

Chapter 3
Drug Profile



3. Drug Profile

3.1 Introduction:

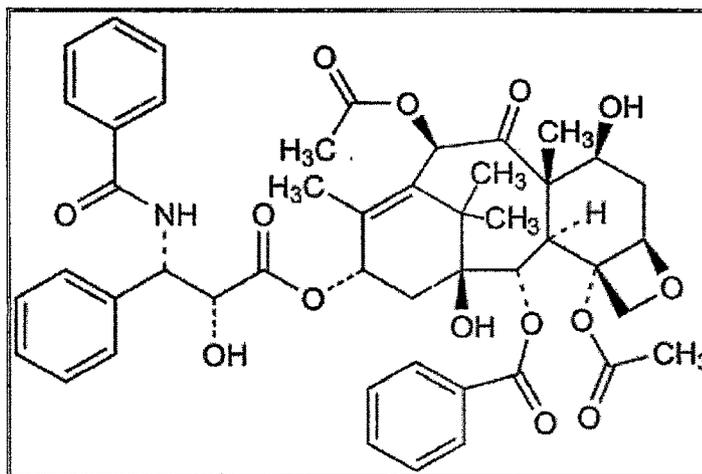
Paclitaxel (PCL) is a taxoid extracted from the bark of Pacific yew and the needles of the English yew. It works against cancer by interfering with mitosis. It binds to microtubules and inhibits their depolymerization into tubulin. PCL blocks a cell's ability to break down the mitotic spindle during mitosis. With the spindle still in place the cell cannot divide into daughter cells.

Description

a) **Chemical name:** [2aR-[2a α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]- β -(Benzoyl-amino)- α -hydroxybenzenepropanoic acid 6,12bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10, 11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca-[3,4]benz[1,2-b]oxet-9-yl ester.

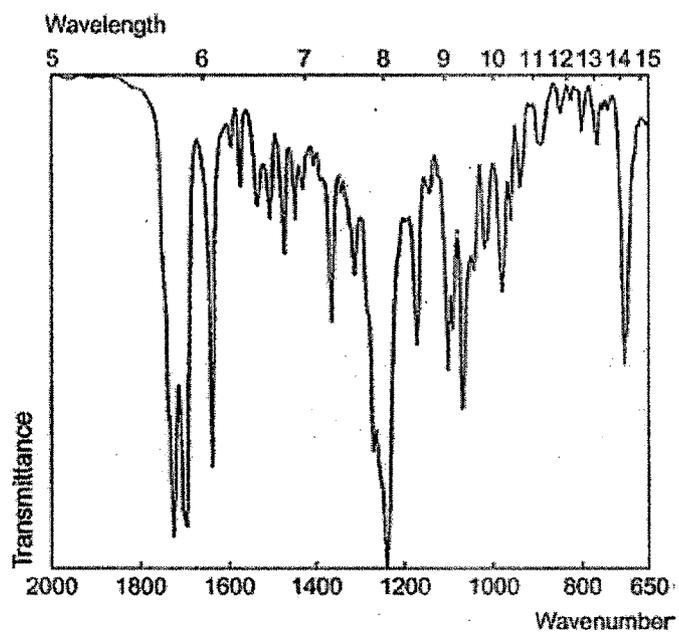
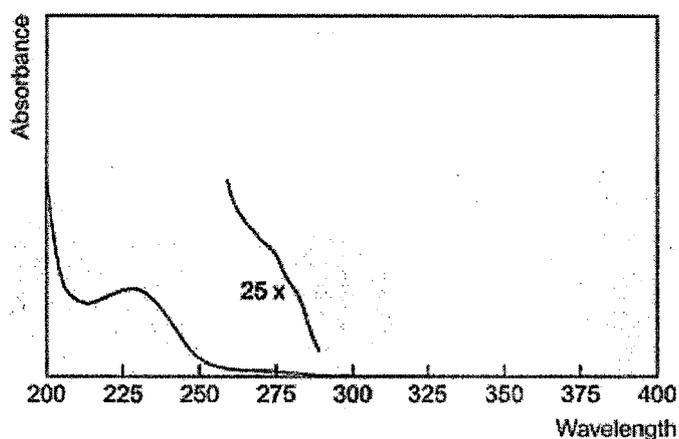
b) Formula

