

## 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, for oral use  
Initial U.S. Approval: 1996

### WARNING: BONE MARROW SUPPRESSION

See full prescribing information for complete boxed warning  
HYCAMTIN can cause severe myelosuppression. Administer only to patients with baseline neutrophil counts of  $\geq 1,500$  cells/mm<sup>3</sup> and a platelet count  $\geq 100,000$  cells/mm<sup>3</sup>. Monitor blood cell counts (5.1).

### RECENT MAJOR CHANGES

Boxed Warning	06S/2014
Dosage and Administration, Dose Modification Guidelines (2.2)	06S/2014
Contraindications, Severe Bone Marrow Depression (4)	Removed 06S/2014
Warnings and Precautions, Embryofetal Toxicity (5.4)	06S/2014
Warnings and Precautions, Drug Interactions (5.5)	Removed 06S/2014

### INDICATIONS AND USAGE

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

### DOSAGE AND ADMINISTRATION

- 2.3 mg/m<sup>2</sup>/day orally once daily for 5 consecutive days repeated every 21 days. (2)
- Renal impairment: Adjust the dose of HYCAMTIN in patients with renal impairment. (2.2)

### DOSAGE FORMS AND STRENGTHS

0.25-mg and 1-mg capsules. (3)

### CONTRAINDICATIONS

- History of severe hypersensitivity reactions to topotecan. (4)

### WARNINGS and PRECAUTIONS

- Bone marrow suppression: Administer HYCAMTIN only to patients with adequate bone marrow reserves. Monitor peripheral blood counts. (5.1) Adjust dose as needed. (2.2)
- Diarrhea: Severe diarrhea can occur and may require hospitalization. (5.2) Withhold for severe diarrhea. Reduce dose upon recovery. (2.2)
- Interstitial lung disease (ILD): Fatal cases have occurred. Permanently discontinue for confirmed ILD. (5.3)
- Embryofetal toxicity: 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 (56%), anemia (25%), and thrombocytopenia (35%). The most common ( $\geq 10\%$ ) non-hematologic adverse reactions (all grades) were nausea (33%), diarrhea (22%), vomiting (21%), alopecia (20%), and fatigue (19%). (6.1)

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

### DRUG INTERACTIONS

- Avoid concomitant use of P-gp and BCRP inhibitors with HYCAMTIN. (7, 12.3)

### USE IN SPECIFIC POPULATIONS

- Geriatric use: Diarrhea was more frequent in patients aged  $\geq 65$  years (28%) compared with those younger than 65 years. (19%) (5.2, 6.1, 8.5)
- Nursing mothers: Discontinue nursing or discontinue HYCAMTIN. (8.3)

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

Revised: ~~xx/xxxx~~ June 2014

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: BONE MARROW SUPPRESSION**

3 **HYCAMTIN<sup>®</sup> can cause severe myelosuppression. Administer only to patients with**  
4 **neutrophil counts of  $\geq 1,500$  cells/mm<sup>3</sup> and platelet counts  $\geq 100,000$  cells/mm<sup>3</sup>. Monitor**  
5 **blood cell counts.**

### 6 **1 INDICATIONS AND USAGE**

7 HYCAMTIN capsules are indicated for the treatment of relapsed small cell lung cancer in  
8 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/m<sup>2</sup>/day orally once daily for 5  
13 consecutive days repeated every 21 days. Round the dose to the nearest 0.25 mg, and prescribe  
14 the minimum number of 1-mg and 0.25-mg capsules. Prescribe the same number of capsules for  
15 each of the 5 dosing days.

16 Take HYCAMTIN capsules with or without food. Swallow capsules whole. Do not chew, crush,  
17 or divide the capsules. Do not prescribe a replacement dose for emesis.

#### 18 **2.2 Dose Modification Guidelines**

##### 19 Hematologic Toxicities:

20 Do not administer subsequent courses of HYCAMTIN capsules until neutrophils recover to  
21 greater than 1,000 cells/mm<sup>3</sup>, platelets recover to greater than 100,000 cells/mm<sup>3</sup>, hemoglobin  
22 levels recover to greater than or equal to 9.0 g/dL (with transfusion if necessary).

- 23 • Dose reduce HYCAMTIN capsules by 0.4 mg/m<sup>2</sup>/day for:
  - 24 ○ neutrophil counts of less than 500 cells/mm<sup>3</sup> associated with fever or infection or
  - 25 lasting for 7 days or more;
  - 26 ○ neutrophil counts of 500 to 1,000 cells/mm<sup>3</sup> lasting beyond day 21 of the treatment
  - 27 course;
  - 28 ○ platelet counts less than 25,000 cells/mm<sup>3</sup>.

##### 29 Diarrhea:

30 Do not administer HYCAMTIN capsules to patients with Grade 3 or 4 diarrhea. After recovery  
31 to Grade 1 or less, reduce the dose of HYCAMTIN by 0.4 mg/m<sup>2</sup>/day for subsequent courses  
32 [see Warnings and Precautions (5.2)].

33 Renal Impairment:

34 The recommended starting doses of HYCAMTIN capsules in patients with moderate and severe  
35 renal impairment are as follows:

36  
37 **Table 1. Dose Reduction Guidelines for Renal Impairment**

Degree of Renal Impairment	Creatinine Clearance <sup>a</sup> (mL/min)	Dose (mg/m <sup>2</sup> )/day
Moderate	30 – 49	1.5 <sup>b</sup>
Severe	<30	0.6 <sup>b</sup>

38 <sup>a</sup> Calculated with the Cockcroft-Gault method using ideal body weight.

