

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20571/S9**

**FINAL PRINTED LABELING**

1 **WARNINGS**

2  
3 CAMPTOSAR Injection should be administered only under the supervision of a physician  
4 who is experienced in the use of cancer chemotherapeutic agents. Appropriate management  
5 of complications is possible only when adequate diagnostic and treatment facilities are  
6 readily available.

7  
8 CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated  
9 by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring  
10 during or shortly after infusion of CAMPTOSAR) may be accompanied by cholinergic  
11 symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and  
12 intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other  
13 cholinergic symptoms may be prevented or ameliorated by atropine (see PRECAUTIONS,  
14 General). Late diarrhea (generally occurring more than 24 hours after administration of  
15 CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and  
16 can be life threatening. Late diarrhea should be treated promptly with loperamide; patients  
17 with severe diarrhea should be carefully monitored and given fluid and electrolyte  
18 replacement if they become dehydrated (see WARNINGS section). Administration of  
19 CAMPTOSAR should be interrupted and subsequent doses reduced if severe diarrhea occurs  
20 (see DOSAGE AND ADMINISTRATION).

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22 Severe myelosuppression may occur (see WARNINGS section).

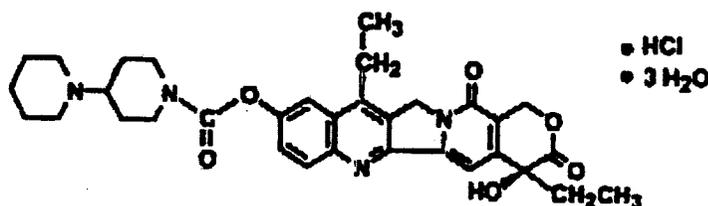
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24 **DESCRIPTION**

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

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

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

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### Irinotecan Hydrochloride

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52 Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical  
53 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  
54 water and organic solvents.

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### 57 CLINICAL PHARMACOLOGY

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

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68 Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is  
69 formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond  
70 between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately  
71 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and  
72 rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative  
73 to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration

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75 versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95%  
76 bound to plasma proteins compared to approximately 50% bound to plasma proteins for  
77 irinotecan (see Pharmacokinetics). The precise contribution of SN-38 to the activity of  
78 CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form  
79 and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the  
80 two forms such that an acid pH promotes the formation of the lactone, while a more basic pH  
81 favors the hydroxy acid anion form.

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

### 85 86 **Pharmacokinetics**

87 After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline  
88 in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12  
89 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to  
90 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to  
91 those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

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93 Over the recommended dose range of 50 to 350 mg/m<sup>2</sup>, the AUC of irinotecan increases  
94 linearly with dose; the AUC of SN-38 increases less than proportionally with dose.  
95 Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour  
96 following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for  
97 irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and  
98 340 mg/m<sup>2</sup> determined in two clinical studies in patients with solid tumors are summarized in  
99 Table 1:

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Table 1. Summary Of Mean ( $\pm$  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 $\pm$ 797	10,200 $\pm$ 3,270	5.8 <sup>a</sup> $\pm$ 0.7	110 $\pm$ 48.5	13.3 $\pm$ 6.01	26.3 $\pm$ 11.9	229 $\pm$ 108	10.4 <sup>a</sup> $\pm$ 3.1
340 (N=6)	3,392 $\pm$ 874	20,604 $\pm$ 6,027	11.7 <sup>b</sup> $\pm$ 1.0	234 $\pm$ 69.6	13.9 $\pm$ 4.00	56.0 $\pm$ 28.2	474 $\pm$ 245	21.0 <sup>b</sup> $\pm$ 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.

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

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

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### 131 Pharmacokinetics in Special Populations

132 *Geriatric:* In studies using the weekly schedule, the terminal half-life of irinotecan was  
 133 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than  
 134 65 years. Dose-normalized AUC<sub>0-24</sub> for SN-38 in patients who were at least 65 years of age  
 135 was 11% higher than in patients younger than 65 years. No change in the starting dose is  
 136 recommended for geriatric patients receiving the weekly dosage schedule of irinotecan.  
 137 The pharmacokinetics of irinotecan given once every 3 weeks has not been studied in the  
 138 geriatric population; a lower starting dose is recommended in patients 70 years or older based  
 139 on clinical toxicity experience with this schedule (see DOSAGE AND  
 140 ADMINISTRATION).

141 *Pediatric:* Information regarding the pharmacokinetics of irinotecan is not available.  
142 *Gender:* The pharmacokinetics of irinotecan do not appear to be influenced by gender.  
143 *Race:* The influence of race on the pharmacokinetics of irinotecan has not been evaluated.  
144 *Hepatic Insufficiency:* The influence of hepatic insufficiency on the pharmacokinetic  
145 characteristics of irinotecan and its metabolites has not been formally studied. Among  
146 patients with known hepatic tumor involvement (a majority of patients), irinotecan and  
147 SN-38 AUC values were somewhat higher than values for patients without liver metastases  
148 (see PRECAUTIONS).  
149 *Renal Insufficiency:* The influence of renal insufficiency on the pharmacokinetics of  
150 irinotecan has not been evaluated.

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### 152 **Drug-Drug Interactions**

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

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

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### 167 **CLINICAL STUDIES**

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

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#### 176 **First-line Therapy in Combination with 5-FU/LV for the Treatment of Metastatic** 177 **Colorectal Cancer**

178 Two phase 3, randomized, controlled, multinational clinical trials support the use of  
179 CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the  
180 colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were  
181 compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus  
182 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily

183 for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was  
184 also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV,  
185 with or without irinotecan.

