

1
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).

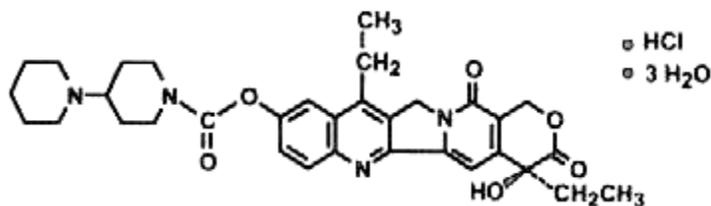
24 Severe myelosuppression may occur (see WARNINGS).

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:



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/m², 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/m² 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 ²)	Irinotecan					SN-38		
	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)	V _z (L/m ²)	CL (L/h/m ²)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)
125 (N=64)	1,660 ± 797	10,200 ± 3,270	5.8 ^a ± 0.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	10.4 ^a ± 3.1
340 (N=6)	3,392 ± 874	20,604 ± 6,027	11.7 ^b ± 1.0	234 ± 69.6	13.9 ± 4.0	56.0 ± 28.2	474 ± 245	21.0 ^b ± 4.3

C_{max} - Maximum plasma concentration

AUC₀₋₂₄ - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion

t_{1/2} - Terminal elimination half-life

V_z - Volume of distribution of terminal elimination phase

CL - Total systemic clearance

^a Plasma specimens collected for 24 hours following the end of the 90-minute infusion.

^b Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

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/m²) to 50% (300 mg/m²).

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

128 *Anticonvulsants:* Exposure to irinotecan and its active metabolite SN-38 is substantially reduced
129 in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing
130 anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for
131 patients taking these anticonvulsants has not been formally defined. The following drugs are also
132 CYP3A4 inducers: rifampin, rifabutin. For patients requiring anticonvulsant treatment, consideration
133 should be given to substituting non-enzyme inducing anticonvulsants at least 2 weeks prior to
134 initiation of irinotecan therapy. Dexamethasone does not appear to alter the pharmacokinetics of
135 irinotecan.

136 *St. John's Wort:* St. John's Wort is an inducer of CYP3A4 enzymes. Exposure to the active
137 metabolite SN-38 is reduced in patients receiving concomitant St. John's Wort. St. John's Wort
138 should be discontinued at least 2 weeks prior to the first cycle of irinotecan, and St. John's Wort is
139 contraindicated during irinotecan therapy.

140 *Ketoconazole*: Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients receiving
141 concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38.
142 Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy and
143 ketoconazole is contraindicated during irinotecan therapy.
144

145 **CLINICAL STUDIES**

146 Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and
147 leucovorin (LV) and as a single agent (see DOSAGE AND ADMINISTRATION). When given as
148 a component of combination-agent treatment, irinotecan was either given with a weekly schedule of
149 bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and a once-
150 every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies
151 of combination and single-agent use are described below.
152

153 **First-Line Therapy in Combination with 5-FU/LV for the Treatment of Metastatic** 154 **Colorectal Cancer**

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

169 In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant
170 improvements in objective tumor response rates, time to tumor progression, and survival when
171 compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line
172 therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens
173 in the control arm. Patient characteristics and major efficacy results are shown in Table 3.
174

