CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

LABELING

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/mm^3 and a platelet count ≥100,000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, blood cell counts should be monitored (5.1).

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- 2.3 mg/m^2/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)
- Pregnancy or breastfeeding. (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)
- Fetal harm may occur when administered to a pregnant woman. HYCAMTIN should not be used by pregnant women. (5.3)

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)

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

Issued: October 2007
HYC:1PI

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 ≥1,500 cells/mm^3 and a platelet count ≥100,000 cells/mm^3. 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/m^2/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/m^2/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/mm^3, platelets recover to >100,000 cells/mm^3, and hemoglobin levels recover to ≥9.0 g/dL (with transfusion if necessary).

For patients who experience severe neutropenia (neutrophils <500 cells/mm^3 associated with fever or infection or lasting for 7 days or more) or neutropenia (neutrophils 500 to 1,000 cells/mm^3 lasting beyond day 21 of the treatment course), the HYCAMTIN capsules dose should be reduced by 0.4 mg/m^2/day for subsequent courses. Doses should be similarly reduced if the platelet count falls below 25,000 cells/mm^3.

For patients who experience Grade 3 or 4 diarrhea, the HYCAMTIN capsules dose should be reduced by 0.4 mg/m^2/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 who are pregnant or breastfeeding, or 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/m^2/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/mm^3) 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/mm^3) 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 ≥1,500 cells/mm^3 and a platelet count ≥100,000 cells/mm^3. 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 Pregnancy

Pregnancy Category D

HYCAMTIN may cause fetal harm when administered to a pregnant woman. The effects of topotecan on pregnant women have not been studied. Women should be warned to avoid becoming pregnant. *[See Contraindications (4).]* In rabbits, an IV dose of 0.10 mg/kg/day (about equal to the clinical IV 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, an IV dose of 0.23 mg/kg/day (about equal to the clinical IV 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. An IV dose of 0.10 mg/kg/day (about half the clinical IV 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. 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.

5.4 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

	HYCAMTIN Capsules + BSC (N = 70)			HYCAMTIN Capsules Thoracic Cancer Population (N = 682)		
Adverse Reaction	**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.

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 Contraindications (4) and Warnings and Precautions (5.3).]*

8.3 Nursing Mothers

HYCAMTIN is contraindicated during breastfeeding *[see Contraindications (4)]*.

Rats excrete high concentrations of topotecan into milk. Lactating female rats given 4.72 mg/m^2 IV (about twice the clinical dose on a mg/m^2 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. Breastfeeding should be discontinued 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 (CLcr = 50-80 mL/min) and moderate renal (CLcr = 30-49 mL/min) impairment, respectively, than in patients with normal renal function (CLcr >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/m^2/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 overdosage with HYCAMTIN capsules. The primary anticipated complication of overdosage would consist of hematological toxicity. The patient

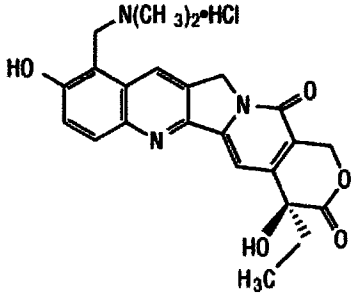
should be observed closely for bone marrow suppression, and supportive measures (such as the prophylactic use of G-CSF and/or antibiotic therapy) should be considered.

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/m^2 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 $AUC_{0-\infty}$ 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 AUC_{0-24} 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/m^2 IV (about 3/5th of the oral clinical dose on a mg/m^2 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/m^2 IV (about 1/6th the oral clinical dose on a mg/m^2 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/m^2/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/m^2/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.