- **Empirical:** C₄₇H₅₁N₁₄O₁₄ contains not less than 97.0% and not more than 102.0% calculated on the anhydrous.
- **Structural:**



- **Molecular weight:** 853.91
- **Appearance and colour:** White to off white crystalline powder.
- **Solubility:** It is virtually insoluble in water and shows poor solubility in most pharmaceutically approved solvents.

Ultraviolet Spectrum. Aqueous acid—227, 273 nm.



- **Melting point:** Melts at around 216-217 °C with decomposition.
- **Category:** Antineoplastic agent
- **Storage:** should be kept in air tight container, protected from light and stored at a room temperature.

3.2 Pharmacology:

Mechanism of action:

PCL is a novel antimicrotubule agent that promotes the assembly of microtubules from tubulin dimmers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, PCL induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Anti-tumor activity:

PCL has activity against a broad band of tumor types, including breast, ovarian, lung, head and neck cancers. PCL has also has activity in other malignancies that are refractory to conventional chemotherapy, including previously treated lymphoma and small cell lung cancers and oesophageal, gastric endometrial, bladder and germ cell tumors. PCL is also active against AIDS-associated Kaposi’s sarcoma.

Pharmacokinetics:

The PCL is highly bound to plasma protein (88-98%). Tissue distribution and binding influence the rate of plasma clearance; PCL shows saturable distribution and non-linear disposition. An agent with non-linear disposition lacks a proportional relationship between dose and the area under the plasma concentration of drug versus time curve (plasma AUC) this causes a disproportionate degree of changes in AUC and in clearance of the drug, even with modest dose alteration. The mean clearance of PCL appears to decrease as the dose is increased if the schedule remains constant. For a dose of 135

mg/m², the clearance rate is 14.7 L/h/ m²; for a dose of 250mg/ m² the clearance rate is 8 L/h/ m². Hence the severity and the duration of toxicity increase disproportionately with dose escalation. Similarly, if the dose of PCL is reduced because of excess toxicity from one cycle to another, it decreases the AUC significantly and may compromise efficacy. The comparison of response rate to dose intensity within across clinical trials is very difficult if different dosing schedules of PCL are used. The nonlinear pharmacokinetics of PCL could be attributed to its vehicle of formulation.

Half-life: 3 to 50 h (non-linear pharmacokinetics, independent of dose and wide inter-patient variability).

Volume of distribution: 200 to about 700 L/m².

Clearance: Plasma, 11.6 to 24.0 L/h/m²; mean, 0.42 L/m²/day (from peritoneal cavity).

Adverse Effects/Uncommon Effects:

Neutropenia, leucopenia, thrombocytopenia, anaemia, hypersensitivity reactions, bradycardia, abnormal ECG, peripheral neuropathy, nausea, vomiting, diarrhoea, mucositis, Injection site reactions like erythema, tenderness, skin discolouration, or swelling at the injection site.

Drug Interaction:

Myelosuppression was more profound when given after Cisplatin than with the alternate sequence. Caution should be exercised when administering PCL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes. Plasma levels of Doxorubicin and its metabolite may be raised when used in combination with PCL.

Route of administration: Parenteral.

Dose:

PCL injection is a clear, colourless to slightly yellow viscous solution. It is supplied as a non-aqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. PCL is available in 30mg (5ml), 100mg (16.7ml) and 300mg (50ml) multidose vials. Each ml of sterile nonpyrogenic solution contains 6mg of PCL,

527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7 % (v/v) dehydrated alcohol, USP.

