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2 **CAMPTOSAR®**  
3 irinotecan hydrochloride injection

4  
5 For Intravenous Use Only  
6

7 **WARNINGS**

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

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

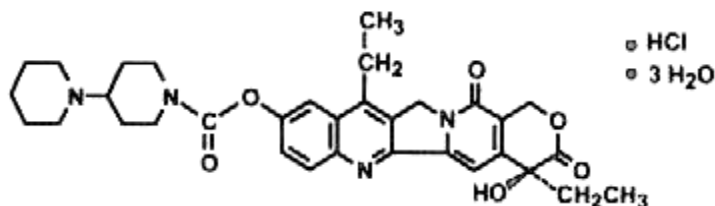
24 Severe myelosuppression may occur (see WARNINGS).  
25

26 **DESCRIPTION**

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

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

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

42  
43

44 Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical  
45 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 water  
46 and organic solvents.

47

### 48 CLINICAL PHARMACOLOGY

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

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

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

70

71 **Pharmacokinetics**

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

77 Over the recommended dose range of 50 to 350 mg/m<sup>2</sup>, the AUC of irinotecan increases  
 78 linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum  
 79 concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of  
 80 a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following  
 81 a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m<sup>2</sup> determined in two clinical  
 82 studies in patients with solid tumors are summarized in Table 1:  
 83

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

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

C<sub>max</sub> - Maximum plasma concentration

AUC<sub>0-24</sub> - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion

t<sub>1/2</sub> - Terminal elimination half-life

V<sub>z</sub> - Volume of distribution of terminal elimination phase

CL - Total systemic clearance

<sup>a</sup> Plasma specimens collected for 24 hours following the end of the 90-minute infusion.

<sup>b</sup> 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.

84  
 85 Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly  
 86 bound to human plasma proteins (approximately 95% bound). The plasma protein to which  
 87 irinotecan and SN-38 predominantly binds is albumin.

88 *Metabolism and Excretion:* The metabolic conversion of irinotecan to the active metabolite  
 89 SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38  
 90 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide had  
 91 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The  
 92 disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan  
 93 is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary  
 94 excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48  
 95 hours following administration of irinotecan in two patients ranged from approximately 25%  
 96 (100 mg/m<sup>2</sup>) to 50% (300 mg/m<sup>2</sup>).

97

98 **Pharmacokinetics in Special Populations**

99 *Geriatric:* In studies using the weekly schedule, the terminal half-life of irinotecan was  
100 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years.  
101 Dose-normalized AUC<sub>0-24</sub> for SN-38 in patients who were at least 65 years of age was 11% higher  
102 than in patients younger than 65 years. No change in the starting dose is recommended for geriatric  
103 patients receiving the weekly dosage schedule of irinotecan.

104 The pharmacokinetics of irinotecan given once every 3 weeks has not been studied in the geriatric  
105 population; a lower starting dose is recommended in patients 70 years or older based on clinical  
106 toxicity experience with this schedule (see DOSAGE AND ADMINISTRATION).

107

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

109

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

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

112 *Hepatic Insufficiency:* The influence of hepatic insufficiency on the pharmacokinetic characteristics  
113 of irinotecan and its metabolites has not been formally studied. Among patients with known hepatic  
114 tumor involvement (a majority of patients), irinotecan and SN-38 AUC values were somewhat  
115 higher than values for patients without liver metastases (see PRECAUTIONS).

116 *Renal Insufficiency:* The influence of renal insufficiency on the pharmacokinetics of irinotecan has  
117 not been evaluated.

118

119 **Drug-Drug Interactions**

120 In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in  
121 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the  
122 drugs were co-administered. Although the C<sub>max</sub> and AUC<sub>0-24</sub> of SN-38, the active metabolite, were  
123 reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV  
124 administration compared with when irinotecan was given alone, this sequence of administration was  
125 used in the combination trials and is recommended (see DOSAGE AND ADMINISTRATION).  
126 Formal in vivo or in vitro drug interaction studies to evaluate the influence of irinotecan on the  
127 disposition of 5-FU and LV have not been conducted.

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

130

131

132

133 **CLINICAL STUDIES**

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

140

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

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

157 In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant  
158 improvements in objective tumor response rates, time to tumor progression, and survival when  
159 compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line  
160 therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens  
161 in the control arm. Patient characteristics and major efficacy results are shown in Table 3.

162

**Table 3. 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
<b>Demographics and Treatment Administration</b>					
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 <sup>a</sup> (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%) <sup>a</sup>					
Irinotecan	72	--	75	87	--
5-FU	71	86	--	86	93
<b>Efficacy Results</b>					
Confirmed Objective Tumor Response Rate <sup>b</sup> (%)	39 (p<0.0001) <sup>c</sup>	21	18	35 (p<0.005) <sup>c</sup>	22
Median Time to Tumor Progression <sup>d</sup> (months)	7.0 (p=0.004) <sup>d</sup>	4.3	4.2	6.7 (p<0.001) <sup>d</sup>	4.4
Median Survival (months)	14.8 (p<0.05) <sup>d</sup>	12.6	12.0	17.4 (p<0.05) <sup>d</sup>	14.1

<sup>a</sup> Study 1: N=225 (irinotecan/5-FU/LV), N=219 (5-FU/LV), N=223 (irinotecan)