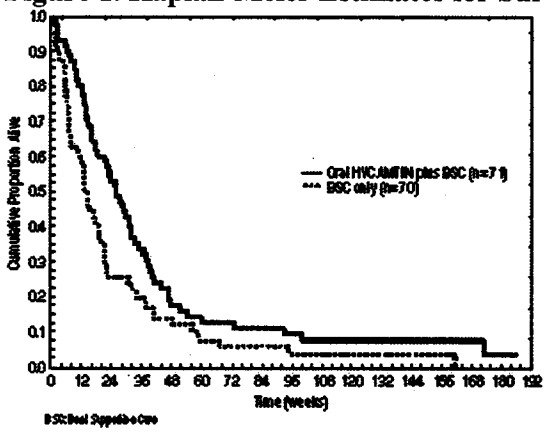
The HYCAMTIN capsules plus BSC arm showed a statistically significant improvement in overall survival compared with the BSC alone arm (Log-rank p = 0.0104). Survival results are shown in Table 2 and Figure 1.

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

1. The National Institute for Occupational Safety and Health. NIOSH Alert. preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Available at: www.cdc.gov/niosh/docs/2004-165/ Accessed October 2, 2007.
2. Occupational Safety and Health Administration. Controlling Occupational Exposure to Hazardous Drugs. OSHA Technical Manual, TED 1-0.15A. Section VI: Chapter 2. Available at: www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html Accessed October 2, 2007.
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006;63:1172-1193.
4. Polovich, M., White, J.M., Kelleher, L.O., eds. *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice.* 2nd ed. Pittsburgh, PA: Oncology Nursing Society: 2005.

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 at controlled room temperature 20° to 25°C (68° to 77°F), with excursions permitted 15° to 30°C (59° to 86°F) [see USP]. 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.

HYCAMTIN is a registered trademark of GlaxoSmithKline.

GlaxoSmithKline
Research Triangle Park, NC 27709

PATIENT INFORMATION

HYCAMTIN® (hi-CAM-tin)
(topotecan) Capsules

Read the Patient Information that comes with HYCAMTIN capsules before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about taking HYCAMTIN capsules?
HYCAMTIN capsules can cause serious side effects:

Decreased blood counts. Taking HYCAMTIN affects your bone marrow and can cause a severe decrease in your blood cell counts (bone marrow suppression) - neutrophils (a type of white blood cell important in fighting bacterial infections), red blood cells (blood cells that carry oxygen to the tissues), and platelets (important for clotting and control of bleeding).

- You should have blood tests regularly to check your blood counts. A decrease in neutrophils (neutropenia) may affect how your body fights infection.
- Your healthcare provider will tell you if your blood counts are too low before you begin treatment with HYCAMTIN.
- Your dose of HYCAMTIN may need to be changed or stopped until your blood counts recover enough after each cycle of treatment.
- Call your healthcare provider right away if you get any of the following signs of infection:
  - fever (temperature of 100.5°F or greater)
  - chills
  - cough
  - burning or pain on urination
- Tell your healthcare provider about any abnormal bleeding or bruising.

Diarrhea. Diarrhea may occur from taking HYCAMTIN capsules, and may be serious enough that you must be treated in the hospital. Tell your healthcare provider right away if you have:

- diarrhea with fever
- diarrhea 3 or more times a day
- diarrhea with stomach-area pain or cramps

See "*What are the possible side effects of HYCAMTIN capsules?*"

What are HYCAMTIN capsules?

HYCAMTIN capsules are prescription medicines you take by mouth. HYCAMTIN capsules are used to treat a certain type of lung cancer called small cell lung cancer. HYCAMTIN capsules may be right for you if:

- your cancer responded to your first chemotherapy
- your cancer came back at least 45 days after you finished your last dose of chemotherapy

HYCAMTIN capsules have not been studied in children.

Who should NOT take HYCAMTIN capsules?

Do not take HYCAMTIN capsules if:

- you are allergic to anything in HYCAMTIN capsules. See the end of this leaflet for a complete list of ingredients in HYCAMTIN capsules.
- the results of your last blood test show blood counts that are too low. Your healthcare provider will tell you.
- you are pregnant or think that you may be pregnant. Taking HYCAMTIN during pregnancy may harm your unborn baby. If you are able to become pregnant, talk with your healthcare provider about how to prevent pregnancy while taking HYCAMTIN.
- you are breastfeeding. Do not breastfeed while you are taking HYCAMTIN.

What else should I tell my healthcare provider before taking HYCAMTIN capsules?

