

1 **CAMPTOSAR®**
2 irinotecan hydrochloride injection
3

4 **WARNINGS**

5 CAMPTOSAR Injection should be administered only under the supervision of a
6 physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate
7 management of complications is possible only when adequate diagnostic and treatment
8 facilities are readily available.

9 CAMPTOSAR can induce both early and late forms of diarrhea that appear to be
10 mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea
11 (occurring during or shortly after infusion of CAMPTOSAR) may be accompanied by
12 cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis,
13 flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea
14 and other cholinergic symptoms may be prevented or ameliorated by atropine (see
15 PRECAUTIONS, General). Late diarrhea (generally occurring more than 24 hours after
16 administration of CAMPTOSAR) can be life threatening since it may be prolonged and may
17 lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly
18 with loperamide. Patients with diarrhea should be carefully monitored and given fluid and
19 electrolyte replacement if they become dehydrated, or antibiotic therapy if they develop ileus,
20 fever, or severe neutropenia (see WARNINGS). Administration of CAMPTOSAR should be
21 interrupted and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND
22 ADMINISTRATION).

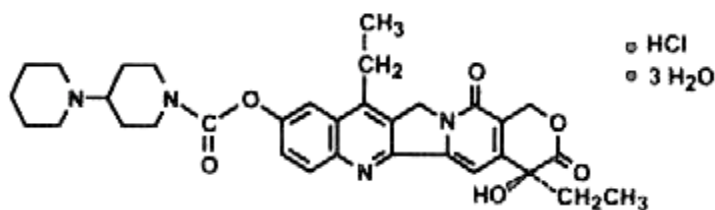
23 Severe myelosuppression may occur (see WARNINGS).
24

25 **DESCRIPTION**

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

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

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



Irinotecan Hydrochloride

43
44

45 Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical
46 formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is slightly soluble in
47 water and organic solvents.

48

49 **CLINICAL PHARMACOLOGY**

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

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

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

73

74 **Pharmacokinetics**

75 After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations
76 decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to
77 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10
78 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar

79 to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in
 80 equilibrium.

81 Over the recommended dose range of 50 to 350 mg/m², the AUC of irinotecan increases
 82 linearly with dose; the AUC of SN-38 increases less than proportionally with dose.
 83 Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour
 84 following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for
 85 irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and
 86 340 mg/m² determined in two clinical studies in patients with solid tumors are summarized in
 87 Table 1:
 88

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 ± 4.00	56.0 ± 28.2	474 ± 245	21.0 ^b ± 4.3

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.

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90

91 Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is
 92 highly bound to human plasma proteins (approximately 95% bound). The plasma protein to
 93 which irinotecan and SN-38 predominantly binds is albumin.

94 *Metabolism and Excretion:* The metabolic conversion of irinotecan to the active metabolite
 95 SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38
 96 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide
 97 had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro.
 98 The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion
 99 of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative
 100 biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide)
 101 over a period of 48 hours following administration of irinotecan in two patients ranged from
 102 approximately 25% (100 mg/m²) to 50% (300 mg/m²).
 103

104 **Pharmacokinetics in Special Populations**

105 *Geriatric:* In studies using the weekly schedule, the terminal half-life of irinotecan was
 106 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than
 107 65 years. Dose-normalized AUC₀₋₂₄ for SN-38 in patients who were at least 65 years of age

108 was 11% higher than in patients younger than 65 years. No change in the starting dose is
109 recommended for geriatric patients receiving the weekly dosage schedule of irinotecan.
110 The pharmacokinetics of irinotecan given once every 3 weeks has not been studied in the
111 geriatric population; a lower starting dose is recommended in patients 70 years or older based
112 on clinical toxicity experience with this schedule (see DOSAGE AND ADMINISTRATION).
113 *Pediatric:* Information regarding the pharmacokinetics of irinotecan is not available.
114 *Gender:* The pharmacokinetics of irinotecan do not appear to be influenced by gender.
115 *Race:* The influence of race on the pharmacokinetics of irinotecan has not been evaluated.
116 *Hepatic Insufficiency:* The influence of hepatic insufficiency on the pharmacokinetic
117 characteristics of irinotecan and its metabolites has not been formally studied. Among
118 patients with known hepatic tumor involvement (a majority of patients), irinotecan and
119 SN-38 AUC values were somewhat higher than values for patients without liver metastases
120 (see PRECAUTIONS).
121 *Renal Insufficiency:* The influence of renal insufficiency on the pharmacokinetics of
122 irinotecan has not been evaluated.

123

124 **Drug-Drug Interactions**

125 In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin
126 (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially
127 altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the
128 active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed
129 by 5-FU and LV administration compared with when irinotecan was given alone, this
130 sequence of administration was used in the combination trials and is recommended (see
131 DOSAGE AND ADMINISTRATION). Formal in vivo or in vitro drug interaction studies to
132 evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been
133 conducted.

134 Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly
135 administered medications have not been formally investigated.