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

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

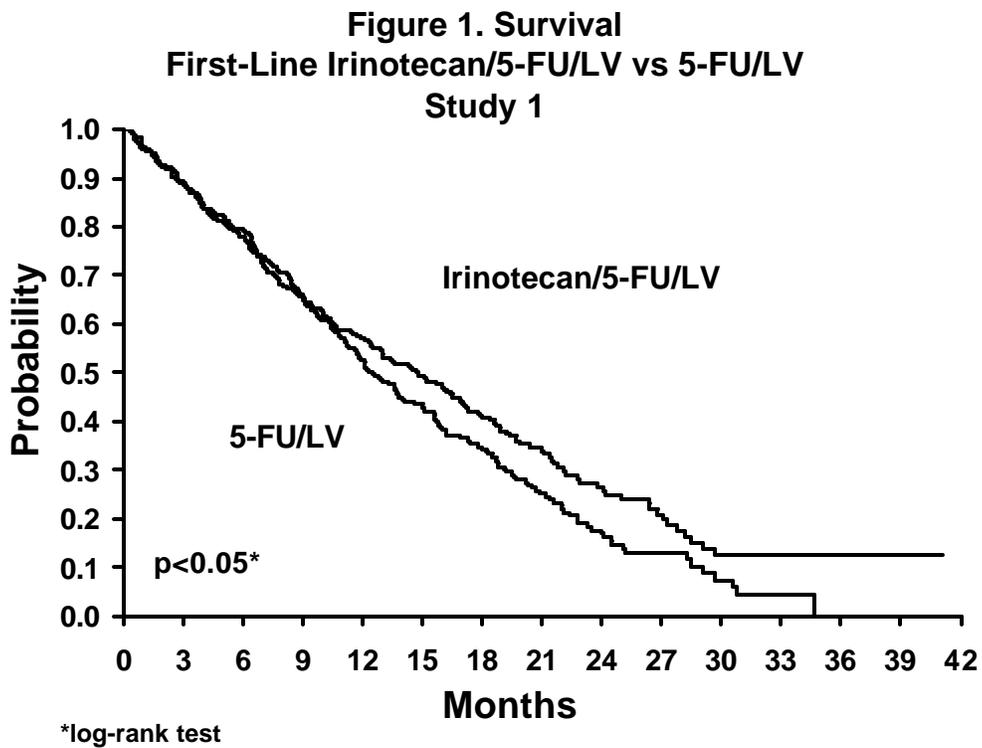
Study 2: N=199 (irinotecan/5-FU/LV), N=186 (5-FU/LV)

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

^c Chi-square test

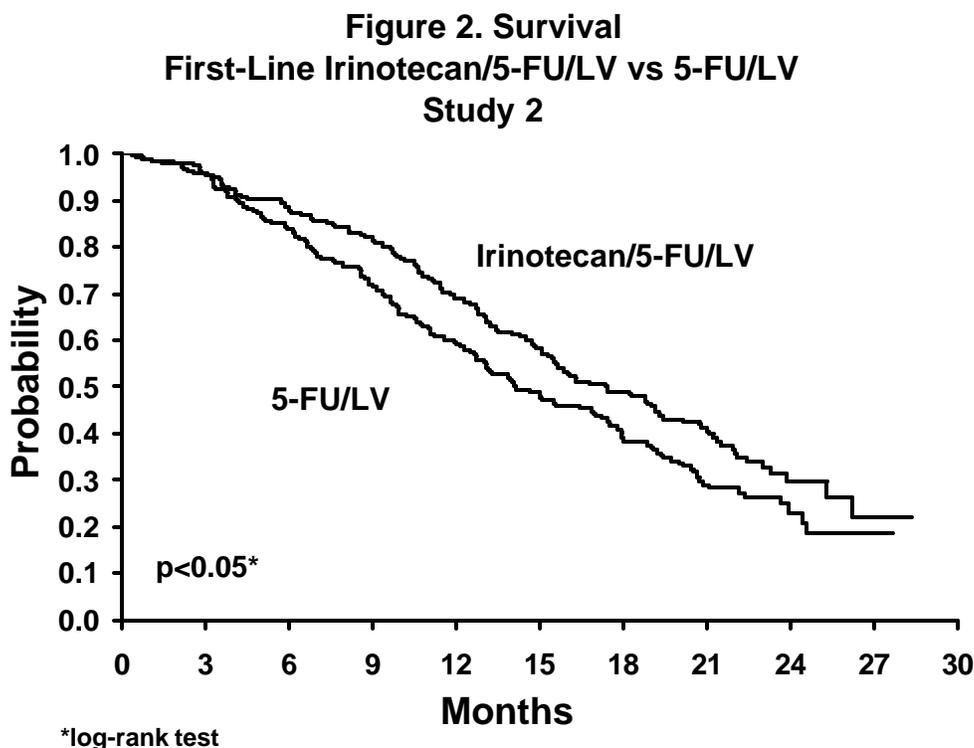
^d Log-rank test

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



182

183



184

185 **Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer After**
186 **5-FU-Based Treatment**

187

188 ***Weekly Dosage Schedule***

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

204 cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen
205 administered for metastatic disease. The results of the individual studies are shown in Table 4.
206

