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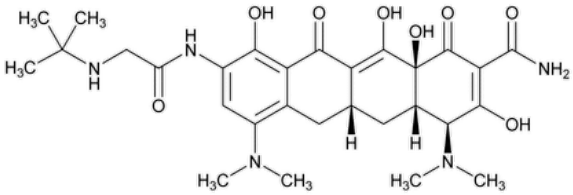
Tigecycline



$C_{29}H_{39}N_5O_8$ 585.65

2-Naphthacenecarboxamide, 4,7-bis(dimethylamino)-9-[[[(1,1-dimethylethyl)amino]acetyl]amino]-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4*S*,4a*S*,5a*R*,12a*S*)-;
(4*S*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide CAS RN®: 220620-09-7; UNII: 70JE2N95KR.

DEFINITION

Tigecycline contains NLT 97.0% and NMT 102.0% of tigecycline ($C_{29}H_{39}N_5O_8$), calculated on the anhydrous and solvent-free basis.

[NOTE—Handle Standards and samples under moisture-controlled conditions to prevent degradation in quantitative applications where degradation could impact results.]

IDENTIFICATION

Change to read:

• **A.** ▲**SPECTROSCOPIC IDENTIFICATION TESTS** ⟨197⟩**,** *Infrared Spectroscopy*: **197K**▲ (CN 1-MAY-2020)

• **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**

Protect solutions containing tigecycline from light using low-actinic glassware. Store these solutions at 10° immediately after preparation and during analysis.

Buffer: 4.35 g/L of dibasic potassium phosphate and 0.93 g/L of edetate disodium, adjusted with phosphoric acid to a pH of 6.2

Mobile phase: Acetonitrile and *Buffer* (140:860)

Diluent: 4.35 g/L of dibasic potassium phosphate and 0.5 g/L of sodium bisulfite, adjusted with 1 N potassium hydroxide to a pH of 8.0

System suitability stock solution: Dissolve 10 mg of USP Tigecycline RS in 10.0 mL of water. Add 1 or 2 drops of trifluoroacetic acid, heat at about 65° for 15 min, and cool.

System suitability solution: Dilute 5.0 mL of the *System suitability stock solution* with water to 50.0 mL.

Standard solution: 0.1 mg/mL of USP Tigecycline RS in *Diluent*

Sample solution: 0.1 mg/mL of Tigecycline in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 248 nm

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

Temperatures

Column: 30°

Autosampler: 10°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

[NOTE—The relative retention times for the tigecycline epimer and tigecycline are about 0.67 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between the tigecycline epimer and tigecycline, *System suitability solution*

Tailing factor: 0.7–1.5, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of tigecycline ($C_{29}H_{39}N_5O_8$) in the portion of Tigecycline 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 Tigecycline RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 97.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

• **ORGANIC IMPURITIES**

Protect solutions containing tigecycline from light using low-actinic glassware. Store these solutions at 10° immediately after preparation and during analysis.

Solution A: Dissolve 4.35 g of dibasic potassium phosphate and 0.93 g of edetate disodium in 950 mL of water. Adjust with phosphoric acid to a pH of 6.4 ± 0.05, and add 50 mL of acetonitrile.

Solution B: Dissolve 4.35 g of dibasic potassium phosphate and 0.93 g of edetate disodium in 500 mL of water. Adjust with phosphoric acid to a pH of 6.4 ± 0.05, and add 500 mL of acetonitrile.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
40	57	43
55	0	100
58	0	100
59	85	15
66	85	15

Diluent: 4.35 g/L of dibasic potassium phosphate and 0.5 g/L of sodium bisulfite, adjusted with 1 N potassium hydroxide to a pH of 8.0

System suitability solution: 0.5 mg/mL of USP Tigecycline RS and 2.4 µg/mL of USP Tigecycline Related Compound B RS in *Diluent*

Standard solution: 0.005 mg/mL of USP Tigecycline RS in *Diluent*

Sensitivity solution: 0.25 µg/mL of USP Tigecycline RS in *Diluent*

Sample solution: 0.5 mg/mL of Tigecycline in *Diluent*

Chromatographic system

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

Mode: LC

Detector: 248 nm

Column: 4.6-mm × 15-cm; 3-µm packing L1

Temperatures

Column: 30°

Autosampler: 10°

Flow rate: 1 mL/min

Injection volume: 25 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between tigecycline related compound B and the tigecycline epimer, *System suitability solution*

