HY:L15
PRESCRIBING INFORMATION

HYCAMTIN â

(topotecan hydrochloride)
For Injection
FOR INTRAVENOUS USE

WARNING

HYCAMTIN (topotecan hydrochloride) for Injection should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Therapy with HYCAMTIN should not be given to patients with baseline neutrophil counts of less than 1,500 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection and death, frequent peripheral blood cell counts should be performed on all patients receiving HYCAMTIN.

DESCRIPTION

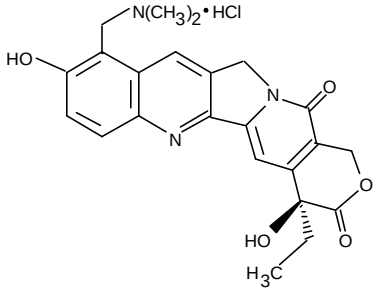
HYCAMTIN (topotecan hydrochloride) is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity.

HYCAMTIN for Injection is supplied as a sterile lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by intravenous infusion.

Inactive ingredients are mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5 to 3.5.

The chemical name for 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. It has the molecular formula $C_{23}H_{23}N_3O_5$•HCl and a molecular weight of 457.9.

Topotecan hydrochloride has the following structural formula:



It is soluble in water and melts with decomposition at 213° to 218°C.

CLINICAL PHARMACOLOGY

Mechanism of Action: Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks.

Pharmacokinetics: The pharmacokinetics of topotecan have been evaluated in cancer patients following doses of 0.5 to 1.5 mg/m^2 administered as a 30-minute infusion. Topotecan exhibits multiexponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

Metabolism and Elimination: Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. In vitro studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway.

In humans, about 30% of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination (see Special Populations).

Special Populations: ***Gender:*** The overall mean topotecan plasma clearance in male patients was approximately 24% higher than that in female patients, largely reflecting difference in body size.

Geriatrics: Topotecan pharmacokinetics have not been specifically studied in an elderly population, but population pharmacokinetic analysis in female patients did not identify age as a significant factor. Decreased renal clearance, which is common in the elderly, is a more important determinant of topotecan clearance (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Race: The effect of race on topotecan pharmacokinetics has not been studied.

Renal Impairment: In patients with mild renal impairment (creatinine clearance of 40 to 60 mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Mean half-life, estimated in 3 renally impaired patients, was about 5.0 hours. Dosage adjustment is recommended for these patients (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment: Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2.0 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen (see DOSAGE AND ADMINISTRATION).

Drug Interactions: Pharmacokinetic studies of the interaction of topotecan with concomitantly administered medications have not been formally investigated. In vitro inhibition studies using marker substrates known to be metabolized by human P450 CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

Pharmacodynamics: The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. When topotecan is administered at a dose of 1.5 mg/m^2/day for 5 days, an 80% to 90% decrease in white blood cell count at nadir is typically observed after the first cycle of therapy.

CLINICAL STUDIES

Ovarian Cancer: HYCAMTIN was studied in 2 clinical trials of 223 patients given topotecan with metastatic ovarian carcinoma. All patients had disease that had recurred on, or was unresponsive to, a platinum-containing regimen. Patients in these 2 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.

One study was a randomized trial of 112 patients treated with HYCAMTIN (1.5 mg/m^2/day × 5 days starting on day 1 of a 21-day course) and 114 patients treated with paclitaxel (175 mg/m^2 over 3 hours on day 1 of a 21-day course). All patients had recurrent ovarian cancer after a platinum-containing regimen or had not responded to at least 1 prior platinum-containing regimen. Patients who did not respond to the study therapy, or who progressed, could be given the alternative treatment.

Response rates, response duration, and time to progression are shown in Table 1.