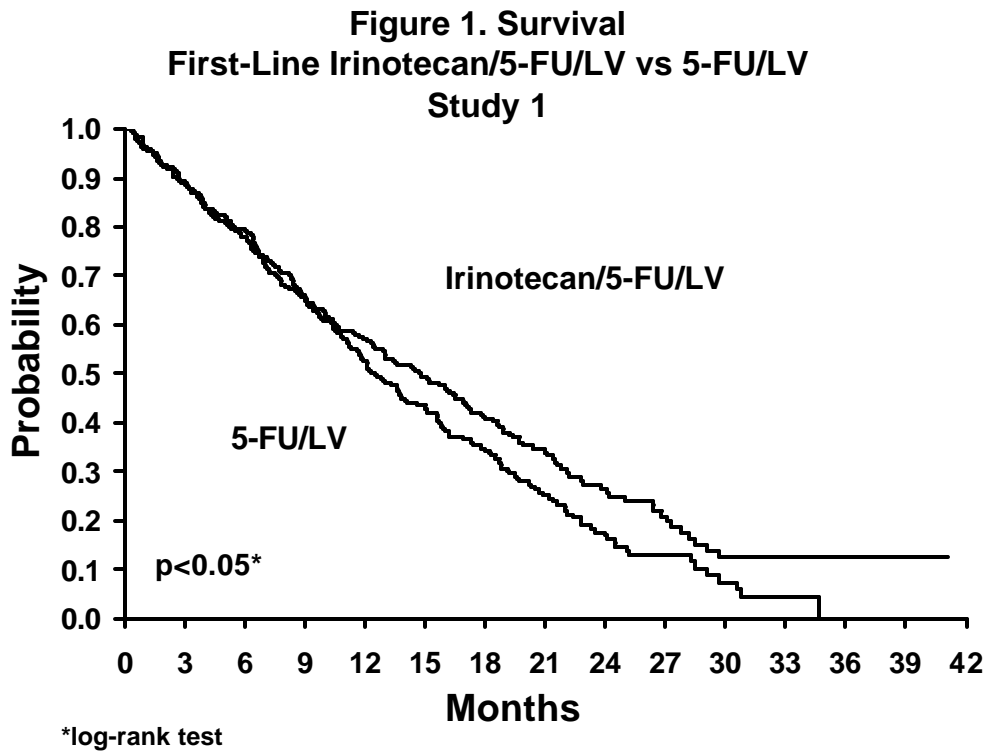
Study 2: N=199 (irinotecan/5-FU/LV), N=186 (5-FU/LV)

<sup>b</sup> Confirmed  $\geq 4$  to 6 weeks after first evidence of objective response

<sup>c</sup> Chi-square test

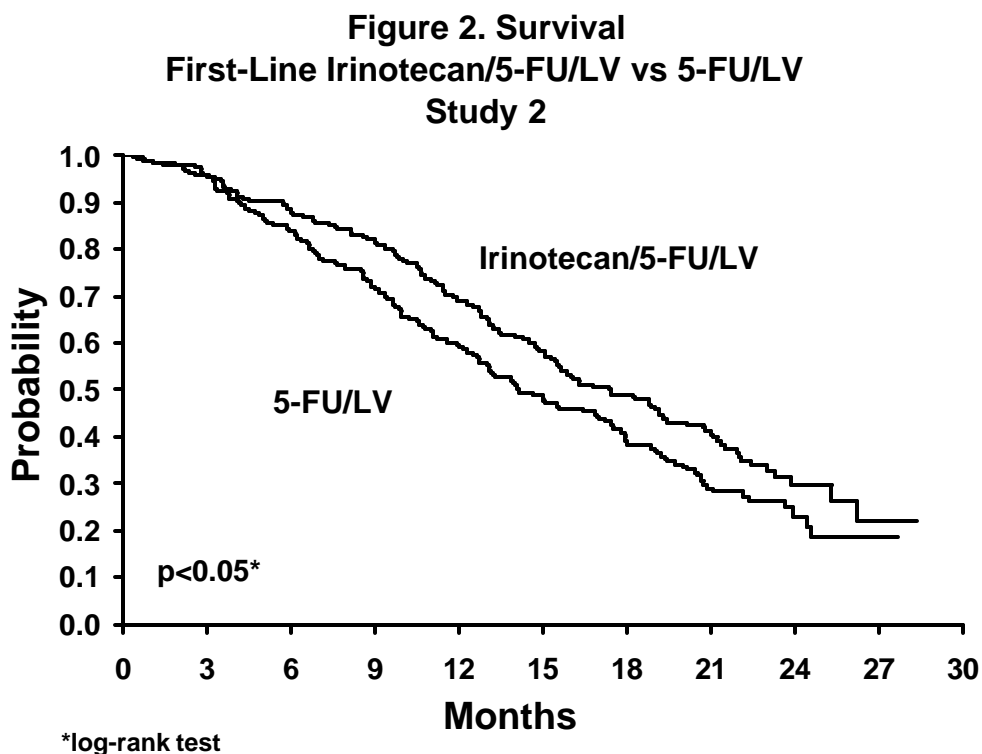
<sup>d</sup> Log-rank test

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



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171



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173 **Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer After**  
174 **5-FU-Based Treatment**

175

176 ***Weekly Dosage Schedule***

177

178 Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59  
179 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the  
180 colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy.

