

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 $\geq 1,500$ cells/mm³ and a platelet count $\geq 100,000$ cells/mm³. 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/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)
- 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 ($\geq 10\%$) 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*

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 Pregnancy
- 5.4 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.

1

2 **FULL PRESCRIBING INFORMATION**

3 **WARNING: BONE MARROW SUPPRESSION**

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

7 **1 INDICATIONS AND USAGE**

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

11 **2 DOSAGE AND ADMINISTRATION**

12 **2.1 Recommended Dosing**

13 The recommended dose of HYCAMTIN capsules is 2.3 mg/m²/day once daily for
14 5 consecutive days repeated every 21 days. Round the calculated oral daily dose to the nearest
15 0.25 mg, and prescribe the minimum number of 1 mg and 0.25 mg capsules. The same number
16 of capsules should be prescribed for each of the 5 dosing days.

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

20 **2.2 Adjustment of Dose in Special Populations**

21 Renal Function Impairment: No dosage adjustment of HYCAMTIN capsules appears
22 to be required for treating patients with mild renal impairment (CLcr = 50-80 mL/min). A dose
23 adjustment of HYCAMTIN capsules to 1.8 mg/m²/day is predicted to adjust the area under the
24 curve (AUC) to the normal range for patients with moderate renal impairment (CLcr = 30-
25 49 mL/min). Insufficient data are available in patients with severe renal impairment
26 (CLcr <30 mL/min) to provide a dosage recommendation for HYCAMTIN capsules [*see Use in*
27 *Specific Populations (8.6)*].

28 **2.3 Dose Modification Guidelines**

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

32 For patients who experience severe neutropenia (neutrophils <500 cells/mm³ associated
33 with fever or infection or lasting for 7 days or more) or neutropenia (neutrophils 500 to
34 1,000 cells/mm³ lasting beyond day 21 of the treatment course), the HYCAMTIN capsules dose
35 should be reduced by 0.4 mg/m²/day for subsequent courses. Doses should be similarly reduced
36 if the platelet count falls below 25,000 cells/mm³.

37 For patients who experience Grade 3 or 4 diarrhea, the Hycamtin capsules dose
38 should be reduced by 0.4 mg/m²/day for subsequent courses [see Warnings and Precautions
39 (5.2)]. Patients with Grade 2 diarrhea may need to follow the same dose modification guidelines.

40 **3 DOSAGE FORMS AND STRENGTHS**

41 Hycamtin capsules contain topotecan hydrochloride expressed as topotecan free base.
42 The 0.25 mg capsules are opaque white to yellowish-white and imprinted with Hycamtin and
43 0.25 mg. The 1 mg capsules are opaque pink and imprinted with Hycamtin and 1 mg.

44 **4 CONTRAINDICATIONS**

45 Hycamtin is contraindicated in patients who have a history of severe hypersensitivity
46 reactions (e.g., anaphylactoid reactions) to topotecan or to any of its ingredients. Hycamtin
47 should not be used in patients who are pregnant or breastfeeding, or in patients with severe bone
48 marrow depression.

49 **5 WARNINGS AND PRECAUTIONS**

50 **5.1 Bone Marrow Suppression**

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

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

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

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

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

67 **Monitoring of Bone Marrow Function:** Hycamtin should be administered only in
68 patients with adequate bone marrow reserves, including a baseline neutrophil count of
69 $\geq 1,500$ cells/mm³ and a platelet count $\geq 100,000$ cells/mm³. Frequent monitoring of peripheral
70 blood cell counts should be instituted during treatment with Hycamtin.

