

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYCAMTIN capsules safely and effectively. See full prescribing information for HYCAMTIN capsules.

HYCAMTIN® (topotecan) Capsules
Initial U.S. Approval: 1996

WARNING: BONE MARROW SUPPRESSION
See full prescribing information for complete boxed warning
HYCAMTIN should be administered only to patients with baseline neutrophil counts of ≥1,500 cells/mm³ and a platelet count ≥100,000 cells/mm³. In order to monitor the occurrence of bone marrow suppression, blood cell counts should be monitored (5.1).

RECENT MAJOR CHANGES
Contraindications (4) 10/2011
Warnings and Precautions, Pregnancy (5.4) 10/2011

INDICATIONS AND USAGE
HYCAMTIN is a topoisomerase inhibitor indicated for treatment of patients with relapsed small cell lung cancer. (1)

DOSAGE AND ADMINISTRATION
• 2.3 mg/m²/day orally once daily for 5 consecutive days repeated every 21 days. (2)
• See dose modification guidelines for patients with bone marrow toxicity or Grade 3 or 4 diarrhea. (2.3)

DOSAGE FORMS AND STRENGTHS
0.25 mg and 1 mg capsules. (3)

CONTRAINDICATIONS
• History of severe hypersensitivity reactions (e.g., anaphylactoid reactions) to topotecan or to any of its ingredients. (4)
• Severe bone marrow depression. (4)

WARNINGS AND PRECAUTIONS
• Bone marrow suppression. HYCAMTIN should be administered only to patients with adequate bone marrow reserves. Peripheral blood counts should be monitored. (5.1) Dose may need to be adjusted. (2.3)

- Topotecan-induced neutropenia can lead to neutropenic colitis. (5.1)
- Diarrhea, including severe diarrhea requiring hospitalization, has been reported during treatment with HYCAMTIN capsules. (5.2) Dose may need to be adjusted. (2.3)
- HYCAMTIN has been associated with reports of interstitial lung disease, some of which have been fatal. (5.3)
- Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus. (5.4, 8.1)

ADVERSE REACTIONS
The most common Grade 3 or 4 hematologic adverse reactions with HYCAMTIN capsules were neutropenia (61%), anemia (25%), and thrombocytopenia (37%). The most common (≥10%) non-hematologic adverse reactions (all grades) were nausea (27%), diarrhea (14%), vomiting (19%), fatigue (11%), and alopecia (10%).

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• Patients should be carefully monitored for adverse reactions when HYCAMTIN capsules are administered with a drug known to inhibit ABCG2 (BCRP) or ABCB1 (P-glycoprotein). (7.1)

USE IN SPECIFIC POPULATIONS
• Geriatric use: Among patients who received HYCAMTIN capsules in 4 thoracic cancer studies, drug-related diarrhea was more frequent in patients ≥65 years of age (28%) compared to those <65 years of age (19%). (5.2) (6.1)
• Nursing Mothers: Discontinue nursing when receiving HYCAMTIN. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: BONE MARROW SUPPRESSION

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
2.2 Adjustment of Dose in Special Populations
2.3 Dose Modification Guidelines
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Bone Marrow Suppression
5.2 Diarrhea
5.3 Interstitial Lung Disease
5.4 Pregnancy
5.5 Drug Interactions
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs That Inhibit Drug Efflux Transporters
7.2 Effects of Topotecan on Drug Metabolizing Enzymes
7.3 Effects of Other Drugs on Topotecan Pharmacokinetics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Small Cell Lung Cancer
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Bone Marrow Suppression
17.2 Pregnancy
17.3 Diarrhea
17.4 FDA-Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: BONE MARROW SUPPRESSION

HYCAMTIN should be administered only to patients with baseline neutrophil counts of $\geq 1,500$ cells/mm³ and a platelet count $\geq 100,000$ cells/mm³. In order to assess the occurrence of bone marrow suppression, blood cell counts should be monitored.

1 INDICATIONS AND USAGE

HYCAMTIN capsules are indicated for the treatment of relapsed small cell lung cancer in patients with a prior complete or partial response and who are at least 45 days from the end of first-line chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended dose of HYCAMTIN capsules is 2.3 mg/m²/day once daily for 5 consecutive days repeated every 21 days. Round the calculated oral daily dose to the nearest 0.25 mg, and prescribe the minimum number of 1 mg and 0.25 mg capsules. The same number of capsules should be prescribed for each of the 5 dosing days.