39 <sup>b</sup> Dose can be increased after the first course by 0.4 mg/m<sup>2</sup>/day if no severe hematologic or  
40 gastrointestinal toxicities occur.

41 **3 DOSAGE FORMS AND STRENGTHS**

42 HYCAMTIN capsules contain topotecan hydrochloride expressed as topotecan free base. The  
43 0.25-mg capsules are opaque white to yellowish-white and imprinted with HYCAMTIN and  
44 0.25 mg. The 1-mg capsules are opaque pink and imprinted with HYCAMTIN and 1 mg.

45 **4 CONTRAINDICATIONS**

46 HYCAMTIN is contraindicated in patients who have a history of severe hypersensitivity  
47 reactions to topotecan.

48 **5 WARNINGS AND PRECAUTIONS**

49 **5.1 Bone Marrow Suppression**

50 Bone marrow suppression (primarily neutropenia) is a dose-limiting toxicity of HYCAMTIN.  
51 Neutropenia is not cumulative over time. The following data on myelosuppression are based on  
52 an integrated safety database from 4 thoracic malignancy trials (N = 682) using HYCAMTIN  
53 capsules at 2.3 mg/m<sup>2</sup>/day for 5 consecutive days. The median day for neutrophil and platelet  
54 nadirs occurred on Day 15.

55 Neutropenia:

56 Grade 4 neutropenia (<500 cells/mm<sup>3</sup>) occurred in 32% of patients with a median duration of  
57 7 days and was most common during Course 1 of treatment (20% of patients). Clinical sequelae  
58 of neutropenia included infection (17%), febrile neutropenia (4%), sepsis (2%), and septic death  
59 (1%). Pancytopenia has been reported.

60 Topotecan can cause fatal typhlitis (neutropenic enterocolitis). Consider the possibility of  
61 typhlitis in patients presenting with fever, neutropenia, and abdominal pain [*see Dosage and*  
62 *Administration (2.2)*].

63 **Thrombocytopenia:**

64 Grade 4 thrombocytopenia (<10,000 cells/mm<sup>3</sup>) occurred in 6% of patients, with a median  
65 duration of 3 days.

66 **Anemia:**

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

68 Administer the first course of HYCAMTIN only to patients with a neutrophil count of  
69  $\geq 1,500$  cells/mm<sup>3</sup> and a platelet count  $\geq 100,000$  cells/mm<sup>3</sup>. Monitor peripheral blood cell counts  
70 frequently during treatment with HYCAMTIN. Refer to Section 2.2 for dose modification  
71 guidelines for hematological toxicities in subsequent courses.

72 **5.2 Diarrhea**

73 Diarrhea, including severe and life-threatening diarrhea requiring hospitalization, can occur  
74 during treatment with HYCAMTIN capsules. Diarrhea caused by HYCAMTIN capsules can  
75 occur at the same time as drug-induced neutropenia and its sequelae. In the 682 patients who  
76 received HYCAMTIN capsules in the 4 lung cancer trials, the incidence of diarrhea caused by  
77 HYCAMTIN capsules was 22%, with 4% Grade 3 and 0.4% Grade 4. The incidence of Grade 3  
78 or 4 diarrhea proximate (within 5 days) to Grade 3 or 4 neutropenia events in the group receiving  
79 HYCAMTIN capsules was 5%. The median time to onset of Grade 2 or worse diarrhea was 9  
80 days in the group receiving HYCAMTIN capsules. Manage diarrhea caused by HYCAMTIN  
81 capsules aggressively. Do not administer HYCAMTIN capsules to patients with Grade 3 or 4  
82 diarrhea. Reduce the dose of HYCAMTIN after recovery to Grade 1 or less [*see Dosage and*  
83 *Administration (2.2)*].

84 **5.3 Interstitial Lung Disease**

85 Interstitial lung disease (ILD), including fatalities, has occurred with HYCAMTIN. Underlying  
86 risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic radiation, and use  
87 of pneumotoxic drugs and/or colony stimulating factors. Monitor patients for pulmonary  
88 symptoms indicative of interstitial lung disease (e.g., cough, fever, dyspnea, and/or hypoxia), and  
89 discontinue HYCAMTIN if a new diagnosis of ILD is confirmed.

90 **5.4 Embryofetal Toxicity**

91 HYCAMTIN can cause fetal harm when administered to a pregnant woman. Topotecan caused  
92 embryoletality, fetotoxicity, and teratogenicity in rats and rabbits when administered during  
93 organogenesis. If this drug is used during pregnancy, or if a patient becomes pregnant while  
94 taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in*  
95 *Specific Populations (8.1)*].

96 Advise females of reproductive potential to use highly effective contraception during treatment  
97 and for at least 1 month after the last dose of HYCAMTIN. Advise patients to contact their  
98 healthcare provider if they become pregnant, or if pregnancy is suspected, while taking

99 | HYCAMTIN [see Use in Specific Populations (8.1, 8.7)].

