PRODUCT INFORMATION

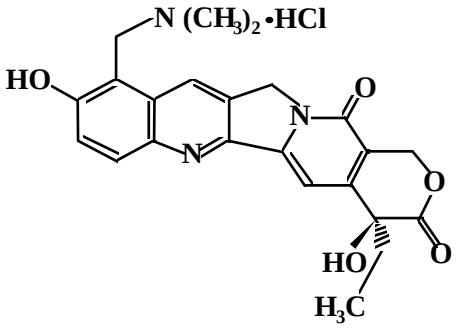
HYCAMTIN® POWDER FOR INJECTION

(Topotecan hydrochloride)

NAME OF THE MEDICINE

HYCAMTIN (topotecan hydrochloride) is a specific inhibitor of topoisomerase-I enzyme. It is a water soluble analogue of camptothecin, a natural substance found in several species of Asian tree. Topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]-quinoline-3,14-(4*H*,12*H*)-dione monohydrochloride. Empirical formula $C_{23}H_{23}N_3O_5$.

Structure:



Molecular Weight**:** 421.453 (free base)

CAS**:** 123948-87-8

DESCRIPTION:

Topotecan is a yellow to green powder with a solubility in water of 80.5 mg/mL at 25ºC. The pKa values obtained for the quinoline, phenol and benzyldimethylamino groups of topotecan hydrochloride were 0.60, 6.99 and 10.50 respectively. The log P value (calculated) at pH 7.4 is – 0.3. The reconstituted solution ranges in colour from yellow to yellow-green. The pH of a 1 mg/mL solution in water is 4.3.

HYCAMTIN powder for i.v. infusion vials also contain tartaric acid, mannitol, hydrochloric acid and sodium hydroxide.

PHARMACOLOGY

The anti-tumour activity of topotecan involves the inhibition of the enzyme topoisomerase-I. This enzyme plays an important role in replication, transcription and DNA damage repair. It is involved in DNA replication, resolving supercoils introduced into DNA by the movement of a replication fork or transcription complex down a double-stranded DNA molecule. Topotecan reversibly inhibits the catalytic action of topoisomerase-I by reducing the initial velocity of catalysis. It inhibits the religation reaction of topoisomerase-I by stabilising the intermediate covalent complex between topoisomerase-I enzyme and strand-cleaved DNA. This results in relaxation of supercoiled DNA.

The cytotoxicity of topotecan results from the production of enzyme-mediated DNA damage. This DNA damage occurs when a replication complex runs into a topotecan-induced cleavable complex. This induces a protein-associated single-strand DNA break. Consequently, topotecan is an S-phase dependent cytotoxic drug.

Pharmacokinetics

The pharmacokinetics of topotecan after intravenous administration have been evaluated in adult cancer patients who received single doses of 2.5 to 22.5 mg/m^2 given as a 30 minute infusion and 0.5 to 1.5 mg/m^2 given as 30 minute infusions on a daily times five schedule.

Distribution

Following intravenous administration, topotecan has a high volume of distribution of about 132 L (80 L/m^2), approximately three times total body water, indicating binding to tissues or intracellular uptake.

In vitro studies indicate that binding of topotecan to plasma proteins was low (35%). Distribution between blood cells and plasma was fairly homogenous resulting in a blood to plasma ratio of approximately 1.2.

Elimination

Following i.v. administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of i.v. topotecan is dose proportional within the range of doses administered. There is little or no accumulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing.

Following a single 30-minute intravenous infusion of topotecan, at doses of 0.5 to 1.5 mg/m^2 topotecan demonstrated a high plasma clearance with mean value of 62 l/h (SD 22 l/h), corresponding to approximately 2/3 liver blood flow. The mean terminal half-life of topotecan lactone ranged from 2 to 3 hours following intravenous administration.

Topotecan appears to be excreted by both biliary and urinary routes. A major route of clearance of topotecan was by hydrolysis of the lactone ring to form the ring-opened hydroxy acid. A variable fraction of the dose (generally 20-60%) was excreted as topotecan or the open ring form in urine.

In an unlabelled mass-balance study in patients with advanced solid tumours, 4 patients received iv topotecan 1.5 mg/m^2 and 4 oral topotecan 2.3 mg/m^2 administered once daily for 5 days. Following IV administration, overall recovery of drug-related material was 71 to 76% of the administered dose. Approximately 51% was excreted as total topotecan and 2.5% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18% of the administered dose while faecal elimination of N-desmethyl topotecan was approximately 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4-9%) of the total drug related material accounted for in the urine and faeces. The topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide in the urine were less than or equal to 2% of the dose.

