

NDA 20-571/S-030
Literature Review Update

July 10, 2006

1 **Camptosar**[®]
2 irinotecan hydrochloride injection
3
4 For Intravenous Use Only

WARNINGS

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6 CAMPTOSAR Injection should be administered only under the supervision of a
7 physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate
8 management of complications is possible only when adequate diagnostic and treatment
9 facilities are readily available. CAMPTOSAR can induce both early and late forms of
10 diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may
11 be severe. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR)
12 may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis,
13 lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause
14 abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or
15 ameliorated by atropine (see PRECAUTIONS, General). Late diarrhea (generally
16 occurring more than 24 hours after administration of CAMPTOSAR) can be life
17 threatening since it may be prolonged and may lead to dehydration, electrolyte
18 imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients
19 with diarrhea should be carefully monitored and given fluid and electrolyte replacement
20 if they become dehydrated or antibiotic therapy if they develop ileus, fever, or severe
21 neutropenia (see WARNINGS). Administration of CAMPTOSAR should be interrupted
22 and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND
23 ADMINISTRATION).

24 Severe myelosuppression may occur (see WARNINGS).

DESCRIPTION

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27 CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic
28 agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically
29 investigated as CPT-11.

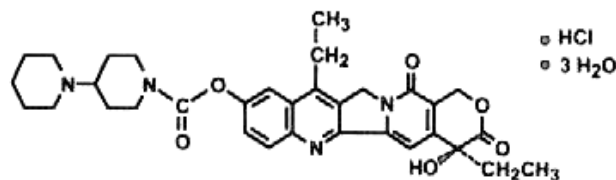
30 CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is
31 available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride
32 and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution
33 contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of
34 sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been
35 adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.
36 CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9%
37 Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is
38 5% Dextrose Injection, USP.

39 Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid
40 extract from plants such as *Camptotheca acuminata*. The chemical name is (S)-4,11-
41 diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]-
42 indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride,
43 trihydrate. Its structural formula is as follows:

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Irinotecan Hydrochloride

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48 Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the
49 empirical formula C₃₃H₃₈N₄O₆•HCl•3H₂O and a molecular weight of 677.19. It is slightly
50 soluble in water and organic solvents.

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52 CLINICAL PHARMACOLOGY

53 Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the
54 enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible
55 single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase
56 I-DNA complex and prevent religation of these single-strand breaks. Current research
57 suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage
58 produced during DNA synthesis when replication enzymes interact with the ternary
59 complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian
60 cells cannot efficiently repair these double-strand breaks.

61 Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-
62 38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate
63 bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is
64 approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I
65 purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that
66 the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the
67 plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to
68 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately
69 50% bound to plasma proteins for irinotecan (see Pharmacokinetics). The precise
70 contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan
71 and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A
72 pH-dependent equilibrium exists between the two forms such that an acid pH promotes
73 the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

74 Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of
75 rodent origin and in human carcinoma xenografts of various histological types.

76 Pharmacokinetics

77 After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations
78 decline in a multiexponential manner, with a mean terminal elimination half-life of about
79 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is
80 about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38
81 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms
82 are in equilibrium.

83 Over the recommended dose range of 50 to 350 mg/m², the AUC of irinotecan

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84 increases linearly with dose; the AUC of SN-38 increases less than proportionally with
85 dose. Maximum concentrations of the active metabolite SN-38 are generally seen within
86 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic
87 parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose
88 levels of 125 and 340 mg/m² determined in two clinical studies in patients with solid
89 tumors are summarized in Table 1:

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**Table 1. Summary of Mean (±Standard Deviation)
Irinotecan and SN-38 Pharmacokinetic
Parameters in Patients with Solid Tumors**

Dose (mg/m ²)	Irinotecan					SN-38		
	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)	V _z (L/m ²)	CL (L/h/m ²)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8 ^a ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4 ^a ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7 ^b ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0 ^b ±4.3

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C_{max} - Maximum plasma concentration
AUC₀₋₂₄ - Area under the plasma concentration-time curve from time
0 to 24 hours after the end of the 90-minute infusion
t_{1/2} - Terminal elimination half-life
V_z - Volume of distribution of terminal elimination phase
CL - Total systemic clearance
^a Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
^b Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer
collection period, these values provide a more accurate reflection of the terminal elimination half-lives
of irinotecan and SN-38.

105 Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is
106 highly bound to human plasma proteins (approximately 95% bound). The plasma protein
107 to which irinotecan and SN-38 predominantly binds is albumin.
108 *Metabolism and Excretion:* The metabolic conversion of irinotecan to the active
109 metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the
110 liver. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl
111 transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is
112 reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity
113 such as the UGT1A1*28 polymorphism. Approximately 10% of the North American
114 population is homozygous for the UGT1A1*28 allele. In a prospective study, in which
115 irinotecan was administered as a single-agent on a once-every-3-week schedule, patients
116 who were homozygous for UGT1A1*28 had a higher exposure to SN-38 than patients
117 with the wild-type UGT1A1 allele (See WARNINGS and DOSAGE AND
118 ADMINISTRATION). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in
119 cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not
120 been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-
121 38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of
122 irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours
123 following administration of irinotecan in two patients ranged from approximately 25%
124 (100 mg/m²) to 50% (300 mg/m²).

125 **Pharmacokinetics in Special Populations**

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126 *Geriatric:* In studies using the weekly schedule, the terminal half-life of irinotecan was
127 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than
128 65 years. Dose-normalized AUC₀₋₂₄ for SN-38 in patients who were at least 65 years of
129 age was 11% higher than in patients younger than 65 years. No change in the starting
130 dose is recommended for geriatric patients receiving the weekly dosage schedule of
131 irinotecan. The pharmacokinetics of irinotecan given once every 3 weeks has not
132 been studied in the geriatric population; a lower starting dose is recommended in
133 patients 70 years or older based on clinical toxicity experience with this schedule
134 (see DOSAGE AND ADMINISTRATION).

135 *Pediatric:* See **Pediatric Use** under **PRECAUTIONS**.

136 *Gender:* The pharmacokinetics of irinotecan do not appear to be influenced by gender.

137 *Race:* The influence of race on the pharmacokinetics of irinotecan has not been
138 evaluated.

139 *Hepatic Insufficiency:* Irinotecan clearance is diminished in patients with hepatic
140 dysfunction while exposure to the active metabolite SN-38 is increased relative to that in
141 patients with normal hepatic function. The magnitude of these effects is proportional to
142 the degree of liver impairment as measured by elevations in total bilirubin and
143 transaminase concentrations. However, the tolerability of irinotecan in patients with
144 hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently,
145 and no recommendations for dosing can be made. See DOSAGE AND
146 ADMINISTRATION and PRECAUTIONS: Patients at Particular Risk Sections.

147 *Renal Insufficiency:* The influence of renal insufficiency on the pharmacokinetics of
148 irinotecan has not been evaluated. Therefore, caution should be undertaken in patients
149 with impaired renal function. Irinotecan is not recommended for use in patients on
150 dialysis.

151 **Drug-Drug Interactions**

152 *5-fluorouracil (5-FU) and leucovorin (LV):* In a phase 1 clinical study involving
153 irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors,
154 the disposition of irinotecan was not substantially altered when the drugs were co-
155 administered. Although the C_{max} and AUC₀₋₂₄ of SN-38, the active metabolite, were
156 reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and
157 LV administration compared with when irinotecan was given alone, this sequence
158 of administration was used in the combination trials and is recommended (see
159 DOSAGE AND ADMINISTRATION). Formal in vivo or in vitro drug interaction
160 studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV
161 have not been conducted.

162 *Anticonvulsants:* Exposure to irinotecan and its active metabolite SN-38 is
163 substantially reduced in adult and pediatric patients concomitantly receiving the
164 CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or
165 carbamazepine. The appropriate starting dose for patients taking these
166 anticonvulsants has not been formally defined. The following drugs are also
167 CYP3A4 inducers: rifampin, rifabutin. For patients requiring anticonvulsant
168 treatment, consideration should be given to substituting non-enzyme inducing
169 anticonvulsants at least 2 weeks prior to initiation of irinotecan therapy.