HYCAMTIN capsules may be taken with or without food. The capsules must be swallowed whole and must not be chewed, crushed, or divided. If your patient vomits after taking the dose of HYCAMTIN, the patient should not take a replacement dose.

2.2 Adjustment of Dose in Special Populations

Renal Function Impairment: No dosage adjustment of HYCAMTIN capsules appears to be required for treating patients with mild renal impairment (CLcr = 50-80 mL/min). A dose adjustment of HYCAMTIN capsules to 1.8 mg/m²/day is predicted to adjust the area under the curve (AUC) to the normal range for patients with moderate renal impairment (CLcr = 30-49 mL/min). Insufficient data are available in patients with severe renal impairment (CLcr <30 mL/min) to provide a dosage recommendation for HYCAMTIN capsules [*see Use in Specific Populations (8.6)*].

2.3 Dose Modification Guidelines

Patients should not be treated with subsequent courses of HYCAMTIN until neutrophils recover to $>1,000$ cells/mm³, platelets recover to $>100,000$ cells/mm³, and hemoglobin levels recover to ≥ 9.0 g/dL (with transfusion if necessary).

For patients who experience severe neutropenia (neutrophils <500 cells/mm³ associated with fever or infection or lasting for 7 days or more) or neutropenia (neutrophils 500 to 1,000 cells/mm³ lasting beyond day 21 of the treatment course), the HYCAMTIN capsules dose should be reduced by 0.4 mg/m²/day for subsequent courses. Doses should be similarly reduced if the platelet count falls below 25,000 cells/mm³.

For patients who experience Grade 3 or 4 diarrhea, the HYCAMTIN capsules dose should be reduced by 0.4 mg/m²/day for subsequent courses [see *Warnings and Precautions* (5.2)]. Patients with Grade 2 diarrhea may need to follow the same dose modification guidelines.

3 DOSAGE FORMS AND STRENGTHS

HYCAMTIN capsules contain topotecan hydrochloride expressed as topotecan free base. The 0.25 mg capsules are opaque white to yellowish-white and imprinted with HYCAMTIN and 0.25 mg. The 1 mg capsules are opaque pink and imprinted with HYCAMTIN and 1 mg.

4 CONTRAINDICATIONS

HYCAMTIN is contraindicated in patients who have a history of severe hypersensitivity reactions (e.g., anaphylactoid reactions) to topotecan or to any of its ingredients. HYCAMTIN should not be used in patients with severe bone marrow depression.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

Bone marrow suppression (primarily neutropenia) is a dose-limiting toxicity of HYCAMTIN. Neutropenia is not cumulative over time. The following data on myelosuppression are based on an integrated safety database from 4 thoracic malignancy studies (N = 682) using HYCAMTIN capsules at 2.3 mg/m²/day for 5 consecutive days. The median day for neutrophil, red blood cell, and platelet nadirs occurred on day 15.

Neutropenia: Grade 4 neutropenia (<500 cells/mm³) occurred in 32% of patients with a median duration of 7 days and was most common during course 1 of treatment (20% of patients). Infection, sepsis, and febrile neutropenia occurred in 17%, 2%, and 4% of patients, respectively. Death due to sepsis occurred in 1% of patients. Pancytopenia has been reported.

Topotecan-induced neutropenia can lead to neutropenic colitis. Fatalities due to neutropenic colitis have been reported. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered. [See *Dosage and Administration* (2.3).]

Thrombocytopenia: Grade 4 thrombocytopenia (<10,000 cells/mm³) occurred in 6% of patients, with a median duration of 3 days.

Anemia: Grade 3 or 4 anemia (<8 g/dL) occurred in 25% of patients.

Monitoring of Bone Marrow Function: HYCAMTIN should be administered only in patients with adequate bone marrow reserves, including a baseline neutrophil count of $\geq 1,500$ cells/mm³ and a platelet count $\geq 100,000$ cells/mm³. Frequent monitoring of peripheral blood cell counts should be instituted during treatment with HYCAMTIN.

5.2 Diarrhea

Diarrhea, including severe diarrhea requiring hospitalization, has been reported during treatment with HYCAMTIN capsules. Diarrhea related to HYCAMTIN capsules can occur at the same time as drug-related neutropenia and its sequelae. Communication with patients prior to drug administration regarding these side effects and proactive management of early and all signs

and symptoms of diarrhea is important. Treatment-related diarrhea is associated with significant morbidity and may be life-threatening. Should diarrhea occur during treatment with HYCAMTIN capsules, physicians are advised to aggressively manage diarrhea. Clinical guidelines describing the aggressive management of diarrhea include specific recommendations on patient communication and awareness, recognition of early warning signs, use of anti-diarrheals and antibiotics, changes in fluid intake and diet, and need for hospitalization.