Table 4. Weekly Dosage Schedule: Study Results

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

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

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

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

207

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

224

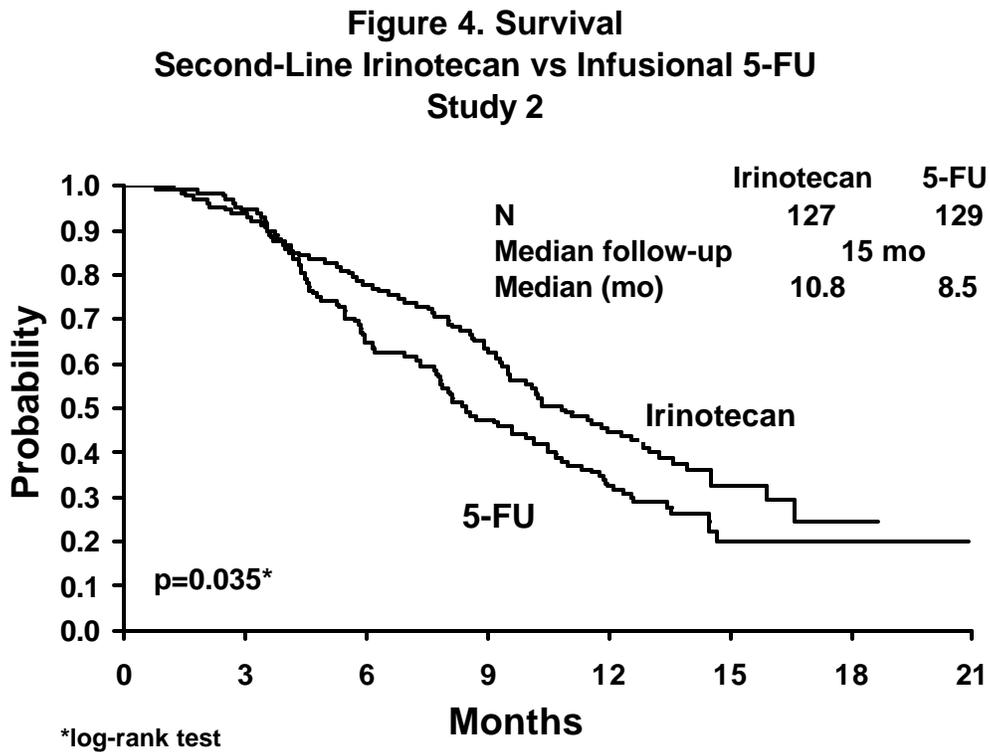
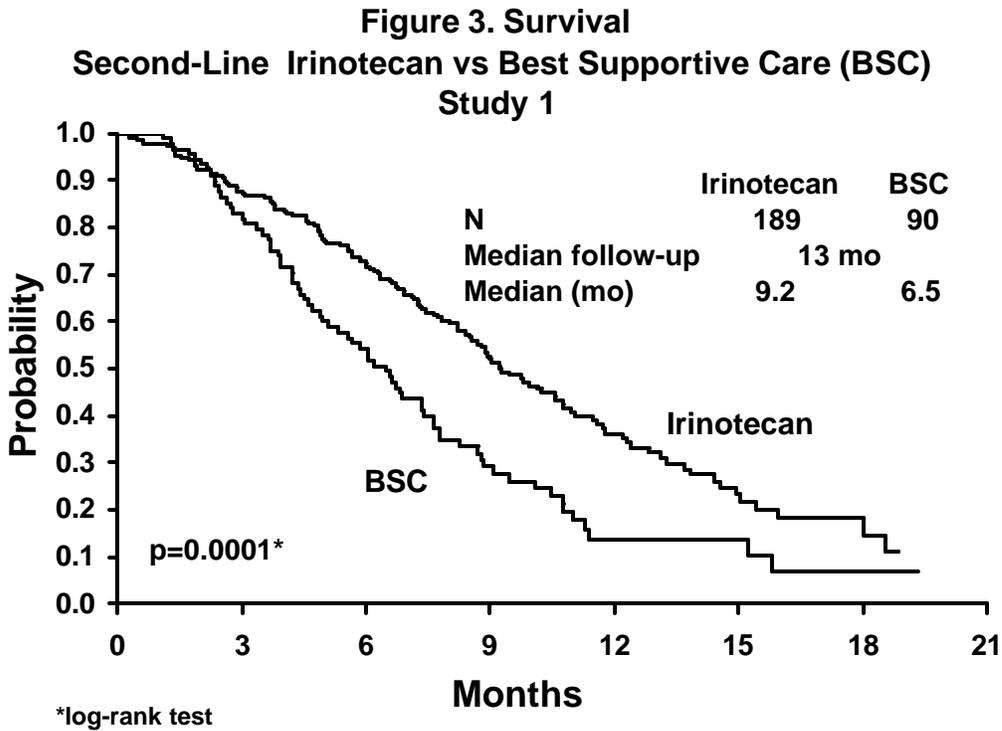
225 ***Once-Every-3-Week Dosage Schedule***

226 *Single-Arm Studies:* Data from an open-label, single-agent, single-arm, multicenter, clinical study
227 involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the
228 treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed
229 following treatment with 5-FU. Patients received a starting dose of 350 mg/m² given by 30-minute
230 intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the
231 intent-to-treat response rate was 12.1% (95% CI,
232 7.0% to 18.1%).