170 Dexamethasone does not appear to alter the pharmacokinetics of irinotecan.

171 *St. John's Wort:* St. John's Wort is an inducer of CYP3A4 enzymes. Exposure to

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172 the active metabolite SN-38 is reduced in patients receiving concomitant St.
173 John's Wort. St. John's Wort should be discontinued at least 2 weeks prior to the
174 first cycle of irinotecan, and St. John's Wort is contraindicated during irinotecan
175 therapy.

176 *Ketoconazole*: Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients
177 receiving concomitant ketoconazole have increased exposure to irinotecan and its
178 active metabolite SN-38. Patients should discontinue ketoconazole at least 1 week
179 prior to starting irinotecan therapy and ketoconazole is contraindicated during
180 irinotecan therapy.

181 *Neuromuscular blocking agents*. Interaction between irinotecan and neuromuscular
182 blocking agents cannot be ruled out. Irinotecan has anticholinesterase activity which
183 may prolong the neuromuscular blocking effects of suxamethonium and the
184 neuromuscular blockade of non-depolarizing drugs may be antagonized.

185 *Atazanavir sulfate*: Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1
186 inhibitor has the potential to increase systemic exposure of SN-38, the active metabolite
187 of irinotecan. Physicians should take this into consideration when co-administering these
188 drugs.

189 **CLINICAL STUDIES**

190 Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU)
191 and leucovorin (LV) and as a single agent (see DOSAGE AND ADMINISTRATION).
192 When given as a component of combination-agent treatment, irinotecan was either given
193 with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional
194 5-FU/LV. Weekly and a once-every-3-week dosage schedules were used for the single-
195 agent irinotecan studies. Clinical studies of combination and single-agent use are
196 described below.

197 **First-Line Therapy in Combination with 5-FU/LV for the Treatment of** 198 **Metastatic Colorectal Cancer**

199 Two phase 3, randomized, controlled, multinational clinical trials support the use of
200 CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of
201 the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were
202 compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-
203 FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given
204 daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly
205 schedule was also included. Study 2 evaluated two different methods of administering
206 infusional 5-FU/LV, with or without irinotecan. In both studies, concomitant medications
207 such as antiemetics, atropine, and loperamide were given to patients for prophylaxis
208 and/or management of symptoms from treatment. In Study 2, a 7-day course of
209 fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for
210 greater than 24 hours despite loperamide or if they developed a fever in addition to
211 diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who
212 developed an absolute neutrophil count (ANC) $<500/\text{mm}^3$, even in the absence of fever or
213 diarrhea. Patients in both studies also received treatment with intravenous antibiotics if
214 they had persistent diarrhea or fever or if ileus developed.

215 In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant
216 improvements in objective tumor response rates, time to tumor progression, and survival
217 when compared with 5-FU/LV alone. These differences in survival were observed in

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218 spite of second-line therapy in a majority of patients on both arms, including crossover to
219 irinotecan-containing regimens in the control arm. Patient characteristics and major
220 efficacy results are shown in Table 2.
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Table 2. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 q 6 weeks	Bolus 5-FU/LV daily x 5 q 4 weeks	Irinotecan weekly x 4 q 6 weeks	Irinotecan + Infusional 5-FU/LV	Infusional 5-FU/LV
Number of Patients	231	226	226	198	187
Demographics and Treatment Administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance Status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary Tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median Time from Diagnosis to Randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior Adjuvant 5-FU Therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median Duration of Study Treatment ^a (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%) ^a					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed Objective Tumor Response Rate ^b (%)	39 (p<0.0001) ^c	21	18	35 (p<0.005) ^c	22
Median Time to Tumor Progression ^d (months)	7.0 (p=0.004) ^d	4.3	4.2	6.7 (p<0.001) ^d	4.4
Median Survival (months)	14.8 (p<0.05) ^d	12.6	12.0	17.4 (p<0.05) ^d	14.1

^a Study 1: N=225 (irinotecan/5-FU/LV),N=219 (5-FU/LV),N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV),N=186 (5-FU/LV)

^b Confirmed ≥ 4 to 6 weeks after first evidence of objective response

^c Chi-square test

^d Log-rank test

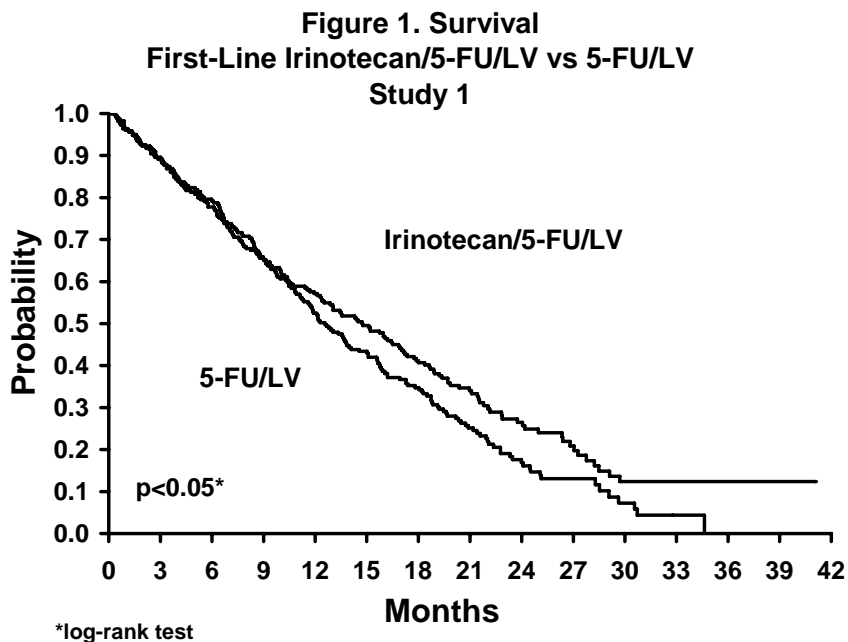
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Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.



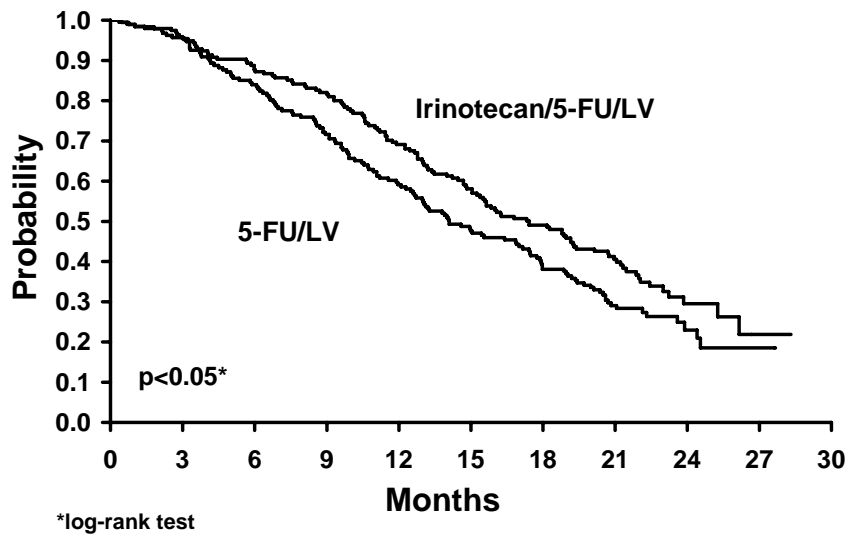
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Figure 2. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 2



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266 **Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer**
267 **After 5-FU-Based Treatment**

268 ***Weekly Dosage Schedule***

269 Data from three open-label, single-agent, clinical studies, involving a total of 304
270 patients in 59 centers, support the use of CAMPTOSAR in the treatment of
271 patients with metastatic cancer of the colon or rectum that has recurred or progressed
272 following treatment with 5-FU-based therapy. These studies were designed to
273 evaluate tumor response rate and do not provide information on actual clinical
274 benefit, such as effects on survival and disease-related symptoms. In each study,
275 CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-
276 minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest
277 period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m²,
278 but the 150-mg/m² dose was poorly tolerated (due to unacceptably high rates of grade 4
279 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was conducted
280 by a single investigator at several regional hospitals. Study 2 was a multicenter study
281 conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in
282 Study 2 received a starting dose of 125 mg/m². Study 3 was a multicenter study that
283 enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m²
284 but was reduced to 100 mg/m² because the toxicity seen at the 125-mg/m² dose was
285 perceived to be greater than that seen in previous studies. All patients in these studies
286 had metastatic colorectal cancer, and the majority had disease that recurred or
287 progressed following a 5-FU-based regimen administered for metastatic disease. The
288 results of the individual studies are shown in Table 3.
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Table 3. Weekly Dosage Schedule: Study Results

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Starting Dose (mg/m ² /wk x 4)	125 ^a	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤ 6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity ^b (median %)	74	67	73	81
Efficacy				
Confirmed Objective Response Rate (%) ^c (95% CI)	21 (9.3 - 32.3)	13 (6.3 - 20.4)	14 (5.5 - 22.6)	9 (3.3 - 14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

^a Nine patients received 150 mg/m² as a starting dose; two (22.2%) responded to CAMPTOSAR.