Of the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, the overall incidence of drug-related diarrhea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. Drug-related diarrhea was more frequent in patients ≥ 65 years of age (28%) compared to those < 65 years of age (19%). [*See Adverse Reactions (6.1) and Use in Specific Populations (8.5).*]

5.3 Interstitial Lung Disease

HYCAMTIN has been associated with reports of interstitial lung disease (ILD), some of which have been fatal [*see Adverse Reactions (6.2)*]. 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 interstitial lung disease (e.g., cough, fever, dyspnea, and/or hypoxia), and HYCAMTIN should be discontinued if a new diagnosis of ILD is confirmed.

5.4 Pregnancy

Pregnancy Category D

HYCAMTIN can cause fetal harm when administered to a pregnant woman. Topotecan caused embryoletality, fetotoxicity, and teratogenicity in rats and rabbits when administered during organogenesis. There are no adequate and well controlled studies of HYCAMTIN in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations, Pregnancy (8.1)*].

5.5 Drug Interactions

P-glycoprotein inhibitors (e.g., cyclosporine A, elacridar, ketoconazole, ritonavir, and saquinavir) can cause significant increases in topotecan exposure. The concomitant use of P-glycoprotein inhibitors with HYCAMTIN capsules should be avoided. [*See Drug Interactions (7.1)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The safety of HYCAMTIN capsules has been evaluated in 682 patients with thoracic cancer (3 recurrent small cell lung cancer [SCLC] studies and 1 recurrent non-small cell lung cancer [NSCLC] study) who received at least one dose of HYCAMTIN capsules. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 1 describes the hematologic and non-hematologic adverse reactions in recurrent SCLC patients treated with HYCAMTIN capsules plus best supportive care (BSC) and in the overall thoracic cancer patient population.

Table 1. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated With HYCAMTIN Capsules Plus BSC and in 4 Thoracic Cancer Studies

Adverse Reaction	HYCAMTIN Capsules + BSC (N = 70)			HYCAMTIN Capsules Thoracic Cancer Population (N = 682)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	94	15	10	98	18	7
Leukopenia	90	25	16	86	29	15
Neutropenia	91	28	33	83	24	32
Thrombocytopenia	81	30	7	81	29	6
Non-hematologic						
Nausea	27	1	0	33	3	0
Diarrhea	14	4	1	22	4	0.4
Vomiting	19	1	0	21	3	0.4
Alopecia	10	0	0	20	0.1	0
Fatigue	11	0	0	19	4	0.1
Anorexia	7	0	0	14	2	0
Asthenia	3	0	0	7	2	0
Pyrexia	7	1	0	5	1	1

BSC = Best Supportive Care.

N = total number of patients treated.

Adverse reactions were graded using NCI Common Toxicity Criteria.

Diarrhea Adverse Reactions: Of the 70 patients who received HYCAMTIN capsules plus BSC, the incidence of drug-related diarrhea was 14%, with 4% Grade 3 and 1% Grade 4.

In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, the incidence of drug-related diarrhea was 22%, with 4% Grade 3 and 0.4% Grade 4. The overall incidence of drug-related diarrhea was more frequent in patients ≥65 years of age (28%, n = 225) with 10% Grade 1, 9% Grade 2, 7% Grade 3, and 1% Grade 4 compared to those <65 years of age (19%, n = 457) with 7% Grade 1, 9% Grade 2, 3% Grade 3, and 0% Grade 4. The incidence of Grade 3 or 4 diarrhea proximate (within 5 days) to Grade 3 or 4 neutropenia events in the HYCAMTIN capsules treatment group was 5%. The median time to onset of Grade 2 or worse diarrhea was 9 days in the HYCAMTIN capsules group.

Deaths Occurring Within 30 Days Following the Last Dose of Study Medication: In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, 39 deaths occurred within 30 days after the last dose of study medication for a reason other than

progressive disease; 13 of these deaths were attributed to hematologic toxicity, 5 were attributed to non-hematologic toxicity, and 21 were attributed to other causes. One patient death (68 years of age) was attributed to treatment-related diarrhea and one death (68 years of age) attributed diarrhea as a contributory event; both patients received HYCAMTIN capsules.