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

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**Table 2. Combination Dosage Schedule: Study Results**

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 q 6 weeks	Bolus 5-FU/LV daily x 5 q 4 weeks	Irinotecan weekly x 4 q 6 weeks	Irinotecan + Infusional 5-FU/LV	Infusional 5-FU/LV
Number of Patients	231	226	226	198	187
<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<.0001) <sup>c</sup>	21	18	35 (p<.005) <sup>c</sup>	22
Median Time to Tumor Progression <sup>d</sup> (months)	7.0 (p=.004) <sup>d</sup>	4.3	4.2	6.7 (p<.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)

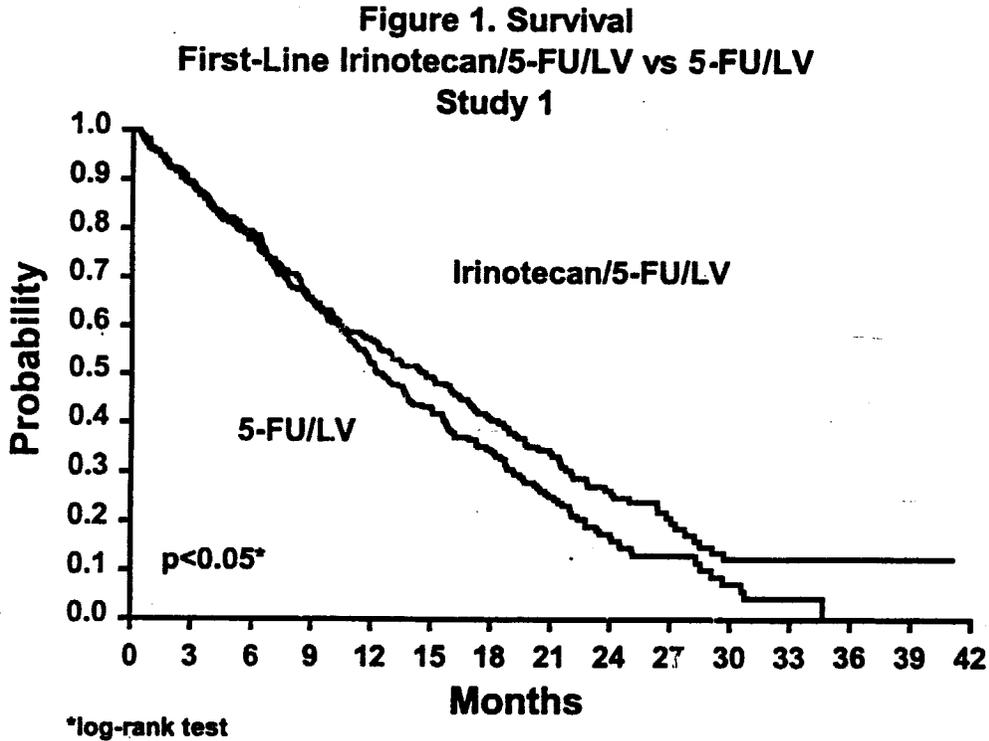
Study 2: N=199 (irinotecan/5-FU/LV), N=186 (5-FU/LV)

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

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

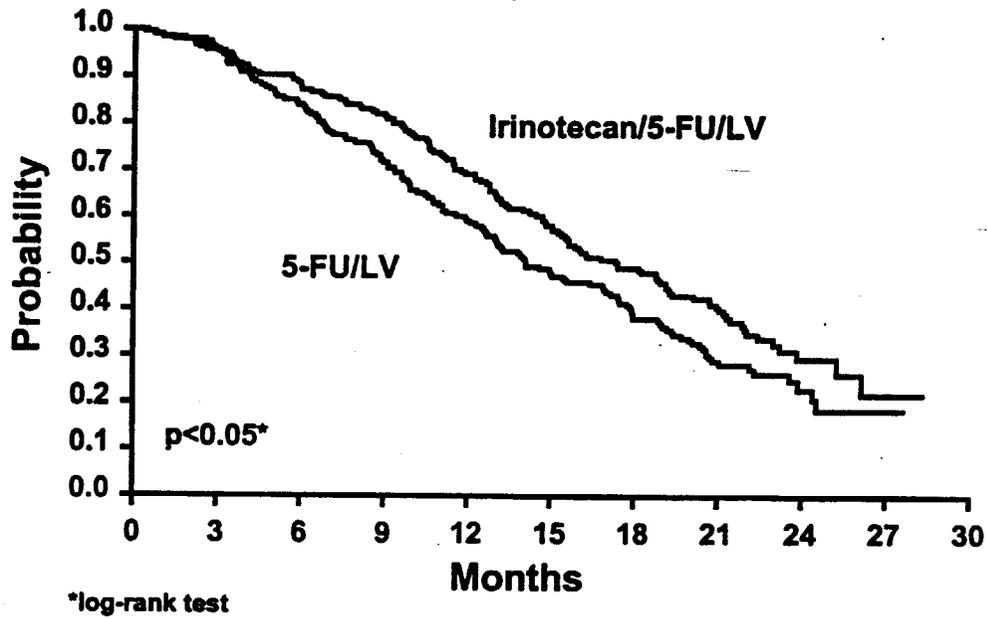
<sup>d</sup> Log-rank test

195 Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV  
196 when response rates and time to tumor progression were examined across the following  
197 demographic and disease-related subgroups (age, gender, ethnic origin, performance status,  
198 extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant  
199 therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier  
200 survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and  
201 2, respectively



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



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

***Weekly Dosage Schedule***

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week courses consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of 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 tolerated (due to unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1 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 enrolled in Study 2 received a starting dose of 125 mg/m<sup>2</sup>. Study 3 was a multicenter study that 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 cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 3.

