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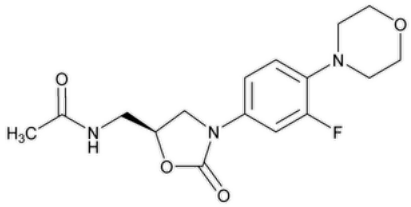
Linezolid



$C_{16}H_{20}FN_3O_4$ 337.35

Acetamide, *N*-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, (*S*)-;

N-[[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide CAS RN®: 165800-03-3.

DEFINITION

Linezolid contains NLT 98.0% and NMT 102.0% of linezolid ($C_{16}H_{20}FN_3O_4$), calculated on the anhydrous, solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020) **:** If a difference appears in the IR spectra of the analyte and the Standard, dissolve equal portions of the test specimen and the USP Reference Standard in equal volumes of methanol. Evaporate the solutions to dryness and perform the test on the residues.

• **B.** 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: 1.4 g/L of monobasic potassium phosphate

Solution A: Methanol, acetonitrile, and *Buffer* (15:5:80)

Solution B: Methanol and *Buffer* (50:50)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	80	20
8	57	43
18	0	100
25	0	100

Return to original conditions, and equilibrate the system for 5 min.

Diluent: Acetonitrile and water (35:65)

System suitability solution: 50 µg/mL each of USP Linezolid RS and USP Linezolid Related Compound D RS in *Diluent*

Standard solution: 0.08 mg/mL of USP Linezolid RS in *Diluent*

Sample solution: 0.08 mg/mL of Linezolid in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 7.5-cm; 3-µm packing L1

Temperatures

Autosampler: 15°

Column: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times for linezolid and linezolid related compound D are about 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 3.0 between linezolid and linezolid related compound D, *System suitability solution*

Tailing factor: NMT 1.5, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of linezolid ($C_{16}H_{20}FN_3O_4$) in the portion of Linezolid 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 Linezolid RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous, solvent-free basis

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.2%
- **ORGANIC IMPURITIES**

Buffer, Solution A, Solution B, Mobile phase, Diluent, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 0.0008 mg/mL of USP Linezolid RS in *Diluent*

Sample solution: 0.8 mg/mL of Linezolid in *Diluent*

System suitability

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

[NOTE—The relative retention times for linezolid and linezolid related compound D are about 1.0 and 1.4, respectively.]

Suitability requirements

Resolution: NLT 3.0 between linezolid and linezolid related compound D, *System suitability solution*

Tailing factor: NMT 1.5, *Standard 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 Linezolid taken:

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

r_U = peak response of each impurity from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Linezolid *N*-oxide[a]	0.20	0.3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Linezolid related compound C (linezolid amine)[b]	0.31	0.2
Desfluoro linezolid (if present)[c,d]	0.63	0.3
Linezolid	1.0	—
Any individual unspecified impurity	—	0.1

[a] (*S*)-4-{4-[5-(Acetamidomethyl)-2-oxooxazolidin-3-yl]-2-fluorophenyl}morpholine 4-oxide.

[b] (*S*)-5-(Aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one.

[c] (*S*)-*N*-{[3-(4-Morpholinophenyl)-2-oxooxazolidin-5-yl]methyl}acetamide.

[d] If possible from the manufacturing process.

• **Enantiomeric Purity**

Mobile phase: Hexane, absolute alcohol, and trifluoroacetic acid (650:350:1)

System suitability solution: 25 µg/mL each of USP Linezolid RS and USP Linezolid R-Isomer RS in absolute alcohol

Sample solution: 0.5 mg/mL of Linezolid in absolute alcohol. Sonicate as needed to dissolve.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L51

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 2.8 times the retention time of linezolid

System suitability

Sample: *System suitability solution*

[Note—The relative retention times for linezolid *R*-isomer and linezolid are 0.84 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between linezolid *R*-isomer and linezolid

Analysis

Sample: *Sample solution*

Calculate the percentage of linezolid *R*-isomer in the portion of Linezolid taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of linezolid *R*-isomer from the *Sample solution*

r_T = sum of the peak responses of both enantiomers from the *Sample solution*

Acceptance criteria: NMT 0.3%

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I, Method Ic*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

• **USP Reference Standards ⟨11⟩**

USP Linezolid RS

USP Linezolid Related Compound D RS

(*R*)-[3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl]methyl methanesulfonate.

$C_{15}H_{19}FN_2O_6S$ 374.38

USP Linezolid R-Isomer RS

N-{[(*R*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

$C_{16}H_{20}FN_3O_4$ 337.35

Topic/Question	Contact	Expert Committee
LINEZOLID	Documentary Standards Support	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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