71 **5.2 Diarrhea**

72 Diarrhea, including severe diarrhea requiring hospitalization, has been reported during
73 treatment with Hycamtin capsules. Diarrhea related to Hycamtin capsules can occur at the
74 same time as drug-related neutropenia and its sequelae. Communication with patients prior to

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

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

87 **5.3 Pregnancy**

88 Pregnancy Category D

89 HYCAMTIN may cause fetal harm when administered to a pregnant woman. The effects
90 of topotecan on pregnant women have not been studied. Women should be warned to avoid
91 becoming pregnant. [*See Contraindications (4).*] In rabbits, an IV dose of 0.10 mg/kg/day (about
92 equal to the clinical IV dose on a mg/m² basis) given on days 6 through 20 of gestation caused
93 maternal toxicity, embryoletality, and reduced fetal body weight. In the rat, an IV dose of
94 0.23 mg/kg/day (about equal to the clinical IV dose on a mg/m² basis) given for 14 days before
95 mating through gestation day 6 caused fetal resorption, microphthalmia, pre-implant loss, and
96 mild maternal toxicity. An IV dose of 0.10 mg/kg/day (about half the clinical IV dose on a
97 mg/m² basis) given to rats on days 6 through 17 of gestation caused an increase in post-
98 implantation mortality. This dose also caused an increase in total fetal malformations. The most
99 frequent malformations were of the eye (microphthalmia, anophthalmia, rosette formation of the
100 retina, coloboma of the retina, ectopic orbit), brain (dilated lateral and third ventricles), skull, and
101 vertebrae. If this drug is used during pregnancy, or if a patient becomes pregnant while taking
102 this drug, the patient should be apprised of the potential hazard to the fetus.

103 **5.4 Drug Interactions**

104 P-glycoprotein inhibitors (e.g., cyclosporine A, elacridar, ketoconazole, ritonavir, and
105 saquinavir) can cause significant increases in topotecan exposure. The concomitant use of P-
106 glycoprotein inhibitors with HYCAMTIN capsules should be avoided. [*See Drug Interactions*
107 *(7.1).*]

108 **6 ADVERSE REACTIONS**

109 **6.1 Clinical Trials Experience**

110 The safety of HYCAMTIN capsules has been evaluated in 682 patients with thoracic
111 cancer (3 recurrent small cell lung cancer [SCLC] studies and 1 recurrent non-small cell lung
112 cancer [NSCLC] study) who received at least one dose of HYCAMTIN capsules. Because
113 clinical trials are conducted under widely varying conditions, adverse reaction rates observed in

114 the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another
 115 drug and may not reflect the rates observed in practice.

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

119
 120 **Table 1. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated**
 121 **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

122 BSC = Best Supportive Care.

123 N = total number of patients treated.

124 Adverse reactions were graded using NCI Common Toxicity Criteria.

125
 126 **Diarrhea Adverse Reactions:** Of the 70 patients who received HYCAMTIN capsules
 127 plus BSC, the incidence of drug-related diarrhea was 14%, with 4% Grade 3 and 1% Grade 4.

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

136 **Deaths Occurring Within 30 Days Following the Last Dose of Study Medication:**

137 In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, 39
138 deaths occurred within 30 days after the last dose of study medication for a reason other than
139 progressive disease; 13 of these deaths were attributed to hematologic toxicity, 5 were attributed
140 to non-hematologic toxicity, and 21 were attributed to other causes. One patient death (68 years
141 of age) was attributed to treatment-related diarrhea and one death (68 years of age) attributed
142 diarrhea as a contributory event; both patients received HYCAMTIN capsules.

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

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

147 **6.2 Postmarketing Experience**

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

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

154 *Immune system disorders:* Allergic manifestations, anaphylactoid reactions.

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

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

158 **7 DRUG INTERACTIONS**

159 **7.1 Drugs That Inhibit Drug Efflux Transporters**

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

167 **7.2 Effects of Topotecan on Drug Metabolizing Enzymes**

168 In vitro inhibition studies using marker substrates known to be metabolized by human
169 cytochromes P450 (CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or
170 CYP4A) or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were
171 not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

172 **7.3 Effects of Other Drugs on Topotecan Pharmacokinetics**

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

175 **8 USE IN SPECIFIC POPULATIONS**

176 **8.1 Pregnancy**

177 Pregnancy Category D. [See Contraindications (4) and Warnings and Precautions (5.3).]

178 **8.3 Nursing Mothers**

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

180 Rats excrete high concentrations of topotecan into milk. Lactating female rats given
181 4.72 mg/m² IV (about twice the clinical dose on a mg/m² basis) excreted topotecan into milk at
182 concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is
183 excreted in human milk. Breastfeeding should be discontinued when women are receiving
184 HYCAMTIN.