**Table 3. 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 objection response.

229 In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304  
230 patients began therapy at the recommended starting dose of 125 mg/m<sup>2</sup>. Among these  
231 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate  
232 of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A  
233 considerably lower response rate was seen with a starting dose of 100 mg/m<sup>2</sup>. The majority of  
234 responses were observed within the first two courses of therapy, but responses did occur in  
235 later courses of treatment (one response was observed after the eighth course). The median  
236 response duration for patients beginning therapy at 125 mg/m<sup>2</sup> was 5.8 months (range, 2.6 to  
237 15.1 months). Of the 304 patients treated in the three studies, response rates to  
238 CAMPTOSAR were similar in males and females and among patients older and younger than  
239 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum  
240 and in patients with single and multiple metastatic sites. The response rate was 18.5% in  
241 patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or  
242 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the  
243 patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had  
244 received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the  
245 same rate as those who had not previously received irradiation.

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

248 *Single-Arm Studies:* Data from an open-label, single-agent, single arm, multicenter, clinical  
249 study involving a total of 132 patients support a once every-3-week dosage schedule of  
250 irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that  
251 recurred or progressed following treatment with 5-FU. Patients received a starting dose of  
252 350 mg/m<sup>2</sup> given by 30-minute intravenous infusion once every 3 weeks. Among the 132  
253 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI,  
254 7.0% to 18.1%).

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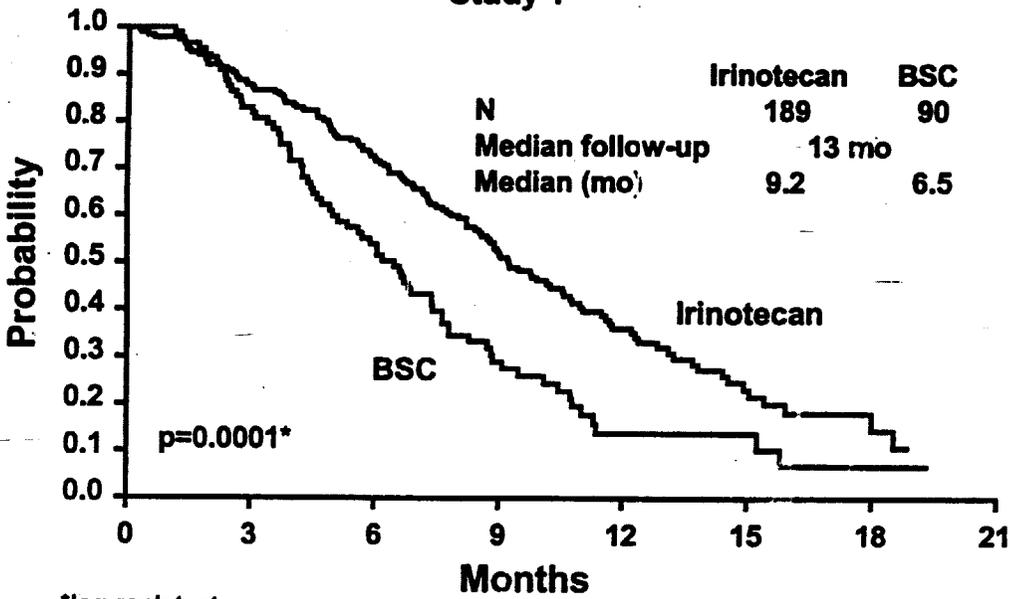
256 *Randomized Trials:* Two multicenter, randomized, clinical studies further support the use of  
257 irinotecan given by the once-every-3-week dosage schedule in patients with metastatic  
258 colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In  
259 the first study, second-line irinotecan therapy plus best supportive care was compared with  
260 best supportive care alone. In the second study, second-line irinotecan therapy was compared  
261 with infusional 5-FU-based therapy. In both studies, irinotecan was administered  
262 intravenously at a starting dose of 350 mg/m<sup>2</sup> over 90 minutes once every 3 weeks. The  
263 starting dose was 300 mg/m<sup>2</sup> for patients who were 70 years and older or who had a  
264 performance status of 2. The highest total dose permitted was 700 mg. Dose reductions  
265 and/or administration delays were permitted in the event of severe hematologic and/or  
266 nonhematologic toxicities while on treatment. Best supportive care was provided to patients  
267 in both arms of Study 1 and included antibiotics, analgesics, corticosteroids, transfusions,  
268 psychotherapy, or any other symptomatic therapy as clinically indicated. Concomitant  
269 medications such as antiemetics, atropine, and loperamide were given to patients in the  
270 irinotecan arm for prophylaxis and/or management of symptoms from treatment. If late

271 diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of  
272 fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the second  
273 study received one of the following 5-FU regimens: (1) LV, 200 mg/m<sup>2</sup> IV over 2 hours;  
274 followed by 5-FU, 400 mg/m<sup>2</sup> IV bolus; followed by 5-FU, 600 mg/m<sup>2</sup> continuous IV  
275 infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m<sup>2</sup> /day  
276 protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m<sup>2</sup> IV over 24 hours  
277 every week for 6 weeks with or without LV, 20 to 500 mg/m<sup>2</sup> /day every week IV for 6  
278 weeks with 2-week rest between courses. Patients were to be followed every 3 to 6 weeks for  
279 1 year.