In addition to the adverse reactions listed previously, the following adverse reactions have been reported with HYCAMTIN for Injection:

- Incidence >10%: Febrile neutropenia, abdominal pain, stomatitis, constipation.
- Incidence 1 to 10%: Sepsis, hypersensitivity (including rash), hyperbilirubinemia, malaise.

6.2 Postmarketing Experience

There is no postmarketing experience with HYCAMTIN capsules. The following adverse reactions have been identified during post-approval use of HYCAMTIN for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Severe bleeding (in association with thrombocytopenia).

Immune system disorders: Allergic manifestations, anaphylactoid reactions.

Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease.

Gastrointestinal disorders: Abdominal pain potentially associated with neutropenic colitis [see Warnings and Precautions (5.1)].

Skin and subcutaneous tissue disorders: Angioedema, severe dermatitis, severe pruritus.

7 DRUG INTERACTIONS

7.1 Drugs That Inhibit Drug Efflux Transporters

Topotecan is a substrate for both ABCB1 [P-glycoprotein (P-gp)] and ABCG2 (BCRP). Elacridar (inhibitor of ABCB1 and ABCG2) administered with HYCAMTIN capsules increased topotecan exposure to approximately 2.5-fold of control. Cyclosporine A (inhibitor of ABCB1, ABCC1 [MRP-1], and CYP3A4) with HYCAMTIN capsules increased topotecan exposure to 2- to 3-fold of control. Patients should be carefully monitored for adverse reactions when HYCAMTIN capsules are administered with a drug known to inhibit these transporters. [See *Clinical Pharmacology* (12.3).]

7.2 Effects of Topotecan on Drug Metabolizing Enzymes

In vitro inhibition studies using marker substrates known to be metabolized by human cytochromes 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.

7.3 Effects of Other Drugs on Topotecan Pharmacokinetics

The pharmacokinetics of topotecan were generally unchanged when coadministered with ranitidine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. [*See Warnings and Precautions (5.4).*]

HYCAMTIN can cause fetal harm when administered to a pregnant woman. In rabbits, an IV dose of 0.10 mg/kg/day (about equal to the clinical IV dose on a mg/m² basis) given on days 6 through 20 of gestation caused maternal toxicity, embryoletality, and reduced fetal body weight. In the rat, an IV dose of 0.23 mg/kg/day (about equal to the clinical IV dose on a mg/m² basis) given for 14 days before mating through gestation day 6 caused fetal resorption, microphthalmia, pre-implant loss, and mild maternal toxicity. An IV dose of 0.10 mg/kg/day (about half the clinical IV dose on a mg/m² 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.

There are no adequate and well controlled studies of HYCAMTIN in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8.3 Nursing Mothers

Rats excrete high concentrations of topotecan into milk. Lactating female rats given 4.72 mg/m² IV (about twice the clinical dose on a mg/m² basis) excreted topotecan into milk at concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from HYCAMTIN, discontinue breastfeeding when women are receiving HYCAMTIN.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 682 patients with thoracic cancer in 4 clinical studies who received HYCAMTIN capsules, 33% (n = 225) were 65 years of age and older, while 4.8% (n = 33) were 75 years of age and older. Treatment-related diarrhea was more frequent in patients ≥65 years of age (28%) compared to those <65 years of age (19%). [*See Warnings and Precautions (5.2) and Adverse Reactions (6.1).*] Among patients ≥65 years of age, those receiving HYCAMTIN capsules plus BSC showed a survival benefit compared to those receiving BSC alone.

There were no apparent differences in the pharmacokinetics of topotecan in elderly patients with creatinine clearance of ≥60 mL/minute [*see Clinical Pharmacology (12.3)*].

This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function [*see Dosage and Administration (2.2)*].

8.6 Renal Impairment

A cross-study analysis of data collected from 217 patients with advanced solid tumors

indicated that exposure ($AUC_{0-\infty}$) to topotecan lactone, the pharmacologically active moiety, was 10% and 20% higher in patients with mild renal ($CL_{Cr} = 50-80$ mL/min) and moderate renal ($CL_{Cr} = 30-49$ mL/min) impairment, respectively, than in patients with normal renal function ($CL_{Cr} >80$ mL/min) [see *Dosage and Administration (2.2)*].

8.7 Hepatic Impairment

In a population pharmacokinetic analysis involving oral topotecan administered at doses of 0.15-2.7 mg/m²/day to 118 cancer patients, the pharmacokinetics of total topotecan did not differ significantly based on patient serum bilirubin, ALT, or AST. No dosage adjustment appeared to be required for patients with impaired hepatic function (serum bilirubin of >1.5 mg/dL).