136

137 **CLINICAL STUDIES**

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

144

145 **First-Line Therapy in Combination with 5-FU/LV for the Treatment of Metastatic 146 Colorectal Cancer**

147 Two phase 3, randomized, controlled, multinational clinical trials support the use of
148 CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the
149 colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were
150 compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus
151 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily
152 for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was

153 also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV,
154 with or without irinotecan. In both studies, concomitant medications such as antiemetics,
155 atropine, and loperamide were given to patients for prophylaxis and/or management of
156 symptoms from treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic
157 prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite
158 loperamide or if they developed a fever in addition to diarrhea. Treatment with oral
159 fluoroquinolone was also initiated in patients who developed an absolute neutrophil count
160 (ANC) $< 500/\text{mm}^3$, even in the absence of fever or diarrhea. Patients in both studies also
161 received treatment with intravenous antibiotics if they had persistent diarrhea or fever or if
162 ileus developed.

163 In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant
164 improvements in objective tumor response rates, time to tumor progression, and survival
165 when compared with 5-FU/LV alone. These differences in survival were observed in spite of
166 second-line therapy in a majority of patients on both arms, including crossover to irinotecan-
167 containing regimens in the control arm. Patient characteristics and major efficacy results are
168 shown in Table 2.

169

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

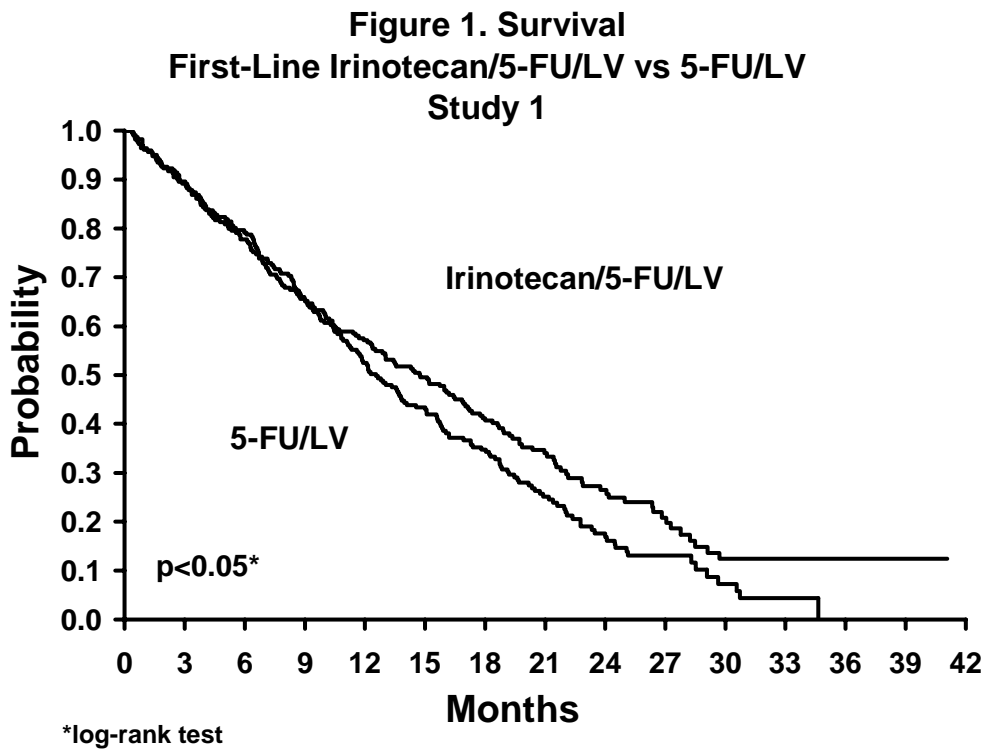
^c Chi-square test

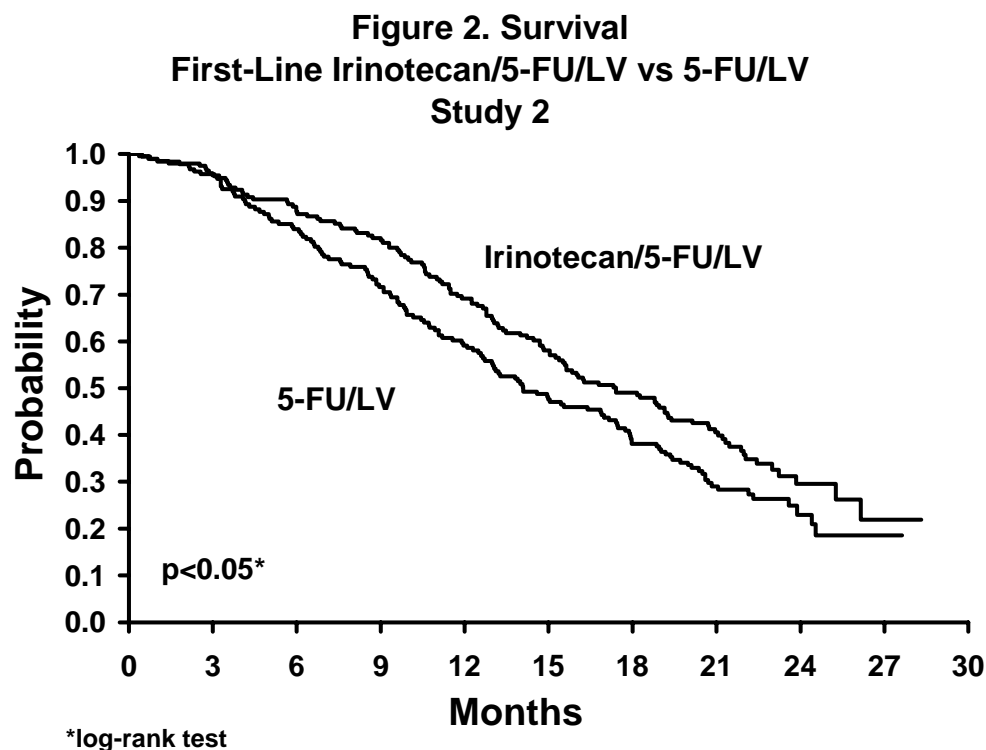
^d Log-rank test

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171 Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV
172 when response rates and time to tumor progression were examined across the following
173 demographic and disease-related subgroups (age, gender, ethnic origin, performance status,
174 extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant
175 therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier
176 survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and
177 2, respectively.
178





180

181 **Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer** 182 **After 5-FU-Based Treatment**

183

184 *Weekly Dosage Schedule*

185 Data from three open-label, single-agent, clinical studies, involving a total of 304 patients
186 in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic
187 cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-
188 based therapy. These studies were designed to evaluate tumor response rate and do not
189 provide information on actual clinical benefit, such as effects on survival and disease-related
