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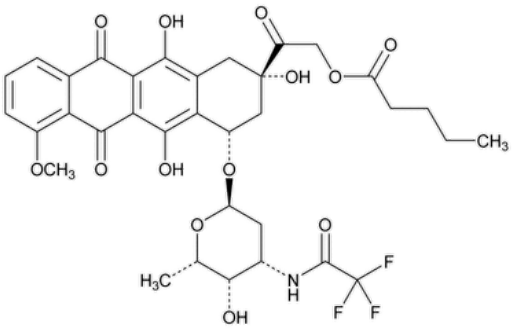
Valrubicin



$C_{34}H_{36}F_3NO_{13}$ 723.64

(2*S*-*cis*)-2-[1,2,3,4,6,11-Hexahydro-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-4-[[2,3,6-trideoxy-3-[(trifluoroacetyl) amino]-α-L-*lyxo*-hexopyranosyl]oxy]-2-naphthacenyl]-2-oxoethyl pentanoate;
(8*S*,10*S*)-8-Glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy]-5,12-naphthacenedione 8^2-valerate CAS RN®: 56124-62-0; UNII: 2C6NUM6878.

DEFINITION

Valrubicin contains NLT 98.0% and NMT 102.0% of $C_{34}H_{36}F_3NO_{13}$, calculated on the anhydrous and solvent-free basis.

[**Caution—**Great care should be taken to prevent inhaling particles of Valrubicin and exposing the skin to it.]

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197M**▲ (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**

Solution A: 3.4 mg/mL of monobasic potassium phosphate adjusted with phosphoric acid to a pH of 3.1

Mobile phase: Acetonitrile and *Solution A* (3:2)

Standard solution: 0.5 mg/mL of USP Valrubicin RS in acetonitrile

Sample solution: 0.5 mg/mL of Valrubicin in acetonitrile

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 5-cm; 1.8-µm packing L1

Flow rate: 1.5 mL/min

Column temperature: 40°

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{34}H_{36}F_3NO_{13}$ in the portion of Valrubicin 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 Valrubicin RS in the *Standard solution* (mg/mL)

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

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

IMPURITIES

Inorganic Impurities

- **Residue on Ignition ⟨281⟩:** NMT 0.2%

Organic Impurities

- **Procedure**

Solution A: Use *Solution A* as directed in the *Assay.*

Solution B: Acetonitrile

Mobile phase: See the gradient table below. [Note—Analysis time is 55 min. The steps that follow are for column washing and re-equilibration.]

Time (min)	Solution A (%)	Solution B (%)
0	75	25
45	40	60
55	40	60
58	20	80
68	20	80
70	75	25
80	75	25

Solution C: Acetonitrile and water (1:1)

Stock standard solution: 2 mg/mL of USP Valrubicin RS in acetonitrile and water (1:1). [Note—Dissolve first in acetonitrile, using 50% of the final volume and dilute with water to volume.]

Standard solution: 0.01 mg/mL of valrubicin in *Solution C*

System suitability solution: 2 mg/mL of USP Valrubicin Resolution Mixture RS in acetonitrile and water (1:1). [Note—Dissolve first in acetonitrile, using 50% of the final volume and dilute with water to volume.]

Sample solution: 2 mg/mL of Valrubicin in acetonitrile and water (1:1). [Note—Dissolve first in acetonitrile, using 50% of the final volume and dilute with water to volume.]

Chromatographic system

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

Mode: LC

Detector: 254 nm

Column: 4.6-mm × 5-cm; 1.8-µm packing L1

Flow rate: 1.5 mL/min

Temperature

Column: 40°

Autosampler: 4°

Injection size: 10 µL

System suitability

Sample: *System suitability solution*

[NOTE—Identify the peaks by the relative retention times listed in *Impurity Table 1*.]

Suitability requirements

Resolution: NLT 2.0 between doxorubicinone and daunorubicin

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Valrubicin taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

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

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

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

F = relative response factor as listed in *Impurity Table 1*

Acceptance criteria

[NOTE—Reporting level is 0.05%.]

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.0%

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Doxorubicin	0.05	1.0	0.15
Doxorubicinone[a]	0.10	0.63	0.15
Daunorubicin	0.12	0.86	0.15
Daunorubicin bromoketal[b]	0.42	1.4	0.15
Doxorubicin valerate[c]	0.48	1.3	0.15
Doxorubicinone valerate[d]	0.76	0.80	0.15
Valrubicin	1.0	—	—
Dianhydrovalrubicin[e]	1.2	0.47	0.15
Any unspecified impurity	—	1.0	0.10

[a] (8*S*,10*S*)-6,8,10,11-Tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.

[b] (8*S*,10*S*)-10-[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-(2-bromo-1,1-dimethoxyethyl)-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tet
rahydrotetracene-5,12-dione.

[c] 2-{(2*S*,4*S*)-4-[(3-Amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl}-2-
oxoethyl pentanoate.

[d] 2-Oxo-2-[(2*S*,4*S*)-2,4,5,12-tetrahydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethyl pentanoate.

[e] 2-(5,12-Dihydroxy-7-methoxy-6,11-dioxo-6,11-dihydrotetracen-2-yl)-2-oxoethyl pentanoate.

SPECIFIC TESTS

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

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.

• **USP Reference Standards** ⟨11⟩

USP Valrubicin RS

USP Valrubicin Resolution Mixture RS

This Reference Standard is a mixture of the following with their chemical names:

Doxorubicin: (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione.

Doxorubicin aglycone: (8*S*,10*S*)-6,8,10,11-tetrahydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydro tetracene-5,12-dione.

Daunorubicin: (8*S*,10*S*)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-6,8,11-trihydroxy-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione.

Daunorubicin bromoketal: (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-(2-bromo-1,1-dimethoxyethyl)-6,8,11-trihydroxy-1-methoxy- 7,8,9,10-tetrahydrotetracene-5,12-dione.

Doxorubicin valerate: 2-{(2*S*,4*S*)-4-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl}-2-oxoethyl pentanoate.

Doxorubicin aglycone valerate: 2-oxo-2-[(2*S*,4*S*)-2,4,5,12-tetrahydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl]ethyl pentanoate.

Valrubicin: (8*S*,10*S*)-8-glycoloyl-7,8,9,10-tetrahydro- 6,8,11-trihydroxy-1-methoxy-10-[[2,3,6-trideoxy-3-(2,2,2-trifluoroacetamido)-α-L-*lyxo*-hexopyranosyl]oxy]-5,12-naphthacenedione 8^2-valerate.

Dianhydrovalrubicin: 2-(5,12-dihydroxy-7-methoxy-6,11-dioxo-6,11-dihydrotetracen-2-yl)-2-oxoethyl pentanoate.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
VALRUBICIN	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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