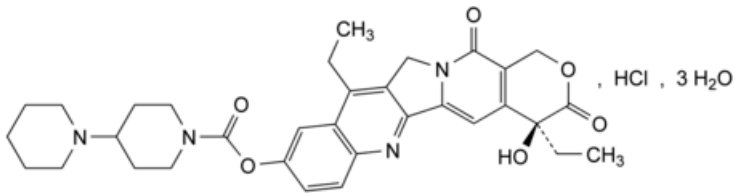
Edition: BP 2025 (Ph. Eur. 11.6 update)

Irinotecan Hydrochloride Trihydrate

General Notices

(Ph. Eur. monograph 2675)



$C_{33}H_{39}ClN_4O_6,3H_2O$ 677 *136572-09-3*

Action and use

Inhibitor of DNA topoisomerase type I; antineoplastic.

Ph Eur

DEFINITION

(4*S*)-4,11-Diethyl-4-hydroxy-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 trihydrate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

Pale yellow or yellow, crystalline powder.

Solubility

Sparingly soluble in water, in ethanol (96 per cent) and in methanol.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).

Comparison irinotecan hydrochloride trihydrate CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

B. Water (see Tests).
C. It gives reaction (a) of chlorides (2.3.1).

Dissolve 0.10 g in water R and dilute to 50 mL with the same solvent.

TESTS

Appearance of solution

The solution is clear (2.2.1) and not more intensely coloured than reference solution GY_2 (2.2.2, Method II).

Dissolve 0.200 g in water R with heating at 80 °C and dilute to 20 mL with the same solvent.

Enantiomeric purity

Liquid chromatography (2.2.29).

Solvent mixture diethylamine R, anhydrous ethanol R (0.4:100 *V/V*).

Test solution Dissolve 15.0 mg of the substance to be examined in the solvent mixture and dilute to 10.0 mL with the solvent mixture.

Reference solution (a) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (b) Dissolve the contents of a vial of irinotecan for system suitability 1 CRS (containing impurity L) in 1 mL of the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: *cellulose derivative of silica gel for chiral separation R* (10 µm).

Mobile phase diethylamine R, anhydrous ethanol R, hexane R (0.2:50:50 *V/V/V*).

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 370 nm.

Injection 20 µL.

Run time 1.5 times the retention time of irinotecan.

Identification of impurities Use the chromatogram obtained with reference solution (b) to identify the peak due to impurity L.

Relative retention With reference to irinotecan (retention time = about 15 min): impurity L = about 0.7.

System suitability:

— resolution: minimum 1.5 between the peaks due to impurity L and irinotecan in the chromatogram obtained with reference solution (b).

Calculation of percentage content:

— for impurity L, use the concentration of irinotecan hydrochloride trihydrate in reference solution (a).

Limit:

— *impurity L*: maximum 0.15 per cent.

Related substances

Liquid chromatography (2.2.29). *Carry out the test protected from light.*

Solvent mixture acetonitrile R, methanol R, mobile phase A (25:25:50 *V/V/V*).

Test solution Dissolve 50.0 mg of the substance to be examined in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (a) Dissolve 50.0 mg of irinotecan hydrochloride trihydrate CRS in the solvent mixture and dilute to 50.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve the contents of a vial of irinotecan for peak identification CRS (containing impurities C and E) in 1 mL of the solvent mixture.

Reference solution (d) Dissolve 5 mg of irinotecan for system suitability 2 CRS (containing impurity M) in the solvent mixture and dilute to 10 mL with the solvent mixture.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: end-capped octadecylsilyl silica gel for chromatography with embedded polar groups R (5 µm).

Mobile phase:

— *mobile phase A*: dissolve 2.72 g of potassium dihydrogen phosphate R in 950 mL of water for chromatography R, adjust to pH 3.5 with dilute phosphoric acid R and dilute to 1000 mL with water for chromatography R;

— *mobile phase B*: methanol R2, acetonitrile R1 (40:60 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	80	20
2 - 42	80 → 30	20 → 70
42 - 47	30	70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

Injection 10 µL of the test solution and reference solutions (b), (c) and (d).

Identification of impurities Use the chromatogram supplied with irinotecan for peak identification CRS and the chromatogram obtained with reference solution (c) to identify the peaks due to impurities C and E; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity M.

Relative retention With reference to irinotecan (retention time = about 17 min): impurity M = about 0.9; impurity C = about 1.3; impurity E = about 1.5.

System suitability:

— resolution: minimum 2.0 between the peaks due to impurity M and irinotecan in the chromatogram obtained with reference solution (d).

Calculation of percentage contents:

— *correction factor*: multiply the peak area of impurity M by 1.3;

— for each impurity, use the concentration of irinotecan hydrochloride trihydrate in reference solution (b).

Limits:

— *impurities C, E, M*: for each impurity, maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

7.0 per cent to 9.0 per cent, determined on 0.100 g.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification.

Injection 5 µL of the test solution and reference solution (a).

Calculate the percentage content of $C_{33}H_{39}ClN_4O_6$ taking into account the assigned content of *irinotecan hydrochloride trihydrate CRS*.