Tailing factor: 0.7–1.5, *Standard solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tigecycline 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 tigecycline from the *Standard solution*

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

C_U = concentration of Tigecycline 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 (%)
Specified unidentified impurity	0.12	0.15
Specified unidentified impurity	0.23	0.15
Tigecycline open ring[a,b]	0.36	0.020
Specified unidentified impurity	0.50	0.15
Tigecycline 12-oxo-11-hydroxy[c]	0.55	0.15
Tigecycline related compound B[d]	0.64	0.25
Tigecycline epimer[e]	0.74	1.0
Specified unidentified impurity	0.76	0.15
Tigecycline	1.0	—
Tigecycline quinone analog[f]	1.3	0.15
Specified unidentified impurity	1.5	0.15

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Minocycline	1.6	0.25
Tigecycline tricyclic analog[g]	1.7	0.15
Specified unidentified impurity	1.9	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	2.2

[a] To be reported if there is a peak with maximum absorbance at either 390 or 640 nm. The impurity is quantitated at 248 nm. The system may resolve two peaks. The limit is for the sum of the two peaks.

[b] (3*S*,4*R*)-7-[2-(*tert*-Butylamino)acetamido]-3-[4-carbamoyl-2-(dimethylamino)-3,5,6-trihydroxybenzyl]-5-(dimethylimino)-1,4,8-trihydroxy-3,4,5,8-tetrahydronaphthalene-2-carboxylate.

[c] (4*S*,4a*S*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)- 3,10,11,12a-tetrahydroxy-1,12-dioxo-1,4,4a,5,12,12a-hexahydro-2-naphthacenecarboxamide.

[d] (4*S*,4a*S*,5a*R*,12a*S*)-9-Amino-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride.

[e] (4*R*,4a*S*,5a*R*,12a*S*)-9-[2-(*tert*-Butylamino)acetamido]-4,7-bis(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-2-naphthacenecarboxamide.

[f] (*S*)-4-({6-[2-(*tert*-Butylamino)acetamido]-8-(dimethylamino)-5-hydroxy-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}methyl)-2,5-dihydroxy-3,6-dioxocyclohexa-1,4-dienecarboxamide.

[g] (1*S*,4a*R*,4b*R*,10a*R*,11a*S*)-7-[2-(*tert*-Butylamino)acetamido]-9-(dimethylamino)-1,4,4a,6-tetrahydroxy-2,5,12-trioxo-1,2,4a,5,10,10a,11,11a-octahydro-1,4b-methanobenzo[*b*]fluorene-3-carboxamide.

SPECIFIC TESTS

• **pH** ⟨791⟩

Sample solution: 10 mg/mL

Acceptance criteria: 7.7–8.2

• **Water Determination,** *Method Ic* ⟨921⟩

Sample solution: 50 mg/mL of Tigecycline in dimethyl sulfoxide

Acceptance criteria: NMT 2.5%

• **Optical Rotation,** *Specific Rotation* ⟨781S⟩

Sample solution: 1 mg/mL in water

Acceptance criteria: −240° to −215° on the anhydrous and solvent-free basis

• **Bacterial Endotoxins Test** ⟨85⟩**:** Where the label states that Tigecycline is sterile or must be subjected to further processing during the preparation of injectable dosage forms, it contains NMT 1 USP Endotoxin Unit/mg of tigecycline.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in air-tight, light-resistant containers under nitrogen, and store refrigerated.

• **Labeling:** Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

• **USP Reference Standards** ⟨11⟩

USP Tigecycline RS

USP Tigecycline Related Compound B RS

(4*S*,4a*S*,5a*R*,12a*S*)-9-Amino-4,7-bis(dimethylamino)-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide hydrochloride.

$C_{23}H_{28}N_4O_7 \cdot HCl$ 508.95

Topic/Question	Contact	Expert Committee
TIGECYCLINE	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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