190 symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles
191 consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a
192 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or
193 150 mg/m², but the 150-mg/m² dose was poorly tolerated (due to unacceptably high rates of
194 grade 4 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was
195 conducted by a single investigator at several regional hospitals. Study 2 was a multicenter
196 study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in
197 Study 2 received a starting dose of 125 mg/m². Study 3 was a multicenter study that enrolled
198 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m² but was reduced
199 to 100 mg/m² because the toxicity seen at the 125-mg/m² dose was perceived to be greater
200 than that seen in previous studies. All patients in these studies had metastatic colorectal

201 cancer, and the majority had disease that recurred or progressed following a 5-FU-based
 202 regimen administered for metastatic disease. The results of the individual studies are shown
 203 in Table 3.
 204

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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206 In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304
207 patients began therapy at the recommended starting dose of 125 mg/m². Among these
208 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate
209 of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A
210 considerably lower response rate was seen with a starting dose of 100 mg/m². The majority of
211 responses were observed within the first two cycles of therapy, but responses did occur in
212 later cycles of treatment (one response was observed after the eighth cycle). The median
213 response duration for patients beginning therapy at 125 mg/m² was 5.8 months (range, 2.6 to
214 15.1 months). Of the 304 patients treated in the three studies, response rates to
215 CAMPTOSAR were similar in males and females and among patients older and younger than
216 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum
217 and in patients with single and multiple metastatic sites. The response rate was 18.5% in
218 patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or
219 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the
220 patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had
221 received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the
222 same rate as those who had not previously received irradiation.

223 224 ***Once-Every-3-Week Dosage Schedule***

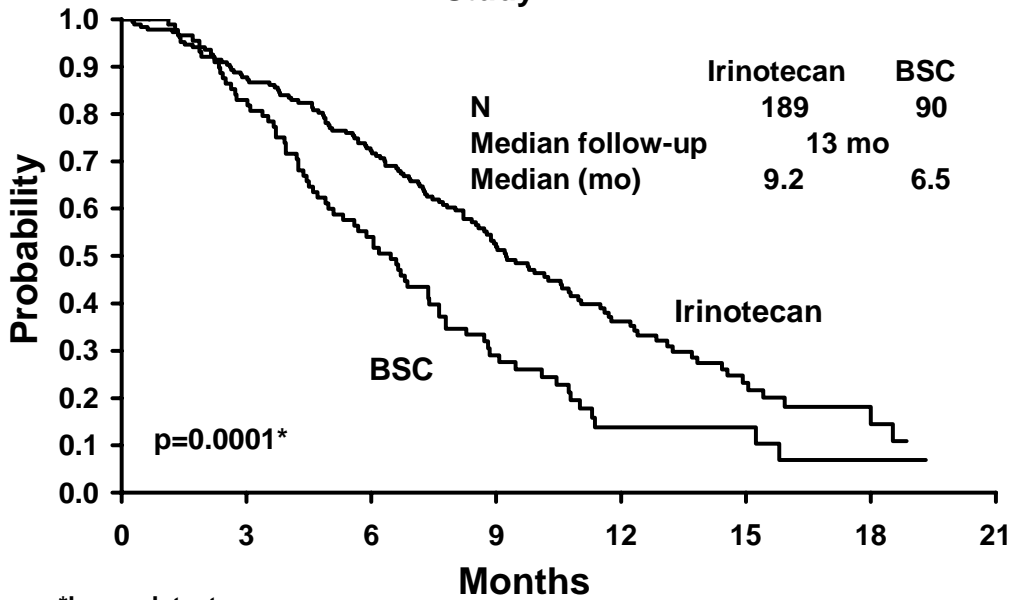
225 *Single-Arm Studies:* Data from an open-label, single-agent, single-arm, multicenter, clinical
226 study involving a total of 132 patients support a once every-3-week dosage schedule of
227 irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that
228 recurred or progressed following treatment with 5-FU. Patients received a starting dose of
229 350 mg/m² given by 30-minute intravenous infusion once every 3 weeks. Among the 132
230 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI,
231 7.0% to 18.1%).