## 100 **6 ADVERSE REACTIONS**

101 The following serious adverse reactions are described below and elsewhere in the labeling:

- 102 • Bone Marrow Suppression [see Warnings and Precautions (5.1)]
- 103 • Diarrhea [see Warnings and Precautions (5.2)]
- 104 • Interstitial Lung Disease [see Warnings and Precautions (5.3)]

### 105 **6.1 Clinical Trials Experience**

106 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
107 observed in the clinical trials of a drug cannot be directly compared with rates in the clinical  
108 trials of another drug and may not reflect the rates observed in practice.

109 The safety of HYCAMTIN capsules was evaluated in 682 patients with lung cancer (3 recurrent  
110 small cell lung cancer [SCLC] trials and 1 recurrent non-small cell lung cancer [NSCLC] trial)  
111 who received at least one dose of HYCAMTIN capsules. Patients in all four trials had advanced  
112 lung malignancies and received prior chemotherapy in the first-line setting. The dose regimen for  
113 HYCAMTIN capsules was 2.3 mg/m<sup>2</sup>/day for five consecutive days every 21 days. The median  
114 number of courses was 3 (range: 1 to 20) in these four trials. Table 2 describes the hematologic  
115 and non-hematologic adverse reactions in recurrent SCLC patients treated with HYCAMTIN  
116 capsules in the overall lung cancer patient population.

117

118 **Table 2. Incidence (≥5%) of Adverse Reactions in Small Cell Lung Cancer Patients Treated**  
 119 **With HYCAMTIN Capsules Plus BSC and in Four Lung Cancer Trials**

Adverse Reaction	HYCAMTIN Capsules + BSC (N = 70)			HYCAMTIN Capsules Lung Cancer Population (N = 682)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
<b>Hematologic</b>						
Anemia	94	15	10	98	18	7
Neutropenia	91	28	33	83	24	32
Thrombocytopenia	81	30	7	81	29	6
<b>Non-hematologic</b>						
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

120 BSC = Best Supportive Care.

121 N = Total number of patients treated.

122 Adverse reactions were graded using NCI Common Toxicity Criteria Version 2.0.

123 **On-Study Death Due to Toxicity of HYCAMTIN:** In the 682 patients who received  
 124 HYCAMTIN capsules in the four lung cancer trials, 39 deaths (6%) occurred within 30 days  
 125 after the last dose for a reason other than progressive disease: 13 due to hematologic toxicity, 5  
 126 due to non-hematologic toxicity (2 from diarrhea), and 21 due to other causes.

## 127 **7 DRUG INTERACTIONS**

128 Topotecan is a substrate for both P-glycoprotein (P-gp) and breast cancer resistance protein  
 129 (BCRP). Inhibitors of these transporters increase the systemic exposure to oral topotecan. Avoid  
 130 concomitant use of P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol,  
 131 clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine,  
 132 itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor,  
 133 verapamil) and BCRP inhibitors (e.g., cyclosporine, eltrombopag) with HYCAMTIN capsules  
 134 [see *Clinical Pharmacology* (12.3)].

## 135 **8 USE IN SPECIFIC POPULATIONS**

### 136 **8.1 Pregnancy**

137 Pregnancy Category D.

138 **Risk Summary:**

139 HYCAMTIN can cause fetal harm when administered to a pregnant woman. Topotecan caused  
140 embryoletality, fetotoxicity, and teratogenicity in rats and rabbits when administered during  
141 organogenesis. If this drug is used during pregnancy, or if the patient becomes pregnant while  
142 taking this drug, inform the patient of the potential hazard to a fetus.

#### 143 Animal Data:

144 In rabbits, an IV dose of 0.10 mg/kg/day (about equal to the clinical IV dose on a mg/m<sup>2</sup> basis)  
145 given on days 6 through 20 of gestation caused maternal toxicity, embryoletality, and reduced  
146 fetal body weight. In the rat, an IV dose of 0.23 mg/kg/day (about equal to the clinical IV dose  
147 on a mg/m<sup>2</sup> basis) given for 14 days before mating through gestation day 6 caused fetal  
148 resorption, microphthalmia, pre-implant loss, and mild maternal toxicity. Administration of an  
149 IV dose of 0.10 mg/kg/day (about half the clinical IV dose on a mg/m<sup>2</sup> basis) to rats on days 6  
150 through 17 of gestation caused an increase in post-implantation mortality. This dose also caused  
151 an increase in total fetal malformations. The most frequent malformations were of the eye  
152 (microphthalmia, anophthalmia, rosette formation of the retina, coloboma of the retina, ectopic  
153 orbit), brain (dilated lateral and third ventricles), skull, and vertebrae.

#### 154 **8.3 Nursing Mothers**

155 It is not known whether topotecan is present in human milk. Lactating rats excrete high  
156 concentrations of topotecan into milk. Female rats given 4.72 mg/m<sup>2</sup> IV (about twice the clinical  
157 dose on a mg/m<sup>2</sup> basis) excreted topotecan into milk at concentrations up to 48-fold higher than  
158 those in plasma. Because many drugs are present in human milk, and because of the potential for  
159 serious adverse reactions in nursing infants from HYCAMTIN, a decision should be made  
160 whether to discontinue nursing or to discontinue the drug, taking into account the importance of  
161 the drug to the mother.