^b Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m²/wk corresponding with 150, 125, and 100 mg/m² starting doses, respectively.

^c Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

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299 In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304
300 patients began therapy at the recommended starting dose of 125 mg/m². Among these
301 193 patients, 2 complete and 27 partial responses were observed, for an overall
302 response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting
303 dose. A considerably lower response rate was seen with a starting dose of 100 mg/m².
304 The majority of responses were observed within the first two cycles of therapy, but
305 responses did occur in later cycles of treatment (one response was observed after the
306 eighth cycle). The median response duration for patients beginning therapy at 125
307 mg/m² was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the
308 three studies, response rates to CAMPTOSAR were similar in males and females and
309 among patients older and younger than 65 years. Rates were also similar in patients with
310 cancer of the colon or cancer of the rectum and in patients with single and multiple
311 metastatic sites. The response rate was 18.5% in patients with a performance status of 0
312 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance
313 status of 3 or 4 have not been studied. Over half of the patients responding to
314 CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous
315 irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as
316 those who had not previously received irradiation.

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318 ***Once-Every-3-Week Dosage Schedule***

319 *Single-Arm Studies:* Data from an open-label, single-agent, single-arm, multicenter,
320 clinical study involving a total of 132 patients support a once every-3-week dosage
321 schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or
322 rectum that recurred or progressed following treatment with 5-FU. Patients received a
323 starting dose of 350 mg/m² given by 30-minute intravenous infusion once every 3
324 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat
325 response rate was 12.1% (95% CI, 7.0% to 18.1%).

326 *Randomized Trials:* Two multicenter, randomized, clinical studies further support the use
327 of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic
328 colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy.
329 In the first study, second-line irinotecan therapy plus best supportive care was compared
330 with best supportive care alone. In the second study, second-line irinotecan therapy was
331 compared with infusional 5-FU-based therapy. In both studies, irinotecan was
332 administered intravenously at a starting dose of 350 mg/m² over 90 minutes once every 3
333 weeks. The starting dose was 300 mg/m² for patients who were 70 years and older or
334 who had a performance status of 2. The highest total dose permitted was 700 mg. Dose
335 reductions and/or administration delays were permitted in the event of severe
336 hematologic and/or nonhematologic toxicities while on treatment. Best supportive care
337 was provided to patients in both arms of Study 1 and included antibiotics, analgesics,
338 corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as
339 clinically indicated. In both studies, concomitant medications such as antiemetics,
340 atropine, and loperamide were given to patients for prophylaxis and/or management of
341 symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite
342 loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients
343 in the control arm of the second study received one of the following 5-FU regimens: (1)

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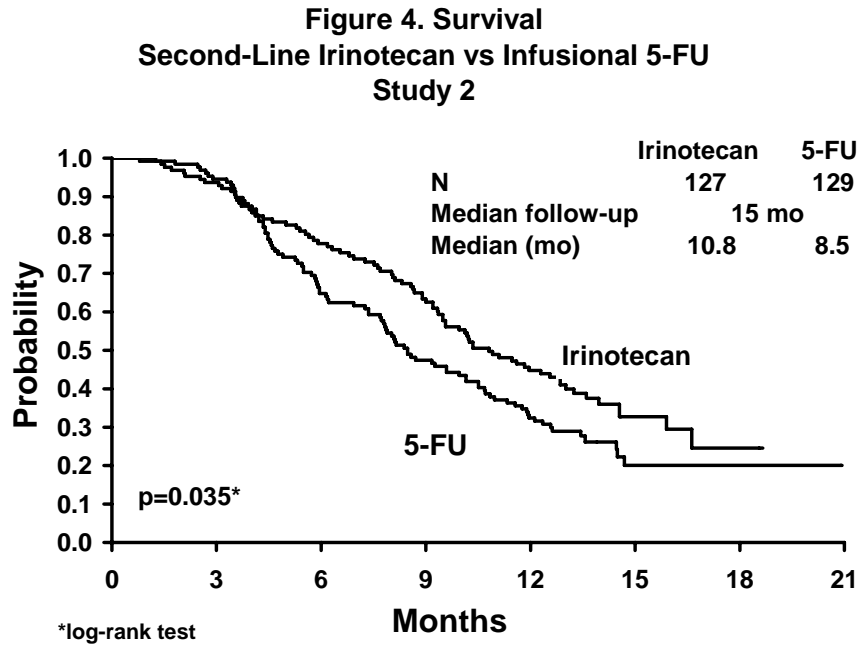
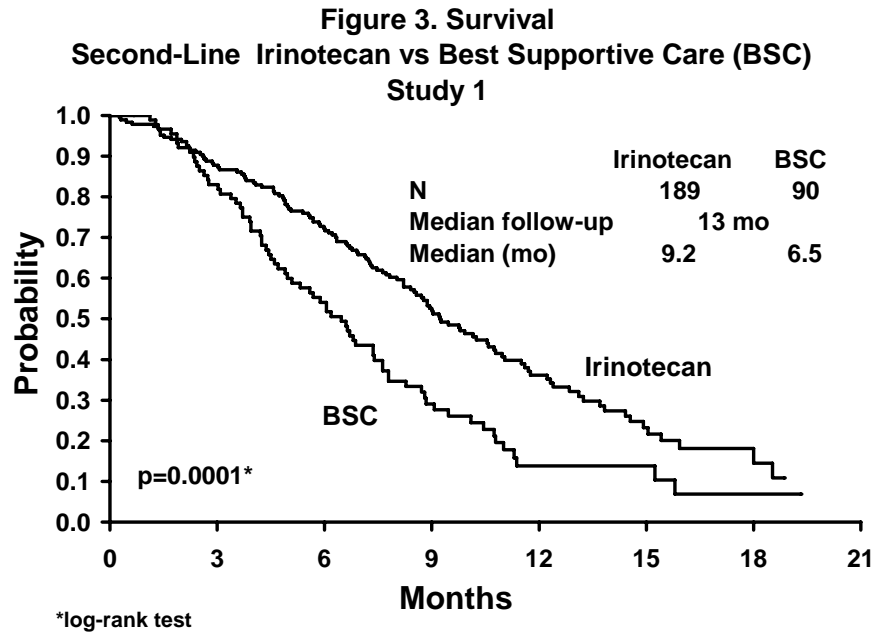
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344 LV, 200 mg/m² IV over 2 hours; followed by 5-FU, 400 mg/m² IV bolus; followed by
345 5-FU, 600 mg/m² continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks;
346 (2) 5-FU, 250 to 300 mg/m²/day protracted continuous IV infusion until toxicity; (3) 5-
347 FU, 2.6 to 3 g/m² IV over 24 hours every week for 6 weeks with or without LV, 20 to
348 500 mg/m²/day every week IV for 6 weeks with 2-week rest between cycles. Patients
349 were to be followed every 3 to 6 weeks for 1 year.