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

250 followed by 5-FU, 600 mg/m² continuous IV infusion over 22 hours on days 1 and 2 every 2
251 weeks; (2) 5-FU, 250 to 300 mg/m²/day protracted continuous IV infusion until toxicity; (3) 5-FU,
252 2.6 to 3 g/m² IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m²/day
253 every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3
254 to 6 weeks for 1 year.

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



275

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

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

^a BSC = best supportive care

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

276

277 In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of
278 each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as “Did
279 pain interfere with daily activities?” (1 = Not at All, to 4 = Very Much) and “Do you have any
280 trouble taking a long walk?” (Yes or No). The answers from the 30 questions were converted into
281 15 subscales, that were scored from 0 to 100, and the global health status subscale that was
282 derived from two questions about the patient’s sense of general well being in the past week. In
283 addition to the global health status subscale, there were five functional (i.e., cognitive, emotional,
284 social, physical, role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia,
285 constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results as
286 summarized in Table 6 are based on patients’ worst post-baseline scores. In Study 1, a multivariate
287 analysis and univariate analyses of the individual subscales were performed and corrected for
288 multivariate testing. Patients receiving irinotecan reported significantly better results for the global
289 health status, on two of five functional subscales, and on four of nine symptom subscales. As
290 expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best
291 supportive care. In Study 2, the multivariate analysis on all 15 subscales did not indicate a
292 statistically significant difference between irinotecan and infusional 5-FU.

293

Table 6. EORTC QLQ-C30: Mean Worst Post-Baseline Score^a

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

^a 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.

294

295

INDICATIONS AND USAGE

296

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.

297

298

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.

299

300

301

CONTRAINDICATIONS

302

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

303

304

305

WARNINGS

306

307

General

308

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).

309

310

311

312

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.

313

314

315

316

317

Diarrhea

318

319

320

321

322

323

324

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).

325

326

327

328

329

330

331

332

333

334

335

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).

336

337

Neutropenia

338

339

340

341

342

343

344

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).

345

346

347

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.

348

Hypersensitivity

349

350

351

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

352

Colitis/Ileus

353

354

355

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

356 **Renal Impairment/Renal Failure**

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

359

360 **Thromboembolism**

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

363

364 **Pregnancy**

365 CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity
366 related to ¹⁴C-irinotecan crosses the placenta of rats following intravenous administration of
367 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times,
368 respectively, the corresponding values in patients administered 125 mg/m²). Administration of 6
369 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and
370 AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered
371 125 mg/m²) and rabbits (about one-half the recommended human weekly starting dose on a mg/m²
372 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-
373 implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses
374 greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about
375 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m²) and in
376 rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a mg/m²
377 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.
378 Irinotecan administered to rat dams for the period following organogenesis through weaning at
379 doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the
380 offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the
381 drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the
382 patient should be apprised of the potential hazard to the fetus. Women of childbearing potential
383 should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

384

385 **PRECAUTIONS**

386

387 **General**

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

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

399 *Treatment of Cholinergic Symptoms:* Prophylactic or therapeutic administration of 0.25 to 1 mg
400 of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in
401 patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing,
402 abdominal cramping, or diarrhea (occurring during or shortly after infusion of CAMPTOSAR).

403 These symptoms are expected to occur more frequently with higher irinotecan doses.

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

410 The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been
411 established. In clinical trials of either dosing schedule, irinotecan was not administered to patients
412 with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver
413 metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. However in
414 clinical trials of the weekly dosage schedule, it has been noted that patients with modestly elevated
415 baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of
416 experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than
417 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; p<0.001). Patients with abnormal
418 glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of
419 myelosuppression when receiving therapy with CAMPTOSAR. An association between baseline
420 bilirubin elevations and an increased risk of late diarrhea has not been observed in studies of the
421 weekly dosage schedule.