#### 162 **8.4 Pediatric Use**

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

#### 164 **8.5 Geriatric Use**

165 Of the 682 patients with thoracic cancer in 4 clinical trials who received HYCAMTIN capsules,  
166 33% (n = 225) were aged 65 years and older, while 4.8% (n = 33) were aged 75 years and older.  
167 Treatment-related diarrhea was more frequent in patients aged ≥65 years (28%) compared with  
168 those younger than 65 years (19%). [*See Warnings and Precautions (5.2), Adverse Reactions*  
169 *(6.1).*]

170 No overall differences in effectiveness were observed between patients 65 years and older and  
171 younger patients.

#### 172 **8.6 Renal Impairment**

173 The systemic exposure to both topotecan lactone and total topotecan increased in patients with  
174 renal impairment compared with that in patients with normal renal function. No dosage

175 adjustment is recommended for patients with mild renal impairment (CLcr = 50-79 mL/min).  
176 Adjust the dose of HYCAMTIN capsules in patients with moderate (CLcr = 30-49 mL/min) and  
177 severe (CLcr <30 mL/min) renal impairment [see Dosage and Administration (2.2), Clinical  
178 Pharmacology (12.3)].

## 179 **8.7 Females and Males of Reproductive Potential**

### 180 Contraception:

181 *Females:* Counsel patients on pregnancy planning and prevention. Advise female patients of  
182 reproductive potential to use highly effective contraception during and for 1 month following  
183 treatment with HYCAMTIN. Advise patients to contact their healthcare provider if they become  
184 pregnant, or if pregnancy is suspected, while taking HYCAMTIN [see Use in Specific  
185 Populations (8.1)].

186 *Males:* HYCAMTIN may damage spermatozoa, resulting in possible genetic and fetal  
187 abnormalities. Advise males with a female sexual partner of reproductive potential to use  
188 effective contraception during and for 3 months after treatment with HYCAMTIN [see  
189 Nonclinical Toxicology (13.1)].

### 190 Infertility:

191 *Females:* In females of reproductive potential, HYCAMTIN may have both acute and long-term  
192 effects on fertility [see Nonclinical Toxicology (13.1)].

193 *Males:* Effects on spermatogenesis have been observed in animals administered HYCAMTIN.  
194 Advise males of the potential risk for impaired fertility and to seek counseling on fertility and  
195 family planning options prior to starting treatment.

## 196 **10 OVERDOSAGE**

197 Overdoses (up to 5-fold of the prescribed dose) occurred in patients treated with HYCAMTIN  
198 capsules. The primary complication of overdosage is bone marrow suppression. The observed  
199 signs and symptoms of overdose are consistent with the known adverse reactions associated with  
200 HYCAMTIN for oral use [see Adverse Reactions (6.1)]. Mucositis has also been reported in  
201 association with overdose.

202 There is no known antidote for overdosage with HYCAMTIN. If an overdose is suspected,  
203 monitor the patient closely for bone marrow suppression, and institute supportive-care measures  
204 (such as the prophylactic use of G-CSF and/or antibiotic therapy) as appropriate.

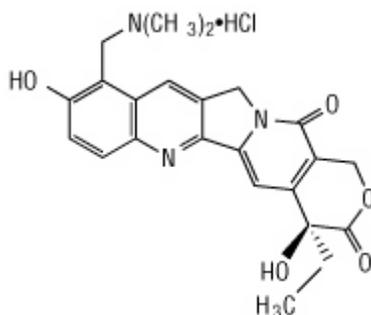
## 205 **11 DESCRIPTION**

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

208 The chemical name for topotecan hydrochloride is (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-  
209 dihydroxy-1H-pyrano[3',4':6,7] indolizino [1,2-b]quinoline-3,14-(4H,12H)-dione

210 monohydrochloride. It has the molecular formula  $C_{23}H_{23}N_3O_5 \cdot HCl$  and a molecular weight of  
211 457.9. It is soluble in water and melts with decomposition at 213° to 218°C.

212 Topotecan hydrochloride has the following structural formula:



213  
214 HYCAMTIN capsules for oral use contain topotecan hydrochloride, the content of which is  
215 expressed as topotecan free base. The excipients are gelatin, glyceryl monostearate,  
216 hydrogenated vegetable oil, and titanium dioxide. The capsules are imprinted with edible black  
217 ink. The 1-mg capsules also contain red iron oxide.

## 218 **12 CLINICAL PHARMACOLOGY**

### 219 **12.1 Mechanism of Action**

220 Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks.  
221 Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single-  
222 strand breaks. The cytotoxicity of topotecan is thought to be due to double-strand DNA damage  
223 produced during DNA synthesis, when replication enzymes interact with the ternary complex  
224 formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair  
225 these double-strand breaks.

### 226 **12.3 Pharmacokinetics**

227 Following administration of HYCAMTIN capsules at doses of 1.2 to 3.1 mg/m<sup>2</sup> administered  
228 daily for 5 days in cancer patients, topotecan exhibited biexponential pharmacokinetics with a  
229 mean terminal half-life of 3 to 6 hours. Total exposure (AUC) increased approximately  
230 proportionally to dose.

#### 231 Absorption:

232 Topotecan is rapidly absorbed with peak plasma concentrations occurring between 1 to 2 hours  
233 following oral administration. The oral bioavailability of topotecan is approximately 40%.  
234 Following a high-fat meal, the extent of exposure was similar in the fed and fasted states, while  
235 T<sub>max</sub> was delayed from 1.5 to 3 hours for topotecan lactone and from 3 to 4 hours for total  
236 topotecan. HYCAMTIN capsules can be given without regard to food.

