

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).

-----**RECENT MAJOR CHANGES**-----

Warnings and Precautions, Interstitial lung disease (5.3) 6/2010

-----**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)
- HYCAMTIN has been associated with reports of interstitial lung disease, some of which have been fatal. (5.3).
- Fetal harm may occur when administered to a pregnant woman. HYCAMTIN should not be used by pregnant women. (5.4)

-----**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.

Revised: 6/2010
HYC:XPI

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: BONE MARROW SUPPRESSION**

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

6 **1 INDICATIONS AND USAGE**

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

10 **2 DOSAGE AND ADMINISTRATION**

11 **2.1 Recommended Dosing**

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

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

19 **2.2 Adjustment of Dose in Special Populations**

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

27 **2.3 Dose Modification Guidelines**

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

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

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

39 **3 DOSAGE FORMS AND STRENGTHS**

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

43 **4 CONTRAINDICATIONS**

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

48 **5 WARNINGS AND PRECAUTIONS**

49 **5.1 Bone Marrow Suppression**

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

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

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

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

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

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

70 **5.2 Diarrhea**

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

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

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

86 **5.3 Interstitial Lung Disease**

87 HYCAMTIN has been associated with reports of interstitial lung disease (ILD), some of
88 which have been fatal [see *Adverse Reactions (6.2)*]. Underlying risk factors include history of
89 ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation, and use of pneumotoxic
90 drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms
91 indicative of interstitial lung disease (e.g., cough, fever, dyspnea, and/or hypoxia), and
92 HYCAMTIN should be discontinued if a new diagnosis of ILD is confirmed.

93 **5.4 Pregnancy**

94 Pregnancy Category D

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

109 **5.5 Drug Interactions**

110 P-glycoprotein inhibitors (e.g., cyclosporine A, elacridar, ketoconazole, ritonavir, and
111 saquinavir) can cause significant increases in topotecan exposure. The concomitant use of P-
112 glycoprotein inhibitors with HYCAMTIN capsules should be avoided. [See *Drug Interactions*
113 *(7.1)*.]

114 **6 ADVERSE REACTIONS**

115 **6.1 Clinical Trials Experience**

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

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

126 **Table 1. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated**
127 **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 |

128 BSC = Best Supportive Care.

129 N = total number of patients treated.

130 Adverse reactions were graded using NCI Common Toxicity Criteria.

131

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

134 In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies,
135 the incidence of drug-related diarrhea was 22%, with 4% Grade 3 and 0.4% Grade 4. The overall
136 incidence of drug-related diarrhea was more frequent in patients ≥65 years of age (28%, n = 225)

137 with 10% Grade 1, 9% Grade 2, 7% Grade 3, and 1% Grade 4 compared to those <65 years of
138 age (19%, n = 457) with 7% Grade 1, 9% Grade 2, 3% Grade 3, and 0% Grade 4. The incidence
139 of Grade 3 or 4 diarrhea proximate (within 5 days) to Grade 3 or 4 neutropenia events in the
140 HYCAMTIN capsules treatment group was 5%. The median time to onset of Grade 2 or worse
141 diarrhea was 9 days in the HYCAMTIN capsules group.

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

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

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

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

153 **6.2 Postmarketing Experience**

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

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

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

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

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

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

165 **7 DRUG INTERACTIONS**

166 **7.1 Drugs That Inhibit Drug Efflux Transporters**

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

174 **7.2 Effects of Topotecan on Drug Metabolizing Enzymes**

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

176 cytochromes P450 (CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or
177 CYP4A) or dihydropyrimidine dehydrogenase indicate that the activities of these enzymes were
178 not altered by topotecan. Enzyme inhibition by topotecan has not been evaluated in vivo.

179 **7.3 Effects of Other Drugs on Topotecan Pharmacokinetics**

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

182 **8 USE IN SPECIFIC POPULATIONS**

183 **8.1 Pregnancy**

184 Pregnancy Category D. [See *Contraindications (4) and Warnings and Precautions (5.4).*]

185 **8.3 Nursing Mothers**

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

187 Rats excrete high concentrations of topotecan into milk. Lactating female rats given
188 4.72 mg/m² IV (about twice the clinical dose on a mg/m² basis) excreted topotecan into milk at
189 concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is
190 excreted in human milk. Breastfeeding should be discontinued when women are receiving
191 HYCAMTIN.

192 **8.4 Pediatric Use**

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

194 **8.5 Geriatric Use**

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

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

203 This drug is known to be excreted by the kidney, and the risk of toxic reactions to this
204 drug may be greater in patients with impaired renal function [see *Dosage and Administration*
205 *(2.2)*].