350 A total of 535 patients were randomized in the two studies at 94 centers. The primary
351 endpoint in both studies was survival. The studies demonstrated a significant overall
352 survival advantage for irinotecan compared with best supportive care (p=0.0001) and
353 infusional 5-FU-based therapy (p=0.035) as shown in Figures 3 and 4. In Study 1, median
354 survival for patients treated with irinotecan was 9.2 months compared with 6.5 months
355 for patients receiving best supportive care. In Study 2, median survival for patients
356 treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving
357 infusional 5-FU-based therapy. Multiple regression analyses determined that patients'
358 baseline characteristics also had a significant effect on survival. When adjusted for
359 performance status and other baseline prognostic factors, survival among patients treated
360 with irinotecan remained significantly longer than in the control populations (p=0.001 for
361 Study 1 and p=0.017 for Study 2). Measurements of pain, performance status, and weight
362 loss were collected prospectively in the two studies; however, the plan for the analysis of
363 these data was defined retrospectively. When comparing irinotecan with best supportive
364 care in Study 1, this analysis showed a statistically significant advantage for irinotecan,
365 with longer time to development of pain (6.9 months versus 2.0 months), time to
366 performance status deterioration (5.7 months versus 3.3 months), and time to > 5%
367 weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with
368 a baseline performance status of 1 or 2 showed an improvement in performance status
369 when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive
370 care (p=0.002). Because of the inclusion of patients with non-measurable disease, intent-
371 to-treat response rates could not be assessed.

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373 In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the
374 start of each cycle of therapy, patients completed a questionnaire consisting of 30
375 questions, such as “Did pain interfere with daily activities?” (1 = Not at All, to 4 = Very
376 Much) and “Do you have any trouble taking a long walk?” (Yes or No). The answers
377 from the 30 questions were converted into 15 subscales, that were scored from 0 to 100,
378 and the global health status subscale that was derived from two questions about the
379 patient’s sense of general well being in the past week. In addition to the global health
380 status subscale, there were five functional (i.e., cognitive, emotional, social, physical,
381 role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia,
382 constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results
383 as summarized in Table 5 are based on patients’ worst post-baseline scores. In Study 1, a
384 multivariate analysis and univariate analyses of the individual subscales were performed
385 and corrected for multivariate testing. Patients receiving irinotecan reported significantly
386 better results for the global health status, on two of five functional subscales, and on four
387 of nine symptom subscales. As expected, patients receiving irinotecan noted significantly
388 more diarrhea than those receiving best supportive care. In Study 2, the multivariate
389 analysis on all 15 subscales did not indicate a statistically significant difference between
390 irinotecan and infusional 5-FU.

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Table 4. Once-Every-3-Week Dosage Schedule: Study Results

	Study 1		Study 2	
	Irinotecan	BSC ^a	Irinotecan	5-FU
Number of Patients	189	90	127	129
Demographics and Treatment Administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median Age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance Status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary Tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU Therapy (%)				
For Metastatic Disease	70	63	58	68
As Adjuvant Treatment	30	37	42	32
Prior Irradiation (%)	26	27	18	20
Duration of Study Treatment (median, months) (Log-rank test)	4.1	--	4.2 (p=0.02)	2.8
Relative Dose Intensity (median %) ^b	94	--	95	81-99
Survival				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

^a BSC = best supportive care

^b Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m²/wk corresponding with 350 and 300 mg/m² starting doses, respectively.

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Table 5. EORTC QLQ-C30: Mean Worst Post-Baseline Score^a

QLQ-C30 Subscale	Study 1			Study 2		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global Health Status	47	37	0.03	53	52	0.9
Functional Scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite Loss	37	57	0.0007	35	38	0.9
Pain Assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial Impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

^aFor the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

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INDICATIONS AND USAGE

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CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. CAMPTOSAR is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

400

CONTRAINDICATIONS

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CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

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WARNINGS

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General

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Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with the “Mayo Clinic” regimen of 5-FU/LV (administration for 4-5 consecutive days every 4 weeks) because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended (see DOSAGE AND ADMINISTRATION, Table 10).

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In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

414

Diarrhea

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CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that

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420 can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be
421 prevented or ameliorated by administration of atropine (see PRECAUTIONS, General,
422 for dosing recommendations for atropine).

423 Late diarrhea (generally occurring more than 24 hours after administration of
424 CAMPTOSAR) can be life threatening since it may be prolonged and may lead to
425 dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly
426 with loperamide (see PRECAUTIONS, Information for Patients, for dosing
427 recommendations for loperamide). Patients with diarrhea should be carefully monitored,
428 should be given fluid and electrolyte replacement if they become dehydrated, and should
429 be given antibiotic support if they develop ileus, fever, or severe neutropenia. After the
430 first treatment, subsequent weekly chemotherapy treatments should be delayed in patients
431 until return of pretreatment bowel function for at least 24 hours without need for anti-
432 diarrhea medication. If grade 2, 3, or 4 late diarrhea occurs subsequent doses of
433 CAMPTOSAR should be decreased within the current cycle (see DOSAGE AND
434 ADMINISTRATION).

435 **Neutropenia**

436 Deaths due to sepsis following severe neutropenia have been reported in patients treated
437 with CAMPTOSAR. Neutropenic complications should be managed promptly with
438 antibiotic support (see PRECAUTIONS). Therapy with CAMPTOSAR should be
439 temporarily omitted during a cycle of therapy if neutropenic fever occurs or if the
440 absolute neutrophil count drops $<1000/\text{mm}^3$. After the patient recovers to an absolute
441 neutrophil count $\geq 1000/\text{mm}^3$, subsequent doses of CAMPTOSAR should be reduced
442 depending upon the level of neutropenia observed (see DOSAGE AND
443 ADMINISTRATION).

444 Routine administration of a colony-stimulating factor (CSF) is not necessary, but
445 physicians may wish to consider CSF use in individual patients experiencing significant
446 neutropenia.

447 **Patients with Reduced UGT1A1 Activity**

448 Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for
449 neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose
450 should be considered for patients known to be homozygous for the UGT1A1*28 allele
451 (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one
452 variant allele and one wild-type allele which results in intermediate UGT1A1 activity)
453 may be at increased risk for neutropenia; however, clinical results have been variable and
454 such patients have been shown to tolerate normal starting doses.

455 **Hypersensitivity**

456 Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions
457 have been observed.

458 **Colitis/Ileus**

459 Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been
460 observed. Patients experiencing ileus should receive prompt antibiotic support (see
461 PRECAUTIONS).

462 **Renal Impairment/Renal Failure**

463 Rare cases of renal impairment and acute renal failure have been identified, usually in
464 patients who became volume depleted from severe vomiting and/or diarrhea.

465 **Thromboembolism**

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466 Thromboembolic events have been observed in patients receiving irinotecan-containing
467 regimens; the specific cause of these events has not been determined.

468 **Pregnancy**

469 CAMPTOSAR may cause fetal harm when administered to a pregnant woman.
470 Radioactivity related to ¹⁴C-irinotecan crosses the placenta of rats following intravenous
471 administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and
472 AUC about 3 and 0.5 times, respectively, the corresponding values in patients
473 administered 125 mg/m²). Administration of 6 mg/kg/day intravenous irinotecan to rats
474 (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times,
475 respectively, the corresponding values in patients administered 125 mg/m²) and rabbits
476 (about one-half the recommended human weekly starting dose on a mg/m² basis) during
477 the period of organogenesis, is embryotoxic as characterized by increased post-
478 implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in
479 rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan
480 C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients
481 administered 125 mg/m²) and in rabbits at 6.0 mg/kg/day (about one-half the
482 recommended human weekly starting dose on a mg/m² basis). Teratogenic effects
483 included a variety of external, visceral, and skeletal abnormalities. Irinotecan
484 administered to rat dams for the period following organogenesis through weaning at
485 doses of 6 mg/kg/day caused decreased learning ability and decreased female body
486 weights in the offspring. There are no adequate and well-controlled studies of irinotecan
487 in pregnant women. If the drug is used during pregnancy, or if the patient becomes
488 pregnant while receiving this drug, the patient should be apprised of the potential hazard
489 to the fetus. Women of childbearing potential should be advised to avoid becoming
490 pregnant while receiving treatment with CAMPTOSAR.

491

492 **PRECAUTIONS**

493 **General**

494 *Care of Intravenous Site:* CAMPTOSAR Injection is administered by intravenous
495 infusion. Care should be taken to avoid extravasation, and the infusion site should be
496 monitored for signs of inflammation. Should extravasation occur, flushing the site with
497 sterile water and applications of ice are recommended.

498 *Premedication with Antiemetics:* Irinotecan is emetogenic. It is recommended that patients
499 receive premedication with antiemetic agents. In clinical studies of the weekly dosage
500 schedule, the majority of patients received 10 mg of dexamethasone given in conjunction
501 with another type of antiemetic agent, such as a 5-HT³ blocker (e.g., ondansetron or
502 granisetron). Antiemetic agents should be given on the day of treatment, starting at least
503 30 minutes before administration of CAMPTOSAR. Physicians should also consider
504 providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent
505 use as needed.