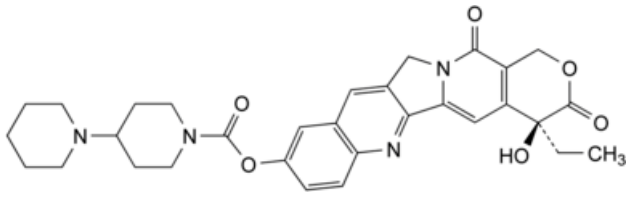
STORAGE

In an airtight container, protected from light.

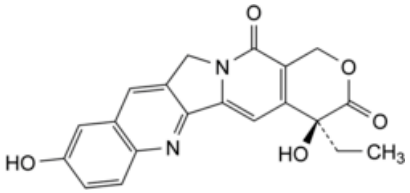
IMPURITIES

Specified impurities *C, E, L, M*.

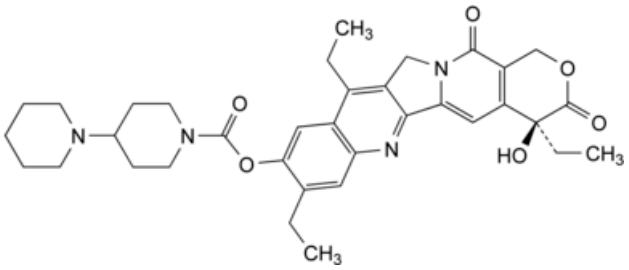
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) *A, B, D, F, G, H, K*.



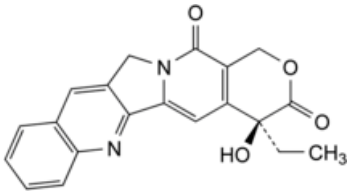
A. (4*S*)-4-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (11-desethyl irinotecan),



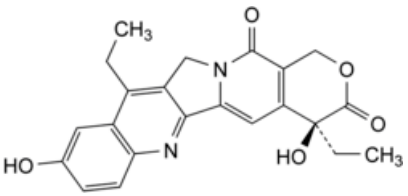
B. (4*S*)-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (9-hydroxycamptothecin),



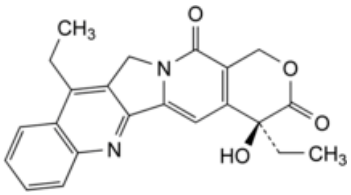
C. (4*S*)-4,8,11-triethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (8-ethyl irinotecan),



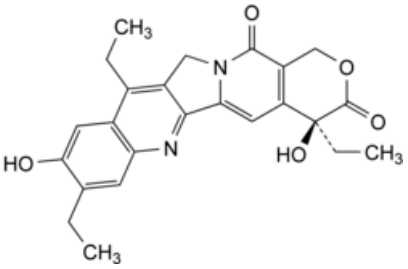
D. (4*S*)-4-ethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (camptothecin),



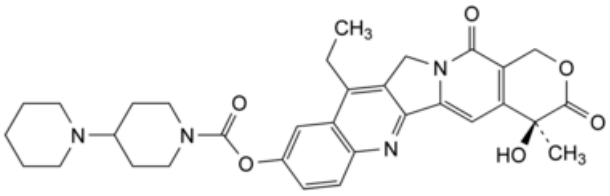
E. (4*S*)-4,11-diethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (11-ethyl-9-hydroxycamptothecin),



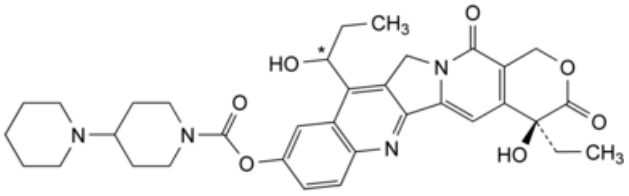
F. (4*S*)-4,11-diethyl-4-hydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (11-ethylcamptothecin),



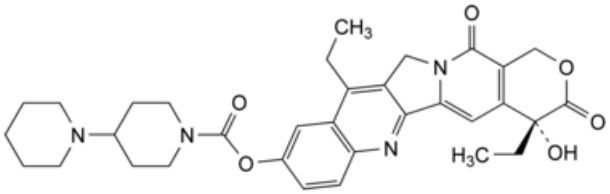
G. (4*S*)-4,8,11-triethyl-4,9-dihydroxy-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione (8,11-diethyl-9-hydroxycamptothecin),



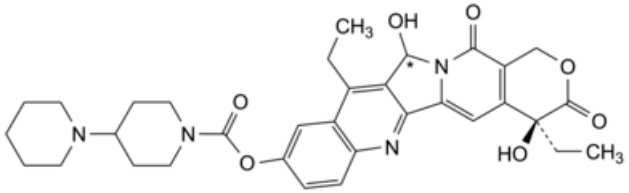
H. (4*S*)-11-ethyl-4-hydroxy-4-methyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3′,4′:6,7]indolizino[1,2-*b*]quinolin-9-yl 1,4′-bipiperidine-1′-carboxylate (4-methyl irinotecan analogue),



K. (4*S*)-4-ethyl-4-hydroxy-11-(1-hydroxypropyl)-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,



L. (4*R*)-4,11-diethyl-4-hydroxy-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 (irinotecan enantiomer),



M. (4*S*)-4,11-diethyl-4,12-dihydroxy-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 (12-hydroxy irinotecan).

Ph Eur