The dose varies between 100 and 250 mg/m² body surface by intravenous infusion over 3 h every 2 to 3 weeks depending on condition and response. Dose may be reduced by 20% in some cases. Pretreated with corticosteroids, antihistaminics and H₂ antagonists.

Pediatrics: Not recommended.

Pregnancy: Not usually prescribed.

Precaution:

PCL therapy should not be given to patients with solid tumors who have baseline neutrophil count less than 1,500 cells/mm³ and should not be given to patients with AIDS- related Kaposi's sarcoma if the baseline neutrophil count is less than 1,000 cells/mm³. In order to monitor the occurrence of bone marrow suppression, primarily Neutropenia, which may be severe and result in infections, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving PCL.

Metabolism:

Taxane metabolism is primarily hepatic and renal clearance is minimal (<5% excretion in urine). PCL is metabolized by hepatic cytochrome P450 enzyme systems and eliminated by biliary excretion. PCL undergoes stereo specific CYP2C8 hydroxylation at the C6' position of the taxane nucleus to form 6- α -hydroxy PCL, the major metabolite. Interestingly, this biotransformation is inhibited by 0.1% v/v Cremophor EL. Under *in-vitro* conditions, the levels of each monohydroxylated species can be influenced by the inductive effects of co-medications. Each monohydroxylated species can be further metabolized, probably by the other pathway, to converge to the dihydroxy taxol metabolite, 6- α -hydroxyl-3'-*p*-hydroxyphenyl-PCL. The half life of total metabolites (5.6 \pm 0.4 h) greatly exceeds that of unchanged taxol (2.9 \pm 0.3 h), but hydroxylation significantly reduces potency in Cytotoxicity assays, although not in microtubule binding assays.

Table 3.1. Analytical methods for PCL

Analyte	Method/Mobile Phase/Column/Remarks	Type of sample	Detection by	Reference
Paclitaxel	C8 (MOS Hypersil, 150 × 4.6 mm i.d., 5 µm). Mobile phase: methanol: acetate buffer (0.02 M, pH 4.5) (65:35), flow rate 2 mL/min.	Biological Fluids	UV detection (λ=227 nm).	Rizzo et. al., 1990
Paclitaxel	(analytical) C18 Radial-Pak cartridge (100 × 8 mm i.d., 10 µm); (guard) C18 (Guard-Pak). Mobile phase: water: acetonitrile (65:35) to (0:100) exponentially over 20 min. Internal standard: N-cyclohexylbenzamide.	Human plasma and urine	UV detection (λ=227 nm)	Longnecker et. al., 1987
Paclitaxel	limit of quantification 5 µg/L	Human Plasma	UV detection (λ=227 nm)	Supko et. al., 1999
Paclitaxel	limit of quantification 25 and 40 µg/L, respectively	Human plasma and urine	UV detection (λ=227 nm)	Martin et. al., 1998
Paclitaxel	limit of quantification 10 µg/L. UV detection (λ=230 nm)	Human Plasma	UV detection (λ=230 nm)	Sparreboom et. al., 1998
Paclitaxel	limit of detection 0.10 µg/L	Human Plasma	UV detection (λ=227 nm)	Rizzo et. al., 1990
Paclitaxel	limit of detection is 0.25 µg/L. MS detection	Human serum	Mass spectrometry	Xu et. al., 2000
Paclitaxel	limit of detection is 42 µg/L	Human serum	Enzyme-linked immunosorbent assay.	Leu et. al., 1993
Paclitaxel	limit of detection 0.3 µg/L	Human Plasma	Competitive inhibition enzyme immunoassay.	Grothaus et. al., 1993

3.3 Marketed Product:

TAXOL[®] (Bristol-Myers Squibb Company) - TAXOL is available in 30 mg (5 ml), 100 mg (16.7 ml), and 300 mg (50 ml) multidose vials.