Special Patient Populations

In a population study with i.v. topotecan, a number of factors including age, weight and ascites had no significant effect on clearance.

Renal impairment

Plasma clearance of i.v. topotecan in patients with mild renal impairment (creatinine clearance 0.68-1 mL/s) decreased to about 67% compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14%. In patients with moderate renal impairment (creatinine clearance 0.33-0.67 mL/s) topotecan plasma clearance was reduced to 34% of the value in control patients.

Volume of distribution also decreased by about 25% which resulted in an increase in mean half-life from 1.9 hours to 4.9 hours.

Hepatic impairment

Plasma clearance of topotecan lactone after i.v. administration in patients with hepatic impairment (serum bilirubin in the range 25.65 to 171 µmol/L) decreased to about 67% when compared with a control group of patients. Topotecan half-life was increased by about 30% but no clear change in volume of distribution was observed. Total topotecan plasma clearance in patients with hepatic impairment only decreased by about 10% compared with the control group of patients.

CLINICAL TRIALS

Powder for i.v. infusion:

Small Cell Lung Carcinoma

In a comparative study of topotecan and the treatment regimen CAV (cyclophosphamide, doxorubicin, vincristine) in patients with relapsed small cell lung carcinoma who had been sensitive to first line chemotherapy (n= 107 and 104, respectively), the response rate (95% C.I.) was 22% (15, 30) versus 15% (8, 22). Median time to progression was 13 weeks versus 12 weeks (hazard ratio 0.86 [0.6, 1.2]), median duration of response was 14 weeks versus 15 weeks (hazard ratio 1.3 [0.6, 2.9]) for topotecan and CAV, respectively. Median overall survival was 25 weeks for topotecan versus 22 weeks for CAV (hazard ratio 1.17 [0.8, 1.6]). In a Symptom Specific Questionnaire, patients treated with topotecan experienced significantly greater relief in the following symptoms: dyspnoea*, hoarseness *, fatigue* and interference with daily activities. The time to worsening of the following symptoms was significantly longer for topotecan-treated patients than for CAV: dyspnoea*, loss of appetite (* $p<0.05$).

In Phase II studies the outcomes for refractory patients were:

Response rates 2 - 7 %, median time to progression 6 – 10 weeks and median survival 16 – 21 weeks. Symptom improvement in refractory patients was comparable to those in sensitive patients.

The response rate in the overall small cell lung carcinoma population (n= 426) was 14% with a response rate of 4% in refractory patients.

Activity has been observed in cerebral metastases in patients (sensitive and refractory) with brain metastases. Of 23 patients in three studies who had measurable brain metastases, 8 (35%) had objective responses.

In a study in patients with extensive small cell lung cancer who had received no prior therapy, 48 patients were treated with topotecan at a dose of 2.0 mg/m^2/day daily for five days and repeated every 21 days. According to the "window of opportunity" design, patients who did not respond after 2 cycles, or who did not achieve complete response after 4 cycles or who had progressive disease at any stage were treated with cisplatin and etoposide or carboplatin and etoposide. The partial response rate achieved after topotecan therapy was 40% and the overall median survival (after "salvage" therapy with cisplatin/carboplatin and etoposide) was 10 months.

Ovarian Carcinoma

HYCAMTIN (topotecan hydrochloride) was studied in four clinical trials of 453 patients with metastatic ovarian carcinoma. All patients had disease that had recurred on, or was unresponsive to, a platinum-containing regimen. Patients in these four studies received an initial dose of 1.5 mg/m^2 given by intravenous infusion over 30 minutes for 5 consecutive days, starting on day 1 of a 21-day course.

In a comparative study of topotecan and paclitaxel in patients previously treated for ovarian carcinoma with platinum-based chemotherapy (n= 112 and 114, respectively), the response rate (95% C.I.) was 21% (18, 28) versus 14% (8, 21) and median time to progression 26 weeks versus 22 weeks (hazard ratio 0.76 [0.6, 1.0]), for topotecan and paclitaxel, respectively. Median overall survival was 63 weeks for topotecan versus 53 weeks for paclitaxel (hazard ratio 0.97 [0.7, 1.3]).

