

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 inhibitor indicated for treatment of patients with relapsed small cell lung cancer. (1)

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

0.25 mg and 1 mg capsules. (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Bone marrow suppression. HYCAMTIN should be administered only to patients with adequate bone marrow reserves. Peripheral blood counts should be monitored. (5.1) Dose may need to be adjusted. (2.3)
- Topotecan-induced neutropenia can lead to neutropenic colitis. (5.1)

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

ADVERSE REACTIONS

The most common Grade 3 or 4 hematologic adverse reactions with HYCAMTIN capsules were neutropenia (61%), anemia (25%), and thrombocytopenia (37%). The most common ($\geq 10\%$) 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)
- Nursing Mothers: Discontinue nursing when receiving HYCAMTIN. (8.3)

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

Issued: Month Year

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

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 (CLcr = 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 (CLcr = 30-
24 49 mL/min). Insufficient data are available in patients with severe renal impairment
25 (CLcr <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 with severe bone marrow depression.

47 **5 WARNINGS AND PRECAUTIONS**

48 **5.1 Bone Marrow Suppression**

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

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

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

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

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

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

69 **5.2 Diarrhea**

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

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

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

85 **5.3 Interstitial Lung Disease**

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

92 **5.4 Pregnancy**

93 Pregnancy Category D

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

100 **5.5 Drug Interactions**

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

105 **6 ADVERSE REACTIONS**

106 **6.1 Clinical Trials Experience**

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

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

116

117 **Table 1. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated**
118 **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

119 BSC = Best Supportive Care.

120 N = total number of patients treated.

121 Adverse reactions were graded using NCI Common Toxicity Criteria.

122

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

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

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

134 In the 682 patients who received HYCAMTIN capsules in the 4 thoracic cancer studies, 39
135 deaths occurred within 30 days after the last dose of study medication for a reason other than

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

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

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

144 **6.2 Postmarketing Experience**

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

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

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

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

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

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

156 **7 DRUG INTERACTIONS**

157 **7.1 Drugs That Inhibit Drug Efflux Transporters**

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

165 **7.2 Effects of Topotecan on Drug Metabolizing Enzymes**

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

170 **7.3 Effects of Other Drugs on Topotecan Pharmacokinetics**

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

173 **8 USE IN SPECIFIC POPULATIONS**

174 **8.1 Pregnancy**

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

176 HYCAMTIN can cause fetal harm when administered to a pregnant woman. In rabbits,
177 an IV dose of 0.10 mg/kg/day (about equal to the clinical IV dose on a mg/m² basis) given on
178 days 6 through 20 of gestation caused maternal toxicity, embryoletality, and reduced fetal body
179 weight. In the rat, an IV dose of 0.23 mg/kg/day (about equal to the clinical IV dose on a mg/m²
180 basis) given for 14 days before mating through gestation day 6 caused fetal resorption,
181 microphthalmia, pre-implant loss, and mild maternal toxicity. An IV dose of 0.10 mg/kg/day
182 (about half the clinical IV dose on a mg/m² basis) given to rats on days 6 through 17 of gestation
183 caused an increase in post-implantation mortality. This dose also caused an increase in total fetal
184 malformations. The most frequent malformations were of the eye (microphthalmia,
185 anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic orbit), brain
186 (dilated lateral and third ventricles), skull, and vertebrae.

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

190 **8.3 Nursing Mothers**

191 Rats excrete high concentrations of topotecan into milk. Lactating female rats given
192 4.72 mg/m² IV (about twice the clinical dose on a mg/m² basis) excreted topotecan into milk at
193 concentrations up to 48-fold higher than those in plasma. It is not known whether the drug is
194 excreted in human milk. Because many drugs are excreted in human milk, and because of the
195 potential for serious adverse reactions in nursing infants from HYCAMTIN, discontinue
196 breastfeeding when women are receiving HYCAMTIN.

197 **8.4 Pediatric Use**

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

199 **8.5 Geriatric Use**

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

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

208 This drug is known to be excreted by the kidney, and the risk of toxic reactions to this
209 drug may be greater in patients with impaired renal function [see Dosage and Administration
210 (2.2)].