3.4 Introduction

Irinotecan (CPT-11)

Irinotecan is a semisynthetic, water-soluble derivative of camptothecin, which is a cytotoxic alkaloid extracted from plants such as *Camptotheca acuminata*. It works against cancer by interfering S-phase of the cell cycle. It inhibits the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication.

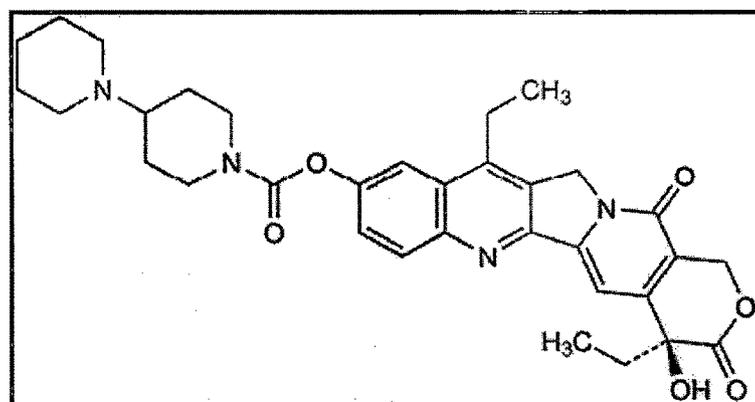
Description

Chemical name:

[1,4'-Bipiperidine]-1'-carboxylic acid (4*S*)-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.

Formula

- Empirical: $C_{33}H_{38}N_4O_6$
- Structural:



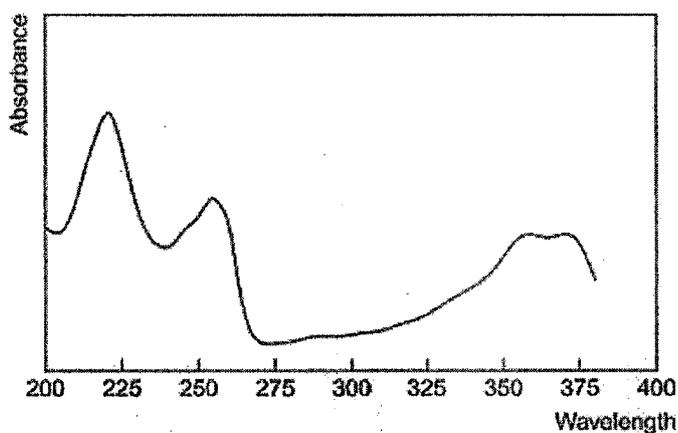
- Molecular weight: 586.7
- Appearance and colour: Pale yellow powder.

Irinotecan Hydrochloride

- **Formula - Empirical:** $C_{33}H_{39}ClN_4O_6$
- **Molecular weight:** 623.2

Irinotecan Hydrochloride Trihydrate (DQ-2805; U-101440E)

- **Formula - Empirical:** $C_{33}H_{38}ClN_4O_6 \cdot HCl \cdot 3H_2O$
- **Molecular weight:** 677.2
- **Solubility:** It is soluble in water and glacial acetic acid; partially soluble in chloroform; slightly soluble in methanol.
- **Appearance and colour:** A pale yellow to yellow crystalline powder.
- **Melting point:** 256.5°.
- **Ultraviolet Spectrum:** Aqueous acid - 221, 254, 359, 372 nm.



- **Category:** Antineoplastic agent
- **Storage:** should be kept in air tight container, protected from light and stored at a room temperature.

3.5 Pharmacology:

Mechanism of action:

Irinotecan and its active metabolite, SN-38, inhibit the action of topoisomerase-I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Irinotecan and SN-38 bind to the topoisomerase I-DNA complex and prevent relegation of the DNA strand, resulting in double-strand DNA breakage and cell death. The precise contribution of SN-38 to the activity of irinotecan in humans is not known. Irinotecan is cell cycle phase-specific (S-phase).

