *System suitability stock solution* in *Mobile phase*

Sample stock solution: Equivalent to 4 mg/mL of clarithromycin from finely powdered Tablets in methanol. [NOTE—Shake by mechanical means for 30 min to disperse and allow any insoluble matter to settle.]