181

182 These studies were designed to evaluate tumor response rate and do not provide information on  
183 actual clinical benefit, such as effects on survival and disease-related symptoms. In each study,

184

185 CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous  
186 infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of

187

188 CAMPTOSAR in these trials were 100, 125, or 150 mg/m<sup>2</sup>, but the 150-mg/m<sup>2</sup> dose was poorly  
189 tolerated (due to unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1

190

191 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study  
2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients

192

enrolled in Study 2 received a starting dose of 125 mg/m<sup>2</sup>. Study 3 was a multicenter study that

193

enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m<sup>2</sup> but was  
reduced to 100 mg/m<sup>2</sup> because the toxicity seen at the 125-mg/m<sup>2</sup> dose was perceived to be

greater than that seen in previous studies. All patients in these studies had metastatic colorectal



192 cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen  
193 administered for metastatic disease. The results of the individual studies are shown in Table 4.  
194

**Table 4. Weekly Dosage Schedule: Study Results**

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Starting Dose (mg/m <sup>2</sup> /wk x 4)	125 <sup>a</sup>	125	125	100
<b>Demographics and Treatment Administration</b>				
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 <sup>b</sup> (median %)	74	67	73	81
<b>Efficacy</b>				
Confirmed Objective Response Rate (%) <sup>c</sup> (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

<sup>a</sup> Nine patients received 150 mg/m<sup>2</sup> as a starting dose; two (22.2%) responded to CAMPTOSAR.

<sup>b</sup> Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m<sup>2</sup>/wk corresponding with 150, 125, and 100 mg/m<sup>2</sup> starting doses, respectively.

<sup>c</sup> Confirmed = 4 to 6 weeks after first evidence of objective response.

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196 In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients  
197 began therapy at the recommended starting dose of 125 mg/m<sup>2</sup>. Among these 193 patients,  
198 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95%  
199 Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response  
200 rate was seen with a starting dose of 100 mg/m<sup>2</sup>. The majority of responses were observed within  
201 the first two cycles of therapy, but responses did occur in later cycles of treatment (one response  
202 was observed after the eighth cycle). The median response duration for patients beginning therapy at  
203 125 mg/m<sup>2</sup> was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three  
204 studies, response rates to CAMPTOSAR were similar in males and females and among patients  
205 older and younger than 65 years. Rates were also similar in patients with cancer of the colon or  
206 cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was  
207 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of  
208 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients  
209 responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received  
210 previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as  
211 those who had not previously received irradiation.

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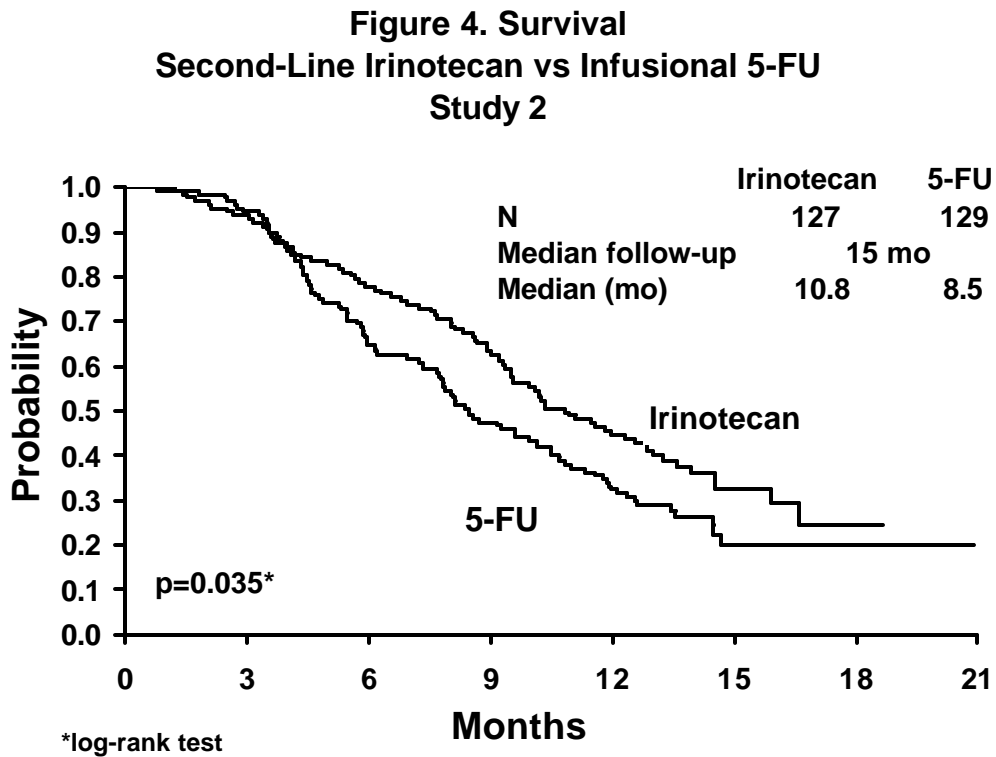
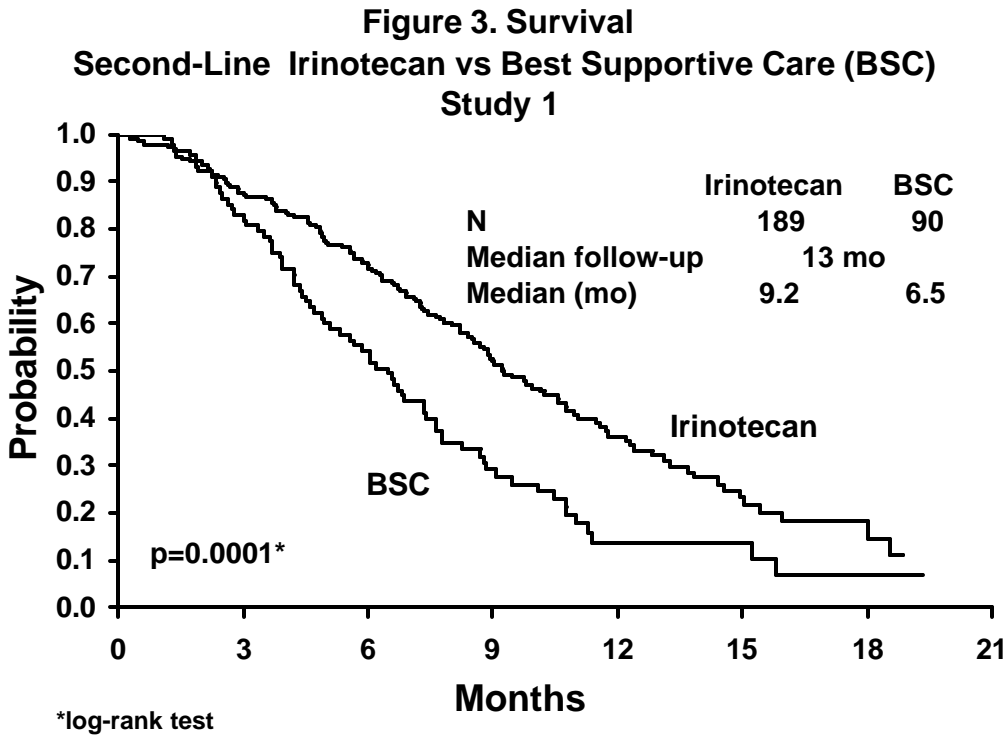
### 213 ***Once-Every-3-Week Dosage Schedule***