206 **8.6 Renal Impairment**

207 A cross-study analysis of data collected from 217 patients with advanced solid tumors
208 indicated that exposure (AUC_{0-∞}) to topotecan lactone, the pharmacologically active moiety, was
209 10% and 20% higher in patients with mild renal (CL_{Cr} = 50-80 mL/min) and moderate renal
210 (CL_{Cr} = 30-49 mL/min) impairment, respectively, than in patients with normal renal function
211 (CL_{Cr} >80 mL/min) [see *Dosage and Administration (2.2)*].

212 **8.7 Hepatic Impairment**

213 In a population pharmacokinetic analysis involving oral topotecan administered at doses
214 of 0.15-2.7 mg/m²/day to 118 cancer patients, the pharmacokinetics of total topotecan did not

215 differ significantly based on patient serum bilirubin, ALT, or AST. No dosage adjustment
216 appeared to be required for patients with impaired hepatic function (serum bilirubin of
217 >1.5 mg/dL).

218 **10 OVERDOSAGE**

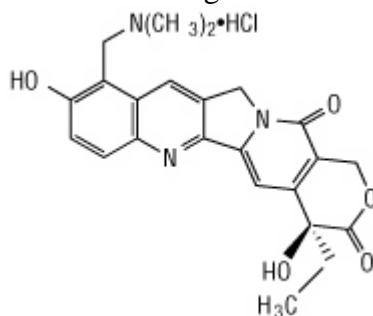
219 There is no known antidote for overdose with HYCAMTIN capsules. The primary
220 anticipated complication of overdose would consist of hematological toxicity. The patient
221 should be observed closely for bone marrow suppression, and supportive measures (such as the
222 prophylactic use of G-CSF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

223 **11 DESCRIPTION**

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

226 The chemical name for topotecan hydrochloride is (*S*)-10-[(dimethylamino)methyl]-4-
227 ethyl-4,9-dihydroxy-1*H*-pyrano[3',4':6,7] indolizino [1,2-*b*]quinoline-3,14-(4*H*,12*H*)-dione
228 monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5 \cdot HCl$ and a molecular weight of
229 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

230 Topotecan hydrochloride has the following structural formula:



231
232 HYCAMTIN capsules contain topotecan hydrochloride, the content of which is
233 expressed as topotecan free base. The major excipients are hydrogenated vegetable oil, glyceryl
234 monostearate, gelatin, and titanium dioxide. The capsules are imprinted with edible black ink.
235 The 1 mg capsules also contain red iron oxide.

236 **12 CLINICAL PHARMACOLOGY**

237 **12.1 Mechanism of Action**

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

244 **12.2 Pharmacodynamics**

245 The dose-limiting toxicity of topotecan is leukopenia. White blood cell count decreases

246 with increasing topotecan dose or topotecan AUC. There is a correlation between topotecan
247 lactone AUC day 1 and percent decrease of leukocytes.

248 **12.3 Pharmacokinetics**

249 The pharmacokinetics of Hycamtin capsules after oral administration have been
250 evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² administered daily for 5 days.
251 Topotecan exhibits biexponential pharmacokinetics with a mean terminal half-life of 3 to
252 6 hours. Total exposure (AUC) increases approximately proportionally with dose. Plasma protein
253 binding of topotecan is about 35%.

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

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

262 Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1
263 (P-gp) and ABCC1 (MRP-1) as well as the metabolizing enzyme CYP3A4, within 4 hours of
264 oral topotecan increased the dose-normalized AUC₀₋₂₄ of topotecan lactone and total topotecan to
265 2.0- to 3-fold of control. [See Drug Interactions (7.1).]

266 **Metabolism and Elimination:** Topotecan undergoes a reversible pH-dependent
267 hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤4,
268 the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at
269 physiologic pH. The mean metabolite:parent AUC ratio was <10% for total topotecan and
270 topotecan lactone.

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

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

283 **13 NONCLINICAL TOXICOLOGY**

284 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

297 **14 CLINICAL STUDIES**

298 **14.1 Small Cell Lung Cancer**

299 HYCAMTIN capsules were studied in patients with relapsed SCLC in a randomized,
300 comparative, open label trial. The patients were prior responders (complete or partial) to first-
301 line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and
302 had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were
303 randomized to HYCAMTIN capsules (2.3 mg/m²/day administered for 5 consecutive days
304 repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to
305 BSC alone. The primary objective was to compare the overall survival between the 2 treatment
306 arms. Patients in the HYCAMTIN capsules plus BSC group received a median of 4 courses
307 (range 1 to 10) and maintained a median dose intensity of HYCAMTIN capsules,
308 3.77 mg/m²/week. The median patient age in the HYCAMTIN capsules plus BSC arm and the
309 BSC alone treatment arm was 60 years and 58 years while the percentage of patients ≥65 years
310 of age was 34% and 29%, respectively. All but 1 patient were Caucasian. The HYCAMTIN
311 capsules plus BSC treatment arm included 68% of patients with extensive disease and 28% with
312 liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver
313 metastases. Both treatment arms recruited 73% males. In the HYCAMTIN capsules plus BSC
314 arm, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC alone arm,
315 26% of patients had prior carboplatin and 51% had prior cisplatin.