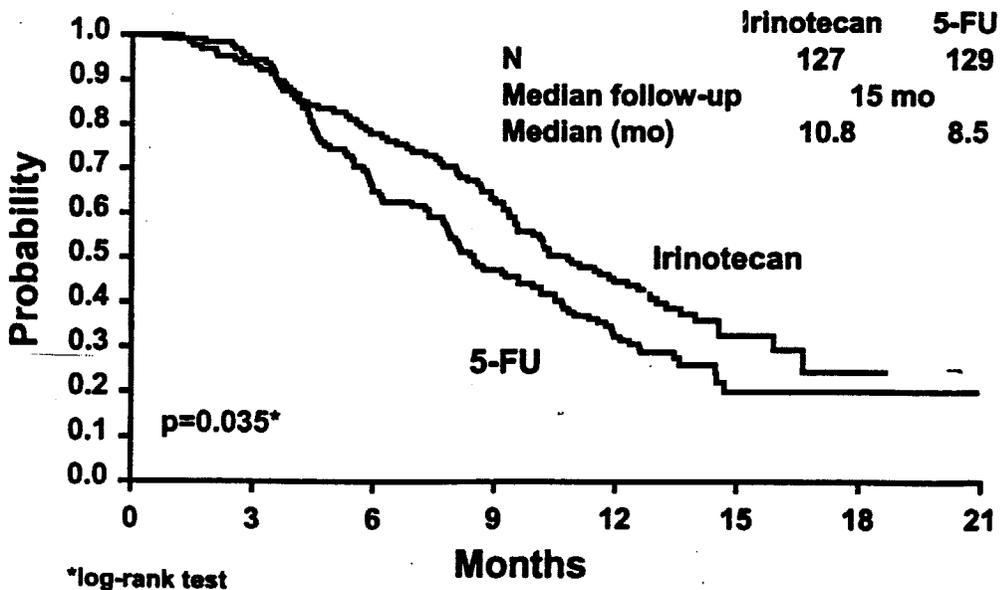
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281 A total of 535 patients were randomized in the two studies at 94 centers. The primary  
282 endpoint in both studies was survival. The studies demonstrated a significant overall survival  
283 advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-  
284 based therapy (p=0.035) as shown in Figures 3 and 4. In Study 1, median survival for patients  
285 treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best  
286 supportive care. In Study 2, median survival for patients treated with irinotecan was 10.8  
287 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy.  
288 Multiple regression analyses determined that patients' baseline characteristics also had a  
289 significant effect on survival. When adjusted for performance status and other baseline  
290 prognostic factors, survival among patients treated with irinotecan remained significantly  
291 longer than in the control populations (p=0.001 for Study 1 and p=0.017 for Study 2).  
292 Measurements of pain, performance status, and weight loss were collected prospectively in  
293 the two studies; however, the plan for the analysis of these data was defined retrospectively.  
294 When comparing irinotecan with best supportive care in Study 1, this analysis showed a  
295 statistically significant advantage for irinotecan, with longer time to development of pain  
296 (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus  
297 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally,  
298 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an  
299 improvement in performance status when treated with irinotecan versus 11.3% (7/62) of  
300 patients receiving best supportive care (p=0.002). Because of the inclusion of patients with  
301 non-measurable disease, intent-to-treat response rates could not be assessed.

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



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



302

**Table 4. 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)
<b>Performance Status (PS)</b>				
0 (%)	47	31	58	54
1 (%)	39	46	35	43
2 (%)	14	23	8	3
<b>Primary Tumor (%)</b>				
Colon	55	52	57	62
Rectum	45	48	43	38
<b>Prior 5-FU Therapy (%)</b>				
For Metastatic Disease	70	63	58	68
As Adjuvant Treatment	30	37	42	32
<b>Prior Irradiation (%)</b>				
	26	27	18	20
<b>Duration of Study Treatment (median, months)</b>				
	4.1	—	4.2 (p=0.02)	2.8
<b>Relative Dose Intensity (median %)<sup>b</sup></b>				
	94	—	95	81-99
<b>Survival</b>				
<b>Survival (median, months)</b>				
	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.

303

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

321

**Table 5. 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.

322

323

324

## INDICATIONS AND USAGE

325

326

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

330

331

332

## CONTRAINDICATIONS

333

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

334

335

336

## WARNINGS

337

338

### General

339

Outside of a well-designed clinical study, CAMPTOSAR 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).

340

341

342

343

344 **Diarrhea**

345 CAMPTOSAR Injection can induce both early and late forms of diarrhea that appear to be  
346 mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion  
347 of CAMPTOSAR) is cholinergic in nature. It is usually transient and only infrequently is  
348 severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis,  
349 lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal  
350 cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated  
351 by administration of atropine (see PRECAUTIONS, General, for dosing recommendations  
352 for atropine).