214 *Single-Arm Studies:* Data from an open-label, single-agent, single-arm, multicenter, clinical study  
215 involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the  
216 treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed  
217 following treatment with 5-FU. Patients received a starting dose of 350 mg/m<sup>2</sup> given by 30-minute  
218 intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the  
219 intent-to-treat response rate was 12.1% (95% CI,  
220 7.0% to 18.1%).

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

238 followed by 5-FU, 600 mg/m<sup>2</sup> continuous IV infusion over 22 hours on days 1 and 2 every 2  
239 weeks; (2) 5-FU, 250 to 300 mg/m<sup>2</sup>/day protracted continuous IV infusion until toxicity; (3) 5-FU,  
240 2.6 to 3 g/m<sup>2</sup> IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m<sup>2</sup>/day  
241 every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3  
242 to 6 weeks for 1 year.

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



263

**Table 5. Once-Every-3-Week Dosage Schedule: Study Results**

	Study 1		Study 2	
	Irinotecan	BSC <sup>a</sup>	Irinotecan	5-FU
Number of Patients	189	90	127	129
<b>Demographics and Treatment Administration</b>				
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 %) <sup>b</sup>	94	--	95	81-99
<b>Survival</b>				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

<sup>a</sup> BSC = best supportive care

<sup>b</sup> Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m<sup>2</sup>/wk corresponding with 350 and 300 mg/m<sup>2</sup> starting doses, respectively.

264

265 In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of  
 266 each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as “Did  
 267 pain interfere with daily activities?” (1 = Not at All, to 4 = Very Much) and “Do you have any  
 268 trouble taking a long walk?” (Yes or No). The answers from the 30 questions were converted into  
 269 15 subscales, that were scored from 0 to 100, and the global health status subscale that was  
 270 derived from two questions about the patient’s sense of general well being in the past week. In  
 271 addition to the global health status subscale, there were five functional (i.e., cognitive, emotional,  
 272 social, physical, role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia,  
 273 constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results as  
 274 summarized in Table 6 are based on patients’ worst post-baseline scores. In Study 1, a multivariate  
 275 analysis and univariate analyses of the individual subscales were performed and corrected for  
 276 multivariate testing. Patients receiving irinotecan reported significantly better results for the global  
 277 health status, on two of five functional subscales, and on four of nine symptom subscales. As  
 278 expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best  
 279 supportive care. In Study 2, the multivariate analysis on all 15 subscales did not indicate a  
 280 statistically significant difference between irinotecan and infusional 5-FU.

281

**Table 6. EORTC QLQ-C30: Mean Worst Post-Baseline Score<sup>a</sup>**

QLQ-C30 Subscale	Study 1			Study 2		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
<b>Global Health Status</b>	47	37	0.03	53	52	0.9
<b>Functional Scales</b>						
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
<b>Symptom Scales</b>						
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

<sup>a</sup> For 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.

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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.

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## CONTRAINDICATIONS

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

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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 12).

295

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.