506 *Treatment of Cholinergic Symptoms:* Prophylactic or therapeutic administration of 0.25 to
507 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically
508 contraindicated) in patients experiencing rhinitis, increased salivation, miosis,
509 lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or
510 shortly after infusion of CAMPTOSAR). These symptoms are expected to occur more
511 frequently with higher irinotecan doses.

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512 *Patients at Particular Risk:* In patients receiving either irinotecan/5-FU/LV or 5-FU/LV
513 in the clinical trials, higher rates of hospitalization, neutropenic fever,
514 thromboembolism, first-cycle treatment discontinuation, and early deaths were observed
515 in patients with a baseline performance status of 2 than in patients with a baseline
516 performance status of 0 or 1. Patients who had previously received pelvic/abdominal
517 radiation and elderly patients with comorbid conditions should be closely monitored.

518 The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been
519 established. In clinical trials of either dosing schedule, irinotecan was not administered to
520 patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of
521 normal if no liver metastasis, or transaminase >5 times the upper limit of normal with
522 liver metastasis. In clinical trials of the weekly dosage schedule, patients with modestly
523 elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly
524 greater likelihood of experiencing first-cycle, grade 3 or 4 neutropenia than those with
525 bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226];
526 $p < 0.001$). Also see CLINICAL PHARMACOLOGY: Pharmacokinetics in Special
527 Populations: *Hepatic Insufficiency*. Patients with deficient glucuronidation of bilirubin,
528 such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when
529 receiving therapy with CAMPTOSAR.

530 Ketoconazole, enzyme-inducing anticonvulsants and St. John's Wort are known to have
531 drug-drug interactions with irinotecan therapy. (See Drug-Drug Interactions sub-section
532 under CLINICAL PHARMACOLOGY)

533 Irinotecan commonly causes neutropenia, leucopenia, and anemia, any of which may be
534 severe and therefore should not be used in patients with severe bone marrow failure.¹
535 Patients must not be treated with irinotecan until resolution of the bowel obstruction.
536 Patients with hereditary fructose intolerance should not be given CAMPTOSAR, as this
537 product contains sorbitol.

538 **Information for Patients**

540 Patients and patients' caregivers should be informed of the expected toxic effects of
541 CAMPTOSAR, particularly of its gastrointestinal complications, such as nausea,
542 vomiting, abdominal cramping, diarrhea, and infection. Each patient should be instructed
543 to have loperamide readily available and to begin treatment for late diarrhea (generally
544 occurring more than 24 hours after administration of CAMPTOSAR) at the first episode
545 of poorly formed or loose stools or the earliest onset of bowel movements more frequent
546 than normally expected for the patient. One dosage regimen for loperamide used in
547 clinical trials consisted of the following (Note: This dosage regimen exceeds the usual
548 dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and
549 then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours.
550 Loperamide is not recommended to be used for more than 48 consecutive hours at these
551 doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg
552 of loperamide every 4 hours. Premedication with loperamide is not recommended. The
553 use of drugs with laxative properties should be avoided because of the potential for
554 exacerbation of diarrhea. Patients should be advised to contact their physician to discuss
555 any laxative use.

556 Patients should be instructed to contact their physician or nurse if any of the following
557 occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of

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558 dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by
559 mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours;
560 or fever or evidence of infection.

561 Patients should be warned about the potential for dizziness or visual disturbances which
562 may occur within 24 hours following the administration of CAMPTOSAR, and advised
563 not to drive or operate machinery if these symptoms occur.

564 Patients should be alerted to the possibility of alopecia.

565 **Laboratory Tests**

566 Careful monitoring of the white blood cell count with differential, hemoglobin, and
567 platelet count is recommended before each dose of CAMPTOSAR.

568 **Drug Interactions**

569 The adverse effects of CAMPTOSAR, such as myelosuppression and diarrhea, would
570 be expected to be exacerbated by other antineoplastic agents having similar adverse
571 effects.

572 Patients who have previously received pelvic/ abdominal irradiation are at increased
573 risk of severe myelosuppression following the administration of CAMPTOSAR. The
574 concurrent administration of CAMPTOSAR with irradiation has not been adequately
575 studied and is not recommended.

576 Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is
577 possible that the administration of dexamethasone as antiemetic prophylaxis may have
578 enhanced the likelihood of this effect. However, serious opportunistic infections have not
579 been observed, and no complications have specifically been attributed to
580 lymphocytopenia.

581 Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually,
582 this has been observed in patients with a history of diabetes mellitus or evidence of
583 glucose intolerance prior to administration of CAMPTOSAR. It is probable that
584 dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some
585 patients.

586 The incidence of akathisia in clinical trials of the weekly dosage schedule was greater
587 (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as
588 CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients).
589 The 8.5% incidence of akathisia, however, is within the range reported for use of
590 prochlorperazine when given as a premedication for other chemotherapies.

591 It would be expected that laxative use during therapy with CAMPTOSAR would
592 worsen the incidence or severity of diarrhea, but this has not been studied.

593 In view of the potential risk of dehydration secondary to vomiting and/or diarrhea
594 induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing
595 with CAMPTOSAR and, certainly, during periods of active vomiting or diarrhea.

596

597 **Drug-Laboratory Test Interactions**

598 There are no known interactions between CAMPTOSAR and laboratory tests.

599 **Carcinogenesis, Mutagenesis & Impairment of Fertility**

600 Long-term carcinogenicity studies with irinotecan were not conducted. Rats were,
601 however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per
602 week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max}
603 and AUC that were about 7.0 times and 1.3 times the respective values in patients

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604 administered 125 mg/m² weekly) and were then allowed to recover for 91 weeks. Under
605 these conditions, there was a significant linear trend with dose for the incidence of
606 combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.
607 Neither irinotecan nor SN-38 was mutagenic in the in vitro Ames assay. Irinotecan was
608 clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in
609 vivo (micronucleus test in mice). No significant adverse effects on fertility and general
610 reproductive performance were observed after intravenous administration of irinotecan in
611 doses of up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive
612 organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg
613 (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times,
614 respectively, the corresponding values in patients administered 125 mg/m² weekly) and
615 dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about
616 one-half and 1/15th, respectively, the corresponding values in patients administered 125
617 mg/m² weekly).

618 **Pregnancy**

619 Pregnancy Category D—see WARNINGS.

620 **Nursing Mothers**

621 Radioactivity appeared in rat milk within 5 minutes of intravenous administration of
622 radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration
623 relative to plasma concentrations. Because many drugs are excreted in human milk and
624 because of the potential for serious adverse reactions in nursing infants, it is
625 recommended that nursing be discontinued when receiving therapy with
626 CAMPTOSAR.

627 **Pediatric Use**

628 The effectiveness of irinotecan in pediatric patients has not been established. Results
629 from two open-label, single arm studies were evaluated. One hundred and seventy
630 children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/
631 m² of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4
632 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by
633 fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients.
634 This adverse event profile was comparable to that observed in adults. In the second
635 phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m² of
636 irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent
637 therapy was followed by multimodal therapy. Accrual to the single agent irinotecan
638 phase was halted due to the high rate (28.6%) of progressive disease and the early deaths
639 (14%). The adverse event profile was different in this study from that observed in adults;
640 the most significant grade 3 or 4 adverse events were dehydration experienced by 6
641 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and
642 hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5
643 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

644 Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric
645 solid-tumor trials at dose levels of 50 mg/m² (60-min infusion, n=48) and 125 mg/m²
646 (90-min infusion, n=6). Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m² for the
647 50mg/m² dose and 16.2 ± 4.6 L/h/m² for the 125 mg/m² dose, which is comparable to that
648 in adults. Dose-normalized SN-38 AUC values were comparable between adults and
649 children. Minimal accumulation of irinotecan and SN-38 was observed in children on

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650 daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

651 **Geriatric Use**

652 Patients greater than 65 years of age should be closely monitored because of a greater
653 risk of late diarrhea in this population (see CLINICAL PHARMACOLOGY,
654 Pharmacokinetics in Special Populations and ADVERSE REACTIONS, Overview
655 of Adverse Events). The starting dose of CAMPTOSAR in patients 70 years and
656 older for the once-every-3-week-dosage schedule should be 300 mg/m² (see
657 DOSAGE AND ADMINISTRATION).