Antitumor activity:

Irinotecan has activity against a broad band of tumor types including colorectal, cervical, esophageal, gastric, lung and pancreatic cancers. It has also activity in other malignancies that are refractory to conventional chemotherapy, including glioma and mesothelioma.

Pharmacokinetics: Irinotecan is approx. 65% (range between 30 and 68%) bound to plasma proteins and SN-38 metabolite 95%. After intravenous administration, irinotecan is metabolized, by carboxylesterase, in the liver to the active metabolite 7-ethyl-10-hydroxycamptothecin, SN-38 and carboxylic acid. SN-38 then undergoes conjugation, by UDP-glucuronyl transferase, to SN-38 glucuronide. Another metabolite 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin (APC) is produced by oxidative attack at the piperidine group. About 20% of the dose is excreted in urine within 24 h, <1% as SN-38 and approx. 3 to 6% as SN-38 glucuronide. Further excretion is via bile.

Half-life: 6 to 12 h; 10 to 20 h for the metabolite SN-38.

Volume of distribution: About 157 L/m².

Clearance: Body clearance, 15 L/m²/h.

Adverse Effects/Uncommon Effects:

Toxicity: Diarrhoea if prolonged and over 24 h can be life threatening. Anemia, leucopenia, Neutropenia, thrombocytopenia, bradycardia, edema, hypotension, fatigue,

fever, weight loss, alopecia, flushing, piloerection, rash, dizziness, insomnia, visual disturbances, abdominal cramp, back pain, head ache, dyspnea.

Drug Interaction:

Anticonvulsants which induce cytochrome P450 (e.g., carbamazepine, phenobarbital, phenytoin) and dexamethasone may decrease therapeutic and toxic effects of Irinotecan where as it may be increased with bevacizumab. Diuretics may worsen dehydration due to irinotecan-induced diarrhea or vomiting. Etoposide causes hepatotoxicity where prochlorperazine interaction causes increased incidence of akathisia (a feeling of "inner restlessness")

Route of administration: Parenteral.

Dose:

The usual dosage range is 40 mg/m² body surface to 250 mg/m² administered three times a week, once a week to once every 3 weeks. One suggested regimen is 125 mg/m² infused over 90 min, once a week for 4 weeks, followed by 2-week rest period. Dose is modified according to toxicity. The maximum dose is 750 mg/m²/day.

Pediatrics: Not recommended. Irinotecan is currently being studied in children.

Pregnancy: Not usually prescribed.

Precaution:

Irinotecan therapy should not be given to patients with solid tumors who had previous pelvic or abdominal radiation, have a greater risk of irinotecan-related toxicities. Caution should be taken in patients with pre-existing lung tumours or nonmalignant pulmonary diseases as this may cause a potentially life-threatening syndrome consisting of dyspnea, fever, and reticulonodular pattern on chest x-ray. In clinical trials the risk of severe neutropenia during the first course of irinotecan therapy may be substantially increased in patients with modest increase in serum bilirubin (17-35 µmol/L). The use of irinotecan in patients with significant hepatic dysfunction has not been established. Individuals with Gilbert's syndrome have deficient uridine diphosphate glucuronosyltransferase activity, which is involved in the elimination of SN-38, the active metabolite of irinotecan. Hence,

Gilbert's syndrome may increase the risk of irinotecan-induced toxicity. There is some evidence linking therapy with topoisomerase I inhibitors, such as irinotecan, to the development of acute leukemias associated with specific chromosomal translocations. Irinotecan and its active metabolite SN-38 were not mutagenic, however, irinotecan was clastogenic in mammalian *in-vitro* and *in-vivo* chromosome tests.

Metabolism:

irinotecan metabolism is primarily hepatic and it is rapidly converted to SN-38 by hepatic carboxylesterase enzymes. Irinotecan and SN-38 undergo reversible, pH-dependent conversion between the active lactone (acidic pH) and inactive hydroxyacid (basic pH) forms. Its active metabolite is SN-38 and inactive metabolites are SN-38 glucuronide, aminopentane carboxylic acid. Excretion through biliary and urinary routes.