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

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

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### **Neutropenia**

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

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

336

### **Hypersensitivity**

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

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### **Colitis/Ileus**

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



344 **Renal Impairment/Renal Failure**

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

347  
348 **Thromboembolism**

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

351  
352 **Pregnancy**

353 CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity  
354 related to <sup>14</sup>C-irinotecan crosses the placenta of rats following intravenous administration of  
355 10 mg/kg (which in separate studies produced an irinotecan C<sub>max</sub> and AUC about 3 and 0.5 times,  
356 respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup>). Administration of 6  
357 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C<sub>max</sub> and  
358 AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered  
359 125 mg/m<sup>2</sup>) and rabbits (about one-half the recommended human weekly starting dose on a mg/m<sup>2</sup>  
360 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-  
361 implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses  
362 greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C<sub>max</sub> and AUC about  
363 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m<sup>2</sup>) and in  
364 rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a mg/m<sup>2</sup>  
365 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.  
366 Irinotecan administered to rat dams for the period following organogenesis through weaning at  
367 doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the  
368 offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the  
369 drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the  
370 patient should be apprised of the potential hazard to the fetus. Women of childbearing potential  
371 should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

372  
373 **PRECAUTIONS**

374  
375 **General**

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

380 *Premedication with Antiemetics:* Irinotecan is emetogenic. It is recommended that patients  
381 receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the  
382 majority of patients received 10 mg of dexamethasone given in conjunction with another type of  
383 antiemetic agent, such as a 5-HT<sup>3</sup> blocker (e.g., ondansetron or granisetron). Antiemetic agents  
384 should be given on the day of treatment, starting at least 30 minutes before administration of  
385 CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g.,  
386 prochlorperazine) for subsequent use as needed.

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

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

398 The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been  
399 established. In clinical trials of either dosing schedule, irinotecan was not administered to patients  
400 with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver  
401 metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. However in  
402 clinical trials of the weekly dosage schedule, it has been noted that patients with modestly elevated  
403 baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of  
404 experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than  
405 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; p<0.001). Patients with abnormal  
406 glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of  
407 myelosuppression when receiving therapy with CAMPTOSAR. An association between baseline  
408 bilirubin elevations and an increased risk of late diarrhea has not been observed in studies of the  
409 weekly dosage schedule.

410

#### 411 **Information for Patients**

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

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

429 Patients should be alerted to the possibility of alopecia.

430

### 431 **Laboratory Tests**

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

434

### 435 **Drug Interactions**

436

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

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

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

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

451 The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%,  
452 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than  
453 when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of  
454 akathisia, however, is within the range reported for use of prochlorperazine when given as a  
455 premedication for other chemotherapies.

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

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

461

### 462 **Drug-Laboratory Test Interactions**

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

464

### 465 **Carcinogenesis, Mutagenesis & Impairment of Fertility**

466 Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however,  
467 administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in  
468 separate studies, the 25 mg/kg dose produced an irinotecan  $C_{max}$  and AUC that were about  
469 7.0 times and 1.3 times the respective values in patients administered 125 mg/m<sup>2</sup> weekly) and were  
470 then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend  
471 with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial  
472 stromal sarcomas. Neither irinotecan nor SN-38 was mutagenic in the in vitro Ames assay.

473 Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells)  
474 and in vivo (micronucleus test in mice). No significant adverse effects on fertility and general  
475 reproductive performance were observed after intravenous administration of irinotecan in doses of  
476 up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive organs was  
477 observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies  
478 produced an irinotecan  $C_{max}$  and AUC about 5 and 1 times, respectively, the corresponding values  
479 in patients administered 125 mg/m<sup>2</sup> weekly) and dogs at 0.4 mg/kg (which in separate studies  
480 produced an irinotecan  $C_{max}$  and AUC about one-half and 1/15<sup>th</sup>, respectively, the corresponding  
481 values in patients administered 125 mg/m<sup>2</sup> weekly).

### 482 **Pregnancy**

483 Pregnancy Category D—see WARNINGS.

### 484 **Nursing Mothers**

485 Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled  
486 irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma  
487 concentrations. Because many drugs are excreted in human milk and because of the potential for  
488 serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when  
489 receiving therapy with CAMPTOSAR.  
490  
491

### 492 **Pediatric Use**

493 The effectiveness of irinotecan in pediatric patients has not been established. Results from two  
494 open-label, single arm studies were evaluated. One hundred and seventy children with refractory  
495 solid tumors were enrolled in one phase 2 trial in which 50 mg/m<sup>2</sup> of irinotecan was infused for 5  
496 consecutive days every 3 weeks. Grade 3- 4 neutropenia was experienced by 54 (31.8%) patients.  
497 Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3- 4 diarrhea was observed in  
498 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the  
499 second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m<sup>2</sup> of  
500 irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was  
501 followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the  
502 high rate (28.6%) of progressive disease and the early deaths (14%) The adverse event profile was  
503 different in this study from that observed in adults; the most significant grade 3 or 4 adverse events  
504 were dehydration experienced by 6 patients (28.6%) associated with severe hypokalaemia in 5  
505 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was  
506 reported in 5 patients (23.8%)(across all courses of therapy and irrespective of causal relationship).  
507  
508

509 Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor  
510 trials at dose levels of 50 mg/m<sup>2</sup> (60-min infusion, n=48) and 125 mg/m<sup>2</sup> (90-min infusion, n=6).  
511 Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m<sup>2</sup> for the 50 mg/m<sup>2</sup> dose and 16.2 ± 4.6  
512 L/h/m<sup>2</sup> for the 125 mg/m<sup>2</sup> dose, which is comparable to that in adults. Dose-normalized SN-38  
513 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and  
514 SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x  
515 2 weeks every 3 weeks].

516  
517

### 518 **Geriatric Use**

519 Patients greater than 65 years of age should be closely monitored because of a greater risk of  
520 late diarrhea in this population (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special  
521 Populations and ADVERSE REACTIONS, Overview of Adverse Events). The starting dose of  
522 CAMPTOSAR in patients 70 years and older for the once-every-3-week- dosage schedule should  
523 be 300 mg/m<sup>2</sup> (see DOSAGE AND ADMINISTRATION).