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

425

426 **Information for Patients**

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

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

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

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

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

Drug Interactions

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

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

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

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

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

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

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

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m² weekly) and were

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

497 **Pregnancy**

498 Pregnancy Category D—see WARNINGS.

500 **Nursing Mothers**

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

507 **Pediatric Use**

508 The effectiveness of irinotecan in pediatric patients has not been established. Results from two
509 open-label, single arm studies were evaluated. One hundred and seventy children with refractory
510 solid tumors were enrolled in one phase 2 trial in which 50 mg/m² of irinotecan was infused for 5
511 consecutive days every 3 weeks. Grade 3- 4 neutropenia was experienced by 54 (31.8%) patients.
512 Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3- 4 diarrhea was observed in
513 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the
514 second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m² of
515 irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was
516 followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the
517 high rate (28.6%) of progressive disease and the early deaths (14%) The adverse event profile was
518 different in this study from that observed in adults; the most significant grade 3 or 4 adverse events
519 were dehydration experienced by 6 patients (28.6%) associated with severe hypokalaemia in 5
520 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was
521 reported in 5 patients (23.8%)(across all courses of therapy and irrespective of causal relationship).
522
523

524 Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor
525 trials at dose levels of 50 mg/m² (60-min infusion, n=48) and 125 mg/m² (90-min infusion, n=6).
526 Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m² for the 50 mg/m² dose and 16.2 ± 4.6
527 L/h/m² for the 125 mg/m² dose, which is comparable to that in adults. Dose-normalized SN-38
528 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and
529 SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x
530 2 weeks every 3 weeks].

531

532

533 **Geriatric Use**

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

539

540 **ADVERSE REACTIONS**

541

542 **First-Line Combination Therapy**

543 A total of 955 patients with metastatic colorectal cancer received the recommended regimens of
544 irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3
545 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received
546 5-FU/LV alone, and 223 patients received irinotecan alone. (See Table 12 in DOSAGE AND
547 ADMINISTRATION for recommended combination-agent regimens.)

548 In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received
549 irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%)
550 received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who
551 received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients
552 who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during
553 thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic
554 fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (6.7%)
555 patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-
556 FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to
557 adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with
558 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who
559 received irinotecan alone.

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

566 adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with
567 5-FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

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

574 Tables 8 and 9 list the clinically relevant adverse events reported in Studies 1 and 2,
575 respectively.
576

Table 8. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies^a

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

Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic events ^c	9.3	--	11.4	--	5.4	--

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

^bComplete hair loss = Grade 2

^c 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.

577

Table 9. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies^a

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

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

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

^c Complete hair loss = Grade 2

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

578

579

580

581

Second-Line Single-Agent Therapy

582

583

Weekly Dosage Schedule

584

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.

592

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%).

597

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/m² starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m² 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.

606

607

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

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

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

^b Occurring > 24 hours after administration of CAMPTOSAR

^c Occurring ≤24 hours after administration of CAMPTOSAR

^d Primarily upper respiratory infections

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

608

609

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

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

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

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

628

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

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

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

^b BSC = best supportive care

^c Hepatic includes events such as ascites and jaundice

^d Cutaneous signs include events such as rash

^e Respiratory includes events such as dyspnea and cough

^f Neurologic includes events such as somnolence

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

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

629

630

Overview of Adverse Events

631

632

633

634

635

636

637

638

639

640

641

642

643

644

645

646

647

648

649

650

651

652

653

654

655

656

657

658

659

660

661

662

663

664

665

666

667

668

669

670

671

Gastrointestinal: Nausea, vomiting, and diarrhea are common adverse events following treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR. For patients starting treatment at the 125-mg/m² weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those patients treated at the 125-mg/m² weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125 mg/m² than in patients given a 100-mg/m² weekly starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In one study of the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43% [25/58] versus 16% [5/32]; p=0.01), but there were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with administration of CAMPTOSAR.

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

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

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

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

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

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

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

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

686

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

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

699

700 **Post-Marketing Experience**

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

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

708

709 **OVERDOSAGE**

710 In U.S. phase 1 trials, single doses of up to 345 mg/m² of irinotecan were administered to
711 patients with various cancers. Single doses of up to 750 mg/m² of irinotecan have been given in non-
712 U.S. trials. The adverse events in these patients were similar to those reported with the
713 recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR.