#### 237 Distribution:

238 Binding of topotecan to plasma proteins is approximately 35%.

239 **Metabolism:**

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

244 **Excretion:**

245 In a mass balance study in 4 patients with advanced solid tumors, the overall recovery of drug-  
246 related material following 5 daily doses of topotecan was 57% of the administered oral dose. In  
247 the urine, 20% of the orally administered dose was excreted as total topotecan and 2% was  
248 excreted as N-desmethyl topotecan [*see Use in Specific Populations (8.6)*].

249 Fecal elimination of total topotecan accounted for 33%, while fecal elimination of N-desmethyl  
250 topotecan was 1.5%. Overall, the N-desmethyl metabolite contributed a mean of  $<6\%$  (range: 4%  
251 to 8%) of the total drug-related material accounted for in the urine and feces. O-glucuronides of  
252 both topotecan and N-desmethyl topotecan have been identified in the urine.

253 **Specific Populations:**

254 ***Age and Gender:*** A cross-study analysis in 217 patients with advanced solid tumors indicated  
255 that age and gender did not significantly affect the pharmacokinetics of oral topotecan.

256 ***Race:*** In patients with normal renal function, the exposures (geometric mean dose-normalized  
257 AUC<sub>inf</sub>) to topotecan lactone and total topotecan each were approximately 30% higher in Asian  
258 patients (n = 7) compared with Caucasian patients (n = 11).

259 In patients with mild renal impairment, the exposure was 30% higher for topotecan lactone in  
260 Asian (n = 7) compared with Caucasian (n = 12) patients, but the exposure to total topotecan was  
261 similar.

262 In patients with moderate renal impairment, the exposure was 60% higher for both topotecan  
263 lactone and total topotecan in Asian (n = 8) compared with Caucasian patients (n = 6).

264 In patients with severe renal impairment, the exposure was 112% higher for topotecan lactone  
265 and 70% higher for total topotecan in Asian (n = 3) compared with Caucasian patients (n = 4).

266 ***Renal Impairment:*** A trial was conducted in 59 patients with advanced cancer who were  
267 grouped based on the degree of their renal function and received HYCAMTIN capsules as shown  
268 in the table below.

269

270 **Table 3. Renal Function Groups With Initial Doses of HYCAMTIN Received**

Renal Function Group	Creatinine Clearance (CL <sub>cr</sub> ) (mL/min)	N	Dose (mg/m <sup>2</sup> ) Once Daily for 5 Days
Normal (without prior P-B CT) <sup>a</sup>	>80	6	2.3
Normal (with prior P-B CT)	>80	12	2.3
Mild renal impairment	50-79	19	1.9 or 2.3
Moderate renal impairment	30-49	14	1.2, 1.5 or 1.8
Severe renal impairment	<30	8	0.6, 0.8 or 1.2

271 <sup>a</sup> P-B CT = platinum-based chemotherapy.

272

273 The exposure (geometric mean dose-normalized AUC<sub>inf</sub>) for topotecan lactone increased by  
 274 34%, 80%, and 114% in Caucasian patients with mild, moderate, and severe renal impairment,  
 275 respectively, compared with that in Caucasian patients with normal renal function. The  
 276 corresponding values for total topotecan in Caucasian patients were 70%, 108%, and 227%,  
 277 respectively. Asian patients with mild, moderate, and severe renal impairment had a 34%, 121%,  
 278 and 247% higher exposure to topotecan lactone, respectively, than Asian patients with normal  
 279 renal function. The corresponding values for total topotecan in Asian patients are 26%, 153%,  
 280 and 331%, respectively. Prior platinum-based chemotherapy (P-B CT) had no effect on the  
 281 systemic exposure to both total topotecan and topotecan lactone in patients with normal renal  
 282 function.

283 No dosage adjustment is recommended for patients with mild renal impairment. Adjust the  
 284 dosage of HYCAMTIN capsules in patients with moderate and severe renal impairment [*see*  
 285 *Dosage and Administration (2.2), Use in Specific Populations (8.6)*].

286 **Hepatic Impairment:** In a population pharmacokinetic analysis involving oral topotecan  
 287 administered at doses of 0.15 to 2.7 mg/m<sup>2</sup>/day to 118 cancer patients, the pharmacokinetics of  
 288 total topotecan did not differ significantly based on patient serum bilirubin, ALT, or AST.

289 **Drug Interactions:**

290 **Effects of Topotecan on Drug-Metabolizing Enzymes:** In vitro inhibition studies using  
 291 marker substrates known to be metabolized by human cytochromes P450 (CYP1A2, CYP2A6,  
 292 CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A) or dihydropyrimidine  
 293 dehydrogenase indicate that the activities of these enzymes were not altered by topotecan.  
 294 Enzyme inhibition by topotecan has not been evaluated in vivo.

295 **Drugs That Inhibit Drug Efflux Transporters:** Following coadministration of escalating doses  
 296 of a dual inhibitor of BCRP and P-gp with oral topotecan, the AUC<sub>inf</sub> of topotecan lactone and  
 297 total topotecan increased approximately 2.5-fold compared with control [*see Drug Interactions*  
 298 *(7.1)*].

