DBL IRINOTECAN INJECTION CONCENTRATE

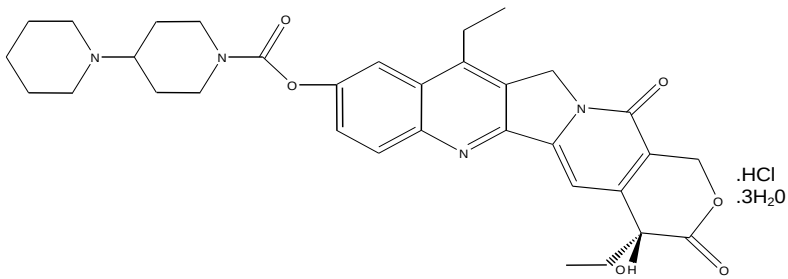
NAME OF THE MEDICINE

Irinotecan hydrochloride trihydrate

CAS No: CAS-136572-09-3

Chemical name: (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride trihydrate

The chemical structure of irinotecan hydrochloride trihydrate is shown below:



DESCRIPTION

DBL IRINOTECAN Injection Concentrate is an antineoplastic agent of the topoisomerase I inhibitor class.

Irinotecan hydrochloride trihydrate is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. It is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6$•HCl•$3H_2O$ and a molecular weight of 677.19. Irinotecan hydrochloride trihydrate is slightly soluble in water and organic solvents.

DBL IRINOTECAN Injection Concentrate is supplied as a sterile, pale yellow, clear, aqueous solution of pH 3.5. It is intended for dilution with 5% Glucose Injection or 0.9% Sodium Chloride

Injection prior to infusion. The 2 mL and 5 mL injections contain 40 mg and 100 mg of irinotecan hydrochloride trihydrate respectively. In addition to irinotecan hydrochloride trihydrate, the ingredients are sorbitol and lactic acid. Sodium hydroxide and hydrochloric acid are used for pH adjustment.

PHARMACOLOGY

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

Irinotecan hydrochloride trihydrate serves as a water-soluble precursor of the lipophilic metabolite SN-38 which is approximately 1000 times as potent as irinotecan hydrochloride trihydrate as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines. However, the precise contribution of SN-38 to the activity of irinotecan hydrochloride trihydrate is unknown. Both irinotecan hydrochloride trihydrate and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. An acidic pH promotes the formation of the lactone whereas a basic pH favours the hydroxy acid anion form.

Administration of irinotecan hydrochloride trihydrate has resulted in antitumour activity in mice bearing cancers of rodent origin and human carcinoma xenografts of various histological types.

Irinotecan hydrochloride trihydrate is a non-competitive inhibitor of acetylcholinesterase and a cholinergic syndrome is associated with its administration (see **ADVERSE EFFECTS**).

Pharmacokinetics

After intravenous infusion of irinotecan hydrochloride trihydrate in humans with various cancers,

irinotecan hydrochloride trihydrate plasma concentrations decline in a multi-exponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. In a study where irinotecan hydrochloride trihydrate was administered at doses of 100-750 mg/m^2 by 30 minute intravenous infusion every three weeks, the plasma terminal elimination half-life was 14.2 ± 7.7 hours for irinotecan hydrochloride trihydrate and 13.8 ± 1.4 hours for SN-38.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan hydrochloride trihydrate increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90 minute infusion of irinotecan hydrochloride trihydrate.

Pharmacokinetic parameters for irinotecan hydrochloride trihydrate and SN-38 following a 90-minute infusion of irinotecan hydrochloride trihydrate at dose levels of 125 and 340 mg/m^2 determined in two clinical studies in patients with solid tumours are summarised in Table 1.

Table 1 – Summary of mean (±standard deviation) irinotecan hydrochloride trihydrate and SN-38 pharmacokinetic parameters in patients with solid tumors

	Irinotecan hydrochloride trihydrate					**SN-38**		
Dose (mg/m^2)	**C_{max} (ng/mL)**	**AUC_{0-24} (ng.hr/mL)**	**$t_{1/2}$ (hr)**	**V_{area} (L/m^2)**	**CL (L/hr/m^2)**	**C_{max} (ng/mL)**	**AUC_{0-24} (ng.hr/mL)**	**$T_{1/2}$ (hr)**
125 (n=64)	1,660 ±797	10,200 ±3,270	5.8[a] ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4[a] ±3.1
340 (n=6)	3,392 ±874	20,604 ±6,027	11.7[b] ±1.0	234 ±69.6	13.9 ±4.00	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max}: Maximum plasma concentration

AUC_{0-24}: 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_{area}: 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 hydrochloride trihydrate and SN-38

In vitro studies indicate that irinotecan hydrochloride trihydrate exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan hydrochloride trihydrate and SN-38 predominantly bind is albumin.