658 **ADVERSE REACTIONS**

659 **First-Line Combination Therapy**

660 A total of 955 patients with metastatic colorectal cancer received the recommended
661 regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or
662 irinotecan alone. In the two phase 3 studies, 370 patients received
663 irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223
664 patients received irinotecan alone. (See Table 10 in DOSAGE AND
665 ADMINISTRATION for recommended combination-agent regimens.)
666

667 In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%)
668 received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone,
669 and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred
670 in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2
671 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1
672 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2
673 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Deaths from any
674 cause within 60 days of first study treatment were reported for 15 (6.7%) patients who
675 received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-
676 FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations
677 due to adverse events were reported for 17 (7.6%) patients who received irinotecan in
678 combination with 5FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26
679 (11.7%) patients who received irinotecan alone.

680 In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%)
681 received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV
682 alone. There was one potentially treatment-related death, which occurred in a patient
683 who received irinotecan in combination with 5-FU/LV (0.7%, neutropenic sepsis).
684 Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%)
685 patients who received irinotecan in combination with 5-FU/LV and 2 (1.4%) patients
686 who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9
687 (6.2%) patients who received irinotecan in combination with 5FU/LV and 1 (0.7%)
688 patient who received 5-FU/LV alone.

689 The most clinically significant adverse events for patients receiving irinotecan-based
690 therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically
691 significant adverse events for patients receiving 5-FU/LV therapy were diarrhea,
692 neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia,
693 neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were
694 observed less often with weekly irinotecan/5-FU/LV than with monthly administration
695 of 5-FU/LV.

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696 Tables 6 and 7 list the clinically relevant adverse events reported in Studies 1 and 2,
697 respectively.

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698

Table 6. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies^a

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly x 4 q 6 weeks N=225		Bolus 5-FU/LV daily x 5 q 4 weeks N=219		Irinotecan weekly x 4 q 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea						
late	84.9	22.7	69.4	13.2	83.0	31.0
grade 3	--	15.1	--	5.9	--	18.4
grade 4	--	7.6	--	7.3	--	12.6
early	45.8	4.9	31.5	1.4	43.0	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24.0	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	--	1.8	--	0	--	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
↑ Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia ^b	43.1	--	26.5	--	46.1	--
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR						
Vasodilatation	9.3	0.9	5.0	0	9.0	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic events ^c	9.3	--	11.4	--	5.4	--

^aSeverity of adverse events based on NCI CTC (version 1.0)

^bComplete hair loss = Grade 2

^cIncludes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

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Table 7. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies^a

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV infusional d 1&2 q 2 weeks N= 145		5-FU/LV infusional d 1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea				
late	72.4	14.4	44.8	6.3
grade 3	--	10.3	--	4.2
grade 4	--	4.1	--	2.1
Cholinergic syndrome ^b	28.3	1.4	0.7	0
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	28.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	--	36.4	--	12.7
grade 4	--	9.8	--	0.7
Leukopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.9	2.1
Neutropenic fever	--	3.4	--	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	--	2.1	--	0
BODY AS A WHOLE				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC & NUTRITIONAL				
↑ Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia ^c	56.6	--	16.8	--
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0
CARDIOVASCULAR				
Hypotension	3.4	1.4	0.7	0
Thromboembolic events ^d	11.7	--	5.6	--

^a Severity of adverse events based on NCI CTC (version 1.0)

^b Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan)

^c Complete hair loss = Grade 2

^d Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

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701 **Second-Line Single-Agent Therapy**

702 ***Weekly Dosage Schedule***

703 In three clinical studies evaluating the weekly dosage schedule, 304 patients with
704 metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-
705 FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within
706 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the
707 deaths were potentially drug-related. These five patients experienced a constellation of
708 medical events that included known effects of CAMPTOSAR. One of these patients
709 died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other
710 patients; these patients recovered with supportive care.

711 One hundred nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times
712 because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be
713 related to administration of CAMPTOSAR. The primary reasons for drug-related
714 hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%);
715 neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or
716 vomiting (4.9%).

717 Adjustments in the dose of CAMPTOSAR were made during the cycle of treatment and
718 for subsequent cycles based on individual patient tolerance. The first dose of at least one
719 cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the
720 125-mg/m² starting dose. Within-cycle dose reductions were required for 32% of the
721 cycles initiated at the 125-mg/m² dose level. The most common reasons for dose
722 reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients
723 discontinued treatment with CAMPTOSAR because of adverse events. The adverse
724 events in Table 8 are based on the experience of the 304 patients enrolled in the three
725 studies described in the CLINICAL STUDIES, Studies Evaluating the Weekly Dosage
726 Schedule, section.

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Table 8. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum^a

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late) ^b	88	31
7-9 stools/day (grade 3)	—	(16)
≥10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early) ^c	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm ³ (grade 3)	—	(15)
<500/mm ³ (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor infection ^d	14	0
Edema	10	1
Abdominal enlargement	10	0
METABOLIC & NUTRITIONAL		
↓ Body weight	30	1
Dehydration	15	4
↑ Alkaline phosphatase	13	4
↑ SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA ^e
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
↑ Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (flushing)	11	0

^a Severity of adverse events based on NCI CTC (version 1.0)

^b Occurring > 24 hours after administration of CAMPTOSAR

^c Occurring ≤24 hours after administration of CAMPTOSAR

^d Primarily upper respiratory infections

^e Not applicable; complete hair loss = NCI grade 2

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730 ***Once-Every-3-Week Dosage Schedule***

731 A total of 535 patients with metastatic colorectal cancer whose disease had recurred or
732 progressed following prior 5-FU therapy participated in the two phase 3 studies: 316
733 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven
734 (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases
735 (1%, 3/316), the deaths were potentially related to irinotecan treatment and were
736 attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One
737 (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was
738 attributed to grade 4 diarrhea.

739 Hospitalizations due to serious adverse events (whether or not related to study
740 treatment) occurred at least once in 60% (188/316) of patients who received irinotecan,
741 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-
742 based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-
743 FU-based therapy discontinued treatment due to adverse events.

744 Of the 316 patients treated with irinotecan, the most clinically significant adverse
745 events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting
746 (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 9 lists the grade 3
747 and 4 adverse events reported in the patients enrolled to all treatment arms of the two
748 studies described in the CLINICAL STUDIES, Studies Evaluating the Once-Every-3-
749 Week Dosage Schedule, section.

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**Table 9. Percent Of Patients Experiencing Grade 3 & 4 Adverse Events
In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy^a**

Adverse Event	Study 1		Study 2	
	Irinotecan N=189	BSC ^b N=90	Irinotecan N=127	5-FU N=129
TOTAL Grade 3/4 Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC & NUTRITIONAL				
Hepatic ^c	9	7	9	6
DERMATOLOGIC				
Hand & foot syndrome	0	0	0	5
Cutaneous signs ^d	2	0	1	3
RESPIRATORY^e	10	8	5	7
NEUROLOGIC^f	12	13	9	4
CARDIOVASCULAR^g	9	3	4	2
OTHER^h	32	28	12	14

^a Severity of adverse events based on NCI CTC (version 1.0)

^b BSC = best supportive care

^c Hepatic includes events such as ascites and jaundice

^d Cutaneous signs include events such as rash

^e Respiratory includes events such as dyspnea and cough

^f Neurologic includes events such as somnolence

^g Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction

^h Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

751

752 **Overview of Adverse Events**

753 *Gastrointestinal:* Nausea, vomiting, and diarrhea are common adverse events following
754 treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting
755 usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies
756 testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea
757 was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage
758 schedule, the median time to onset of late diarrhea was 11 days following
759 administration of CAMPTOSAR. For patients starting treatment at the 125-mg/m²
760 weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those

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761 patients treated at the 125-mg/m² weekly dose who experienced grade 3 or 4 late
762 diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency
763 of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125
764 mg/m² than in patients given a 100-mg/m² weekly starting dose (34% [65/193] versus
765 23% [24/102]; p=0.08). The frequency of grade 3 and 4 late diarrhea by age was
766 significantly greater in patients ≥65 years than in patients <65 years (40% [53/133]
767 versus 23% [40/171]; p=0.002). In one study of the weekly dosage treatment, the
768 frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female
769 patients (43% [25/58] versus 16% [5/32]; p=0.01), but there were no gender differences
770 in the frequency of grade 3 and 4 late diarrhea in the other two studies of the weekly
771 dosage treatment schedule. Colonic ulceration, sometimes with
772 gastrointestinal bleeding, has been observed in association with
773 administration of CAMPTOSAR.