Table 1. Efficacy of HYCAMTIN Versus Paclitaxel in Ovarian Cancer

Parameter	**HYCAMTIN (n = 112)**	**Paclitaxel (n = 114)**
Complete response rate	5%	3%
Partial response rate	16%	11%
Overall response rate	21%	14%
95% Confidence interval	13 to 28%	8 to 20%
(p-value)	(0.20)	
Response duration* (weeks)	n = 23	n = 16
Median	25.9	21.6
95% Confidence interval hazard-ratio	22.1 to 32.9	16.0 to 34.0
(HYCAMTIN:paclitaxel)	0.78	
(p-value)	(0.48)	
Time to progression (weeks)		
Median	18.9	14.7
95% Confidence interval hazard-ratio	12.1 to 23.6	11.9 to 18.3
(HYCAMTIN:paclitaxel)	0.76	
(p-value)	(0.07)	
Survival (weeks)		
Median	63.0	53.0
95% Confidence interval hazard-ratio	46.6 to 71.9	42.3 to 68.7
(HYCAMTIN:paclitaxel)	0.97	
(p-value)	(0.87)	

*The calculation for duration of response was based on the interval between first response and time to progression.

The median time to response was 7.6 weeks (range 3.1 to 21.7) with HYCAMTIN compared to 6.0 weeks (range 2.4 to 18.1) with paclitaxel. Consequently, the efficacy of HYCAMTIN may not be achieved if patients are withdrawn from treatment prematurely.

In the crossover phase, 8 of 61 (13%) patients who received HYCAMTIN after paclitaxel had a partial response and 5 of 49 (10%) patients who received paclitaxel after HYCAMTIN had a response (2 complete responses).

HYCAMTIN was active in ovarian cancer patients who had developed resistance to platinum-containing therapy, defined as tumor progression while on, or tumor relapse within 6 months after completion of, a platinum-containing regimen. One complete and 6 partial responses were seen in 60 patients, for a response rate of 12%. In the same study, there were no complete responders and 4 partial responders on the paclitaxel arm, for a response rate of 7%.

HYCAMTIN was also studied in an open-label, non-comparative trial in 111 patients with recurrent ovarian cancer after treatment with a platinum-containing regimen, or who had not responded to 1 prior platinum-containing regimen. The response rate was 14% (95% CI = 7% to

20%). The median duration of response was 22 weeks (range 4.6 to 41.9 weeks). The time to progression was 11.3 weeks (range 0.7 to 72.1 weeks). The median survival was 67.9 weeks (range 1.4 to 112.9 weeks).

Small Cell Lung Cancer: HYCAMTIN was studied in 426 patients with recurrent or progressive small cell lung cancer in 1 randomized, comparative study and in 3 single-arm studies.

Randomized Comparative Study: In a randomized, comparative, Phase 3 trial, 107 patients were treated with HYCAMTIN (1.5 mg/m^2/day × 5 days starting on day 1 of a 21-day course) and 104 patients were treated with CAV (1,000 mg/m^2 cyclophosphamide, 45 mg/m^2 doxorubicin, 2 mg vincristine administered sequentially on day 1 of a 21-day course). All patients were considered sensitive to first-line chemotherapy (responders who then subsequently progressed ≥60 days after completion of first-line therapy). A total of 77% of patients treated with HYCAMTIN and 79% of patients treated with CAV received platinum/etoposide with or without other agents as first-line chemotherapy.

Response rates, response duration, time to progression, and survival are shown in Table 2.

Table 2. Efficacy of HYCAMTIN Versus CAV (cyclophosphamide-doxorubicin-vincristine) in Small Cell Lung Cancer Patients Sensitive to First-Line Chemotherapy