232 *Randomized Trials:* Two multicenter, randomized, clinical studies further support the use of
233 irinotecan given by the once-every-3-week dosage schedule in patients with metastatic
234 colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In
235 the first study, second-line irinotecan therapy plus best supportive care was compared with
236 best supportive care alone. In the second study, second-line irinotecan therapy was compared
237 with infusional 5-FU-based therapy. In both studies, irinotecan was administered
238 intravenously at a starting dose of 350 mg/m² over 90 minutes once every 3 weeks. The
239 starting dose was 300 mg/m² for patients who were 70 years and older or who had a
240 performance status of 2. The highest total dose permitted was 700 mg. Dose reductions
241 and/or administration delays were permitted in the event of severe hematologic and/or
242 nonhematologic toxicities while on treatment. Best supportive care was provided to patients
243 in both arms of Study 1 and included antibiotics, analgesics, corticosteroids, transfusions,
244 psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies,
245 concomitant medications such as antiemetics, atropine, and loperamide were given to patients
246 for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted
247 for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic
248 prophylaxis was given. Patients in the control arm of the second study received one of the
249 following 5-FU regimens: (1) LV, 200 mg/m² IV over 2 hours; followed by 5-FU, 400
250 mg/m² IV bolus; followed by 5-FU, 600 mg/m² continuous IV infusion over 22 hours on days

251 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m² /day protracted continuous IV infusion
252 until toxicity; (3) 5-FU, 2.6 to 3 g/m² IV over 24 hours every week for 6 weeks with or
253 without LV, 20 to 500 mg/m² /day every week IV for 6 weeks with 2-week rest between
254 cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

255 A total of 535 patients were randomized in the two studies at 94 centers. The primary
256 endpoint in both studies was survival. The studies demonstrated a significant overall survival
257 advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-
258 based therapy (p=0.035) as shown in Figures 3 and 4. In Study 1, median survival for
259 patients treated with irinotecan was 9.2 months compared with 6.5 months for patients
260 receiving best supportive care. In Study 2, median survival for patients treated with irinotecan
261 was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based
262 therapy. Multiple regression analyses determined that patients' baseline characteristics also
263 had a significant effect on survival. When adjusted for performance status and other baseline
264 prognostic factors, survival among patients treated with irinotecan remained significantly
265 longer than in the control populations (p=0.001 for Study 1 and p=0.017 for Study 2).
266 Measurements of pain, performance status, and weight loss were collected prospectively in
267 the two studies; however, the plan for the analysis of these data was defined retrospectively.
268 When comparing irinotecan with best supportive care in Study 1, this analysis showed a
269 statistically significant advantage for irinotecan, with longer time to development of pain
270 (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus
271 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally,
272 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an
273 improvement in performance status when treated with irinotecan versus 11.3% (7/62) of
274 patients receiving best supportive care (p=0.002). Because of the inclusion of patients with
275 non-measurable disease, intent-to-treat response rates could not be assessed.
276

Figure 3. Survival
Second-Line Irinotecan vs Best Supportive Care (BSC)
Study 1



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Figure 4. Survival
Second-Line Irinotecan vs Infusional 5-FU
Study 2

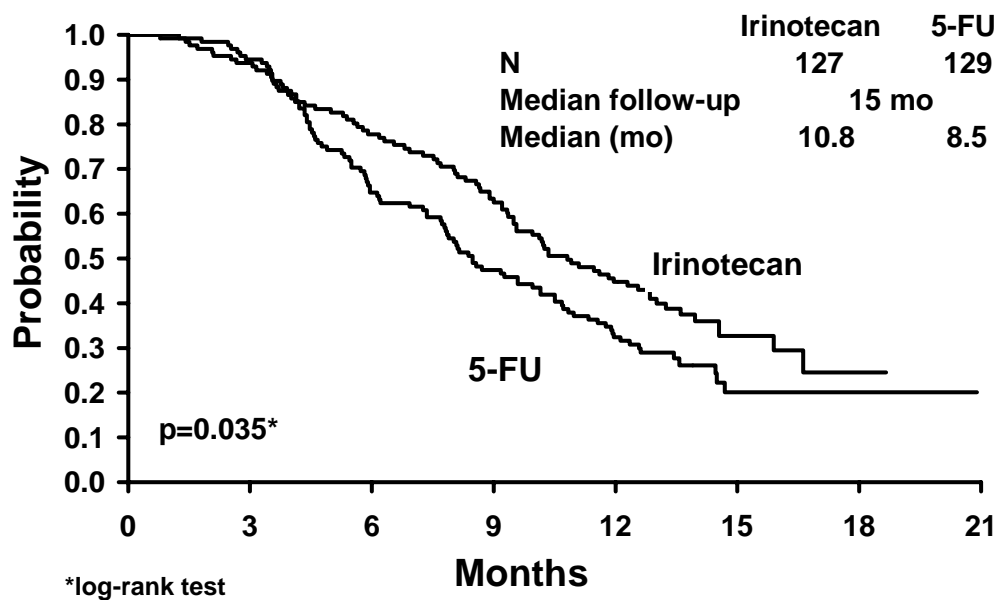


Table 4. Once-Every-3-Week Dosage Schedule: Study Results

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

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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CONTRAINDICATIONS

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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).