10 OVERDOSAGE

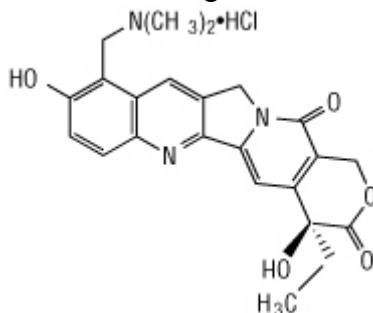
There is no known antidote for overdose with HYCAMTIN capsules. The primary anticipated complication of overdose would consist of hematological toxicity. The patient should be observed closely for bone marrow suppression, and supportive measures (such as the prophylactic use of G-CSF and/or antibiotic therapy) should be considered.

11 DESCRIPTION

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

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 $C_{23}H_{23}N_3O_5 \cdot HCl$ and a molecular weight of 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

Topotecan hydrochloride has the following structural formula:



HYCAMTIN capsules contain topotecan hydrochloride, the content of which is expressed as topotecan free base. The major excipients are hydrogenated vegetable oil, glyceryl monostearate, gelatin, and titanium dioxide. The capsules are imprinted with edible black ink. The 1 mg capsules also contain red iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases with increasing topotecan dose or topotecan AUC. There is a correlation between topotecan lactone AUC day 1 and percent decrease of leukocytes.

12.3 Pharmacokinetics

The pharmacokinetics of HYCAMTIN capsules after oral administration have been evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² administered daily for 5 days. Topotecan exhibits biexponential pharmacokinetics with a mean terminal half-life of 3 to 6 hours. Total exposure (AUC) increases approximately proportionally with dose. Plasma protein binding of topotecan is about 35%.

Absorption: Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours following oral administration. The oral bioavailability of topotecan was about 40%. Following a high-fat meal, the extent of exposure was similar in the fed and fasted states, while t_{max} was delayed from 1.5 to 3 hours (topotecan lactone) and from 3 to 4 hours (total topotecan), respectively. HYCAMTIN capsules can be given without regard to food.

Following coadministration of the ABCG2 (BCRP) and ABCB1 (P-gp) inhibitor elacridar (GF120918) at 100 to 1,000 mg doses with oral topotecan, the AUC_{0-∞} of topotecan lactone and total topotecan increased approximately 2.5-fold.

Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1 (P-gp) and ABCC1 (MRP-1) as well as the metabolizing enzyme CYP3A4, within 4 hours of oral topotecan increased the dose-normalized AUC₀₋₂₄ of topotecan lactone and total topotecan to 2.0- to 3-fold of control. [*See Drug Interactions (7.1).*]

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. The mean metabolite:parent AUC ratio was <10% for total topotecan and topotecan lactone.

In a mass balance study in 4 patients with advanced solid tumors, the overall recovery of drug-related material following 5 daily doses of topotecan was 57% of the administered oral dose. In the urine, 20% of the oral administered dose was excreted as total topotecan and 2% was excreted as N-desmethyl topotecan [*see Use in Specific Populations (8.6)*]. Fecal elimination of total topotecan accounted for 33% while fecal elimination of N-desmethyl topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of <6% (range 4 to 8%) of the total drug-related material accounted for in the urine and feces. O-glucuronides of both topotecan and N-desmethyl topotecan have been identified in the urine.

Age, Gender, and Race: A cross-study analysis in 217 patients with advanced solid tumors indicated that age and gender did not significantly affect the pharmacokinetics of oral topotecan. There are insufficient data to determine an effect of race on pharmacokinetics of oral topotecan.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity testing of topotecan has not been done. Nevertheless, topotecan 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.

Topotecan given to female rats prior to mating at a dose of 1.4 mg/m² IV (about 3/5th of the oral clinical dose on a mg/m² basis) caused superovulation possibly related to inhibition of follicular atresia. This dose given to pregnant female rats also caused increased pre-implantation loss. Studies in dogs given 0.4 mg/m² IV (about 1/6th the oral clinical dose on a mg/m² basis) of topotecan daily for a month suggest that treatment may cause an increase in the incidence of multinucleated spermatogonial giant cells in the testes. Topotecan may impair fertility in women and men.