299 Administration of oral cyclosporine A (15 mg/kg), an inhibitor of P-gp, multidrug-resistance-  
300 associated protein (MRP-1), and cytochrome P450 3A4 (CYP3A4) within 4 hours of oral  
301 topotecan increased the dose-normalized  $AUC_{0-24h}$  of topotecan lactone and total topotecan 2.0-  
302 to 3.0-fold compared with control [see *Drug Interactions (7.1)*].

303 *Effect of pH-Elevating Agents:* The pharmacokinetics of oral topotecan were unchanged when  
304 coadministered with ranitidine.

### 305 **13 NONCLINICAL TOXICOLOGY**

#### 306 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

312 Topotecan given to female rats prior to mating at a dose of  $1.4 \text{ mg/m}^2$  IV (about 0.6 times the  
313 oral clinical dose on a  $\text{mg/m}^2$  basis) caused superovulation possibly related to inhibition of  
314 follicular atresia. This dose given to pregnant female rats also caused increased pre-implantation  
315 loss. Studies in dogs given  $0.4 \text{ mg/m}^2$  IV (about 0.2 times the oral clinical dose on a  $\text{mg/m}^2$   
316 basis) of topotecan daily for a month suggest that treatment may cause an increase in the  
317 incidence of multinucleated spermatogonial giant cells in the testes. Topotecan may impair  
318 fertility in women and men.

### 319 **14 CLINICAL STUDIES**

#### 320 **14.1 Small Cell Lung Cancer**

321 The efficacy of HYCAMTIN capsules was studied in 141 patients with relapsed SCLC in a  
322 randomized, controlled, open-label trial. The patients were prior responders (complete or partial)  
323 to first-line chemotherapy, were not considered candidates for standard intravenous  
324 chemotherapy, and had relapsed at least 45 days from the end of first-line chemotherapy.  
325 Seventy-one patients were randomized to HYCAMTIN capsules ( $2.3 \text{ mg/m}^2/\text{day}$  administered  
326 for 5 consecutive days repeated every 21 days) and Best Supportive Care (BSC) and 70 patients  
327 were randomized to BSC alone. The primary objective was to compare the overall survival  
328 between the treatment arms. Patients in the arm receiving HYCAMTIN capsules plus BSC  
329 received a median of 4 courses (range: 1 to 10) and maintained a median dose intensity of  
330  $3.77 \text{ mg/m}^2/\text{week}$ . The median patient age in the arm receiving HYCAMTIN capsules plus BSC  
331 and the BSC-alone treatment arm was 60 years and 58 years while the percentage of patients  
332 aged  $\geq 65$  years was 34% and 29%, respectively. The majority of patients were Caucasian  
333 (99.3%) and male (73%). Eighty percent of patients receiving HYCAMTIN capsules plus BSC  
334 previously received carboplatin or cisplatin, and 77% of patients in the BSC-alone arm received  
335 prior carboplatin or cisplatin. The arm receiving HYCAMTIN capsules plus BSC included 68%

336 of patients with extensive disease and 28% with liver metastasis. In the BSC- alone arm, 61% of  
 337 patients had extensive disease and 20% had liver metastases. Both treatment arms recruited 73%  
 338 males. In the arm receiving HYCAMTIN capsules plus BSC, 18% of patients had prior  
 339 carboplatin and 62% had prior cisplatin. In the BSC-alone arm, 26% of patients had prior  
 340 carboplatin and 51% had prior cisplatin.

341 The arm receiving HYCAMTIN capsules plus BSC showed a statistically significant  
 342 improvement in overall survival compared with the BSC-alone arm (Log-rank  $P = 0.0104$ ).  
 343 Survival results are shown in Table 3 and Figure 1.  
 344

345 **Table 4. Overall Survival in Patients With Small Cell Lung Cancer With HYCAMTIN**  
 346 **Capsules Plus BSC Compared With BSC Alone**

	Treatment Group	
	HYCAMTIN Capsules + BSC (N = 71)	BSC (N = 70)
<b>Median (months) (95% CI)</b>	6.0 (4.2, 7.3)	3.2 (2.6, 4.3)
<b>Hazard ratio (95% CI)</b>	0.64 (0.45, 0.90)	
Log-rank $P$ -value	0.0104	