Metabolism

The complete disposition of irinotecan hydrochloride trihydrate has not been fully elucidated in humans. Irinotecan hydrochloride trihydrate is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) mediating glucuronidation of SN-38 to form the inactive metabolite SN-38 glucuronide (SN-38G). The metabolic conversion of irinotecan hydrochloride trihydrate occurs primarily in the liver. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several pharmacologically inactive oxidation products, one of which can be hydrolysed by carboxylesterase to release SN-38. Irinotecan is oxidised by cytochrome P450 isozyme 3A4 (CYP3A4) to yield two relatively inactive metabolites, APC (7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin) and the minor metabolite, NPC (7-ethyl-10-(4-amino-1-piperidino)carbonyloxycamptothecin.

Excretion

The disposition of irinotecan hydrochloride trihydrate has not been fully elucidated in humans. In studies of patients with various cancers the urinary excretion of irinotecan hydrochloride trihydrate was 11% to 20% of the administered dose; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan hydrochloride trihydrate and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan hydrochloride trihydrate in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in Special Populations

Geriatric (≥65 years): In studies where irinotecan hydrochloride trihydrate was administered weekly, the terminal half-life of irinotecan hydrochloride trihydrate was 6.0 hours in patients who were 65 years or older, and 5.5 hours in patients younger than 65 years. Dose-normalised AUC_{0-24} for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. There are no kinetic data on the use of the once-every-three-week dosage schedule in elderly patients. A lower starting dose is recommended in patients 65 years and older based on clinical toxicity experienced with this dosage regimen (see **DOSAGE AND ADMINISTRATION**).

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

Irinotecan hydrochloride trihydrate clearance is diminished in patients with hepatic dysfunction while relative exposure to the active metabolite SN-38 is increased. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in serum total bilirubin and transaminase concentrations (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency: The influence of renal insufficiency on the pharmacokinetics of irinotecan hydrochloride trihydrate has not been evaluated.

Pharmacokinetics in Combination Therapy: In a phase I clinical study involving irinotecan hydrochloride trihydrate, fluorouracil (fluorouracil), and leucovorin (LV) in 26 patients with solid tumours the disposition of irinotecan hydrochloride trihydrate was not substantially altered when the drugs were co-administered. However, C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan hydrochloride trihydrate was followed by fluorouracil and LV administration compared with when irinotecan hydrochloride trihydrate was given alone. Formal *in vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan hydrochloride trihydrate on the disposition of fluorouracil and LV have

not been conducted.

CLINICAL TRIALS

Irinotecan hydrochloride trihydrate has been studied in clinical trials in combination with fluorouracil and LV as a first line agent in metastatic colorectal cancer and as a single agent used after failure of initial therapy. Weekly and once every 3 weeks dosage schedules were studied using irinotecan hydrochloride trihydrate as the single agent. Weekly and once every 2 week schedules were studied with irinotecan hydrochloride trihydrate used in combination treatment. Patients with a WHO performance status of 3 or 4 have not been studied in clinical trials (refer to Table 2).

Table 2: WHO scale for performance status

WHO scale	Performance status
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Combination therapy for first-line treatment of metastatic colorectal cancer

Two randomised, open-label, controlled, multinational, phase III clinical trials support the use of irinotecan hydrochloride trihydrate as first-line treatment of patients with metastatic carcinoma of the colon or rectum. The dosing regimens of these studies are given in Table 3.

Table 3: Dosage regimen of the studies evaluating the first line treatment of metastatic colorectal cancer

Arm	Agent	Study 1 Dosing Regimen	Study 2 Dosing Regimen
A	Irinotecan HCl	125 mg/m^2 irinotecan HCl IV infusion over 90 mins. Treatment was administered	N/A