211 **8.6 Renal Impairment**

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

213 indicated that exposure ($AUC_{0-\infty}$) to topotecan lactone, the pharmacologically active moiety, was
214 10% and 20% higher in patients with mild renal ($CL_{cr} = 50-80$ mL/min) and moderate renal
215 ($CL_{cr} = 30-49$ mL/min) impairment, respectively, than in patients with normal renal function
216 ($CL_{cr} >80$ mL/min) [see *Dosage and Administration (2.2)*].

217 **8.7 Hepatic Impairment**

218 In a population pharmacokinetic analysis involving oral topotecan administered at doses
219 of 0.15-2.7 mg/m²/day to 118 cancer patients, the pharmacokinetics of total topotecan did not
220 differ significantly based on patient serum bilirubin, ALT, or AST. No dosage adjustment
221 appeared to be required for patients with impaired hepatic function (serum bilirubin of
222 >1.5 mg/dL).

223 **10 OVERDOSAGE**

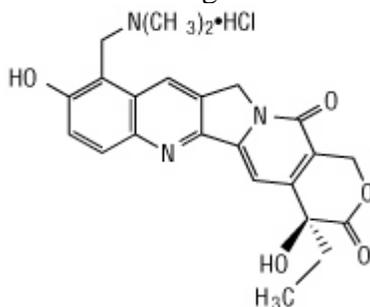
224 There is no known antidote for overdosage with Hycamtin capsules. The primary
225 anticipated complication of overdosage would consist of hematological toxicity. The patient
226 should be observed closely for bone marrow suppression, and supportive measures (such as the
227 prophylactic use of G-CSF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

228 **11 DESCRIPTION**

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

231 The chemical name for topotecan hydrochloride is (S)-10-[(dimethylamino)methyl]-4-
232 ethyl-4,9-dihydroxy-1H-pyrano[3',4':6,7]indolizino [1,2-b]quinoline-3,14-(4H,12H)-dione
233 monohydrochloride. It has the molecular formula $C_{23}H_{23}N_3O_5 \cdot HCl$ and a molecular weight of
234 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

235 Topotecan hydrochloride has the following structural formula:



236
237 Hycamtin capsules contain topotecan hydrochloride, the content of which is
238 expressed as topotecan free base. The major excipients are hydrogenated vegetable oil, glyceryl
239 monostearate, gelatin, and titanium dioxide. The capsules are imprinted with edible black ink.
240 The 1 mg capsules also contain red iron oxide.

241 **12 CLINICAL PHARMACOLOGY**

242 **12.1 Mechanism of Action**

243 Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand

244 breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents religation of these
245 single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA
246 damage produced during DNA synthesis, when replication enzymes interact with the ternary
247 complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently
248 repair these double strand breaks.

249 **12.2 Pharmacodynamics**

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

253 **12.3 Pharmacokinetics**

254 The pharmacokinetics of HYCAMTIN capsules after oral administration have been
255 evaluated in cancer patients following doses of 1.2 to 3.1 mg/m² administered daily for 5 days.
256 Topotecan exhibits biexponential pharmacokinetics with a mean terminal half-life of 3 to
257 6 hours. Total exposure (AUC) increases approximately proportionally with dose. Plasma protein
258 binding of topotecan is about 35%.

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

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

267 Administration of oral cyclosporine A (15 mg/kg), an inhibitor of transporters ABCB1
268 (P-gp) and ABCC1 (MRP-1) as well as the metabolizing enzyme CYP3A4, within 4 hours of
269 oral topotecan increased the dose-normalized AUC₀₋₂₄ of topotecan lactone and total topotecan to
270 2.0- to 3-fold of control. [See *Drug Interactions (7.1)*.]