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

716

717 **DOSAGE AND ADMINISTRATION**

718 **Combination-Agent Dosage**

719 ***Dosage Regimens***

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

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

726

Table 12. Combination-Agent Dosage Regimens & Dose Modifications^a

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU	Starting Dose & Modified Dose Levels (mg/m ²)		
		Starting Dose	Dose Level -1	Dose Level -2
		125	100	75
20	20	20		
500	400	300		
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion ^b	Starting Dose & Modified Dose Levels (mg/m ²)		
		Starting Dose	Dose Level -1	Dose Level -2
		180	150	120
200	200	200		
400	320	240		
600	480	360		

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

^bInfusion follows bolus administration.

727

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

732

733 ***Dose Modifications***

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

742 A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less.
 743 Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If
 744 the patient has not recovered, consideration should be given to discontinuing therapy. Provided
 745 intolerable toxicity does not develop, treatment with additional cycles of CAMPTOSAR/5-FU/LV
 746 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 ^a (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy ^b
No toxicity	Maintain dose level	Maintain dose level
Neutropenia 1 (1500 to 1999/ mm^3) 2 (1000 to 1499/ mm^3) 3 (500 to 999/ mm^3) 4 (<500/ 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
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea 1 (2-3 stools/day > pretx ^c) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 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
Other nonhematologic toxicities^d 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>

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

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

^c Pretreatment

^d Excludes alopecia, anorexia, asthenia

747

748 **Single-Agent Dosage Schedules**

749

750 ***Dosage Regimens***

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

754

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

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

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

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

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

755

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

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

763

764 ***Dose Modifications***

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

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

777

Table 15. Recommended Dose Modifications For Single-Agent Schedules^a

A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, and the platelet count has recovered to $\geq 100,000/\text{mm}^3$, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade ^b (Value)	During a Cycle of Therapy	At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle ^a	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	$\uparrow 25 \text{ mg/m}^2$ up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia 1 (1500 to 1999/ mm^3) 2 (1000 to 1499/ mm^3) 3 (500 to 999/ mm^3) 4 (<500/ mm^3)	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 25 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
Neutropenic fever	Omit dose until resolved, then $\downarrow 50 \text{ mg/m}^2$ when resolved	$\downarrow 50 \text{ mg/m}^2$	$\downarrow 50 \text{ mg/m}^2$
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea 1 (2-3 stools/day > pretx ^c) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Maintain dose level $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2, then $\downarrow 25 \text{ mg/m}^2$ Omit dose until resolved to \leq grade 2 then $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 25 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$	Maintain dose level Maintain dose level $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$
Other nonhematologic^d toxicities 1 2 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 $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$ $\downarrow 50 \text{ mg/m}^2$

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

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

^c Pretreatment

^d Excludes alopecia, anorexia, asthenia

778

779 **Preparation & Administration Precautions**

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

786

787 **Preparation of Infusion Solution**

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

790 CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in
791 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final
792 concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, CAMPTOSAR was administered
793 in 250 mL to 500 mL of 5% Dextrose Injection, USP.

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

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

808

809 **HOW SUPPLIED**

810 Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate
811 salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range,
812 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

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

815 2 mL NDC 0009-7529-02

816 5 mL NDC 0009-7529-01

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

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

823

824 Rx only

825

826 **REFERENCES**

827

- 828 1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations
829 for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
- 830 2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC:
831 Division of Safety, National Institutes of Health; 1983. US Dept of Health and Human Services,
832 Public Health Service publication NIH 83-2621.

- 833 3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. *JAMA*.
834 1985;253:1590-1592.
- 835 4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic
836 agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on
837 Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179
838 Longwood Avenue, Boston, MA 02115.
- 839 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of
840 antineoplastic agents. *Med J Australia*. 1983;1:426-428.
- 841 6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the
842 Mount Sinai Medical Center. *CA-A Cancer J for Clin*. 1983;33:258-263.
- 843 7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling
844 cytotoxic and hazardous drugs. *Am J Hosp Pharm*. 1990;47:1033-1049.
- 845 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.).
846 *Am J Health-SystPharm*. 1996;53-1669-1685

847
848

849 Manufactured by Pharmacia & Upjohn Company
850 A subsidiary of Pharmacia Corporation
851 Kalamazoo, Michigan 49001, USA
852 Licensed from Yakult Honsha Co., LTD, Japan, and Daiichi Pharmaceutical Co., LTD, Japan

853
854 ~~Revised May 2002~~

816 907 113

855 ~~Draft November 2003~~

856 ~~June 24, 2004~~ December 3, 2004

692839