353

354 Late diarrhea (generally occurring more than 24 hours after administration of  
355 CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and  
356 can be life threatening. Late diarrhea should be treated promptly with loperamide (see  
357 PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide).  
358 Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte  
359 replacement if they become dehydrated. National Cancer Institute (NCI) grade 3 diarrhea is  
360 defined as an increase of 7 to 9 stools daily, or incontinence, or severe cramping and NCI  
361 grade 4 diarrhea is defined as an increase of  $\geq 10$  stools daily, or grossly bloody stool, or need  
362 for parenteral support. If grade 3 or 4 late diarrhea occurs, administration of CAMPTOSAR  
363 should be delayed until the patient recovers and subsequent doses should be decreased (see  
364 DOSAGE and ADMINISTRATION).

365

366 **Myelosuppression**

367 Deaths due to sepsis following severe myelosuppression have been reported in patients  
368 treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily omitted  
369 during a course of therapy if neutropenic fever occurs or if the absolute neutrophil count  
370 drops below  $1000/\text{mm}^3$ . After the patient recovers to an absolute neutrophil count  $\geq$   
371  $1000/\text{mm}^3$ , subsequent doses of CAMPTOSAR should be reduced depending upon the level  
372 of myelosuppression observed (see DOSAGE AND ADMINISTRATION).

373

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

376

377 **Hypersensitivity**

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

380

381 **Celitis/Ileus**

382 Cases of colitis complicated by ulceration, bleeding, ileus or what was described as toxic  
383 megacolon have been observed rarely. Cases of ileus without preceding colitis have also  
384 been observed rarely.

385

386 **Renal Impairment/Renal Failure**

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

389

390 **Pregnancy**

391 CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity  
392 related to <sup>14</sup>C-irinotecan crosses the placenta of rats following intravenous administration of  
393 10 mg/kg (which in separate studies produced an irinotecan C<sub>max</sub> and AUC about 3 and  
394 0.5 times, respectively, the corresponding values in patients administered 125 mg/m<sup>2</sup>).

395 Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies  
396 produced an irinotecan C<sub>max</sub> and AUC about 2 and 0.2 times, respectively, the corresponding  
397 values in patients administered 125 mg/m<sup>2</sup>) and rabbits (about one-half the recommended  
398 human weekly starting dose on a mg/m<sup>2</sup> basis) during the period of organogenesis, is  
399 embryotoxic as characterized by increased post-implantation loss and decreased numbers of  
400 live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in  
401 separate studies produced an irinotecan C<sub>max</sub> and AUC about 2/3 and 1/40th, respectively, of  
402 the corresponding values in patients administered 125 mg/m<sup>2</sup>) and in rabbits at 6.0 mg/kg/day  
403 (about one-half the recommended human weekly starting dose on a mg/m<sup>2</sup> basis).

404 Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.

405 Irinotecan administered to rat dams for the period following organogenesis through weaning  
406 at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights  
407 in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant  
408 women. If the drug is used during pregnancy, or if the patient becomes pregnant while  
409 receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women  
410 of childbearing potential should be advised to avoid becoming pregnant while receiving  
411 treatment with CAMPTOSAR.

412

413

414 **PRECAUTIONS.**

415

416 **General**

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

421 *Premedication with Antiemetics:* Irinotecan is emetogenic. It is recommended that patients  
422 receive premedication with antiemetic agents. In clinical studies of the weekly dosage  
423 schedule, the majority of patients received 10 mg of dexamethasone given in conjunction  
424 with another type of antiemetic agent, such as a 5-HT<sub>3</sub> blocker (e.g., ondansetron or  
425 granisetron). Antiemetic agents should be given on the day of treatment, starting at least  
426 30 minutes before administration of CAMPTOSAR. Physicians should also consider

427 providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as  
428 needed.

429 *Treatment of Cholinergic Symptoms:* Prophylactic or therapeutic administration of 0.25 to  
430 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically  
431 contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation,  
432 diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after  
433 infusion of CAMPTOSAR). These symptoms are expected to occur more frequently with  
434 higher irinotecan doses.

435 *Patients at Particular Risk:* Physicians should exercise particular caution in monitoring the  
436 effects of CAMPTOSAR in the elderly ( $\geq 65$  years) and in patients who had previously  
437 received pelvic/abdominal irradiation (see ADVERSE REACTIONS).

438

439 The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been  
440 established. In clinical trials of either dosing schedule, irinotecan was not administered to  
441 patients with serum bilirubin  $>2.0$  mg/dL, or transaminase  $>3$  times the upper limit of normal  
442 if no liver metastasis, or transaminase  $>5$  times the upper limit of normal with liver  
443 metastasis.

444

445 However in clinical trials of the weekly dosage schedule, it has been noted that patients with  
446 modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a  
447 significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than  
448 those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7%  
449 [47/226];  $p < 0.001$ ). Patients with abnormal glucuronidation of bilirubin, such as those with  
450 Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy  
451 with CAMPTOSAR. An association between baseline bilirubin elevations and an increased  
452 risk of late diarrhea has not been observed in studies of the weekly dosage schedule.

453

#### 454 **Information for Patients**

455 Patients and patients' caregivers should be informed of the expected toxic effects of  
456 CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting,  
457 and diarrhea. Each patient should be instructed to have loperamide readily available and to  
458 begin treatment for late diarrhea (generally occurring more than 24 hours after administration  
459 of CAMPTOSAR) at the first episode of poorly formed or loose stools or the earliest onset of  
460 bowel movements more frequent than normally expected for the patient. One dosage regimen  
461 for loperamide used in clinical trials consisted of the following (Note: This dosage regimen  
462 exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late  
463 diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours.  
464 During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should  
465 also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is  
466 not recommended.