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.

322

323 **Diarrhea**

324 CAMPTOSAR can induce both early and late forms of diarrhea that appear to be
325 mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion
326 of CAMPTOSAR) is cholinergic in nature. It is usually transient and only infrequently is
327 severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis,
328 lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal
329 cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated
330 by administration of atropine (see PRECAUTIONS, General, for dosing recommendations
331 for atropine).

332 Late diarrhea (generally occurring more than 24 hours after administration of
333 CAMPTOSAR) can be life threatening since it may be prolonged and may lead to
334 dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with
335 loperamide (see PRECAUTIONS, Information for Patients, for dosing recommendations for
336 loperamide). Patients with diarrhea should be carefully monitored, should be given fluid and
337 electrolyte replacement if they become dehydrated, and should be given antibiotic support if
338 they develop ileus, fever, or severe neutropenia. After the first treatment, subsequent weekly
339 chemotherapy treatments should be delayed in patients until return of pretreatment bowel
340 function for at least 24 hours without need for antidiarrhea medication. If grade 2, 3, or 4 late
341 diarrhea occurs subsequent doses of CAMPTOSAR should be decreased within the current
342 cycle (see DOSAGE AND ADMINISTRATION).

343

344 **Neutropenia**

345 Deaths due to sepsis following severe neutropenia have been reported in patients treated
346 with CAMPTOSAR. Neutropenic complications should be managed promptly with antibiotic
347 support (see PRECAUTIONS). Therapy with CAMPTOSAR should be temporarily omitted
348 during a cycle of therapy if neutropenic fever occurs or if the absolute neutrophil count drops
349 $<1500/\text{mm}^3$. After the patient recovers to an absolute neutrophil count $\geq 1500/\text{mm}^3$,
350 subsequent doses of CAMPTOSAR should be reduced depending upon the level of
351 neutropenia observed (see DOSAGE AND ADMINISTRATION).

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

355

356 **Hypersensitivity**

357 Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have
358 been observed.

359

360 **Colitis/Ileus**

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

364

365 **Renal Impairment/Renal Failure**

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

368 **Thromboembolism**

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

372 **Pregnancy**

373 CAMPTOSAR may cause fetal harm when administered to a pregnant woman.
374 Radioactivity related to ¹⁴C-irinotecan crosses the placenta of rats following intravenous
375 administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC
376 about 3 and 0.5 times, respectively, the corresponding values in patients administered
377 125 mg/m²). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate
378 studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the
379 corresponding values in patients administered 125 mg/m²) and rabbits (about one-half the
380 recommended human weekly starting dose on a mg/m² basis) during the period of
381 organogenesis, is embryotoxic as characterized by increased post-implantation loss and
382 decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2
383 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and
384 1/40th, respectively, of the corresponding values in patients administered 125 mg/m²) and in
385 rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a
386 mg/m² basis). Teratogenic effects included a variety of external, visceral, and skeletal
387 abnormalities. Irinotecan administered to rat dams for the period following organogenesis
388 through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased
389 female body weights in the offspring. There are no adequate and well-controlled studies of
390 irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes
391 pregnant while receiving this drug, the patient should be apprised of the potential hazard to
392 the fetus. Women of childbearing potential should be advised to avoid becoming pregnant
393 while receiving treatment with CAMPTOSAR.

395 **PRECAUTIONS.**

396 **General**

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

401 *Premedication with Antiemetics:* Irinotecan is emetogenic. It is recommended that patients
402 receive premedication with antiemetic agents. In clinical studies of the weekly dosage
403 schedule, the majority of patients received 10 mg of dexamethasone given in conjunction
404 with another type of antiemetic agent, such as a 5-HT³ blocker (e.g., ondansetron or
405 granisetron). Antiemetic agents should be given on the day of treatment, starting at least
406 30 minutes before administration of CAMPTOSAR. Physicians should also consider
407 providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as
408 needed.
409
410

411 *Treatment of Cholinergic Symptoms:* Prophylactic or therapeutic administration of 0.25 to
412 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically
413 contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation,
414 diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after
415 infusion of CAMPTOSAR). These symptoms are expected to occur more frequently with
416 higher irinotecan doses.