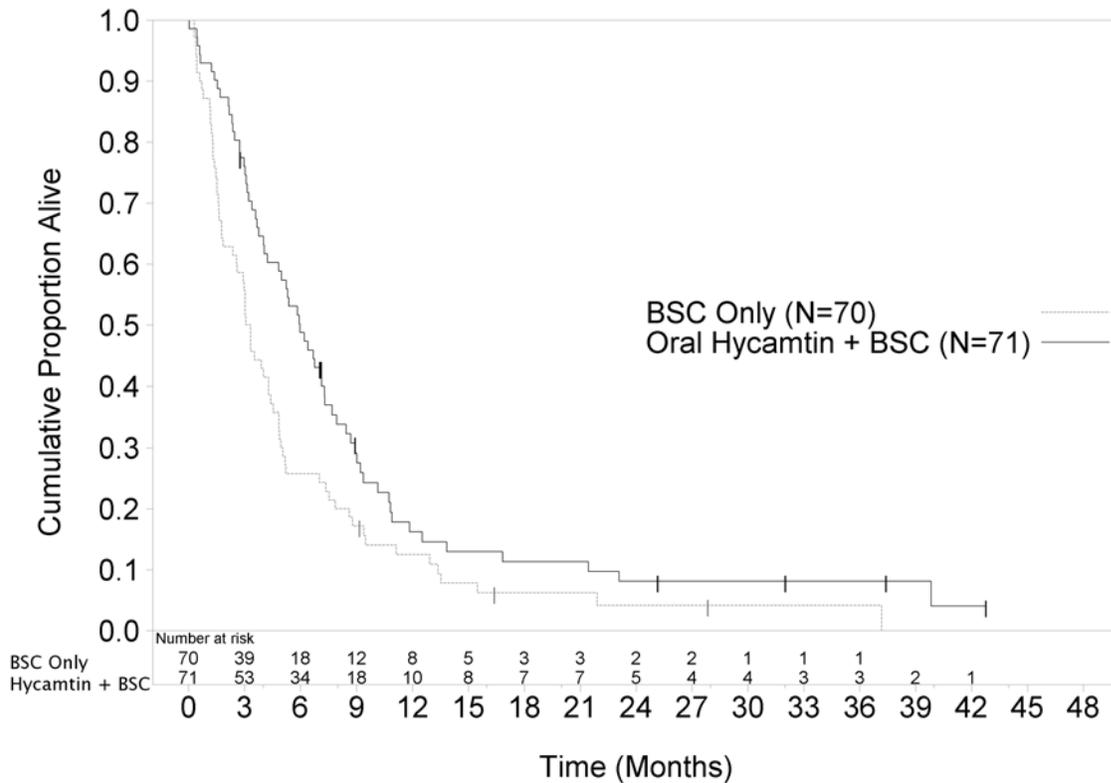
347 BSC = Best Supportive Care.

348 N = Total number of patients randomized.

349 CI = Confidence interval.

350

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



BSC: Best Supportive Care

352  
353

354 **15 REFERENCES**

355 1. “OSHA Hazardous Drugs.” OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>.

356 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

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

363 HYCAMTIN is a cytotoxic drug. Follow applicable special handling and disposable procedures.<sup>1</sup>

364 **17 PATIENT COUNSELING INFORMATION**

365 *Advise the patient to read the FDA-approved patient labeling (Patient Information)*

- 366 • **Bone Marrow Suppression**  
367 Inform patients that HYCAMTIN decreases blood cell counts such as white blood cells,  
368 platelets, and red blood cells. Instruct patients to notify their healthcare provider promptly for  
369 fever or other signs of infection such as chills, cough, or burning pain on urination. Advise  
370 patients that frequent blood tests will be performed while taking HYCAMTIN to monitor for  
371 bone marrow suppression [*see Warnings and Precautions (5.1)*].
- 372 • **Embryofetal Toxicity**  
373 Advise patients on pregnancy planning and prevention. Advise females of reproductive potential  
374 to use highly effective contraception during treatment and for 1 month following treatment with  
375 HYCAMTIN [*see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.7)*].
- 376 Advise males with a female sexual partner of reproductive potential to use effective  
377 contraception during and for 3 months after treatment [*see Nonclinical Toxicology (13.1)*].
- 378 • **Nursing Mothers**  
379 Advise patients to discontinue nursing during treatment with HYCAMTIN [*see Use in Specific*  
380 *Populations 8.1, 8.7*].
- 381 • **Infertility**  
382 Advise male and female patients of the potential risk for impaired fertility and possible family  
383 planning options.
- 384 • **Diarrhea**  
385 Inform patients that HYCAMTIN capsules cause diarrhea which may be severe and life-  
386 threatening. Instruct patients how to manage and/or prevent diarrhea and to inform their  
387 physician if severe diarrhea occurs during treatment with HYCAMTIN capsules [*see Warnings*  
388 *and Precautions (5.2)*].

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390 HYCAMTIN is a registered trademark of the GSK group of companies.  
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394 GlaxoSmithKline  
395 Research Triangle Park, NC 27709  
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## PATIENT INFORMATION

### HYCAMTIN® (hi-CAM-tin) (topotecan) capsules

**What is the most important information I should know about HYCAMTIN capsules?**

**HYCAMTIN capsules can cause serious side effects, including:**

**Decreased blood counts.** HYCAMTIN capsules affects your bone marrow and can cause a severe decrease in your blood cell counts (bone marrow suppression) including 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.** HYCAMTIN capsules can cause severe and life-threatening diarrhea that may need to be treated in 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?”** for more information about side effects.

439 **What are HYCAMTIN capsules?**

440 HYCAMTIN capsules is a prescription used to treat small cell lung cancer that has  
441 come back (relapsed).

442 HYCAMTIN capsules may be right for you if:

- 443 • your cancer responded to your first chemotherapy, and
- 444 • it has been at least 45 days after you finished your last dose of chemotherapy

445

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

447

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

449 Do not take HYCAMTIN if:

- 450 • you are allergic to topotecan. See the end of this leaflet for a complete list of  
451 ingredients in HYCAMTIN capsules.