Parameter	**HYCAMTIN (n = 107)**	**CAV (n = 104)**
Complete response rate	0%	1%
Partial response rate	24%	17%
Overall response rate	24%	18%
Difference in overall response rates	6%	
95% Confidence interval of the difference	(–6 to 18%)	
Response duration* (weeks)	n = 26	n = 19
Median	14.4	15.3
95% Confidence interval hazard-ratio	13.1 to 18.0	13.1 to 23.1
(HYCAMTIN:CAV)	1.42 (0.73 to 2.76)	
(p-value)	(0.30)	
Time to progression (weeks)		
Median	13.3	12.3
95% Confidence interval hazard-ratio	11.4 to 16.4	11.0 to 14.1
(HYCAMTIN:CAV)	0.92 (0.69 to 1.22)	
(p-value)	(0.55)	
Survival (weeks)		
Median	25.0	24.7
95% Confidence interval hazard-ratio	20.6 to 29.6	21.7 to 30.3
(HYCAMTIN:CAV)	1.04 (0.78 to 1.39)	
(p-value)	(0.80)	

*The calculation for duration of response was based on the interval between first response and

time to progression.

The time to response was similar in both arms: HYCAMTIN median of 6 weeks (range 2.4 to 15.7) versus CAV median 6 weeks (range 5.1 to 18.1).

Changes on a disease-related symptom scale in patients who received HYCAMTIN or who received CAV are presented in Table 3. It should be noted that not all patients had all symptoms, nor did all patients respond to all questions. Each symptom was rated on a 4-category scale with an improvement defined as a change in 1 category from baseline sustained over 2 courses. Limitations in interpretation of the rating scale and responses preclude formal statistical analysis.

Table 3. Percentage of Patients With Symptom Improvement[*]: HYCAMTIN Versus CAV in Patients With Small Cell Lung Cancer

Symptom	HYCAMTIN (n = 107)		CAV (n = 104)	
	n[†]	(%)	n[†]	(%)
Shortness of breath	68	(28)	61	(7)
Interference with daily activity	67	(27)	63	(11)
Fatigue	70	(23)	65	(9)
Hoarseness	40	(33)	38	(13)
Cough	69	(25)	61	(15)
Insomnia	57	(33)	53	(19)
Anorexia	56	(32)	57	(16)
Chest pain	44	(25)	41	(17)
Hemoptysis	15	(27)	12	(33)

[*]Defined as improvement sustained over at least 2 courses compared to baseline.

[†] Number of patients with baseline and at least 1 post-baseline assessment.

Single-Arm Studies: HYCAMTIN was also studied in 3 open-label, non-comparative trials in a total of 319 patients with recurrent or progressive small cell lung cancer after treatment with first-line chemotherapy. In all 3 studies, patients were stratified as either sensitive (responders who then subsequently progressed ≥90 days after completion of first-line therapy) or refractory (no response to first-line chemotherapy or who responded to first-line therapy and then progressed within 90 days of completing first-line therapy). Response rates ranged from 11% to 31% for sensitive patients and 2% to 7% for refractory patients. Median time to progression and median survival were similar in all 3 studies and the comparative study.

INDICATIONS AND USAGE

HYCAMTIN is indicated for the treatment of:

- metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.
- small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to

chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy (see CLINICAL STUDIES).

CONTRAINDICATIONS

HYCAMTIN is contraindicated in patients who have a history of hypersensitivity reactions to topotecan or to any of its ingredients. HYCAMTIN should not be used in patients who are pregnant or breast-feeding, or those with severe bone marrow depression.

WARNINGS

Bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of topotecan. Neutropenia is not cumulative over time. The following data on myelosuppression with topotecan is based on the combined experience of 879 patients with metastatic ovarian cancer or small cell lung cancer.

Neutropenia: Grade 4 neutropenia (<500 cells/mm^3) was most common during course 1 of treatment (60% of patients) and occurred in 39% of all courses, with a median duration of 7 days. The nadir neutrophil count occurred at a median of 12 days. Therapy-related sepsis or febrile neutropenia occurred in 23% of patients, and sepsis was fatal in 1%.

Thrombocytopenia: Grade 4 thrombocytopenia (<25,000/mm^3) occurred in 27% of patients and in 9% of courses, with a median duration of 5 days and platelet nadir at a median of 15 days. Platelet transfusions were given to 15% of patients in 4% of courses.