467

468 The use of drugs with laxative properties should be avoided because of the potential for  
469 exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any  
470 laxative use.

471

472 Patients should consult their physician if vomiting occurs, fever or evidence of infection  
473 develops, or if symptoms of dehydration, such as fainting, light-headedness, or dizziness, are  
474 noted following therapy with CAMPTOSAR.

475

476 Patients should be alerted to the possibility of alopecia.

477

#### 478 **Laboratory Tests**

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

481

#### 482 **Drug Interactions**

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

485

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

490

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

495

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

500

501 The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%,  
502 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR  
503 than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence  
504 of akathisia, however, is within the range reported for use of prochlorperazine when given as  
505 a premedication for other chemotherapies.

506

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

509

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

513

#### 514 **Drug-Laboratory Test Interactions**

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

516

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

518 Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however,  
519 administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13  
520 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan  $C_{max}$  and AUC that  
521 were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m<sup>2</sup>  
522 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a  
523 significant linear trend with dose for the incidence of combined uterine horn endometrial  
524 stromal polyps and endometrial stromal sarcomas. Neither irinotecan nor SN-38 was  
525 mutagenic in the in vitro Ames assay. Irinotecan was clastogenic both in vitro (chromosome  
526 aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). No  
527 significant adverse effects on fertility and general reproductive performance were observed  
528 after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and  
529 rabbits. However, atrophy of male reproductive organs was observed after multiple daily  
530 irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an  
531 irinotecan  $C_{max}$  and AUC about 5 and 1 times, respectively, the corresponding values in  
532 patients administered 125 mg/m<sup>2</sup> weekly) and dogs at 0.4 mg/kg (which in separate studies  
533 produced an irinotecan  $C_{max}$  and AUC about one-half and 1/15th, respectively, the  
534 corresponding values in patients administered 125 mg/m<sup>2</sup> weekly).

535

#### 536 **Pregnancy**

537 Pregnancy Category D—see WARNINGS.

538

#### 539 **Nursing Mothers**

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

545

546 **Pediatric Use**

547 The safety and effectiveness of CAMPTOSAR in pediatric patients have not been  
548 established.

549

550 **Geriatric Use**

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

556

557

558 **ADVERSE REACTIONS**

559

560 ***First-Line Combination Therapy***

561 A total of 955 patients with metastatic colorectal cancer received the recommended regimens  
562 of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone (see Table 9  
563 in DOSAGE AND ADMINISTRATION). In the two phase 3 studies, 370 patients received  
564 irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223  
565 patients received irinotecan alone.

566

567 In Study 1, 49 (7.3%) patients died within 30 days of study treatment: 21 (9.3%) received  
568 irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%)  
569 received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%)  
570 patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis),  
571 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding  
572 during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone  
573 (2 neutropenic fever). Discontinuations due to adverse events were reported for 17 (7.6%)  
574 patients who received irinotecan in combination with 5-FU/LV, 14 (6.4%) patients who  
575 received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

576

577 In Study 2, 10 (3.5%) patients died within 30 days of study treatment: 6 (4.1%) received  
578 irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was  
579 one potentially treatment-death, which occurred in a patient who received irinotecan in  
580 combination with 5-FU/LV (0.7%, neutropenic sepsis). Discontinuations due to adverse  
581 events were reported for 9 (6.2%) patients who received irinotecan in combination with  
582 5-FU/LV and 1 (0.7%) patients who received 5-FU/LV alone.

583

584 The most clinically significant adverse events (all grades 1-4) for patients receiving  
585 irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The  
586 most clinically significant adverse events for patients receiving 5-FU/LV therapy were  
587 diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia,

588 neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were  
589 observed less often with weekly irinotecan/5-FU/LV than with monthly administration of  
590 5-FU/LV.

591

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

594

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

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
<b>TOTAL Adverse Events</b>	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>a</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

595

<b>CARDIOVASCULAR</b>						
Vasodilatation	9.3	0.9	5.0	0	9.0	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thrombophlebitis	5.3	2.7	6.8	3.2	3.1	1.8
Pulmonary embolus	2.7	2.7	1.4	1.4	0.9	0.4
Myocardial infarction	1.3	1.3	0	0	0.4	0.4

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

596

597

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

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV infusional D1&2 q 2 weeks N= 145		5-FU/LV infusional D1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
<b>TOTAL Events</b>	100	72.4	100	39.2
<b>GASTROINTESTINAL</b>				
Diarrhea				
late	68.3	14.5	44.8	6.3
grade 3	--	10.3	--	4.2
grade 4	--	4.1	--	2.1
Cholinergic syndrome <sup>a</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	44.1	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	26.7	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	90.0	2.1
Neutropenic fever	--	9.3	--	2.3
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>b</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

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

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

598

26

599 **Second-Line Single-Agent Therapy**

600

601 ***Weekly Dosage Schedule***

602 In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic  
603 carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based  
604 therapy were treated with CAMPTOSAR Injection. Seventeen of the patients died within  
605 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were  
606 potentially drug-related. These five patients experienced a constellation of medical events  
607 that included known effects of CAMPTOSAR. One of these patients died of neutropenic  
608 sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients  
609 recovered with supportive care.