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

423 The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been
424 established. In clinical trials of either dosing schedule, irinotecan was not administered to
425 patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal
426 if no liver metastasis, or transaminase >5 times the upper limit of normal with liver
427 metastasis. However in clinical trials of the weekly dosage schedule, it has been noted that
428 patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have
429 had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than
430 those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7%
431 [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with
432 Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy
433 with CAMPTOSAR. An association between baseline bilirubin elevations and an increased
434 risk of late diarrhea has not been observed in studies of the weekly dosage schedule.

435

436 **Information for Patients**

437 Patients and patients' caregivers should be informed of the expected toxic effects of
438 CAMPTOSAR, particularly of its gastrointestinal complications, such as nausea, vomiting,
439 abdominal cramping, diarrhea, and infection. Each patient should be instructed to have
440 loperamide readily available and to begin treatment for late diarrhea (generally occurring
441 more than 24 hours after administration of CAMPTOSAR) at the first episode of poorly
442 formed or loose stools or the earliest onset of bowel movements more frequent than normally
443 expected for the patient. One dosage regimen for loperamide used in clinical trials consisted
444 of the following (Note: This dosage regimen exceeds the usual dosage recommendations for
445 loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the
446 patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of
447 loperamide every 4 hours. Premedication with loperamide is not recommended. The use of
448 drugs with laxative properties should be avoided because of the potential for exacerbation of
449 diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

450 Patients should be instructed to contact their physician or nurse if any of the following
451 occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of
452 dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth
453 due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or
454 evidence of infection.

455 Patients should be alerted to the possibility of alopecia.

456

457 **Laboratory Tests**

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

460

461 **Drug Interactions**

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

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

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

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

476 The incidence of akathisia in clinical trials of the weekly dosage schedule was greater
477 (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as
478 CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The
479 8.5% incidence of akathisia, however, is within the range reported for use of
480 prochlorperazine when given as a premedication for other chemotherapies.

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

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

486

487 **Drug-Laboratory Test Interactions**

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

489

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

491 Long-term carcinogenicity studies with irinotecan were not conducted. Rats were,
492 however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week
493 for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC
494 that were about 7.0 times and 1.3 times the respective values in patients administered
495 125 mg/m² weekly) and were then allowed to recover for 91 weeks. Under these conditions,
496 there was a significant linear trend with dose for the incidence of combined uterine horn
497 endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan nor SN-38
498 was mutagenic in the in vitro Ames assay. Irinotecan was clastogenic both in vitro
499 (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in
500 mice). No significant adverse effects on fertility and general reproductive performance were

501 observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats
502 and rabbits. However, atrophy of male reproductive organs was observed after multiple daily
503 irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an
504 irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in
505 patients administered 125 mg/m² weekly) and dogs at 0.4 mg/kg (which in separate studies
506 produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the
507 corresponding values in patients administered 125 mg/m² weekly).

508 **Pregnancy**

509 Pregnancy Category D—see WARNINGS.

510 **Nursing Mothers**

511
512 Radioactivity appeared in rat milk within 5 minutes of intravenous administration of
513 radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration
514 relative to plasma concentrations. Because many drugs are excreted in human milk and
515 because of the potential for serious adverse reactions in nursing infants, it is recommended
516 that nursing be discontinued when receiving therapy with CAMPTOSAR.
517

518 **Pediatric Use**

519 The safety and effectiveness of CAMPTOSAR in pediatric patients have not been
520 established.
521

522 **Geriatric Use**

523 Patients greater than 65 years of age should be closely monitored because of a greater risk
524 of late diarrhea in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in
525 Special Populations and ADVERSE REACTIONS, Overview of Adverse Events). The
526 starting dose of CAMPTOSAR in patients 70 years and older for the once-every-3-week-
527 dosage schedule should be 300 mg/m² (see DOSAGE AND ADMINISTRATION).
528

529 **ADVERSE REACTIONS**

530 **First-Line Combination Therapy**

531
532 A total of 955 patients with metastatic colorectal cancer received the recommended
533 regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In
534 the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362
535 patients received 5-FU/LV alone, and 223 patients received irinotecan alone. (See Table 10
536 in DOSAGE AND ADMINISTRATION for recommended combination-agent regimens.)
537

538 In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%)
539 received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and
540 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2
541 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic
542 fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1
543 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received
544 irinotecan alone (2 neutropenic fever). Deaths from any cause within 60 days of first study
545 treatment were reported for 15 (6.7%) patients who received irinotecan in combination with

546 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone, and 15 (6.7%) patients who
547 received irinotecan alone. Discontinuations due to adverse events were reported for 17
548 (7.6%) patients who received irinotecan in combination with 5-FU/LV, 14 (6.4%) patients
549 who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

550 In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%)
551 received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone.
552 There was one potentially treatment-death, which occurred in a patient who received
553 irinotecan in combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause
554 within 60 days of first study treatment were reported for 3 (2.1%) patients who received
555 irinotecan in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone.
556 Discontinuations due to adverse events were reported for 9 (6.2%) patients who received
557 irinotecan in combination with 5-FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

558 The most clinically significant adverse events for patients receiving irinotecan-based
559 therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically
560 significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia,
561 neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined
562 as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with
563 weekly irinotecan/5-FU/LV than with monthly administration of 5-FU/LV.