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

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

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

288 **13 NONCLINICAL TOXICOLOGY**

289 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

302 **14 CLINICAL STUDIES**

303 **14.1 Small Cell Lung Cancer**

304 HYCAMTIN capsules were studied in patients with relapsed SCLC in a randomized,
305 comparative, open label trial. The patients were prior responders (complete or partial) to first-
306 line chemotherapy, were not considered candidates for standard intravenous chemotherapy, and
307 had relapsed at least 45 days from the end of first-line chemotherapy. Seventy-one patients were
308 randomized to HYCAMTIN capsules (2.3 mg/m²/day administered for 5 consecutive days
309 repeated every 21 days) and Best Supportive Care (BSC) and 70 patients were randomized to
310 BSC alone. The primary objective was to compare the overall survival between the 2 treatment
311 arms. Patients in the HYCAMTIN capsules plus BSC group received a median of 4 courses
312 (range 1 to 10) and maintained a median dose intensity of HYCAMTIN capsules,
313 3.77 mg/m²/week. The median patient age in the HYCAMTIN capsules plus BSC arm and the
314 BSC alone treatment arm was 60 years and 58 years while the percentage of patients ≥65 years
315 of age was 34% and 29%, respectively. All but 1 patient were Caucasian. The HYCAMTIN
316 capsules plus BSC treatment arm included 68% of patients with extensive disease and 28% with
317 liver metastasis. In the BSC alone arm, 61% of patients had extensive disease and 20% had liver
318 metastases. Both treatment arms recruited 73% males. In the HYCAMTIN capsules plus BSC
319 arm, 18% of patients had prior carboplatin and 62% had prior cisplatin. In the BSC alone arm,
320 26% of patients had prior carboplatin and 51% had prior cisplatin.

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

323 shown in Table 2 and Figure 1.

324

325 **Table 2. Overall Survival in Small Cell Lung Cancer Patients With HYCAMTIN Capsules**
 326 **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	

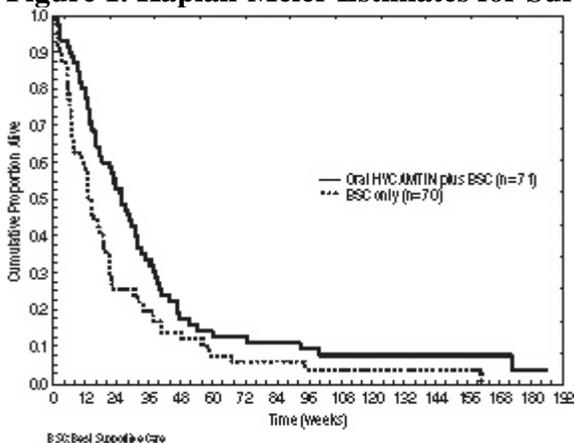
327 BSC = Best Supportive Care.

328 N = total number of patients randomized.

329 CI = Confidence Interval.

330

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



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333

334 **15 REFERENCES**

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345 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

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

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

359 **17 PATIENT COUNSELING INFORMATION**

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

361 **17.1 Bone Marrow Suppression**

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

367 **17.2 Pregnancy**

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

370 **17.3 Diarrhea**

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

374 **17.4 FDA-Approved Patient Labeling**

375 See separate leaflet.

376

377 HYCAMTIN is a registered trademark of GlaxoSmithKline.

378



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380 GlaxoSmithKline

381 Research Triangle Park, NC 27709

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PATIENT INFORMATION

**HYCAMTIN[®] (hi-CAM-tin)
(topotecan) Capsules**

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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.

427 HYCAMTIN capsules may be right for you if:

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

430

431 It is not known if HYCAMTIN is safe and effective in children.

432

433 **Who should not take HYCAMTIN capsules?**

434 Do not take HYCAMTIN capsules if:

- 435 • you are allergic to anything in HYCAMTIN capsules. See the end of this leaflet for a
436 complete list of ingredients in HYCAMTIN capsules.
- 437 • the results of your last blood test show blood counts that are too low. Your healthcare
438 provider will tell you.

