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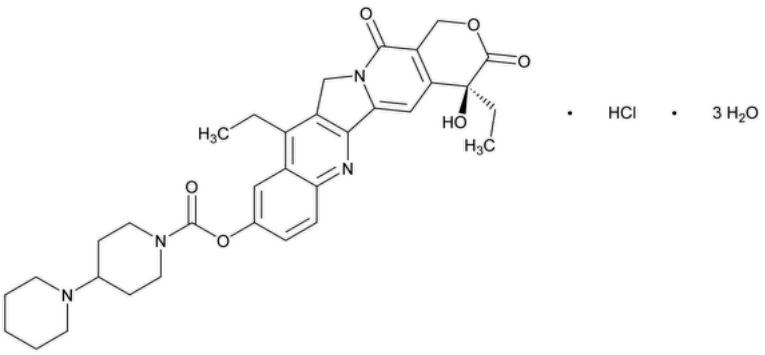
Irinotecan Hydrochloride



$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ Anhydrous: 623.14 Trihydrate: 677.18

[1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester, monohydrochloride, trihydrate, (*S*)-;

(+)-7-Ethyl-10-hydroxycamptothecine 10-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate CAS RN®: 136572-09-3; UNII: 042LAQ1IIS.

DEFINITION

Irinotecan Hydrochloride contains NLT 98.0% and NMT 102.0% of $C_{33}H_{38}N_4O_6 \cdot HCl$, calculated on the anhydrous basis.

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 the irinotecan (*S*-enantiomer) peak in the *Identification solution,* as obtained in the test for *Limit of Irinotecan Hydrochloride Enantiomer*.

• **C. Identification Tests—General, *Chloride* ⟨191⟩:** A 2-mg/mL solution meets the requirements of the tests.

ASSAY

• **Procedure**

Solution A: 2.8 g/L of monobasic sodium phosphate monohydrate and 1.8 g/L of 1-octanesulfonic acid sodium salt monohydrate in water

Mobile phase: Acetonitrile, methanol, and *Solution A* (17:24:59)

Diluent: Use *Mobile phase* adjusted with diluted hydrochloric acid to a pH of 3.65 ± 0.15.

Standard solution: 1 mg/mL of USP Irinotecan Hydrochloride RS in *Diluent*

Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 255 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 15 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of irinotecan hydrochloride ($C_{33}H_{38}N_4O_6 \cdot HCl$) in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

• **Limit of Irinotecan Hydrochloride Enantiomer**

Mobile phase: Hexane, dehydrated alcohol, and diethylamine (250:250:1)

Diluent: Dehydrated alcohol and diethylamine (250:1)

System suitability solution: 0.1 mg/mL each of USP Irinotecan Hydrochloride RS and USP Irinotecan Related Compound D RS in *Diluent*

Identification solution: 1 mg/mL of USP Irinotecan Hydrochloride RS in *Diluent*. [Note—This solution is used for *Identification* test *B*.]

Standard solution: 1.5 µg/mL of USP Irinotecan Related Compound D RS in *Diluent*

Sensitivity solution: 0.5 µg/mL of USP Irinotecan Related Compound D RS in *Diluent*, from the *Standard solution*

Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 370 nm

Column: 4.6-mm × 25-cm; 10-µm packing L40

Flow rate: 1.0 mL/min

Injection size: 20 µL

System suitability

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

[Note—The relative retention times for irinotecan related compound D (*R*-enantiomer) and irinotecan (*S*-enantiomer) are 0.7 and 1.00, respectively.]

Suitability requirements

Resolution: NLT 2.5 between irinotecan related compound D and irinotecan, *System suitability solution*

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

Sensitivity: The irinotecan related compound D peak should be visible, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of irinotecan hydrochloride *R*-enantiomer in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area of irinotecan related compound D from the *Sample solution*

r_S = peak area of irinotecan related compound D from the *Standard solution*

C_S = concentration of USP Irinotecan Related Compound D RS in the *Standard solution* (mg/mL)

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

Acceptance criteria

***R*-enantiomer:** NMT 0.15%

[Note—On the basis of the synthetic route, perform either *Organic Impurities Procedure 1* or *Organic Impurities Procedure 2*.]