774 *Hematology:* CAMPTOSAR commonly causes neutropenia, leukopenia
775 (including lymphocytopenia), and anemia. Serious thrombocytopenia is
776 uncommon. When evaluated in the trials of weekly administration, the
777 frequency of grade 3 and 4 neutropenia was significantly higher in patients who
778 received previous pelvic/abdominal irradiation than in those who had not received
779 such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). In these same
780 studies, patients with baseline serum total bilirubin levels of 1.0 mg/dL or
781 more also had a significantly greater likelihood of experiencing first-cycle
782 grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0
783 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). There were no
784 significant differences in the frequency of grade 3 and 4 neutropenia by age or
785 gender. In the clinical studies evaluating the weekly dosage schedule,
786 neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater)
787 occurred in 3% of the patients; 6% of patients received G-CSF for the treatment
788 of neutropenia. NCI grade 3 or 4 anemia was noted in 7% of the patients
789 receiving weekly treatment; blood transfusions were given to 10% of the patients in these
790 trials.

791 *Body as a Whole:* Asthenia, fever, and abdominal pain are generally the most
792 common events of this type.

793 *Cholinergic Symptoms:* Patients may have cholinergic symptoms of rhinitis,
794 increased salivation, miosis, lacrimation, diaphoresis, flushing, and
795 intestinal hyperperistalsis that can cause abdominal cramping and early
796 diarrhea. If these symptoms occur, they manifest during or shortly after drug
797 infusion. They are thought to be related to the anticholinesterase activity of
798 the irinotecan parent compound and are expected to occur more frequently with
799 higher irinotecan doses.

800 *Hepatic:* In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4
801 liver enzyme abnormalities were observed in fewer than 10% of patients. These events
802 typically occur in patients with known hepatic metastases.

803 *Dermatologic:* Alopecia has been reported during treatment with CAMPTOSAR.
804 Rashes have also been reported but did not result in discontinuation of treatment.

805 *Respiratory:* Severe pulmonary events are infrequent. In the clinical studies
806 evaluating the weekly dosage schedule, NCI grade 3 or 4 dyspnea was reported in

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807 4% of patients. Over half the patients with dyspnea had lung metastases; the extent to
808 which malignant pulmonary involvement or other preexisting lung disease may have
809 contributed to dyspnea in these patients is unknown.

810 Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during
811 irinotecan therapy. Interstitial pulmonary disease can be fatal. Risk factors possibly
812 associated with the development of interstitial pulmonary disease include pre-existing
813 lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors.
814 Patients with risk factors should be closely monitored for respiratory symptoms before
815 and during irinotecan therapy.

816 *Neurologic:* Insomnia and dizziness can occur, but are not usually considered to be
817 directly related to the administration of CAMPTOSAR. Dizziness may sometimes
818 represent symptomatic evidence of orthostatic hypotension in patients with
819 dehydration.

820 *Cardiovascular:* Vasodilation (flushing) may occur during administration of
821 CAMPTOSAR. Bradycardia may also occur, but has not required intervention.
822 These effects have been attributed to the cholinergic syndrome sometimes
823 observed during or shortly after infusion of CAMPTOSAR. Thromboembolic events
824 have been observed in patients receiving CAMPTOSAR; the specific cause of
825 these events has not been determined.

826 **Other Non-U.S. Clinical Trials**

827 Irinotecan has been studied in over 1100 patients in Japan. Patients in these
828 studies had a variety of tumor types, including cancer of the colon or rectum,
829 and were treated with several different doses and schedules. In general, the
830 types of toxicities observed were similar to those seen in U.S. trials with
831 CAMPTOSAR. There is some information from Japanese trials that patients
832 with considerable ascites or pleural effusions were at increased risk for
833 neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome,
834 consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was
835 observed in a small percentage of patients in early Japanese studies. The
836 contribution of irinotecan to these preliminary events was difficult to assess
837 because these patients also had lung tumors and some had preexisting
838 nonmalignant pulmonary disease. As a result of these observations, however,
839 clinical studies in the United States have enrolled few patients with
840 compromised pulmonary function, significant ascites, or pleural effusions.

841 **Post-Marketing Experience**

842 The following events have been identified during postmarketing use of
843 CAMPTOSAR in clinical practice. Infrequent cases of ulcerative and ischemic colitis
844 have been observed. This can be complicated by ulceration, bleeding, ileus, obstruction,
845 and infection, including typhlitis. Patients experiencing ileus should receive prompt
846 antibiotic support (see PRECAUTIONS). Rare cases of intestinal perforation have
847 been reported. Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes
848 have been observed.

849 Hypersensitivity reactions including severe anaphylactic or anaphylactoid
850 reactions have also been observed (see WARNINGS).

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853 Rare cases of hyponatremia mostly related with diarrhea and vomiting have been
854 reported. Transient and mild to moderate increases in serum levels of transaminases
855 (i.e., AST and ALT) in the absence of progressive liver metastasis; transient increase of
856 amylase and occasionally transient increase of lipase have been very rarely reported.

857 Infrequent cases of renal insufficiency including acute renal failure, hypotension or
858 circulatory failure have been observed in patients who experienced episodes of
859 dehydration associated with diarrhea and/or vomiting, or sepsis (see WARNINGS).

860 Early effects such as muscular contraction or cramps and paresthesia have been
861 reported.

862

863 **OVERDOSAGE**

864 In U.S. phase 1 trials, single doses of up to 345 mg/m² of irinotecan were
865 administered to patients with various cancers. Single doses of up to 750
866 mg/m² of irinotecan have been given in non-U.S. trials. The adverse events in
867 these patients were similar to those reported with the recommended dosage
868 and regimen. There have been reports of overdosage at doses up to approximately twice
869 the recommended therapeutic dose, which may be fatal. The most significant adverse
870 reactions reported were severe neutropenia and severe diarrhea. There is no known
871 antidote for overdosage of CAMPTOSAR. Maximum supportive care should
872 be instituted to prevent dehydration due to diarrhea and to treat any infectious
873 complications.

874

875 **DOSAGE AND ADMINISTRATION**

876 **Dosage in Patients with Reduced UGT1A1 Activity**

877 **When administered in combination with other agents, or as a single-agent, a**
878 **reduction in the starting dose by at least one level of CAMPTOSAR should be**
879 **considered for patients known to be homozygous for the UGT1A1*28 allele (See**
880 **CLINICAL PHARMACOLOGY and WARNINGS). However, the precise dose**
881 **reduction in this patient population is not known and subsequent dose modifications**
882 **should be considered based on individual patient tolerance to treatment (See Tables**
883 **10-13).**

884 **Combination-Agent Dosage**

885 ***Dosage Regimens***

886 ***CAMPTOSAR Injection in Combination with 5-Fluorouracil (5-FU) and Leucovorin (LV)***

887 CAMPTOSAR should be administered as an intravenous infusion over
888 90 minutes (see Preparation of Infusion Solution). For all regimens, the dose of LV
889 should be administered immediately after CAMPTOSAR, with the administration of
890 5-FU to occur immediately after receipt of LV. CAMPTOSAR should
891 be used as recommended; the currently recommended regimens are
892 shown in Table 10.

893

Table 10. Combination-Agent Dosage Regimens & Dose Modifications^a

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR	125 mg/m ² IV over 90 min, d 1,8,15,22		
	LV	20 mg/m ² IV bolus, d 1,8,15,22		
	5-FU	500 mg/m ² IV bolus, d 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m²)		
		Starting Dose	Dose Level -1	Dose Level -2

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	CAMPTOSAR		125	100	75
	LV		20	20	20
	5-FU		500	400	300
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR		180 mg/m ² IV over 90 min, d 1,15,29		
	LV		200 mg/m ² IV over 2 h, d 1,2,15,16,29,30		
	5-FU	Bolus	400 mg/m ² IV bolus, d 1,2,15,16,29,30		
	5-FU	Infusion ^b	600 mg/m ² IV over 22 h, d 1,2,15,16,29,30		
				Starting Dose & Modified Dose Levels (mg/m²)	
			Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR		180	150	120
	LV		200	200	200
	5-FU	Bolus	400	320	240
	5-FU	Infusion ^b	600	480	360

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^aDose reductions beyond dose level -2 by decrements of ≈20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

^bInfusion follows bolus administration.