524

### 525 **ADVERSE REACTIONS**

526

#### 527 **First-Line Combination Therapy**

528 A total of 955 patients with metastatic colorectal cancer received the recommended regimens of  
529 irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3  
530 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received  
531 5-FU/LV alone, and 223 patients received irinotecan alone. (See Table 12 in DOSAGE AND  
532 ADMINISTRATION for recommended combination-agent regimens.)

533 In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received  
534 irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%)  
535 received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who  
536 received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients  
537 who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during  
538 thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic  
539 fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (6.7%)  
540 patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-  
541 FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to  
542 adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with  
543 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who  
544 received irinotecan alone.

545 In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received  
546 irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one  
547 potentially treatment-related death, which occurred in a patient who received irinotecan in  
548 combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause within 60 days of  
549 first study treatment were reported for 3 (2.1%) patients who received irinotecan in combination  
550 with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone. Discontinuations due to

551 adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with  
552 5-FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

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

559 Tables 8 and 9 list the clinically relevant adverse events reported in Studies 1 and 2,  
560 respectively.  
561

**Table 8. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies<sup>a</sup>**

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
<b>GASTROINTESTINAL</b>						
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
<b>HEMATOLOGIC</b>						
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
<b>BODY AS A WHOLE</b>						
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
<b>METABOLIC &amp; NUTRITIONAL</b>						
↑ Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
<b>DERMATOLOGIC</b>						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia <sup>b</sup>	43.1	--	26.5	--	46.1	--
<b>RESPIRATORY</b>						
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
<b>NEUROLOGIC</b>						
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
<b>CARDIOVASCULAR</b>						
Vasodilatation	9.3	0.9	5.0	0	9.0	0

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Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic events <sup>c</sup>	9.3	--	11.4	--	5.4	--

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<sup>a</sup>Severity of adverse events based on NCI CTC (version 1.0)

<sup>b</sup>Complete hair loss = Grade 2

<sup>c</sup>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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**Table 9. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies<sup>a</sup>**

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
<b>TOTAL Adverse Events</b>	100	72.4	100	39.2
<b>GASTROINTESTINAL</b>				
Diarrhea				
late	72.4	14.4	44.8	6.3
grade 3	--	10.3	--	4.2
grade 4	--	4.1	--	2.1
Cholinergic syndrome <sup>b</sup>	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
<b>HEMATOLOGIC</b>				
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
<b>BODY AS A WHOLE</b>				
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
<b>METABOLIC &amp; NUTRITIONAL</b>				
↑ Bilirubin	19.1	3.5	35.9	10.6
<b>DERMATOLOGIC</b>				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia <sup>c</sup>	56.6	--	16.8	--
<b>RESPIRATORY</b>				
Dyspnea	9.7	1.4	4.9	0
<b>CARDIOVASCULAR</b>				
Hypotension	3.4	1.4	0.7	0
Thromboembolic events <sup>d</sup>	11.7	--	5.6	--

<sup>a</sup> Severity of adverse events based on NCI CTC (version 1.0)

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

<sup>c</sup> Complete hair loss = Grade 2

<sup>d</sup> 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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## **Second-Line Single-Agent Therapy**

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### ***Weekly Dosage Schedule***

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

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

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Adjustments in the dose of CAMPTOSAR were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The first dose of at least one cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m<sup>2</sup> starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m<sup>2</sup> dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 10 are based on the experience of the 304 patients enrolled in the three studies described in the CLINICAL STUDIES, Studies Evaluating the Weekly Dosage Schedule, section.

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**Table 10. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum<sup>a</sup>**

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
<b>GASTROINTESTINAL</b>		
Diarrhea (late) <sup>b</sup>	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) <sup>c</sup>	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
<b>HEMATOLOGIC</b>		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm <sup>3</sup> (grade 3)	—	(15)
<500/mm <sup>3</sup> (grade 4)	—	(12)
<b>BODY AS A WHOLE</b>		
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 <sup>d</sup>	14	0
Edema	10	1
Abdominal enlargement	10	0
<b>METABOLIC &amp; NUTRITIONAL</b>		
↓ Body weight	30	1
Dehydration	15	4
↑ Alkaline phosphatase	13	4
↑ SGOT	10	1
<b>DERMATOLOGIC</b>		
Alopecia	60	NA <sup>e</sup>
Sweating	16	0
Rash	13	1
<b>RESPIRATORY</b>		
Dyspnea	22	4
↑ Coughing	17	0
Rhinitis	16	0
<b>NEUROLOGIC</b>		
Insomnia	19	0
Dizziness	15	0
<b>CARDIOVASCULAR</b>		
Vasodilation (flushing)	11	0

<sup>a</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>b</sup> Occurring > 24 hours after administration of CAMPTOSAR

<sup>c</sup> Occurring ≤24 hours after administration of CAMPTOSAR

<sup>d</sup> Primarily upper respiratory infections

<sup>e</sup> Not applicable; complete hair loss = NCI grade 2

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

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

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

608 Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all  
609 grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic  
610 symptoms (47%), and neutropenia (30%). Table 11 lists the grade 3 and 4 adverse events reported  
611 in the patients enrolled to all treatment arms of the two studies described in the CLINICAL  
612 STUDIES, Studies Evaluating the Once-Every-3-Week Dosage Schedule, section.