Arm	Agent	Study 1 Dosing Regimen	Study 2 Dosing Regimen
		once weekly for four weeks with treatment resuming on Day 43.	
B1	Irinotecan HCl LV fluorouracil	125 mg/m^2 irinotecan HCl IV infusion over 90 mins followed immediately by 20 mg/m^2 LV administered as an IV bolus injection and then 500 mg/m^2 fluorouracil as an IV bolus injection. Treatment was administered once weekly for four weeks with treatment resuming on Day 43 (Saltz regimen)[a].	80 mg/m^2 IV infusion over 90 mins of irinotecan HCl plus a 500 mg/m^2 LV IV infusion over two hours followed immediately by an 2300 mg/m^2 fluorouracil IV infusion over 24 hours. Treatment was administered once weekly for six weeks with treatment resuming on Day 50 (AIO regimen)[a]
B2	Irinotecan HCl LV fluorouracil	N/A	180 mg/m^2 IV infusion over 90 mins of irinotecan HCl on day 1, plus one hour later a 200 mg/m^2 LV IV infusion over two hours followed immediately by a 400 mg/m^2 fluorouracil IV bolus injection and a 600 mg/m^2 fluorouracil IV infusion over 22 hours on days 1 and 2. Treatment was administered every two weeks (de Gramont regimen)[a]
C1	LV fluorouracil	20 mg/m^2 LV administered as an IV bolus injection followed immediately by 425 mg/m^2 fluorouracil as an IV bolus injection. Treatment was given for 5 consecutive days with the treatment repeating on Day 29 (Mayo Clinic regimen)[a].	500 mg/m^2 LV IV infusion over two hours followed immediately by a 2600 mg/m^2 fluorouracil IV infusion over 24 hours. Administration was weekly for six weeks with treatment resuming on Day 50 (AIO regimen)[a]
C2	LV	N/A	200 mg/m^2 LV IV infusion over two hours

Arm	Agent	Study 1 Dosing Regimen	Study 2 Dosing Regimen
	fluorouracil		followed immediately by a 400 mg/m^2 fluorouracil IV bolus injection and a 600 mg/m^2 fluorouracil IV infusion over 22 hours on days 1 and 2. Treatment was administered every two weeks (de Gramont regimen)[a]

[a] Based on the Saltz, Mayo Clinic, de Gramont and Association of Medical Oncology of the German Cancer Society (AIO) dosing regimens

In both studies, concomitant medications such as anti-emetics, atropine and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In study 2, if late diarrhoea persisted for greater than 24 hours despite loperamide, a 7 day course of fluoroquinolone antibiotic prophylaxis was given. Treatment with oral fluoroquinolone was initiated in patients whose diarrhoea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhoea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) <0.5 x 10^9/L, even in the absence of fever or diarrhoea. Patients also received treatment with intravenous antibiotics if they had persistent diarrhoea or fever or if ileus developed.

In both studies the combination of irinotecan hydrochloride trihydrate /fluorouracil/LV therapy resulted in significant improvements in objective tumour response rate, time to tumour progression (TTP) and survival when compared with fluorouracil/LV alone. These differences in survival were observed despite the use of post-study second-line therapy, including irinotecan-containing regimens in patients in the control arm. Patient characteristics and major efficacy results are shown in Table 4.

Table 4: Combination therapy in first line treatment of metastatic colorectal cancer: Study Results

	Study 1			**Study 2**	
Demographics and Treatment Administration	**Irinotecan HCl fluorouracil/LV**	**fluorouracil/ LV**	**Irinotecan HCl**	**Irinotecan HCl fluorouracil /LV**	**fluorouracil /LV**
Number of Patients	231	226	226	198	187
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 (%)[a]					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Median Primary Tumour (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median Time from Diagnosis to Randomisation (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 fluorouracil Therapy (%)	89	92	90	74	76
No	11	8	10	26	24
Yes					
Median Duration of Study Treatment (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)					
Irinotecan	72	--	75	87	--
Fluorouracil	71	86	--	86	93
Efficacy Results					
Confirmed Objective Tumour Response Rate[b] (%) [95% CI]	39 [33-46]	21 [16-27]	18 [13-24]	35 [28-42]	22 [16-29]
Median Time to Tumour Progression (months) [95% CI]	7.0 [5.4-8.0]	4.3 [3.7-4.6]	4.2 [3.9-5.0]	6.7 [5.7-8.0]	4.4 [3.2-5.5]

	Study 1			Study 2	
Demographics and Treatment Administration	**Irinotecan HCl fluorouracil/LV**	**fluorouracil/ LV**	**Irinotecan HCl**	**Irinotecan HCl fluorouracil /LV**	**fluorouracil /LV**
Median Survival (months) [95% CI]	14.8 [12.3-17.1]	12.6 [11.1-14.6]	12.0 [11.3-13.5]	17.4 [15.2-20.2]	14.1 [12.6-17.4]

[a] Refer to *Table 2*

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

Improvement was noted when response rates and time to tumour progression were examined across all demographic and disease-related subgroups (as categorised by age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities), with irinotecan hydrochloride trihydrate-based combination therapy relative to fluorouracil/LV.