The response rate in the whole ovarian carcinoma programme (n=392, all previously treated with cisplatin or cisplatin and paclitaxel) was 16%. In patients refractory to, or relapsing within three months after cisplatin therapy (n=186), the response rate was 10%.

These data should be evaluated in the context of the overall safety profile of the drug, in particular to the important haematological toxicity. (See **ADVERSE EFFECTS** section).

Cervical carcinoma

In a randomised, comparative phase III trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n=147) was compared with cisplatin alone (n=146) for the treatment of confirmed Stage IV-B or recurrent or persistent carcinoma of the cervix where curative treatment with surgery and/or radiation was not considered appropriate. No patient had received primary chemotherapy with cisplatin or any other cytotoxic agent. Approximately 56% of both treatment groups had received prior cisplatin as a radiotherapy sensitiser. Treatment was planned for a total of 6 cycles. The median number of cycles received was 4 in the combination arm and 3 in the cisplatin arm. The primary efficacy results of this study are presented below in Table 1.

Table 1. Efficacy Results of study GOG 0179

Efficacy endpoint	**Topotecan + Cisplatin (n=147)**	**Cisplatin monotherapy (n = 146)**
Overall Survival		
Median (95% C.I.) in months	9.4 (7.9, 11.9)	6.5 (5.8, 8.8)
Hazard Ratio (95% C.I.) Log rank p-value	0.76 (0.59-0.98) p= 0.033*	
1 Year survival rate (95% C.I.)	40.4% (32.3, 48.5)	28% (20.6, 35.4)
2 Year survival rate (95% C.I.)	11.9% (5.5, 18.3)	7.1 (2.0, 12.2)
Progression-Free Survival		
Median (95% C.I.) in months	4.6 (3.5, 5.7)	2.9 (2.6, 3.5)
Hazard Ratio, 95% C.I. Log rank p-value	0.76 (0.60, 0.97) p= 0.026	
Overall Response Rate (%)	24%	12%
Pearson Chi-square p-value	0.0073	
Complete Response Rate	10%	3%

* Log-rank p-value was significant as it was less than the two-sided nominal significance level of 0.044 after adjusting for interim analysis.

There were four (3%) deaths reported as related / possibly related to treatment in the combination arm and none in the cisplatin arm. In 3 of these cases early progressive disease was reported as the predominant cause of death with treatment related toxicity

cited as a contributory factor. The combination arm was associated with increased haematological toxicity (see **ADVERSE EFFECTS**).

Secondary endpoints of Quality of Life (QoL) was assessed using the Functional Assessment of Cancer Therapy-Cervix Cancer, Brief Pain Inventory as well as the UNISCALE. QoL readings were taken prior to randomisation, prior to cycles 2 and 5 of treatment and 9 months post-randomisation. Compared to cisplatin alone, the increased haematological toxicity seen with the combination of topotecan and cisplatin, did not significantly reduce the patient QoL outcomes.

Capsules:

Small Cell Lung Carcinoma

An open label phase III trial (SK&F 104864/478) compared oral topotecan (2.3 mg/m^2/day for 5 consecutive days every 21 days) plus Best Supportive Care [BSC] [n=71] with BSC alone [n=70] in patients who had relapsed at least 45 days from the end of first-line therapy [median time to progression [TTP] from first-line therapy: 84 days for oral topotecan + BSC, 90 days for BSC]. Patients received a median number of 4 courses with a range of 1-10 courses. Oral topotecan plus BSC group had a statistically significant and clinically meaningful improvement in overall survival compared with the BSC alone group in the ITT population (Log-rank p=0.0104). The median survival for patients treated with topotecan + BSC was 25.9 weeks [95% C.I. 18.3, 31.6] compared to 13.9 weeks [95% C.I. 11.1, 18.6] for patients receiving BSC alone. The unadjusted hazard ratio for oral topotecan plus BSC relative to BSC alone was 0.64 (95% C.I.: 0.45, 0.90).

Odds ratios (OR) for symptom benefit (improvement) using a Generalised Estimating Equations (GEE) model analysis of patients' self-reports on the Patient Symptom Assessment in Lung Cancer (PSALC) scale showed a consistent trend towards symptom benefit with oral topotecan plus BSC relative to BSC alone across all of the 9 lung cancer symptoms which were assessed. In addition, a significant symptom benefit for shortness of breath (OR=2.18: 95% C.I.: 1.09, 4.38), interference with sleep (OR=2.16: 95% C.I.: 1.15, 4.06) and fatigue (OR=2.29: 95% C.I.: 1.25, 4.19) was observed.