613

**Table 11. Percent Of Patients Experiencing Grade 3 & 4 Adverse Events  
In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy<sup>a</sup>**

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

<sup>a</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>b</sup> BSC = best supportive care

<sup>c</sup> Hepatic includes events such as ascites and jaundice

<sup>d</sup> Cutaneous signs include events such as rash

<sup>e</sup> Respiratory includes events such as dyspnea and cough

<sup>f</sup> Neurologic includes events such as somnolence

<sup>g</sup> Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction

<sup>h</sup> Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

614

615 **Overview of Adverse Events**

616 *Gastrointestinal:* Nausea, vomiting, and diarrhea are common adverse events following treatment  
617 with CAMPTOSAR and can be severe. When observed, nausea and vomiting usually occur during  
618 or shortly after infusion of CAMPTOSAR. In the clinical studies testing the every 3-week-dosage  
619 schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the  
620 clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was  
621 11 days following administration of CAMPTOSAR. For patients starting treatment at the  
622 125-mg/m<sup>2</sup> weekly dose, the median duration of any grade of late diarrhea was 3 days. Among  
623 those patients treated at the 125-mg/m<sup>2</sup> weekly dose who experienced grade 3 or 4 late diarrhea,  
624 the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late  
625 diarrhea was somewhat greater in patients starting treatment at 125 mg/m<sup>2</sup> than in patients given a  
626 100-mg/m<sup>2</sup> weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The frequency of  
627 grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients  
628 <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In one study of the weekly dosage  
629 treatment, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in  
630 female patients (43% [25/58] versus 16% [5/32]; p=0.01), but there were no gender differences in  
631 the frequency of grade 3 and 4 late diarrhea in the other two studies of the weekly dosage treatment  
632 schedule. Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in  
633 association with administration of CAMPTOSAR.

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

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

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

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

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

659 *Respiratory:* Severe pulmonary events are infrequent. In the clinical studies evaluating the weekly  
660 dosage schedule, NCI grade 3 or 4 dyspnea was reported in 4% of patients. Over half the patients  
661 with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other  
662 preexisting lung disease may have contributed to dyspnea in these patients is unknown.

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

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

671

### 672 **Other Non-U.S. Clinical Trials**

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

684

### 685 **Post-Marketing Experience**

686 The following events have been identified during post-marketing use of CAMPTOSAR  
687 in clinical practice. Cases of colitis complicated by ulceration, bleeding, ileus, or infection have been  
688 observed. There have been rare cases of renal impairment and acute renal failure, generally in  
689 patients who became infected and/or volume depleted from severe gastrointestinal toxicities (see  
690 WARNINGS).

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

693

### 694 **OVERDOSAGE**

695 In U.S. phase 1 trials, single doses of up to 345 mg/m<sup>2</sup> of irinotecan were administered to  
696 patients with various cancers. Single doses of up to 750 mg/m<sup>2</sup> of irinotecan have been given in non-  
697 U.S. trials. The adverse events in these patients were similar to those reported with the  
698 recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR.

699 Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat  
 700 any infectious complications.

701

702 **DOSAGE AND ADMINISTRATION**

703 **Combination-Agent Dosage**

704 ***Dosage Regimens***

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

706 CAMPTOSAR should be administered as an intravenous infusion over 90 minutes (see  
 707 Preparation of Infusion Solution). For all regimens, the dose of LV should be administered  
 708 immediately after CAMPTOSAR, with the administration of 5-FU to occur immediately after  
 709 receipt of LV. CAMPTOSAR should be used as recommended; the currently recommended  
 710 regimens are shown in Table 12.

711

**Table 12. Combination-Agent Dosage Regimens & Dose Modifications<sup>a</sup>**

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU	Starting Dose & Modified Dose Levels (mg/m <sup>2</sup> )		
		Starting Dose	Dose Level -1	Dose Level -2
		125 mg/m <sup>2</sup> IV over 90 min, d 1,8,15,22 20 mg/m <sup>2</sup> IV bolus, d 1,8,15,22 500 mg/m <sup>2</sup> IV bolus, d 1,8,15,22	125	100
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 <sup>b</sup>	Starting Dose & Modified Dose Levels (mg/m <sup>2</sup> )		
		Starting Dose	Dose Level -1	Dose Level -2
		180 mg/m <sup>2</sup> IV over 90 min, d 1,15,29 200 mg/m <sup>2</sup> IV over 2 h, d 1,2,15,16,29,30 400 mg/m <sup>2</sup> IV bolus, d 1,2,15,16,29,30 600 mg/m <sup>2</sup> IV over 22 h, d 1,2,15,16,29,30	180	150
CAMPTOSAR	180	150	120	
LV	200	200	200	
5-FU Bolus	400	320	240	
5-FU Infusion <sup>b</sup>	600	480	360	

<sup>a</sup>Dose 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.

<sup>b</sup>Infusion follows bolus administration.

712

713 Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were  
 714 not included in clinical studies. It is recommended that patients receive premedication with  
 715 antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in  
 716 patients experiencing cholinergic symptoms. See PRECAUTIONS, General.

717

718 ***Dose Modifications***



719 Patients should be carefully monitored for toxicity and assessed prior to each treatment. Doses  
720 of CAMPTOSAR and 5-FU should be modified as necessary to accommodate individual patient  
721 tolerance to treatment. Based on the recommended dose-levels described in Table 12,  
722 Combination-Agent Dosage Regimens & Dose Modifications, subsequent doses should be adjusted  
723 as suggested in Table 13, Recommended Dose Modifications for Combination Schedules. All dose  
724 modifications should be based on the worst preceding toxicity. After the first treatment, patients with  
725 active diarrhea should return to pre-treatment bowel function without requiring antidiarrhea  
726 medications for at least 24 hours before the next chemotherapy administration.