• **Organic Impurities Procedure 1 (for Material Labeled as Produced by a Synthetic Process)**

Mobile phase, Diluent, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability stock solution: 0.01 mg/mL each of USP Irinotecan Related Compound B RS and USP Irinotecan Related Compound C RS in methanol

System suitability solution: 1.0 µg/mL each of USP Irinotecan Related Compound B RS and USP Irinotecan Related Compound C RS in *Diluent*, from *System suitability stock solution*

Standard solution: 2.0 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*

Sensitivity solution: 0.5 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*

System suitability

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

Suitability requirements

Resolution: NLT 1.1 between irinotecan related compound B and irinotecan related compound C, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each impurity in the portion of Irinotecan Hydrochloride taken:

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

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

r_S = peak area of irinotecan from the *Standard solution*

C_S = concentration of irinotecan hydrochloride in the *Standard solution* (mg/mL)

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

Acceptance criteria

Individual impurities: See *Table 1*. [NOTE—Disregard any impurity peaks less than 0.05%.]

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Irinotecan related compound B	0.55	0.15
Irinotecan related compound C	0.60	0.10
Irinotecan hydrochloride	1.0	—
Any unspecified impurity	—	0.10
Total impurities	—	0.5

- **ORGANIC IMPURITIES PROCEDURE 2 (FOR MATERIAL LABELED AS PRODUCED BY A SEMI-SYNTHETIC PROCESS)**

Solution A: 2.72 g/L of monobasic potassium phosphate in water. Adjust with dilute phosphoric acid (1 in 20) to a pH of 3.5 ± 0.05.

Solution B: Acetonitrile and methanol (3:2)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
40	30	70
45	30	70
50	80	20
55	80	20

Diluent: Acetonitrile, methanol, and *Solution A* (1:1:2)

System suitability solution: 0.1 mg/mL each of USP Irinotecan Hydrochloride RS and USP Irinotecan Related Compound A RS in *Diluent*

Standard solution: 1 µg/mL of USP Irinotecan Hydrochloride RS in *Diluent*

Sample solution: 1 mg/mL of Irinotecan Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between irinotecan and irinotecan related compound A, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Irinotecan Hydrochloride taken:

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

r_U = peak area of each individual impurity from the *Sample solution*

r_S = peak area of irinotecan from the *Standard solution*

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

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

F = relative response factor for each individual impurity (see *Table 3*)

Acceptance criteria

Individual impurities: See *Table 3*. [NOTE—Disregard any unspecified impurity peaks less than 0.05%.]

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
7-Desethyl irinotecan[a]	0.82	0.77	0.15
Irinotecan	1.00	—	—
Irinotecan related compound A[b]	1.15	1.4	0.15
11-Ethyl irinotecan[c]	1.27	0.63	0.15
Camptothecin[d]	1.35	1.4	0.15
Irinotecan related compound B[e]	1.50	1.3	0.15
7-Ethylcamptothecin[f]	1.76	1.2	0.15
7,11-Diethyl-10-hydroxy camptothecin[g]	2.05	0.65	0.15
Any unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.50

[a] (*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4'-bipiperidine)-1'-carboxylate.

[b] (*S*)-4-Ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

[c] (*S*)-4,8,11-Triethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione-9-yl (1,4'-bipiperidine)-1'-carboxylate.

[d] (*S*)-4-Ethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

[e] (*S*)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

[f] (*S*)-4,11-Diethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

[g] (*S*)-4,8,11-Triethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

SPECIFIC TESTS

• **Microbial Enumeration Tests ⟨61⟩** and **Tests for Specified Microorganisms ⟨62⟩:** The total aerobic microbial count does not exceed 1000 cfu/g, and the total combined molds and yeasts count does not exceed 100 cfu/g.

• **Water Determination, *Method I* ⟨921⟩:** Between 7.0% and 9.0%

ADDITIONAL REQUIREMENTS

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

• **Labeling:** If a test for *Organic Impurities* other than *Procedure 1* is used, the labeling states the test with which the article complies.

• **USP Reference Standards ⟨11⟩**

USP Irinotecan Hydrochloride RS

USP Irinotecan Related Compound A RS

(*S*)-4-Ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione.

$C_{20}H_{16}N_2O_5$ 364.35

USP Irinotecan Related Compound B RS

(*S*)-4,11-Diethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione.

$C_{22}H_{20}N_2O_5$ 392.40

USP Irinotecan Related Compound C RS

11-Ethyl-4-hydroxy-4-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl (1,4'-bipiperidine)-1'-carboxylate hydrochloride.

$C_{32}H_{36}N_4O_6 \cdot HCl$ 609.11

USP Irinotecan Related Compound D RS

(*R*)-9-[(1,4'-Bipiperidine)-1'-carbonyloxy]-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline hydrochloride, trihydrate.

$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3\,H_2O$ 677.18

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

Topic/Question	Contact	Expert Committee
IRINOTECAN HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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