In another open label phase III trial (SK&F 104864/396), the efficacy of oral 2.3 mg/m^2/day for 5 consecutive days every 21 days, [n=153] and intravenous 1.5 mg/m^2/day 30 min infusion for 5 consecutive days every 21 days, [n=151] topotecan was compared in patients with sensitive disease, i.e. who had relapsed at least 90 days after completion of one first-line regimen [median TTP 176 days versus 190 days respectively]. Patients received a median number of 4 courses in both arms with a range of 1-19 courses for oral topotecan and a range of 1-14 courses for i.v. topotecan. The overall response rate was 18.3% (95% C.I.: 12.2, 24.4) for oral topotecan and 21.9% (95% C.I.: 15.3, 28.5) for intravenous topotecan. The difference in the response rate (oral — i.v.) was —3.55% (95% C.I.: —12.55, 5.45) i.e. the study did not show non inferiority in the primary endpoint of response rate based on the 10% absolute margin. Median survival was 33.0 weeks (95% C.I.: 29.1, 42.4) in the oral group and 35.0 weeks [95% C.I.: 31.0, 37.14] in the intravenous group. The unadjusted hazard ratio for oral topotecan relative to i.v. topotecan was 0.88 (95% C.I.: 0.7, 1.11). Oral and i.v. topotecan were associated with similar symptom palliation in patients with relapsed sensitive SCLC as assessed from patient's self-reports on the Functional Assessment of Cancer Therapy (FACT-L).

In another open label phase II trial (SK & F 104864/065), the efficacy of oral [2.3 mg/m^2/day for 5 consecutive days every 21 days, n=52] and intravenous [1.5 mg/m^2/day 30 min infusion for 5 consecutive days every 21 days, n=54] topotecan was compared in patients with sensitive disease, i.e. who had relapsed at least 3 months after completion of one first-line regimen. Patients in both arms received a median number of courses of 4 with a range of 1-12 courses. The overall response rate was 23.1% (95%

C.I.: 11.6, 34.5) for oral topotecan and 14.8% (95% C.I.: 5.3, 24.3) for intravenous topotecan. The difference in the response rate (oral-i.v.) was 8.3% (95% C.I.: —6.6, 23.1). Median survival was 32.3 weeks [95% C.I.: 26.3, 40.9] in the oral group and 25.1 weeks [95% C.I.: 21.1, 33.0] in the intravenous group. The unadjusted hazard ratio for oral topotecan relative to i.v. topotecan was 0.88 (95% C.I.: 0.59, 1.31). The study was not designed to assess non-inferiority between oral and intravenous topotecan.

INDICATIONS

HYCAMTIN powder for i.v. infusion is indicated as single agent therapy for the treatment of patients with:

- Small cell lung carcinoma after failure of first line chemotherapy.
- Metastatic carcinoma of the ovary after failure of first-line or subsequent therapy.

HYCAMTIN powder for i.v. infusion is indicated in combination with cisplatin for the treatment of patients with:

- Histologically confirmed Stage IV-B, recurrent, or persistent carcinoma of the cervix, which is not amenable to curative treatment with surgery and/or radiation therapy.

CONTRAINDICATIONS

Hycamtin is contraindicated in:

- Patients with a history of severe hypersensitivity reactions to topotecan or any of its excipients (see **DESCRIPTION**).
- Women who are pregnant or breast feeding.
- Persons who already have severe bone marrow depression prior to starting the first course, as evidenced by baseline neutrophil count of $< 1.5 \times 10^9$/L and/or a platelet count of less than 100×10^9/L)

PRECAUTIONS

Topotecan should be initiated under the direction of a physician experienced in the use of cytotoxic agents.

Haematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see **DOSAGE AND ADMINISTRATION**). Prior to administration of the first course of HYCAMTIN, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/L, a platelet count of $\geq 100 \times 10^9$/L and a haemoglobin level of ≥ 9 g/dL (after transfusion if necessary).

Patients who experience prolonged severe neutropenia, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, should either be given a reduced topotecan dose or prophylactic G-CSF in subsequent courses. If neutropenia is not adequately managed with G-CSF administration, the topotecan dose should be reduced.

Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. In patients presenting with fever, neutropenia and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.

As with other cytotoxic drugs, topotecan can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with topotecan (see **ADVERSE EFFECTS**).

As with other myelosuppressive cytotoxics, greater myelosuppression is likely to be seen when topotecan is used in patients who have received extensive previous chemotherapy and when used in combination with other myelosuppressive cytotoxics. Dose reduction of topotecan may be required in these circumstances.

Topotecan has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (See **ADVERSE EFFECTS**). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnoea and/or hypoxia), and topotecan should be discontinued if a new diagnosis of ILD is confirmed.

There is no evidence that topotecan will affect the ability of a patient to drive or operate machinery. However, caution should be observed when driving or operating machinery if fatigue and asthenia persist.

Dose adjustment may be necessary if topotecan is administered in combination with other cytotoxic agents (see **INTERACTIONS WITH OTHER MEDICINES**).

Carcinogenicity

The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and resulting from its mechanism of action, topotecan is genotoxic to mammalian cells and must be considered to be carcinogenic.

Genotoxicity

Topotecan was mutagenic to L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not cause mutations in bacterial cells.

Effects on Fertility

Topotecan caused superovulation in female rats when given before mating at 1.36 mg/m^2/day. This effect should therefore be taken into account for women of childbearing age.

Use in Pregnancy (Category D)

Topotecan is contraindicated in pregnancy. There is no information on the use of topotecan in pregnant women. As with other cytotoxic drugs, topotecan may cause foetal harm when administered to pregnant women. Women should be advised to avoid becoming pregnant during therapy with topotecan and to inform the treating physician immediately should this occur.

Topotecan was also shown to cause embryo-foetal toxicity when given to rats (0.59 mg/m^2/day) and rabbits (1.25 mg/m^2/day) at doses less than the clinical intravenous dose in humans (1.5 mg/m^2/day). A dose of 0.59 mg/m^2/day was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae). These effects have been

observed with other topoisomerase-I inhibitors and would therefore appear to be a class effect.

Use in Lactation

Topotecan is contraindicated during lactation. Topotecan has been shown to be excreted in the milk of lactating rats. As there is the potential for serious adverse reactions in nursing infants, nursing must be discontinued at the start of therapy.

Use in Children

The use of topotecan in children is not recommended as only limited data are available.

INTERACTIONS WITH OTHER MEDICINES

With the exception of the studies looking at the interaction of topotecan with other cytotoxics, possible interactions of topotecan with concomitantly administered medications have not been formally investigated.

As with other myelosuppressive cytotoxics, greater myelosuppression is likely to be seen when topotecan is used in combination with other myelosuppressive cytotoxics, thereby necessitating dose reduction.

In vitro, topotecan did not inhibit human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A, nor did it inhibit the human cytosolic enzymes dihydropyrimidine or xanthine oxidase. In population studies, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of topotecan.

When topotecan (0.75 mg/m^2/day for 5 consecutive days) and cisplatin (60 mg/m^2/day on Day 1) were administered intravenously in 13 patients with ovarian cancer, mean topotecan plasma clearance on Day 5 was slightly reduced compared to values on Day 1. As a result, systemic exposure of total topotecan, as measured by AUC and Cmax, on Day 5 were increased by 12% (95% C.I.; 2%, 24%) and 23% (95% C.I.; -7%, 63%), respectively. No pharmacokinetic data are available following topotecan (0.75 mg/m^2/day for 3 consecutive days) and cisplatin (50 mg/m^2/day on Day 1) in patients with cervical cancer.

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Following co administration of the ABCG2 (BCRP) and the ABCB1 (P-gp) inhibitor, elacridar (GF120918) at 100 to 1,000 mg with intravenous topotecan increased the $AUC_{0\text{-}inf}$ of topotecan lactone and total topotecan approximately 1.2-fold, respectively.

ADVERSE EFFECTS

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and less than 1/10), uncommon (greater than or equal to 1/1,000 and less than 1/100), rare (greater than or equal to 1/10,000 and less than 1/1,000) and very rare (less than 1/10,000) including isolated reports and not known (cannot be estimated from the available data). Very common, common and uncommon events were generally determined from clinical trial data.

Topotecan clinical trials usually did not include a placebo arm, therefore background rates were not taken into account when assigning frequency categories and all reports of these adverse events have been used.