Anemia: Grade 3/4 anemia (<8 g/dL) occurred in 37% of patients and in 14% of courses. Median nadir was at day 15. Transfusions were needed in 52% of patients in 22% of courses.

In ovarian cancer, the overall treatment-related death rate was 1%. In the comparative study in small cell lung cancer, however, the treatment-related death rates were 5% for HYCAMTIN and 4% for CAV.

Monitoring of Bone Marrow Function: HYCAMTIN should be administered only in patients with adequate bone marrow reserves, including baseline neutrophil count of at least 1,500 cells/mm^3 and platelet count at least 100,000/mm^3. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with HYCAMTIN. Patients should not be treated with subsequent courses of HYCAMTIN until neutrophils recover to >1,000 cells/mm^3, platelets recover to >100,000 cells/mm^3, and hemoglobin levels recover to 9.0 g/dL (with transfusion if necessary). Severe myelotoxicity has been reported when HYCAMTIN is used in combination with cisplatin (see Drug Interactions).

Pregnancy: HYCAMTIN may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. If topotecan is used during a patient's pregnancy, or if a patient becomes pregnant while taking topotecan, she should be warned of the potential hazard to the fetus. Fecund women should be warned to avoid becoming pregnant. In rabbits, a dose of 0.10 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given on days 6 through 20 of gestation caused maternal toxicity, embryolethality, and reduced fetal body weight. In the rat, a dose of 0.23 mg/kg/day (about equal to the clinical dose on a mg/m^2 basis) given for 14 days before mating through gestation day 6 caused fetal resorption,

microphthalmia, pre-implant loss, and mild maternal toxicity. A dose of 0.10 mg/kg/day (about half the clinical dose on a mg/m^2 basis) given to rats on days 6 through 17 of gestation caused an increase in post-implantation mortality. This dose also caused an increase in total fetal malformations. The most frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull, and vertebrae.

PRECAUTIONS

General: Inadvertent extravasation with HYCAMTIN has been associated only with mild local reactions such as erythema and bruising.

Information for Patients: As with other chemotherapeutic agents, HYCAMTIN may cause asthenia or fatigue; if these symptoms occur, caution should be observed when driving or operating machinery.

Hematology: Monitoring of bone marrow function is essential (see WARNINGS and DOSAGE AND ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity testing of topotecan has not been performed. Topotecan, however, is known to be genotoxic to mammalian cells and is a probable carcinogen. 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.

Drug Interactions: Concomitant administration of G-CSF can prolong the duration of neutropenia, so if G-CSF is to be used, it should not be initiated until day 6 of the course of therapy, 24 hours after completion of treatment with HYCAMTIN.

Myelosuppression was more severe when HYCAMTIN was given in combination with cisplatin in Phase 1 studies. In a reported study on concomitant administration of cisplatin 50 mg/m^2 and HYCAMTIN at a dose of 1.25 mg/m^2/day $\times$ 5 days, 1 of 3 patients had severe neutropenia for 12 days and a second patient died with neutropenic sepsis. There are no adequate data to define a safe and effective regimen for HYCAMTIN and cisplatin in combination.

Greater myelosuppression is also likely to be seen when HYCAMTIN is used in combination with other cytotoxic agents, thereby necessitating a dose reduction. However, when combining HYCAMTIN with platinum agents (e.g., cisplatin or carboplatin), a distinct sequence-dependent interaction on myelosuppression has been reported. Coadministration of a platinum agent on day 1 of HYCAMTIN dosing required lower doses of each agent compared to coadministration on day 5 of the HYCAMTIN dosing schedule.

Pregnancy: Pregnancy Category D. (See WARNINGS.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Breast-feeding should be discontinued when women are receiving HYCAMTIN (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the 879 patients with metastatic ovarian cancer or small cell lung cancer in

clinical studies of HYCAMTIN, 32% (n = 281) were 65 years of age and older, while 3.8% (n = 33) were 75 years of age and older. No overall differences in effectiveness or safety were observed between these patients and younger adult patients. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

There were no apparent differences in the pharmacokinetics of topotecan in elderly patients, once the age-related decrease in renal function was considered (see CLINICAL PHARMACOLOGY).