610

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

617

618 Adjustments in the dose of CAMPTOSAR were made during the course of treatment and for  
619 subsequent courses based on individual patient tolerance. The first dose of at least one course  
620 of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m<sup>2</sup>  
621 starting dose. Within-course dose reductions were required for 32% of the courses initiated at  
622 the 125-mg/m<sup>2</sup> dose level. The most common reasons for dose reduction were late diarrhea,  
623 neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with  
624 CAMPTOSAR because of adverse events. The adverse events in Table 8 are based on the  
625 experience of the 304 patients enrolled in the three studies described in the CLINICAL  
626 STUDIES, Studies Evaluating the Weekly Dosage Schedule, section.

627

628

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

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
<b>GASTROINTESTINAL</b>		
Diarrhea (late) <sup>a</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>b</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>c</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>d</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> Occurring > 24 hours after administration of CAMPTOSAR

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

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

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

629

630

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

632 A total of 535 patients with metastatic colorectal cancer whose disease had recurred or  
633 progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received  
634 irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients  
635 treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the  
636 deaths were potentially related to irinotecan treatment and were attributed to neutropenic  
637 infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with  
638 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

639

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

645

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

652

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

Adverse Event	Study 1		Study 2	
	Irinotecan n=189	BSC <sup>a</sup> n=90	Irinotecan n=127	5-FU n=129
<b>TOTAL Grade 3/4 Adverse Events</b>	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>b</sup>	9	7	9	6
<b>DERMATOLOGIC</b>				
Hand & foot syndrome	0	0	0	5
Cutaneous signs <sup>c</sup>	2	0	1	3
<b>RESPIRATORY <sup>d</sup></b>	10	8	5	7
<b>NEUROLOGIC <sup>e</sup></b>	12	13	9	4
<b>CARDIOVASCULAR <sup>f</sup></b>	9	3	4	2
<b>OTHER <sup>g</sup></b>	32	28	12	14

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

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

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

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

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

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

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

653

654

655 **Overview of Adverse Events**

656 *Gastrointestinal:* Nausea, vomiting, and diarrhea are common adverse events following  
 657 treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting  
 658 usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies

659 testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5  
660 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule,  
661 the median time to onset of late diarrhea was 11 days following administration of  
662 CAMPTOSAR. For patients starting treatment at the 125 mg/m<sup>2</sup> weekly dose, the median  
663 duration of any grade of late diarrhea was 3 days. Among those patients treated at the  
664 125 mg/m<sup>2</sup> weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of  
665 the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was  
666 somewhat greater in patients starting treatment at 125 mg/m<sup>2</sup> than in patients given a  
667 100 mg/m<sup>2</sup> weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The  
668 frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years  
669 than in patients <65 years (40% [53/133] versus 23% [40/171]; p = 0.002). In one study of  
670 the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly  
671 greater in male than in female patients (43% [25/58] versus 16% [5/32]; p = 0.01), but there  
672 were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two  
673 studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with  
674 gastrointestinal bleeding, has been observed in association with administration of  
675 CAMPTOSAR.

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

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

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

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

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

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

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

711 *Cardiovascular:* Vasodilation (flushing) may occur during administration of CAMPTOSAR.  
712 Bradycardia may also occur, but has not required intervention. These effects have been  
713 attributed to the cholinergic syndrome sometimes observed during or shortly after infusion of  
714 CAMPTOSAR.

715

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

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

729

#### 730 **Post-Marketing Experience**

731 The following events have been identified during post-marketing use of CAMPTOSAR  
732 in clinical practice. The events, which have been chosen for inclusion due to either their  
733 seriousness, frequency of reporting, possible causal connection to CAMPTOSAR, or a  
734 combination of these factors, include: rare cases of colitis complicated by ulceration,  
735 bleeding, ileus, or what was described as toxic megacolon; rare cases of ileus without  
736 preceding colitis; and rare cases of renal impairment and acute renal failure, generally in  
737 patients who became volume depleted from severe vomiting and/or diarrhea (see  
738 WARNINGS).

739

740 Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have  
741 been observed (see WARNINGS).

742

743 **OVERDOSAGE**

744

745 In U.S. phase 1 trials, single doses of up to 345 mg/m<sup>2</sup> of irinotecan were administered to  
746 patients with various cancers. Single doses of up to 750 mg/m<sup>2</sup> of irinotecan have been given  
747 in non-US trials. The adverse events in these patients were similar to those reported with the  
748 recommended dosage and regimen. There is no known antidote for overdosage of  
749 CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to  
750 diarrhea and to treat any infectious complications.

751

752 **DOSAGE AND ADMINISTRATION**

753

754 **Combination-Agent Dosage**

755

756 *Dosage Regimens*

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

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

763

764

**Table 10. Combination-Agent Dosage Regimens & Dose Modifications<sup>a</sup>**

Regimen 1 6-wk course with bolus 5-FU/LV (next course 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	100	75
20	20	20		
500	400	300		

Regimen 2 6-wk course with infusional 5-FU/LV (next course 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	150	120
200	200	200		
400	320	240		
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 courses may be continued indefinitely as long as patients continue to experience clinical benefit.

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

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

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**Dose Modifications**

Patients should be carefully monitored for toxicity, and 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.