The following frequencies are estimated at the standard recommended doses of topotecan according to indication.

Infections and Infestations

Very Common:	Infection
Common:	Sepsis (see **PRECAUTIONS**)

Blood and lymphatic system disorders

Very Common:	Anaemia, febrile neutropenia, leucopenia, neutropenia, (see Gastrointestinal disorders), thrombocytopenia
Common:	Pancytopenia
Not known	Severe bleeding (associated with thrombocytopenia)

Immune system disorders

Common:	Hypersensitivity, including rash

Metabolism and nutrition disorders

Very Common:	Anorexia (which may be severe)

Respiratory, thoracic and mediastinal disorders

Rare:	Interstitial lung disease

Gastrointestinal disorders

Very Common:	Diarrhoea[#] (see **PRECAUTIONS**), nausea and vomiting (all of which may be severe), abdominal pain*, constipation and stomatitis.

[#]Drug-related diarrhoea in patients greater than 65 years of age was 10%.

*Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see **PRECAUTIONS**).

Hepatobiliary disorders

Common:	Hyperbilirubinaemia, Elevated ALT and AST

Skin and subcutaneous disorders

Very common:	Alopecia

General disorders and administrative site conditions

Very common:	Asthenia, fatigue, pyrexia
Common:	Malaise
Rare:	Extravasation[#]

[#]These reactions have been mild and have not generally required specific therapy.

Central and Peripheral Nervous System

Common:	Headache, dizziness, paraesthesia.
Uncommon:	Hypoesthesia, neuropathy, peripheral neuropathy, paresis.

Respiratory:

Common:	Dyspnoea (4%). coughing, epistaxis, pharyngitis, rhinitis, respiratory disorder.

No evidence of significant cardiotoxicity, neurotoxicity or major organ toxicity has been observed with HYCAMTIN.

Powder for i.v. infusion

Table 2. Incidence of Haematological adverse experiences in small cell lung and ovarian carcinoma (N= 879) patients treated with intravenous topotecan

Haematological Adverse experiences		Incidence (% patients)	Incidence (% courses)
Neutropenia	Severe (n count <0.5 x 10^9/L)	78	39
	Moderate (n count 0.5-0.9 x 10^9/L)	16	30
	All cases by patient		
	fever[1]	11	4
	infection[1]	27	10
	sepsis	4	1
Severe Neutropenia	and fever[1]	5	2
	and fever[1] or infection[1]	19	6
	and fever[1] or infection[1] and sepsis[2]	23	7
Leucopoenia	Severe (white blood cells <1.0 x 10^9/L)	32	11
	Moderate (white blood cells 1.0-1.9 x 10^9/L)	53	43
Thrombocytopenia[3]	Severe (platelets < 25 x 10^9/L)	27	9
	Moderate (platelets 25-49.9 x 10^9/L)	25	16
Anaemia[4]	Moderate to severe (Hb≤ 7.9 g/dL)	37	15
	Mild (Hb 8-10 g/dL)	52	56

1 Fever (CTC grade ≥ 2) or febrile neutropenia; infection (CTC grade ≥ 2)
2 All cases of sepsis regardless of association with neutropenia
3 Severe sequelae associated with thrombocytopenia were uncommon (1.6% of patients). Platelet transfusions were given in 15% of patients (4% courses)
4 Red cell transfusions were given in 52% of patients (22% courses)

Haematologic: In dose-finding studies, the dose-limiting toxicity was found to be haematological. Toxicity was generally predictable and reversible. No evidence of cumulative toxicity was seen. In patients with small cell lung or ovarian carcinoma the onset of neutropenia and thrombocytopenia was generally within 2 weeks of treatment and in the majority of cases lasted no more than 7 days. In 11% of courses severe neutropenia lasted more than 7 days.

Among all patients treated in clinical studies (including both those with severe neutropenia and those who did not develop severe neutropenia), 13% (5% of courses) developed fever and 27% (10% of courses) developed infection. In addition 5% of all patients treated (1% of courses) developed sepsis.