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Data in the following section are based on the combined experience of 453 patients with metastatic ovarian carcinoma, and 426 patients with small cell lung cancer treated with HYCAMTIN. Table 4 lists the principal hematologic toxicities, and Table 5 lists non-hematologic toxicities occurring in at least 15% of patients.

Table 4. Summary of Hematologic Adverse Events in Patients Receiving HYCAMTIN

Hematologic Adverse Event	**Patients n = 879 % Incidence**	**Courses n = 4124 % Incidence**
Neutropenia		
<1,500 cells/mm^3	97	81
<500 cells/mm^3	78	39
Leukopenia		
<3,000 cells/mm^3	97	80
<1,000 cells/mm^3	32	11
Thrombocytopenia		
<75,000/mm^3	69	42
<25,000/mm^3	27	9
Anemia		
<10 g/dL	89	71
<8 g/dL	37	14
Sepsis or fever/infection with grade 4 neutropenia	23	7
Platelet transfusions	15	4
RBC transfusions	52	22

Table 5. Summary of Non-hematologic Adverse Events in Patients Receiving HYCAMTIN

Non-hematologic Adverse Event	All Grades % Incidence		Grade 3 % Incidence		Grade 4 % Incidence	
	n = 879 Patients	n = 4124 Courses	n = 879 Patients	n = 4124 Courses	n = 879 Patients	n = 4124 Courses
Gastrointestinal						
Nausea	64	42	7	2	1	<1
Vomiting	45	22	4	1	1	<1
Diarrhea	32	14	3	1	1	<1
Constipation	29	15	2	1	1	<1
Abdominal pain	22	10	2	1	2	<1
Stomatitis	18	8	1	<1	<1	<1
Anorexia	19	9	2	1	<1	<1
Body as a Whole						
Fatigue	29	22	5	2	0	0
Fever	28	11	1	<1	<1	<1
Pain*	23	11	2	1	1	<1
Asthenia	25	13	4	1	2	<1
Skin/Appendages						
Alopecia	49	54	NA	NA	NA	NA
Rash†	16	6	1	<1	0	0
Respiratory System						
Dyspnea	22	11	5	2	3	1
Coughing	15	7	1	<1	0	0
CNS/Peripheral Nervous System						
Headache	18	7	1	<1	<1	0

*Pain includes body pain, back pain, and skeletal pain.

†Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

Premedications were not routinely used in these clinical studies.

Hematologic: (See WARNINGS.)

Gastrointestinal: The incidence of nausea was 64% (8% grade 3/4), and vomiting occurred in 45% (6% grade 3/4) of patients (see Table 5). The prophylactic use of antiemetics was not routine in patients treated with HYCAMTIN. Thirty-two percent of patients had diarrhea (4% grade 3/4), 29% constipation (2% grade 3/4), and 22% had abdominal pain (4% grade 3/4). Grade 3/4 abdominal pain was 6% in ovarian cancer patients and 2% in small cell lung cancer patients.

Skin/Appendages: Total alopecia (grade 2) occurred in 31% of patients.

Central and Peripheral Nervous System: Headache (18% of patients) was the most frequently reported neurologic toxicity. Paresthesia occurred in 7% of patients but was generally grade 1.
Liver/Biliary: Grade 1 transient elevations in hepatic enzymes occurred in 8% of patients. Greater elevations, grade 3/4, occurred in 4%. Grade 3/4 elevated bilirubin occurred in <2% of patients.
Respiratory: The incidence of grade 3/4 dyspnea was 4% in ovarian cancer patients and 12% in small cell lung cancer patients.

Table 6 shows the grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/paclitaxel comparator trial in ovarian cancer.