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

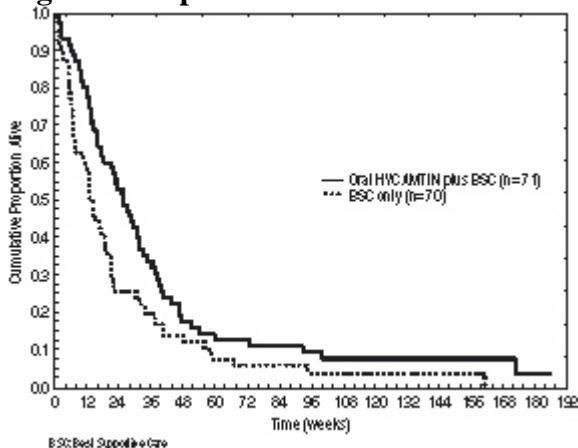
319

320 **Table 2. Overall Survival in Small Cell Lung Cancer Patients With HYCAMTIN Capsules**
 321 **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 | |

322 BSC = Best Supportive Care.
 323 N = total number of patients randomized.
 324 CI = Confidence Interval.

325
 326 **Figure 1. Kaplan-Meier Estimates for Survival**



327
 328

329 **15 REFERENCES**

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 331 Occupational Exposure to Antineoplastic and Other Hazardous Drugs in HealthCare Settings.
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 339 *and Recommendations for Practice.* 2nd ed. Pittsburgh, PA: Oncology Nursing Society: 2005.

340 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

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

355 **17 PATIENT COUNSELING INFORMATION**

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

357 **17.1 Bone Marrow Suppression**

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

363 **17.2 Pregnancy**

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

366 **17.3 Diarrhea**

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

370 **17.4 FDA-Approved Patient Labeling**

371 See separate leaflet.

372
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374



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376 GlaxoSmithKline
377 Research Triangle Park, NC 27709
378

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41

42 **What are HYCAMTIN capsules?**

43 HYCAMTIN capsules are prescription medicines you take by mouth. HYCAMTIN
44 capsules are used to treat a certain type of lung cancer called small cell lung cancer.

45 HYCAMTIN capsules may be right for you if:

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

49

50 HYCAMTIN capsules have not been studied in children.

51

52 **Who should NOT take HYCAMTIN capsules?**

53 Do not take HYCAMTIN capsules if:

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

62

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

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

69

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

72

73 **How should I take HYCAMTIN capsules?**

- 74 • **Take HYCAMTIN capsules exactly as your doctor prescribes them.**
- 75 • Your healthcare provider may want you to take both 1 mg and 0.25 mg capsules
76 together to make up your complete dose. You must be able to tell the difference
77 between the capsules. The 1 mg capsule is a pink color and the 0.25 mg capsule is a
78 white to yellowish-white color.
- 79 • Take HYCAMTIN capsules once a day for 5 days in a row. This treatment will
80 normally be repeated every 3 weeks (a treatment cycle). Your healthcare provider

81 will decide how long you will take HYCAMTIN capsules.

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

99

100 **What should I avoid while taking HYCAMTIN capsules?**

101 HYCAMTIN may make you feel drowsy or sleepy both during and for several days after
102 treatment. If you feel tired or weak, do not drive and do not use heavy tools or operate
103 machinery.

104

105 **What are the possible side effects of HYCAMTIN capsules?**

106 HYCAMTIN can cause serious side effects including decreased blood counts and
107 diarrhea. See “What is the most important information I should know about HYCAMTIN
108 capsules?”

109

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

- 111 • stomach problems such as nausea (feeling sick) and vomiting
112 • tiredness
113 • hair loss
114 • weakness
115 • lung problems (may include being short of breath)

116

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

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

122

123 **How should I store HYCAMTIN capsules?**

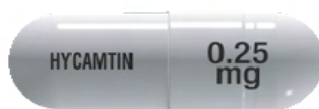
- 124 • Store HYCAMTIN capsules at normal room temperature between 68°-77°F (20°-
125 25°C). Protect from light and heat.
126 • Dispose of HYCAMTIN capsules that are out of date or no longer needed.
127 • **Keep HYCAMTIN capsules and all other medicines out of the reach of children.**

128

129 **What are the ingredients in HYCAMTIN capsules?**

130 **Active Ingredient:** Topotecan

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



134



135

136

(capsules shown larger than actual size)

137

138 **General information about HYCAMTIN capsules**

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

144

145 This leaflet summarizes the most important information about HYCAMTIN capsules. If
146 you would like more information, talk with your healthcare provider. You can ask your
147 pharmacist or healthcare provider for information about HYCAMTIN capsules that is
148 written for health professionals. For more information you can call toll-free 1-888-825-
149 5249 or visit www.gsk.com.

150

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