564 Tables 6 and 7 list the clinically relevant adverse events reported in Studies 1 and 2,
565 respectively.
566

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.

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.

571 **Second-Line Single-Agent Therapy**

572

573 ***Weekly Dosage Schedule***

574 In three clinical studies evaluating the weekly dosage schedule, 304 patients with
575 metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-
576 based therapy were treated with CAMPTOSAR. Seventeen of the patients died within
577 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were
578 potentially drug-related. These five patients experienced a constellation of medical events
579 that included known effects of CAMPTOSAR. One of these patients died of neutropenic
580 sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients
581 recovered with supportive care.

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

588 Adjustments in the dose of CAMPTOSAR were made during the cycle of treatment and
589 for subsequent cycles based on individual patient tolerance. The first dose of at least one
590 cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the
591 125-mg/m² starting dose. Within-cycle dose reductions were required for 32% of the cycles
592 initiated at the 125-mg/m² dose level. The most common reasons for dose reduction were late
593 diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with
594 CAMPTOSAR because of adverse events. The adverse events in Table 8 are based on the
595 experience of the 304 patients enrolled in the three studies described in the CLINICAL
596 STUDIES, Studies Evaluating the Weekly Dosage Schedule, section.

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598

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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Once-Every-3-Week Dosage Schedule

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A total of 535 patients with metastatic colorectal cancer whose disease had recurred or

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progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received

604 irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients
605 treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the
606 deaths were potentially related to irinotecan treatment and were attributed to neutropenic
607 infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with
608 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

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

614 Of the 316 patients treated with irinotecan, the most clinically significant adverse events
615 (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%),
616 cholinergic symptoms (47%), and neutropenia (30%). Table 9 lists the grade 3 and 4 adverse
617 events reported in the patients enrolled to all treatment arms of the two studies described in
618 the CLINICAL STUDIES, Studies Evaluating the Once-Every-3-Week Dosage Schedule,
619 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

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Overview of Adverse Events

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Gastrointestinal: Nausea, vomiting, and diarrhea are common adverse events following treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the

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629 median time to onset of late diarrhea was 11 days following administration of
630 CAMPTOSAR. For patients starting treatment at the 125-mg/m² weekly dose, the median
631 duration of any grade of late diarrhea was 3 days. Among those patients treated at the
632 125-mg/m² weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of
633 the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was
634 somewhat greater in patients starting treatment at 125 mg/m² than in patients given a
635 100-mg/m² weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The
636 frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years
637 than in patients <65 years (40% [53/133] versus 23% [40/171]; p = 0.002). In one study of
638 the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly
639 greater in male than in female patients (43% [25/58] versus 16% [5/32]; p = 0.01), but there
640 were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two
641 studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with
642 gastrointestinal bleeding, has been observed in association with administration of
643 CAMPTOSAR.

644 *Hematology:* CAMPTOSAR commonly causes neutropenia, leukopenia (including
645 lymphocytopenia), and anemia. Serious thrombocytopenia is uncommon. When evaluated in
646 the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was
647 significantly higher in patients who received previous pelvic/abdominal irradiation than in
648 those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p = 0.04). In
649 these same studies, patients with baseline serum total bilirubin levels of 1.0 mg/dL or more
650 also had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia
651 than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18%
652 [47/266]; p<0.001). There were no significant differences in the frequency of grade 3 and 4
653 neutropenia by age or gender. In the clinical studies evaluating the weekly dosage schedule,
654 neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater)
655 occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of
656 neutropenia. NCI grade 3 or 4 anemia was noted in 7% of the patients receiving weekly
657 treatment; blood transfusions were given to 10% of the patients in these trials.

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

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

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

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

671 *Respiratory:* Severe pulmonary events are infrequent. In the clinical studies evaluating the
672 weekly dosage schedule, NCI grade 3 or 4 dyspnea was reported in 4% of patients. Over half
673 the patients with dyspnea had lung metastases; the extent to which malignant pulmonary

674 involvement or other preexisting lung disease may have contributed to dyspnea in these
675 patients is unknown.

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

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

684

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

686 Irinotecan has been studied in over 1100 patients in Japan. Patients in these studies had a
687 variety of tumor types, including cancer of the colon or rectum, and were treated with several
688 different doses and schedules. In general, the types of toxicities observed were similar to
689 those seen in US trials with CAMPTOSAR. There is some information from Japanese trials
690 that patients with considerable ascites or pleural effusions were at increased risk for
691 neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of
692 dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small
693 percentage of patients in early Japanese studies. The contribution of irinotecan to these
694 preliminary events was difficult to assess because these patients also had lung tumors and
695 some had preexisting nonmalignant pulmonary disease. As a result of these observations,
696 however, clinical studies in the United States have enrolled few patients with compromised
697 pulmonary function, significant ascites, or pleural effusions.