Table 6. Comparative Toxicity Profiles for Ovarian Cancer Patients Randomized to Receive HYCAMTIN or Paclitaxel

Adverse Event	**HYCAMTIN**		**Paclitaxel**	
	Patients n = 112	**Courses n = 597**	**Patients n = 114**	**Courses n = 589**
Hematologic Grade 3/4	**%**	**%**	**%**	**%**
Grade 4 neutropenia (<500 cells/mL)	80	36	21	9
Grade 3/4 anemia (Hgb <8 g/dL)	41	16	6	2
Grade 4 thrombocytopenia (<25,000 plts/mL)	27	10	3	<1
Fever/Grade 4 neutropenia	23	6	4	1
Documented sepsis	5	1	2	<1
Death related to sepsis	2	NA	0	NA
Non-hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	5	1	4	1
Constipation	5	1	0	0
Diarrhea	6	2	1	<1
Intestinal obstruction	5	1	4	1
Nausea	10	3	2	<1
Stomatitis	1	<1	1	<1
Vomiting	10	2	3	<1
Constitutional				
Anorexia	4	1	0	0
Dyspnea	6	2	5	1
Fatigue	7	2	6	2
Malaise	2	<1	2	<1

Neuromuscular				
Arthralgia	1	<1	3	<1
Asthenia	5	2	3	1
Chest pain	2	<1	1	<1
Headache	1	<1	2	1
Myalgia	0	0	3	2
Pain[*]	5	1	7	2
Skin/Appendages				
Rash[†]	0	0	1	<1
Liver/Biliary				
Increased hepatic enzymes[‡]	1	<1	1	<1

[*]Pain includes body pain, skeletal pain, and back pain.

[†]Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

[‡]Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT, and increased hepatic enzymes.

Premedications were not routinely used in patients randomized to HYCAMTIN, whereas patients receiving paclitaxel received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

Table 7 shows the grade 3/4 hematologic and major non-hematologic adverse events in the topotecan/CAV comparator trial in small cell lung cancer.

Table 7. Comparative Toxicity Profiles for Small Cell Lung Cancer Patients Randomized to Receive HYCAMTIN or CAV

Adverse Event	**HYCAMTIN**		**CAV**	
	Patients n = 107	**Courses n = 446**	**Patients n = 104**	**Courses n = 359**
Hematologic Grade 3/4	**%**	**%**	**%**	**%**
Grade 4 neutropenia (<500 cells/mL)	70	38	72	51
Grade 3/4 anemia (Hgb <8 g/dL)	42	18	20	7
Grade 4 thrombocytopenia (<25,000 plts/mL)	29	10	5	1
Fever/Grade 4 neutropenia	28	9	26	13
Documented sepsis	5	1	5	1
Death related to sepsis	3	NA	1	NA
Non-hematologic Grade 3/4				
Gastrointestinal				
Abdominal pain	6	1	4	2
Constipation	1	<1	0	0
Diarrhea	1	<1	0	0

Nausea	8	2	6	2
Stomatitis	2	<1	1	<1
Vomiting	3	<1	3	1
Constitutional				
Anorexia	3	1	4	2
Dyspnea	9	5	14	7
Fatigue	6	4	10	3
Neuromuscular				
Asthenia	9	4	7	2
Headache	0	0	2	<1
Pain*	5	2	7	4
Respiratory System				
Coughing	2	1	0	0
Pneumonia	8	2	6	2
Skin/Appendages				
Rash†	1	<1	1	<1
Liver/Biliary				
Increased hepatic enzymes‡	1	<1	0	0

* Pain includes body pain, skeletal pain, and back pain.

†Rash also includes pruritus, rash erythematous, urticaria, dermatitis, bullous eruption, and maculopapular rash.

‡Increased hepatic enzymes includes increased SGOT/AST, increased SGPT/ALT, and increased hepatic enzymes.

Premedications were not routinely used in patients randomized to HYCAMTIN, whereas patients receiving CAV received routine pretreatment with corticosteroids, diphenhydramine, and histamine receptor type 2 blockers.