439

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

441 **Before you take HYCAMTIN capsules, tell your healthcare provider if you:**

- 442 • are pregnant or may become pregnant. HYCAMTIN capsules may harm your unborn baby.
443 You should not become pregnant while you are taking HYCAMTIN capsules.
- 444 • are breastfeeding or plan to breastfeed. It is not known if HYCAMTIN passes into your
445 breast milk or if it can harm your baby. You and your healthcare provider should decide if
446 you will take HYCAMTIN or breast feed. You should not do both.
- 447
- 448 • **Tell your healthcare provider about all the medicines you take**, including prescription
449 and non-prescription medicines, vitamins, and herbal supplements. HYCAMTIN capsules
450 and other medicines may affect each other causing side effects. Especially tell your
451 healthcare provider if you are taking: cyclosporine (SANDIMMUNE[®], GENGRAF[®],
452 NEORAL[®]), ketoconazole (NIZORAL[®], EXTINA[®]), ritonavir (NORVIR[®], KALETRA[®]),
453 saquinavir (INVIRASE[®]).
- 454 • Know your medicines. Keep a list of your medicines and show it to your healthcare provider
455 and pharmacist when you get a new medicine.

456

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

- 458 • **Take HYCAMTIN capsules exactly as your doctor prescribes them.**
- 459 • Your healthcare provider may want you to take both 1 mg and 0.25 mg capsules together to
460 make up your complete dose. You must be able to tell the difference between the capsules.
461 The 1 mg capsule is a pink color and the 0.25 mg capsule is a white to yellowish-white color.
- 462 • Take HYCAMTIN capsules once a day for 5 days in a row. This treatment will normally be
463 repeated every 3 weeks (a treatment cycle). Your healthcare provider will decide how long
464 you will take HYCAMTIN capsules.
- 465 • Swallow HYCAMTIN capsules whole with water. Do not open, chew, or crush HYCAMTIN
466 capsules. HYCAMTIN capsules may be taken with or without food.

- 467 • If any of the HYCAMTIN capsules are broken or leaking, do not touch them with your bare
468 hands. Carefully dispose of the capsules, and then wash your hands well with soap and water.
469 • If you get any of the contents of HYCAMTIN capsules on your skin or in your eyes, do the
470 following:
471 • Wash the area of skin well with soap and water right away,
472 • Wash your eyes right away with gently flowing water for at least 15 minutes.
473 • Call your healthcare provider if you get a skin reaction or if you get the medicine in your
474 eyes.
475 • If you take too much HYCAMTIN, contact your healthcare provider right away.
476 • If you forget to take HYCAMTIN at any time, do not double the dose to make up for a
477 forgotten dose. Wait and take the next scheduled dose. Let your healthcare provider know
478 that you missed a dose.
479 • If you vomit after taking your HYCAMTIN, do not take another dose on the same day. Let
480 your healthcare provider know right away that you have vomited.

481

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

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

486

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

488 HYCAMTIN can cause serious side effects including:

- 489 • See “What is the most important information I should know about HYCAMTIN capsules?”
490 • Lung problems that can cause death. Tell your healthcare provider right away if you have
491 **new or worse** symptoms of coughing, fever, shortness of breath, or problems breathing.
492 Your healthcare provider may tell you to stop taking HYCAMTIN capsules.

493

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

- 495 • stomach problems such as nausea (feeling sick) and vomiting
496 • tiredness
497 • hair loss
498 • weakness

499

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

505

506 These are not all of the possible side effects of HYCAMTIN capsules. For more information, ask

507 your doctor or pharmacist.

508

509 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
510 800-FDA-1088.

511

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

- 513 • Store HYCAMTIN capsules in a refrigerator between 36° to 46°F (2° and 8°C).
- 514 • Keep the bottle of HYCAMTIN capsules in the carton that it comes in to protect it from light.
- 515 • Dispose of HYCAMTIN capsules that are out of date or no longer needed.
- 516 • **Keep HYCAMTIN capsules and all other medicines out of the reach of children.**

517

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

519 **Active Ingredient:** Topotecan

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



523



524

525

(capsules shown larger than actual size)

526

527 **General information about HYCAMTIN capsules**

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

533

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

539

540 This patient information leaflet has been approved by the US Food and Drug Administration.

541

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