185 **8.4 Pediatric Use**

186 Safety and effectiveness in pediatric patients have not been established.

187 **8.5 Geriatric Use**

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

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

196 This drug is known to be excreted by the kidney, and the risk of toxic reactions to this
197 drug may be greater in patients with impaired renal function [see Dosage and Administration
198 (2.2)].

199 **8.6 Renal Impairment**

200 A cross-study analysis of data collected from 217 patients with advanced solid tumors
201 indicated that exposure (AUC_{0-∞}) to topotecan lactone, the pharmacologically active moiety, was
202 10% and 20% higher in patients with mild renal (CL_{cr} = 50-80 mL/min) and moderate renal
203 (CL_{cr} = 30-49 mL/min) impairment, respectively, than in patients with normal renal function
204 (CL_{cr} >80 mL/min) [see Dosage and Administration (2.2)].

205 **8.7 Hepatic Impairment**

206 In a population pharmacokinetic analysis involving oral topotecan administered at doses
207 of 0.15-2.7 mg/m²/day to 118 cancer patients, the pharmacokinetics of total topotecan did not
208 differ significantly based on patient serum bilirubin, ALT, or AST. No dosage adjustment
209 appeared to be required for patients with impaired hepatic function (serum bilirubin of
210 >1.5 mg/dL).

211 **10 OVERDOSAGE**

212 There is no known antidote for overdosage with HYCAMTIN capsules. The primary
213 anticipated complication of overdosage would consist of hematological toxicity. The patient

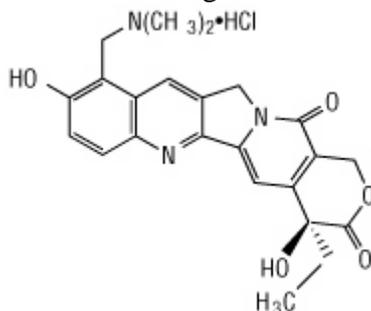
214 should be observed closely for bone marrow suppression, and supportive measures (such as the
215 prophylactic use of G-CSF and/or antibiotic therapy) should be considered.

216 11 DESCRIPTION

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

219 The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-
220 ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione
221 monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5 \cdot HCl$ and a molecular weight of
222 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

223 Topotecan hydrochloride has the following structural formula:



224
225 HYCAMTIN capsules contain topotecan hydrochloride, the content of which is
226 expressed as topotecan free base. The major excipients are hydrogenated vegetable oil, glyceryl
227 monostearate, gelatin, and titanium dioxide. The capsules are imprinted with edible black ink.
228 The 1 mg capsules also contain red iron oxide.

229 12 CLINICAL PHARMACOLOGY

230 12.1 Mechanism of Action

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

237 12.2 Pharmacodynamics

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

241 12.3 Pharmacokinetics

242 The pharmacokinetics of HYCAMTIN capsules after oral administration have been
243 evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² administered daily for 5 days.
244 Topotecan exhibits biexponential pharmacokinetics with a mean terminal half-life of 3 to
245 6 hours. Total exposure (AUC) increases approximately proportionally with dose. Plasma protein

246 binding of topotecan is about 35%.

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

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

255 Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1
256 (P-gp) and ABCC1 (MRP-1) as well as the metabolizing enzyme CYP3A4, within 4 hours of
257 oral topotecan increased the dose-normalized AUC_{0-24} of topotecan lactone and total topotecan to
258 2.0- to 3-fold of control. [See Drug Interactions (7.1).]

259 **Metabolism and Elimination:** Topotecan undergoes a reversible pH-dependent
260 hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At $pH \leq 4$,
261 the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at
262 physiologic pH. The mean metabolite:parent AUC ratio was $<10\%$ for total topotecan and
263 topotecan lactone.

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

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

276 **13 NONCLINICAL TOXICOLOGY**

277 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

278 Carcinogenicity testing of topotecan has not been done. Nevertheless, topotecan is known
279 to be genotoxic to mammalian cells and is a probable carcinogen. Topotecan was mutagenic to
280 L5178Y mouse lymphoma cells and clastogenic to cultured human lymphocytes with and
281 without metabolic activation. It was also clastogenic to mouse bone marrow. Topotecan did not
282 cause mutations in bacterial cells.