Postmarketing Reports of Adverse Events: Reports of adverse events in patients taking HYCAMTIN received after market introduction, which are not listed above, include the following:

Hematologic: *Rare*: Severe bleeding (in association with thrombocytopenia).

Skin/Appendages: *Rare:* Severe dermatitis, severe pruritus.

Body as a Whole: *Infrequent:* Allergic manifestations; *rare:* Anaphylactoid reactions, angioedema.

OVERDOSAGE

There is no known antidote for overdosage with HYCAMTIN. The primary anticipated complication of overdosage would consist of bone marrow suppression.

One patient on a single-dose regimen of 17.5 mg/m^2 given on day 1 of a 21-day cycle had received a single dose of 35 mg/m^2. This patient experienced severe neutropenia (nadir of 320/mm^3) 14 days later but recovered without incident.

The LD_{10} in mice receiving single intravenous infusions of HYCAMTIN was 75 mg/m^2 (CI

95%: 47 to 97).

DOSAGE AND ADMINISTRATION

Prior to administration of the first course of HYCAMTIN, patients must have a baseline neutrophil count of >1,500 cells/mm^3 and a platelet count of >100,000 cells/mm^3. The recommended dose of HYCAMTIN is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. In the absence of tumor progression, a minimum of 4 courses is recommended because tumor response may be delayed. The median time to response in 3 ovarian clinical trials was 9 to 12 weeks, and median time to response in 4 small cell lung cancer trials was 5 to 7 weeks. In the event of severe neutropenia during any course, the dose should be reduced by 0.25 mg/m^2 for subsequent courses. Doses should be similarly reduced if the platelet count falls below 25,000 cells/mm^3. Alternatively, in the event of severe neutropenia, G-CSF may be administered following the subsequent course (before resorting to dose reduction) starting from day 6 of the course (24 hours after completion of topotecan administration).

Adjustment of Dose in Special Populations: ***Hepatic Impairment:*** No dosage adjustment appears to be required for treating patients with impaired hepatic function (plasma bilirubin >1.5 to <10 mg/dL).

Renal Functional Impairment: No dosage adjustment appears to be required for treating patients with mild renal impairment (Cl_{cr} 40 to 60 mL/min.). Dosage adjustment to 0.75 mg/m^2 is recommended for patients with moderate renal impairment (20 to 39 mL/min.). Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation.

Elderly Patients: No dosage adjustment appears to be needed in the elderly other than adjustments related to renal function (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

PREPARATION FOR ADMINISTRATION

Precautions: HYCAMTIN is a cytotoxic anticancer drug. As with other potentially toxic compounds, HYCAMTIN should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If HYCAMTIN solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If HYCAMTIN contacts mucous membranes, flush thoroughly with water.

Preparation for Intravenous Administration: Each HYCAMTIN 4-mg vial is reconstituted with 4 mL Sterile Water for Injection. Then the appropriate volume of the reconstituted solution is diluted in either 0.9% Sodium Chloride Intravenous Infusion or 5% Dextrose Intravenous Infusion prior to administration.

Because the lyophilized dosage form contains no antibacterial preservative, the reconstituted product should be used immediately.

STABILITY

Unopened vials of HYCAMTIN are stable until the date indicated on the package when stored

between 20° and 25°C (68° and 77°F) [see USP] and protected from light in the original package. Because the vials contain no preservative, contents should be used immediately after reconstitution.

Reconstituted vials of HYCAMTIN diluted for infusion are stable at approximately 20° to 25°C (68° to 77°F) and ambient lighting conditions for 24 hours.

HOW SUPPLIED

HYCAMTIN for Injection is supplied in 4-mg (free base) single-dose vials.

NDC 0007-4201-01 (package of 1)

NDC 0007-4201-05 (package of 5)

Storage: Store the vials protected from light in the original cartons at controlled room temperature between 20° and 25°C (68° and 77°F) [see USP].

Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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