781

782

783

A new course 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

784 therapy. Provided intolerable toxicity does not develop, treatment with additional courses of  
 785 CAMPTOSAR/5-FU/LV may be continued indefinitely as long as patients continue to  
 786 experience clinical benefit.  
 787

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

A new course 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 Course of Therapy	At the Start of Subsequent Courses of Therapy <sup>b</sup>
No toxicity	Maintain dose level	Maintain dose level
<b>Neutropenia</b>		
1 (1500 to 1999/ $\text{mm}^3$ )	Maintain dose level	Maintain dose level
2 (1000 to 1499/ $\text{mm}^3$ )	↓ 1 dose level	Maintain dose level
3 (500 to 999/ $\text{mm}^3$ )	Omit dose, then ↓ 1 dose level when resolved to $\leq$ grade 2	↓ 1 dose level
4 (< 500/ $\text{mm}^3$ )	Omit dose, then ↓ 2 dose levels when resolved to $\leq$ grade 2	↓ 2 dose levels
Neutropenic fever (grade 4 neutropenia & $\geq$ grade 2 fever)	Omit dose, then ↓ 2 dose levels when resolved	↓ 2 dose levels
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy and at the start of subsequent courses 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> )	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose, then ↓ 1 dose level when resolved to $\leq$ grade 2	↓ 1 dose level
4 ( $\geq$ 10 stools/day > pretx)	Omit dose, then ↓ 2 dose levels when resolved to $\leq$ grade 2	↓ 2 dose levels
<b>Other nonhematologic Toxicities</b>		
1	Maintain dose level	Maintain dose level
2	↓ 1 dose level	Maintain dose level
3	Omit dose, then ↓ 1 dose level when resolved to $\leq$ grade 2	↓ 1 dose level
4	Omit dose, then ↓ 2 dose levels when resolved to $\leq$ grade 2	↓ 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>

<sup>a</sup>National Cancer Institute Common Toxicity Criteria

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

<sup>c</sup>Pretreatment

788

789

790 **Single-Agent Dosage Schedules**

791 ***Dosage Regimens***

792

793 CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both  
 794 the weekly and once-every-3-week dosage schedules (see Preparation of Infusion Solution).

795 Single-agent dosage regimens are shown in Table 12.

796  
 797

**Table 12. 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>		
	<b>Starting Dose</b>	<b>Dose Level -1</b>	<b>Dose Level -2</b>
	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>		
	<b>Starting Dose</b>	<b>Dose Level -1</b>	<b>Dose Level -2</b>
	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 courses may be continued indefinitely as long as patients continue to experience clinical benefit.

798

799

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

805

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

809

### 810 ***Dose Modifications***

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

817

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

824

**Table 13. Recommended Dose Modifications For Single-Agent Schedules<sup>a</sup>**

A new course 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 Course of Therapy		At the Start of the Next Courses of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Course <sup>a</sup>	
	Weekly	Weekly	Weekly	Once Every 3 Week
No toxicity	Maintain dose level		↑ 25 mg/m <sup>2</sup> up to a maximum dose of 150 mg/m <sup>2</sup>	Maintain dose level
Neutropenia 1 (1500 to 1999/mm <sup>3</sup> ) 2 (1000 to 1499/mm <sup>3</sup> ) 3 (500 to 999/mm <sup>3</sup> ) 4 (<500/mm <sup>3</sup> )	Maintain dose level ↓ 25 mg/m <sup>2</sup> Omit dose, then ↓ 25 mg/m <sup>2</sup> when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m <sup>2</sup> when resolved to ≤ grade 2		Maintain dose level Maintain dose level ↓ 25 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>	Maintain dose level Maintain dose level ↓ 50 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓ 50 mg/m <sup>2</sup> when resolved		↓ 50 mg/m <sup>2</sup>	↓ 50 mg/m <sup>2</sup>
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses 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 <sup>c</sup> ) 2 (4-6 stools/day > pretx <sup>c</sup> ) 3 (7-9 stools/day > pretx <sup>c</sup> ) 4 (≥ 10 stools/day > pretx <sup>c</sup> )	Maintain dose level ↓ 25 mg/m <sup>2</sup> Omit dose, then ↓ 25 mg/m <sup>2</sup> when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m <sup>2</sup> when resolved to ≤ grade 2		Maintain dose level Maintain dose level ↓ 25 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>	Maintain dose level Maintain dose level ↓ 50 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>
Other nonhematologic toxicities 1 2 3 4	Maintain dose level ↓ 25 mg/m <sup>2</sup> Omit dose, then ↓ 25 mg/m <sup>2</sup> when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m <sup>2</sup> when resolved to ≤ grade 2		Maintain dose level ↓ 25 mg/m <sup>2</sup> ↓ 25 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>	Maintain dose level ↓ 50 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup> ↓ 50 mg/m <sup>2</sup>

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

<sup>b</sup> National Cancer Institute Common Toxicity Criteria

<sup>c</sup> Pretreatment

827

828 **Preparation & Administration Precautions**

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

835

836 **Preparation of Infusion Solution**

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

839

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

844

845 The solution is physically and chemically stable for up to 24 hours at room temperature  
846 (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose  
847 Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and  
848 protected from light are physically and chemically stable for 48 hours. Refrigeration of  
849 admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low  
850 and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of  
851 CAMPTOSAR may result in precipitation of the drug and should be avoided. Because of  
852 possible microbial contamination during dilution, it is advisable to use the admixture  
853 prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to  
854 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium  
855 Chloride Injection, USP, the solutions should be used within 6 hours if kept at room  
856 temperature (15° to 30°C, 59° to 86°F).

857

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

861

862

863 **HOW SUPPLIED**

864 Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate  
865 salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to  
866 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

867

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

870           2 mL           NDC 0009-7529-02  
871           5 mL           NDC 0009-7529-01

872

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

876

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

880

881 Rx only

882

#### 883 REFERENCES

884

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902

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