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

**Table 13. 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 <sup>a</sup> (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy <sup>b</sup>
No toxicity	Maintain dose level	Maintain dose level
<b>Neutropenia</b> 1 (1500 to 1999/ $\text{mm}^3$ ) 2 (1000 to 1499/ $\text{mm}^3$ ) 3 (500 to 999/ $\text{mm}^3$ ) 4 (<500/ $\text{mm}^3$ )	Maintain dose level ↓ 1 dose level Omit dose until resolved to $\leq$ grade 2, then ↓ 1 dose level Omit dose until resolved to $\leq$ grade 2, then ↓ 2 dose levels	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
<b>Neutropenic fever</b>	Omit dose until resolved, then ↓ 2 dose levels	
<b>Other hematologic toxicities</b>	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.	
<b>Diarrhea</b> 1 (2-3 stools/day > pretx <sup>c</sup> ) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 ( $\geq 10$ stools/day > pretx)	Delay dose until resolved to baseline, then give same dose Omit dose until resolved to baseline, then ↓ 1 dose level Omit dose until resolved to baseline, then ↓ 1 dose level Omit dose until resolved to baseline, then ↓ 2 dose levels	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
<b>Other nonhematologic toxicities<sup>d</sup></b> 1 2 3 4	Maintain dose level Omit dose until resolved to $\leq$ grade 1, then ↓ 1 dose level Omit dose until resolved to $\leq$ grade 2, then ↓ 1 dose level Omit dose until resolved to $\leq$ grade 2, then ↓ 2 dose levels  <i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR</i>	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels  <i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.</i>

<sup>a</sup> National Cancer Institute Common Toxicity Criteria (version 1.0)

<sup>b</sup> Relative to the starting dose used in the previous cycle

<sup>c</sup> Pretreatment

<sup>d</sup> Excludes alopecia, anorexia, asthenia

732

733 **Single-Agent Dosage Schedules**

734

735 ***Dosage Regimens***

736 CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the  
 737 weekly and once-every-3-week dosage schedules (see Preparation of Infusion Solution). Single-  
 738 agent dosage regimens are shown in Table 14.

739

**Table 14. Single-Agent Regimens of CAMPTOSAR and Dose Modifications**

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

<sup>a</sup>Subsequent doses may be adjusted as high as 150 mg/m<sup>2</sup> or to as low as 50 mg/m<sup>2</sup> in 25 to 50 mg/m<sup>2</sup> decrements depending upon individual patient tolerance.

<sup>b</sup>Subsequent doses may be adjusted as low as 200 mg/m<sup>2</sup> in 50 mg/m<sup>2</sup> decrements depending upon individual patient tolerance.

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

740

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

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

748

749 ***Dose Modifications***

750 Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should be  
 751 modified as necessary to accommodate individual patient tolerance to treatment. Based on  
 752 recommended dose-levels described in Table 14, Single-Agent Regimens of CAMPTOSAR and  
 753 Dose Modifications, subsequent doses should be adjusted as suggested in Table 15, Recommended  
 754 Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the  
 755 worst preceding toxicity.

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

762

**Table 15. Recommended Dose Modifications For Single-Agent Schedules<sup>a</sup>**

**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 <sup>b</sup> (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 <sup>a</sup>	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	$\uparrow 25 \text{ mg/m}^2$ up to a maximum dose of $150 \text{ mg/m}^2$	Maintain dose level
<b>Neutropenia</b> 1 (1500 to 1999/ $\text{mm}^3$ ) 2 (1000 to 1499/ $\text{mm}^3$ ) 3 (500 to 999/ $\text{mm}^3$ ) 4 (<500/ $\text{mm}^3$ )	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 $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
<b>Neutropenic fever</b>	Omit dose until resolved, then $\downarrow 50 \text{ mg/m}^2$ when resolved	$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
<b>Other hematologic toxicities</b>	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.		
<b>Diarrhea</b> 1 (2-3 stools/day > pretx <sup>c</sup> ) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 ( $\geq 10$ 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 $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
<b>Other nonhematologic<sup>d</sup> toxicities</b> 1 2 3 4	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 $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$

<sup>a</sup> All dose modifications should be based on the worst preceding toxicity

<sup>b</sup> National Cancer Institute Common Toxicity Criteria (version 1.0)

<sup>c</sup> Pretreatment

<sup>d</sup> Excludes alopecia, anorexia, asthenia

763

764 **Preparation & Administration Precautions**

765 As with other potentially toxic anticancer agents, care should be exercised in the handling and  
 766 preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is  
 767 recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and  
 768 thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush  
 769 thoroughly with water. Several published guidelines for handling and disposal of anticancer agents  
 770 are available.<sup>1-7</sup>

771

772 **Preparation of Infusion Solution**

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

775 CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in  
776 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final  
777 concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, CAMPTOSAR was administered  
778 in 250 mL to 500 mL of 5% Dextrose Injection, USP.

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

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

793

#### 794 **HOW SUPPLIED**

795 Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate  
796 salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range,  
797 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

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

800 2 mL NDC 0009-7529-02

801 5 mL NDC 0009-7529-01

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

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

808

809 Rx only

810

#### 811 **REFERENCES**

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