283 Topotecan given to female rats prior to mating at a dose of 1.4 mg/m^2 IV (about $3/5^{\text{th}}$ of
284 the oral clinical dose on a mg/m^2 basis) caused superovulation possibly related to inhibition of

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

290 **14 CLINICAL STUDIES**

291 **14.1 Small Cell Lung Cancer**

292 HYCAMTIN capsules were studied in patients with relapsed SCLC in a randomized,
 293 comparative, open label trial. The patients were prior responders (complete or partial) to first-
 294 line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and
 295 had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were
 296 randomized to HYCAMTIN capsules (2.3 mg/m²/day administered for 5 consecutive days
 297 repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to
 298 BSC alone. The primary objective was to compare the overall survival between the 2 treatment
 299 arms. Patients in the HYCAMTIN capsules plus BSC group received a median of 4 courses
 300 (range 1 to 10) and maintained a median dose intensity of HYCAMTIN capsules,
 301 3.77 mg/m²/week. The median patient age in the HYCAMTIN capsules plus BSC arm and the
 302 BSC alone treatment arm was 60 years and 58 years while the percentage of patients ≥65 years
 303 of age was 34% and 29%, respectively. All but 1 patient were Caucasian. The HYCAMTIN
 304 capsules plus BSC treatment arm included 68% of patients with extensive disease and 28% with
 305 liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver
 306 metastases. Both treatment arms recruited 73% males. In the HYCAMTIN capsules plus BSC
 307 arm, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC alone arm,
 308 26% of patients had prior carboplatin and 51% had prior cisplatin.

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

312

313 **Table 2. Overall Survival in Small Cell Lung Cancer Patients With HYCAMTIN Capsules**
 314 **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	

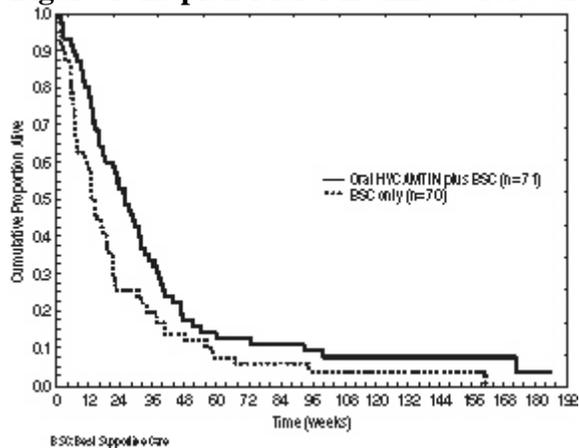
315 BSC = Best Supportive Care.

316 N = total number of patients randomized.

317 CI = Confidence Interval.

318

319 **Figure 1. Kaplan-Meier Estimates for Survival**



320

321

322 **15 REFERENCES**

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

333 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

338 Store at controlled room temperature 20° to 25°C (68° to 77°F), with excursions
 339 permitted 15° to 30°C (59° to 86°F) [see USP]. Store the bottles protected from light in the
 340 original outer cartons.

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

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

347 the eyes.

348 **17 PATIENT COUNSELING INFORMATION**

349 *See FDA-approved patient labeling (17.4).*

350 **17.1 Bone Marrow Suppression**

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

356 **17.2 Pregnancy**

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

359 **17.3 Diarrhea**

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

363 **17.4 FDA-Approved Patient Labeling**

364 See separate leaflet.

365

366 HYCAMTIN is a registered trademark of GlaxoSmithKline.

367



368

369 GlaxoSmithKline

370 Research Triangle Park, NC 27709

371

372 ©2007, GlaxoSmithKline. All rights reserved.

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.

HYCAMTIN is a registered trademark of GlaxoSmithKline.

The following are registered trademarks of their respective owners: GENGRAF/Abbott Laboratories; NEORAL and SANDIMMUNE/Novartis Pharmaceuticals Corporation.



GlaxoSmithKline
Research Triangle Park, NC 27709

©2007, GlaxoSmithKline. All rights reserved.

Issued: October 2007
HYC:1PIL