698

699 **Post-Marketing Experience**

700 The following events have been identified during post-marketing use of CAMPTOSAR
701 in clinical practice. Cases of colitis complicated by ulceration, bleeding, ileus, or infection
702 have been observed. There have been rare cases of renal impairment and acute renal failure,
703 generally in patients who became infected and/or volume depleted from severe
704 gastrointestinal toxicities (see WARNINGS). Hypersensitivity reactions including severe
705 anaphylactic or anaphylactoid reactions have also been observed (see WARNINGS).

706

707 **OVERDOSAGE**

708 In U.S. phase 1 trials, single doses of up to 345 mg/m² of irinotecan were administered to
709 patients with various cancers. Single doses of up to 750 mg/m² of irinotecan have been given
710 in non-U.S. trials. The adverse events in these patients were similar to those reported with the
711 recommended dosage and regimen. There is no known antidote for overdose of
712 CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to
713 diarrhea and to treat any infectious complications.

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715 **DOSAGE AND ADMINISTRATION**

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717 **Combination-Agent Dosage**

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719 ***Dosage Regimens***

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

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

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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 LV 5-FU	125 mg/m ² IV over 90 min, d 1,8,15,22 20 mg/m ² IV bolus, d 1,8,15,22 500 mg/m ² IV bolus, d 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m ²)		
		Starting Dose	Dose Level -1	Dose Level -2
	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 LV 5-FU Bolus 5-FU Infusion ^b	180 mg/m ² IV over 90 min, d 1,15,29 200 mg/m ² IV over 2 h, d 1,2,15,16,29,30 400 mg/m ² IV bolus, d 1,2,15,16,29,30 600 mg/m ² IV over 22 h, d 1,2,15,16,29,30		
		Starting Dose & Modified Dose Levels (mg/m ²)		
		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

^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.

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Dose Modifications

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

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

**Table 11. Recommended Dose Modifications for
CAMPTOSAR/5-Fluorouracil(5-FU)/Leucovorin (LV) Combination Schedules**

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. 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 therapy

Toxicity NCI CTC grade ^a (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy ^b
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/ mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/ mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/ mm^3)	Omit dose until resolved to \leq grade 2, then ↓ 1 dose level	↓ 1 dose level
4 ($<500/\text{mm}^3$)	Omit dose until resolved to \leq grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia 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)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day $>$ pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day $>$ pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	↓ 1 dose level
4 (≥ 10 stools/day $>$ pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other nonhematologic toxicities^d		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to \leq grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to \leq grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to \leq grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	<i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR</i>	<i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.</i>

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

^b Relative to the starting dose used in the previous cycle

^c Pretreatment

^d Excludes alopecia, anorexia, asthenia

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754 **Single-Agent Dosage Schedules**

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756 ***Dosage Regimens***

757 CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for
758 both the weekly and once-every-3-week dosage schedules (see Preparation of Infusion
759 Solution). Single-agent dosage regimens are shown in Table 12.

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Table 12. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Weekly Regimen^a	125 mg/m ² IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels^c (mg/m²)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen^b	350 mg/m ² IV over 90 min, once every 3 wks ^c		
	Starting Dose & Modified Dose Levels (mg/m²)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

^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.

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

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A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: age \geq 65 years, prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin $>$ 2 mg/dL cannot be recommended since such patients were not included in clinical studies.

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Dose Modifications

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

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

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 Week
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) 2 (1000 to 1499/ mm^3) 3 (500 to 999/ mm^3) 4 (<500/ mm^3)	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 25 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
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) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2 then $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 25 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
Other nonhematologic^d toxicities 1 2 34	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 50 \text{ mg/m}^2$	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ $\downarrow 25 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$	Maintain dose level $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$

^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

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787 **Preparation & Administration Precautions**

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

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795 **Preparation of Infusion Solution**

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

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

802 The solution is physically and chemically stable for up to 24 hours at room temperature
803 (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose
804 Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and
805 protected from light are physically and chemically stable for 48 hours. Refrigeration of
806 admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low
807 and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of
808 CAMPTOSAR may result in precipitation of the drug and should be avoided. Because of
809 possible microbial contamination during dilution, it is advisable to use the admixture
810 prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to
811 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium
812 Chloride Injection, USP, the solutions should be used within 6 hours if kept at room
813 temperature (15° to 30°C, 59° to 86°F).

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

817

818 **HOW SUPPLIED**

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

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

824 2 mL NDC 0009-7529-02

825 5 mL NDC 0009-7529-01

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

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

832

833 **Rx only**

834

835 **REFERENCES**

- 836 1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH
837 Publication No. 83-2621. For sale by the Superintendent of Documents, US Government
838 Printing Office, Washington, DC 20402.
- 839 2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985;
840 253(11): 1590-2.
- 841 3. National Study Commission on Cytotoxic Exposure. Recommendations for handling
842 cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study
843 Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied
844 Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
- 845 4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe
846 handling of antineoplastic agents. Med J Australia 1983;1:426-8.
- 847 5. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai
848 Medical Center. CA-A Cancer J for Clinicians, 1983; Sept./Oct., 258-63.
- 849 6. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling
850 cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033-49.
- 851 7. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice
852 Guidelines). Am J Health-Syst Pharm 1996;53:1669-85.

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