14 CLINICAL STUDIES

14.1 Small Cell Lung Cancer

HYCAMTIN capsules were studied in patients with relapsed SCLC in a randomized, comparative, open label trial. The patients were prior responders (complete or partial) to first-line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were randomized to HYCAMTIN capsules (2.3 mg/m²/day administered for 5 consecutive days repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to BSC alone. The primary objective was to compare the overall survival between the 2 treatment arms. Patients in the HYCAMTIN capsules plus BSC group received a median of 4 courses (range 1 to 10) and maintained a median dose intensity of HYCAMTIN capsules, 3.77 mg/m²/week. The median patient age in the HYCAMTIN capsules plus BSC arm and the BSC alone treatment arm was 60 years and 58 years while the percentage of patients ≥65 years of age was 34% and 29%, respectively. All but 1 patient were Caucasian. The HYCAMTIN capsules plus BSC treatment arm included 68% of patients with extensive disease and 28% with liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver metastases. Both treatment arms recruited 73% males. In the HYCAMTIN capsules plus BSC arm, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC alone arm, 26% of patients had prior carboplatin and 51% had prior cisplatin.

The HYCAMTIN capsules plus BSC arm showed a statistically significant improvement in overall survival compared with the BSC alone arm (Log-rank p = 0.0104). Survival results are

shown in Table 2 and Figure 1.

Table 2. Overall Survival in Small Cell Lung Cancer Patients With Hycamtin Capsules Plus BSC Compared With BSC Alone

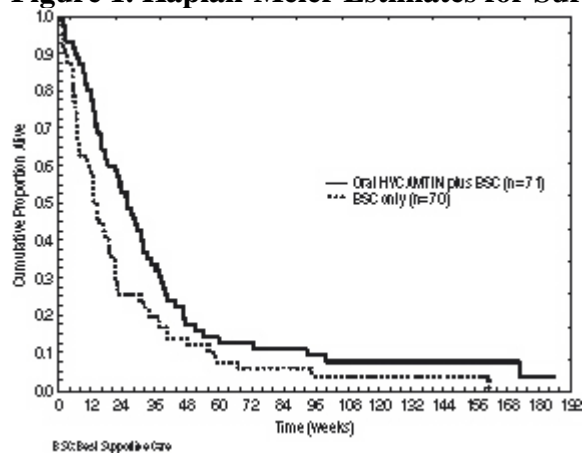
	Treatment Group	
	Hycamtin Capsules + BSC (N = 71)	BSC (N = 70)
Median (weeks) (95% CI)	25.9 (18.3, 31.6)	13.9 (11.1, 18.6)
Hazard ratio (95% CI)	0.64 (0.45, 0.90)	
Log-rank p-value	0.0104	

BSC = Best Supportive Care.

N = total number of patients randomized.

CI = Confidence Interval.

Figure 1. Kaplan-Meier Estimates for Survival



15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

The 0.25 mg HYCAMTIN capsules are opaque white to yellowish-white imprinted with HYCAMTIN and 0.25 mg and are available in bottles of 10: NDC 0007-4205-11.

The 1 mg HYCAMTIN capsules are opaque pink imprinted with HYCAMTIN and 1 mg and are available in bottles of 10: NDC 0007-4207-11.

Store refrigerated 2° to 8°C (36° to 46°F). Store the bottles protected from light in the original outer cartons.

Procedures for proper handling and disposal of anticancer drugs should be used. Several guidelines on this subject have been published.¹⁻⁴

HYCAMTIN capsules should not be opened or crushed. Direct contact of the capsule contents with the skin or mucous membranes should be avoided. If such contacts occur, wash thoroughly with soap and water or wash the eyes immediately with gently flowing water for at least 15 minutes. Consult the healthcare provider in case of a skin reaction or if the drug gets in the eyes.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (17.4).

17.1 Bone Marrow Suppression

Patients should be informed that HYCAMTIN decreases blood cell counts such as white blood cells, platelets, and red blood cells. Patients who develop fever or other signs of infection such as chills, cough, or burning pain on urination while on therapy should notify their physician promptly. Patients should be told that frequent blood tests will be performed while taking HYCAMTIN to monitor for the occurrence of bone marrow suppression.

17.2 Pregnancy

Patients should be advised to use effective contraceptive measures to prevent pregnancy and to avoid breastfeeding during treatment with HYCAMTIN.

17.3 Diarrhea

Patients should be informed that HYCAMTIN capsules cause diarrhea which may be severe in some cases. Patients should be told how to manage and/or prevent diarrhea and to inform their physician if severe diarrhea occurs during treatment with HYCAMTIN capsules.

17.4 FDA-Approved Patient Labeling

See separate leaflet.

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