Table 3: Incidence of all related/possibly-related Non-haematological adverse experiences in small cell lung and ovarian carcinoma (N= 879) patients treated with intravenous topotecan

Non Haematological (related/possibly-related) Adverse experiences		Incidence (% patients) All cases	Incidence (% patients) Grade 3/4
Gastrointestinal			
Nausea		56	5
Vomiting		36	3
Diarrhoea		21	2
Stomatitis		17	1.5
Constipation		10	0.2
Abdominal pain		6	0.9
Fatigue		24	3.5
Asthenia		18	3.4
Alopecia	Total	31	N/A
	Partial	16	N/A
Other Events			
Anorexia		13	1
Rash		8	0.2
Malaise		5	1.1
Hyperbilirubinaemia		1	0.8

N/A - Not Applicable

Table 4 : Number (%) of patients with haematological toxicity by worst CTC grade and with interventions in cervical carcinoma, treated population

	Cisplatin (n=144)		Intravenous Topotecan/Cisplatin (n=140)	
Haematological Toxicity[a]	N	%	N	%
Leucopenia				
Grade 3	1	1	58	41
Grade 4	0	0	35	25
Total	43	30	128	91
ANC-AGC				
Grade 3	1	1	36	26
Grade 4	1	1	67	48
Total	28	19	125	89
Thrombocytopenia				
Grade 3	5	3	36	26
Grade 4	0	0	10	7
Total	21	15	104	74
Haemoglobin				
Grade 3	28	19	47	34
Grade 4	5	3	9	6
Total	130	90	131	94

	Cisplatin (n=144)		Intravenous Topotecan/Cisplatin (n=140)	
Number of patients with interventions for haematological toxicity, treated population				
Intervention type				
G-CSF	5	3.47	37	26.40
Platelet Transfusion	1	0.69	16	11.40
RBC Transfusion	49	34.00	68	48.60
Erythropoietin	38	26.40	51	36.40

Abbrev: CTC = common toxicity criteria; ANC/AGC – absolute neutrophil count/absolute granulocyte count; G-CSF = granulocyte colony stimulating factor, RBC = red blood cells
[a] – toxicity is based on patients worst grade for the study as determined by the investigator

Postmarketing Data

The following adverse reactions have been reported during post-marketing experience with Hycamtin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse reactions are listed according to system organ classes in MedDRA.

	Frequency
Gastrointestinal disorders	
Gastrointestinal perforation	Not known
General disorders and administration site conditions	
Mucosal inflammation	Not known

DOSAGE AND ADMINISTRATION

HYCAMTIN powder for i.v. infusion must be reconstituted and further diluted before use (see Instructions for Use/Handling).

Prior to administration of the first course of HYCAMTIN, patients must have a baseline neutrophil count of $\geq 1.5 \times 10^9$/L, a platelet count of $\geq 100 \times 10^9$/L and a haemoglobin level of ≥ 9 g/dL (after transfusion if necessary).

Populations

Adults and Elderly

Ovarian and small cell lung carcinoma

The recommended dose of HYCAMTIN is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, with a 3 week interval between the start of each course. A minimum of 4 courses is recommended in the absence of definite tumour progression since median time to response in clinical trials was 8 - 11.7 weeks in ovarian cancer and 6.1 weeks in small cell lung cancer.

Subsequent doses

Topotecan should not be readministered unless the neutrophil count is ≥ 1 x 10^9/L, the platelet count is ≥ 100 x 10^9/L, and the haemoglobin level is ≥ 9g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medications (e.g. G-CSF) or to dose reduce to maintain neutrophil counts.

If dosage reduction is chosen for patients who experience severe neutropenia (neutrophil count < 0.5 x 10^9/L) for 7 days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m^2/day to 1.25 mg/m^2/day (or subsequently down to 1.0 mg/m^2/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/L.

In clinical trials, HYCAMTIN powder for i.v. infusion was discontinued if the dose had to be reduced below 1.0 mg/m^2.

Cervical Cancer

Initial Dose:

The recommended dose of topotecan is 0.75 mg/m^2 administered as 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m^2 and following the topotecan dose. This treatment schedule is repeated every 21 days for 6 courses or until progressive disease.

Subsequent doses

Topotecan should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10^9/L, the platelet count is more than or equal to 100 x 10^9/L, and the haemoglobin level is more than or equal to 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer topotecan with other medications (e.g. G-CSF) or to dose reduce to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 0.5 x 10^9/L for seven days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose of topotecan should be reduced by 20% to 0.60 mg/m^2 for subsequent courses (or subsequently down to 0.45 mg/m^2/day).