Table 3.2. Analytical methods for Irinotecan

Analyte	Method/Mobile Phase/Column/Remarks	Type of sample	Detection by	Reference
Irinotecan, SN-38 and other active metabolites	Columns: (analytical) ODS (Hypersil, 100 × 4.6 mm i.d., 5 µm), (guard) 100 RP-18 (LiChrospher, 4 × 4 mm, 5 µm). Column temperature: 50°. Mobile phase: (A) methanol: ammonium acetate (100 mM) containing tetrabutylammonium sulfate (10 mM) (35:65), adjusted to pH 5.5 with hydrochloric acid; (B) (30:70), adjusted to pH 5.3. Flow rate, 1 mL/min. Retention times: 8.3 min (A); 16.1 min (B)	Human Plasma (A) Human plasma, urine and feces (B)	Fluorescence detection (λ_{ex} =355 nm, λ_{em} =515 nm).	De Bruijn et. al., 1997 (A); Sparreboom et. al., 1998 (B)
Irinotecan and SN-38	Columns: (analytical) TSK gel ODS-80Ts (150 × 4.6 mm i.d., 5 µm), (guard) TSK guard gel ODS-120T (15 × 3.2 mm i.d.). Column temperature: 30°. Mobile phase: acetonitrile: sodium hydrogen phosphate (50 mM) (28:72)	Human plasma	Fluorescence detection (λ_{ex} =380 nm, λ_{em} =556 nm)	Sumiyoshi et. al., 1995

	containing sodium 1-heptanesulfonate, adjusted to pH 3.0 with orthophosphoric acid. Flow rate, 1 mL/min. IS: camptothecin. Retention time: irinotecan, 5.4 min; IS, 8.8 min			
Irinotecan	Columns: (analytical) C18 (Zorbax SB, 150 × 4.6 mm, 3.5 μm), (guard) C18 (Chromapack, 10 × 3 mm). Mobile phase: acetonitrile: ammonium acetate (100 mM, pH 6.4): triethylamine (15.6:80:0.1) containing tetrabutylammonium phosphate (5 mM). Flow rate, 1.5 mL/min. Retention time: irinotecan (carboxylate form), 5.7 min; (lactone form), 11.2 min	Human plasma	Fluorescence detection ($\lambda_{ex}=375\text{nm}$, $\lambda_{em}=460\text{nm}$).	Herben et. al., 1998
Irinotecan, (CPT-11), SN-38	Column: (analytical) C18 (Nova-Pak, 100 × 5 mm, 4 μm), (guard) C18 (Nova-Pak, Guard-Pak). Mobile phase: acetonitrile: ammonium acetate (75 mM, pH 6.4) (22:78) containing tetrabutylammonium phosphate (5 mM). Retention time: irinotecan (carboxylate form), 4.2 min; (lactone form), 8.2 min	Human plasma	Fluorescence detection ($\lambda_{ex}=355\text{nm}$, $\lambda_{em}=515\text{nm}$).	Rivory et. al., 1994
Irinotecan and SN-38	Limit of quantification of irinotecan 1.0 μg/L and 0.5 μg/L for the metabolite, SN-38	Human Plasma	Fluorescence detection	Herben et. al., 1998
Irinotecan, SN-38 and other active metabolites	Limit of quantification is 100 μg/L	Human Plasma, Urine and faeces	Fluorescence detection	Sparreboom et. al., 1998

3.6 Marketed Product:

CAMPTOSAR® (Pfizer): 40 mg, 100 mg vials; Mayne Pharma Irinotecan: 40 mg, 100 mg and 500 mg vials. Each ml contains 20 mg irinotecan hydrochloride trihydrate.

3.7 REFERENCES

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