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. HYCAMTIN capsules and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you are taking cyclosporine (SANDIMMUNE, GENGRAF, NEORAL).

Know your medicines. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take HYCAMTIN capsules?

- **Take HYCAMTIN capsules exactly as your doctor prescribes them.**
- Your healthcare provider may want you to take both 1 mg and 0.25 mg capsules together to make up your complete dose. You must be able to tell the difference between the capsules. The 1 mg capsule is a pink color and the 0.25 mg capsule is a white to yellowish-white color.
- Take HYCAMTIN capsules once a day for 5 days in a row. This treatment will

normally be repeated every 3 weeks (a treatment cycle). Your healthcare provider will decide how long you will take HYCAMTIN capsules.

- Swallow HYCAMTIN capsules whole with water. Do not open, chew, or crush HYCAMTIN capsules. HYCAMTIN capsules may be taken with or without food.
- If any of the HYCAMTIN capsules are broken or leaking, do not touch them with your bare hands. Carefully dispose of the capsules, and then wash your hands well with soap and water.
- If you get any of the contents of HYCAMTIN capsules on your skin or in your eyes, do the following:
  - Wash the area of skin well with soap and water right away,
  - Wash your eyes right away with gently flowing water for at least 15 minutes.
  - Call your healthcare provider if you get a skin reaction or if you get the medicine in your eyes.
- If you take too much HYCAMTIN, contact your healthcare provider right away.
- If you forget to take HYCAMTIN at any time, do not double the dose to make up for a forgotten dose. Wait and take the next scheduled dose. Let your healthcare provider know that you missed a dose.
- If you vomit after taking your HYCAMTIN, do not take another dose on the same day. Let your healthcare provider know right away that you have vomited.

What should I avoid while taking HYCAMTIN capsules?
HYCAMTIN may make you feel drowsy or sleepy both during and for several days after treatment. If you feel tired or weak, do not drive and do not use heavy tools or operate machinery.

What are the possible side effects of HYCAMTIN capsules?
HYCAMTIN can cause serious side effects including decreased blood counts and diarrhea. See "What is the most important information I should know about HYCAMTIN capsules?"

The following side effects have been reported in patients taking HYCAMTIN capsules:

- stomach problems such as nausea (feeling sick) and vomiting
- tiredness
- hair loss
- weakness

Tell your healthcare provider if you have any side effect that bothers you or does not go away. Your healthcare provider may change your dose of HYCAMTIN to a dose that is better for you or may stop your treatment with HYCAMTIN for a while. This can help reduce the side effects and may keep them from getting worse. Let your healthcare

provider know if this helps or does not help your side effects.

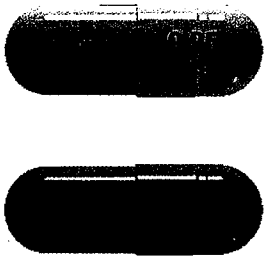
How should I store HYCAMTIN capsules?

- Store HYCAMTIN capsules at normal room temperature between 68°-77°F (20°-25°C). Protect from light and heat.
- Dispose of HYCAMTIN capsules that are out of date or no longer needed.
- **Keep HYCAMTIN capsules and all other medicines out of the reach of children.**

What are the ingredients in HYCAMTIN capsules?

Active Ingredient: Topotecan

Inactive Ingredients: Hydrogenated vegetable oil, glyceryl monostearate, gelatin, and titanium dioxide. The 1 mg capsules also contain red iron oxide. The capsules are imprinted with edible black ink.



(capsules shown larger than actual size)

General information about HYCAMTIN capsules

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information leaflets. Only your doctor knows what treatment is best for you. Do not use HYCAMTIN capsules for a condition for which it was not prescribed by your healthcare provider. Do not give HYCAMTIN capsules to other people, even if they have the same condition that you have. It may harm them.

This leaflet summarizes the most important information about HYCAMTIN capsules. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about HYCAMTIN capsules that is written for health professionals. For more information you can call toll-free 1-888-825-5249 or visit www.gsk.com.

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