Doses should be similarly reduced if the platelet count falls below 25 x 10^9/L.

Special Populations

- **Children**

Use in children is not recommended as only limited data are available.

- **Elderly**

No overall differences in effectiveness were observed between patients over 65 years and younger adult patients.

Use in Renal Impairment

Monotherapy

No dosage adjustment is required in patients with a creatinine clearance ≥ 0.66 mL/s. The recommended dose in patients with creatinine clearance between 0.33 and 0.65 mL/s is 0.75 mg/m^2/day. Insufficient data is available to make a recommendation for patients with a creatinine clearance < 0.33 mL/s. Advice on dosing of topotecan for

patients with moderate renal impairment (0.33 to 0.65 mL/s) is based on studies involving patients with advanced cancer.

Combination therapy

It is recommended that topotecan in combination with cisplatin for the treatment of cervical cancer only be initiated in patients with serum creatinine less than or equal to 132.6 µmol/L. If, during topotecan/cisplatin combination therapy serum creatinine exceeds 132.6 µmol/L, it is recommended that the full prescribing information be consulted for any advice on cisplatin dose reduction/continuation. If cisplatin is discontinued, there are insufficient data regarding continuing monotherapy with topotecan in patients with cervical cancer.

Use in Hepatic Impairment

Monotherapy

No dosage adjustment is required in patients with hepatic impairment (serum bilirubin in the range 25.65 to 171 µmol/L). Hepatically impaired patients were able to tolerate 1.5 mg/m^2 for five days every three weeks although a small reduction in topotecan clearance was observed.

Dosage in combination

There is currently insufficient information to make a recommendation with respect to the use of topotecan in combination with other cytotoxics in first line patients. Dose adjustment may be necessary if topotecan is administered in combination with other cytotoxic agents (see **INTERACTIONS WITH OTHER MEDICINES**).

Instructions for Use/Handling:

HYCAMTIN 4mg vials are reconstituted with 4mL sterile Water for Injection. HYCAMTIN 1 mg vials are reconstituted with 1.1 mL sterile Water for Injections, which ensures that a full 1 mL of solution can be withdrawn from the vial. For infusion, the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride BP intravenous infusion solution or 5% Glucose intravenous infusion solution prior to administration.

Reconstituted vials are stable for up to 24 hours at 5°C and 30°C. Diluted solutions are chemically and physically stable for up to 24 hours at temperatures up to 30°C. The lyophilised dosage form contains no antibacterial preservative. In accordance with good pharmaceutical practice, it is recommended that the product be used as soon as possible after reconstitution and dilution. Otherwise, it should be refrigerated at 2-8°C for not more than 24 hours.

The normal procedures for proper handling and disposal of anticancer drugs should be adopted, including:

- Personnel should be trained to reconstitute the drug.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling this drug during reconstitution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in a high-risk, waste disposal bag for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

OVERDOSAGE

Overdoses (up to 10 fold of the prescribed dose) have been reported in patients being treated with intravenous topotecan. The primary anticipated complication of overdosage would consist of bone marrow suppression. The observed signs and symptoms for overdose are consistent with the known adverse reactions associated with Hycamtin (see **ADVERSE EFFECTS**). In addition, elevated hepatic enzymes and mucositis have been reported following overdose.

There is no known antidote for topotecan overdosage. Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

HYCAMTIN powder for i.v. infusion is presented in single use glass vials containing sterile lyophilised powder for reconstitution. Each 17 mL vial contains topotecan hydrochloride equivalent to 4 mg topotecan as the free base. Each 5 mL vial contains topotecan hydrochloride equivalent to 1 mg as the free base.

Not all strengths or pack sizes may be distributed in Australia.

Lyophilised HYCAMTIN vials stored at temperatures up to 30°C have a shelf-life of 36 months.

The lyophilised dosage form contains no antibacterial preservative. In accordance with good pharmaceutical practice, it is recommended that the product be used as soon as possible after reconstitution and dilution. Otherwise, it should be refrigerated at 2-8°C for not more than 24 hours.

Before reconstitution the product must be protected from light during long-term storage by being retained in its carton.

NAME AND ADDRESS OF THE SPONSOR

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54 Waterloo Road
MACQUARIE PARK NSW 2113

POISON SCHEDULE OF THE MEDICINE: S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 20 August 2009

DATE OF THE MOST RECENT AMENDMENT: 21 September 2017