452

453 **What should I tell my healthcare provider before taking HYCAMTIN  
454 capsules?**

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

- 456 • have kidney problems
- 457 • are pregnant or plan to become pregnant. HYCAMTIN capsules can harm your  
458 unborn baby. You should not become pregnant while you are taking HYCAMTIN  
459 capsules.
  - 460 ○ Females who can become pregnant should use effective birth control  
461 (contraception) during treatment with HYCAMTIN and for 1 month  
462 after treatment.
  - 463 ○ If you are a male and your female sexual partner is able to become  
464 pregnant, you should use effective birth control during treatment with  
465 HYCAMTIN and for 3 months after treatment.
  - 466 ○ Talk to your healthcare provider about birth control options to prevent  
467 pregnancy while you are taking HYCAMTIN.
  - 468 ○ Tell your healthcare provider right away if you or your female partner  
469 becomes pregnant while taking HYCAMTIN.
- 470 • are breastfeeding or plan to breastfeed. It is not known if HYCAMTIN passes into  
471 your breast milk. You and your healthcare provider should decide if you will take  
472 HYCAMTIN or breastfeed. You should not do both.

473

474 **Tell your healthcare provider about all the medicines you take**, including  
475 prescription and over-the-counter medicines, vitamins, and herbal supplements.  
476 Know the medicines you take. Keep a list of them to show your healthcare provider  
477 and pharmacist when you get a new medicine.

478

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

- 480 • Take HYCAMTIN capsules exactly as your healthcare provider tells you to take it.  
481 • Your healthcare provider will tell you how many HYCAMTIN capsules to take and  
482 when to take them.  
483 • Your healthcare provider may change your dose if needed.  
484 • Your healthcare provider may want you to take both 1-mg and 0.25-mg  
485 capsules together to make up your complete dose. You must be able to tell the  
486 difference between the capsules. The 1-mg capsule is a pink color and the 0.25-  
487 mg capsule is a white to yellowish-white color.  
488 • Take HYCAMTIN one time a day for 5 days in a row. This treatment will normally  
489 be repeated every 3 weeks (a treatment cycle). Your healthcare provider will  
490 decide how long you will take HYCAMTIN capsules.  
491 • Swallow HYCAMTIN capsules whole. Do not open, chew, or crush HYCAMTIN  
492 capsules.  
493 • Take HYCAMTIN with or without food.  
494 • If any of the HYCAMTIN capsules are broken or leaking, do not touch them with  
495 your bare hands. Carefully throw away (dispose of) the capsules, and then wash  
496 your hands well with soap and water.  
497 • If you get any of the contents of HYCAMTIN capsules on your skin or in your  
498 eyes, do the following:  
499     o Wash the area of skin well with soap and water right away.  
500     o Wash your eyes right away with gently flowing water for at least 15  
501 minutes.  
502     o Call your healthcare provider if you get a skin reaction or get  
503 HYCAMTIN in your eyes.  
504 • If you take too much HYCAMTIN, call your healthcare provider right away.  
505 • If you vomit after taking your HYCAMTIN, just take the next scheduled dose. Do  
506 not take another dose on the same day.

507  
508 **What are the possible side effects of HYCAMTIN capsules?**

509 **HYCAMTIN can cause serious side effects including:**

- 510 • See "What is the most important information I should know about HYCAMTIN  
511 capsules?"  
512 • **Lung problems that can cause death.** Tell your healthcare provider right  
513 away if you have **new or worse** symptoms of coughing, fever, shortness of  
514 breath, or problems breathing. Your healthcare provider may tell you to stop  
515 taking HYCAMTIN capsules.

516  
517 The most common side effects of HYCAMTIN include:

- 518 • nausea

- 519 • diarrhea
- 520 • vomiting
- 521 • hair loss
- 522 • tiredness

523  
524 HYCAMTIN may cause short-term and long-term fertility problems in females. This  
525 could affect your ability to become pregnant.

526  
527 HYCAMTIN may cause lower sperm count problems in men. This could affect your  
528 ability to father a child and cause birth defects. Talk to your healthcare provider  
529 about family planning options that might be right for you.

530  
531 Tell your healthcare provider if you have any side effect that bothers you or does  
532 not go away.

533  
534 These are not all of the possible side effects of HYCAMTIN capsules. For more  
535 information, ask your healthcare provider or pharmacist.

536  
537 Call your doctor for medical advice about side effects. You may report side effects  
538 to FDA at 1-800-FDA-1088.

- 539
- 540 **How should I store HYCAMTIN capsules?**
- 541 • Store HYCAMTIN capsules in a refrigerator between 36°F to 46°F (2°C to 8°C).
  - 542 • Keep the bottle of HYCAMTIN capsules in the carton that it comes in to protect it  
543 from light.
  - 544 • Ask your healthcare provider or pharmacist how to safely throw away any  
545 unused or expired HYCAMTIN.

546  
547 **Keep HYCAMTIN capsules and all medicines out of the reach of children.**

548  
549 **General information about HYCAMTIN capsules**

550 Medicines are sometimes prescribed for purposes other than those listed in a  
551 Patient Information leaflet. Do not use HYCAMTIN for a condition for which it was  
552 not prescribed. Do not give HYCAMTIN to other people, even if they have the same  
553 symptoms that you have. It may harm them.

554  
555 You can ask your pharmacist or healthcare provider for information about  
556 HYCAMTIN that is written for health professionals.

557  
558 For more information go to [www.gsk.com](http://www.gsk.com) or call 1-888-825-5249.

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

**Active ingredient:** topotecan hydrochloride

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

This Patient Information has been approved by the U.S. Food and Drug Administration.

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