894

895 Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is
896 insufficient information to recommend a dose in these patients. It is recommended
897 that patients receive premedication with antiemetic agents. Prophylactic or
898 therapeutic administration of atropine should be considered in
899 patients experiencing cholinergic symptoms. See PRECAUTIONS,
900 General.

901 **Dose Modifications**

902 Patients should be carefully monitored for toxicity and assessed prior to each treatment.
903 Doses of CAMPTOSAR and 5-FU should be modified as necessary to accommodate
904 individual patient tolerance to treatment. Based on the recommended
905 dose-levels described in Table 10, Combination-Agent Dosage Regimens &
906 Dose Modifications, subsequent doses should be adjusted as
907 suggested in Table 11, Recommended Dose Modifications for Combination
908 Schedules. All dose modifications should be based on the worst preceding
909 toxicity. After the first treatment, patients with active diarrhea should
910 return to pre-treatment bowel function without requiring anti-diarrhea medications for
911 at least 24 hours before the next chemotherapy administration.

912 A new cycle of therapy should not begin until the toxicity has
913 recovered to NCI grade 1 or less. Treatment maybe delayed 1 to 2
914 weeks to allow for recovery from treatment-related toxicity. If the
915 patient has not recovered, consideration should be given to
916 discontinuing therapy. Provided intolerable toxicity does not
917 develop, treatment with additional cycles of CAMPTOSAR/5-FU/LV may
918 be continued indefinitely as long as patients continue to experience clinical
919 benefit.

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^aSubsequent doses may be adjusted as high as 150 mg/m² or to as low as 50 mg/m² in 25 to 50 mg/m² decrements depending upon individual patient tolerance.

^bSubsequent doses may be adjusted as low as 200 mg/m² in 50 mg/m² decrements depending upon individual patient tolerance.

^cProvided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

930

931 A reduction in the starting dose by one dose level of CAMPTOSAR may be
932 considered for patients with any of the following conditions: age ≥ 65 years,
933 prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin
934 levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because
935 there is insufficient information to recommend a dose in these patients.

936 It is recommended that patients receive premedication with antiemetic agents.
937 Prophylactic or therapeutic administration of atropine should be considered in patients
938 experiencing cholinergic symptoms. See PRECAUTIONS, General.

939 ***Dose Modifications***

940 Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should
941 be modified as necessary to accommodate individual patient tolerance to
942 treatment. Based on recommended dose-levels described in Table 12,
943 Single-Agent Regimens of CAMPTOSAR and Dose Modifications,
944 subsequent doses should be adjusted as suggested in Table 13, Recommended Dose
945 Modifications for Single-Agent Schedules. All dose modifications should be based on the
946 worst preceding toxicity.

947 A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1
948 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-
949 related toxicity. If the patient has not recovered, consideration should be
950 given to discontinuing this combination therapy. Provided intolerable toxicity does not
951 develop, treatment with additional cycles of CAMPTOSAR may be continued
952 indefinitely as long as patients continue to experience clinical benefit.

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Table 13. Recommended Dose Modifications For Single-Agent Schedules^a

A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, and the platelet count has recovered to $\geq 100,000/\text{mm}^3$, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.				
Worst Toxicity NCI Grade ^b (Value)	During a Cycle of Therapy		At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle ^a	
	Weekly		Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level		$\uparrow 25 \text{ mg/m}^2$ up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia				
1 (1500 to 1999/ mm^3)	Maintain dose level		Maintain dose level	Maintain dose level
2 (1000 to 1499/ mm^3)	$\downarrow 25 \text{ mg/m}^2$		Maintain dose level	Maintain dose level
3 (500 to 999/ mm^3)	Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$		$\downarrow 25 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
4 ($< 500/\text{mm}^3$)	Omit dose until resolved to \leq grade 2, then $\downarrow 50 \text{ mg/m}^2$		$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
Neutropenic fever	Omit dose until resolved, then $\downarrow 50 \text{ mg/m}^2$ when resolved		$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.			
Diarrhea				
1 (2-3 stools/day $>$ pretx ^c)	Maintain dose level		Maintain dose level	Maintain dose level
2 (4-6 stools/day $>$ pretx)	$\downarrow 25 \text{ mg/m}^2$		Maintain dose level	Maintain dose level
3 (7-9 stools/day $>$ pretx)	Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$		$\downarrow 25 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
4 (≥ 10 stools/day $>$ pretx)	Omit dose until resolved to \leq grade 2 then $\downarrow 50 \text{ mg/m}^2$		$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
Other nonhematologic^d toxicities				
1	Maintain dose level		Maintain dose level	Maintain dose level
2	$\downarrow 25 \text{ mg/m}^2$		$\downarrow 25 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
3	Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$		$\downarrow 25 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
4	Omit dose until resolved to \leq grade 2, then $\downarrow 50 \text{ mg/m}^2$		$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$

^a All dose modifications should be based on the worst preceding toxicity

^b National Cancer Institute Common Toxicity Criteria (version 1.0)

^c Pretreatment

^d Excludes alopecia, anorexia, asthenia

954

955 **Preparation & Administration Precautions**

956 As with other potentially toxic anticancer agents, care should be exercised in the
957 handling and preparation of infusion solutions prepared from CAMPTOSAR Injection.
958 The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin,
959 wash the skin immediately and thoroughly with soap and water. If
960 CAMPTOSAR contacts the mucous membranes, flush thoroughly with water.
961 Several published guidelines for handling and disposal of anticancer agents are
962 available.¹⁻⁷

963 **Preparation of Infusion Solution**

964 Inspect vial contents for particulate matter and repeat inspection when drug product is
965 withdrawn from vial into syringe.

966 CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be
967 diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection,
968 USP, to a final concentration range of 0.12 to 2.8 mg/mL. In most clinical trials,
969 CAMPTOSAR was administered in 250 mL to 500 mL of 5% Dextrose
970 Injection, USP.

971 The solution is physically and chemically stable for up to 24 hours at
972 room temperature (approximately 25°C) and in ambient fluorescent lighting.
973 Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated
974 temperatures (approximately 2° to 8°C), and protected from light are physically and
975 chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium
976 Chloride Injection, USP, is not recommended due to a low and sporadic

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977 incidence of visible particulates. Freezing CAMPTOSAR and admixtures of
978 CAMPTOSAR may result in precipitation of the drug and should be
979 avoided. Because of possible microbial contamination during
980 dilution, it is advisable to use the admixture prepared with 5%Dextrose
981 Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the
982 case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride
983 Injection, USP, the solutions should be used within 6 hours if kept at room temperature
984 (15° to 30°C, 59° to 86°F).

985 Other drugs should not be added to the infusion solution. Parenteral drug
986 products should be inspected visually for particulate matter and discoloration prior
987 to administration whenever solution and container permit.

988 **HOW SUPPLIED**

989 Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the
990 basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When
991 necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or
992 hydrochloric acid.

993 CAMPTOSAR Injection is available in single-dose amber glass vials in the
994 following package sizes:

995 2 mL NDC 0009-7529-02

996 5 mL NDC 0009-7529-01

997

998 This is packaged in a backing/plastic blister to protect against inadvertent
999 breakage and leakage. The vial should be inspected for damage and visible
1000 signs of leaks before removing the backing/plastic blister. If damaged,
1001 incinerate the unopened package.

1002 Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from
1003 light. It is recommended that the vial (and backing/plastic blister) should remain in the
1004 carton until the time of use.

1005

1006 **Rx only**

1007

1008 **REFERENCES**

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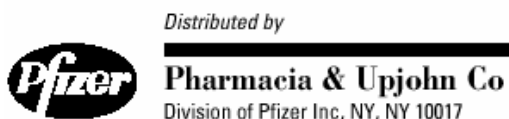
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Camptosar brand of irinotecan hydrochloride injection



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1036 Licensed from Yakult Honsha Co., LTD, Japan, and Daiichi Pharmaceutical
1037 Co., LTD, Japan
1038
1039 Revised June 2006
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ⁱ Addendum to the Expert Report on the clinical documentation, in patients with impaired hepatic function. D. Larrey, February 2001.