The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both studies. While there was no statistical evidence that there were significant differences between irinotecan hydrochloride trihydrate/fluorouracil/LV combination and fluorouracil/LV alone with regard to quality of life (QOL) improvement, descriptive evidence suggested a general trend favouring QOL improvement or less-worsening in favour of the irinotecan hydrochloride trihydrate combination regimen.

Single Agent Treatment in Recurrent or Progressive Metastatic Colorectal Cancer After fluorouracil Based Treatment: Weekly Dosage Schedule

Three multicentre, open-label, phase II studies, all utilising repeated cycles of once weekly treatment with irinotecan hydrochloride trihydrate for 4 consecutive weeks, followed by a two week rest period were conducted in a total of 304 patients in the United States. These studies were designed to evaluate tumour response rate and toxicity with irinotecan hydrochloride trihydrate in patients with metastatic colorectal cancer that recurred or progressed following a prior fluorouracil based chemotherapeutic regimen. Starting doses of irinotecan hydrochloride trihydrate in these trials were 100, 125 or 150 mg/m^2, with 150 mg/m^2 proving to be poorly tolerated due to unacceptably high rates of grade 4 late diarrhoea and febrile neutropenia. The

results of the studies are shown in Table 5.

Table 5: Phase II clinical studies with the once weekly dosage schedule

	Study			
	A	B	C[a]	C[a]
Number of patients	48	90	64	102
Dose (mg/m^2/wk x 4)	125[b]	125	125	100
Prior fluorouracil therapy (%)				
For metastatic disease	81.3	65.5	73.4	67.7
≤6 months after adjuvant	14.6	6.7	26.6	27.5
>6 months after adjuvant	2.1	15.6	0.0	2.0
Classification unknown	2.1	12.2	0.0	2.9
Duration of treatment (median, months)	5.4	3.5	3.9	3.3
Median relative dose intensity (%)[c]	74	67	73	81
Objective response rate (%)[d] [95% CI]	20.8 [9.3 - 32.3]	13.3 [6.3 - 20.4]	14.1 [5.5 - 22.6]	8.8 [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

[a] The initial dose in Study C was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity at the starting dose was perceived to be greater than seen in previous studies. Results are analysed separately for the two starting doses

[b] Nine patients received 150 mg/m^2 as a starting dose; 2 (22.2%) responded to irinotecan hydrochloride trihydrate

[c] Relative dose intensity for irinotecan hydrochloride trihydrate based on planned dose intensity of 100, 83.3 and 66.7 mg/m^2/wk corresponding with 150, 125 and 100 mg/m^2 starting doses respectively

[d] There were 2 complete responses and 38 partial responses

Of the 304 patients treated in the phase II studies, response rates to irinotecan hydrochloride trihydrate were similar in males and females and among patients younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum, and in patients with single and multiple metastatic sites. Response rate was 18.5% in patients with a WHO performance status of 0, and 8.2% in patients with a performance status of 1 or 2.

The response rates with irinotecan hydrochloride trihydrate were unaffected by whether or not patients had responded to prior fluorouracil based treatment given for metastatic disease. Patients who had received previous irradiation to the pelvis also responded to irinotecan hydrochloride trihydrate at approximately the same rate as those who had not previously received irradiation.

Overall, across the pivotal studies, stable disease was documented in 148 (48.7%) of the 304 patients in the intent to treat population and in 145 (55.6%) of the 261 patients in the evaluable population. Consistent with the results in Study C, a somewhat greater percentage of patients who were treated with the 125 mg/m^2 starting dose (53.4%; 103/193) than with the 100 mg/m^2 starting dose (39.2%; 40/102) had stable disease during therapy.

Once Every 3 Week Dosage Schedule

Two phase III, multicentre, randomised studies were conducted with a three weekly dosage regimen in patients with metastatic colorectal cancer whose disease had recurred or progressed following fluorouracil therapy (n = 535). Second-line irinotecan hydrochloride trihydrate was compared with best supportive care in one study and with infusional fluorouracil-based therapy in the second study. The primary endpoint in both studies was survival. Parameters of clinical benefit and quality of life were also assessed. The starting dose was 350 mg/m^2 infused intravenously over 90 minutes to a maximum total dose of 700 mg. For patients 70 years or older and for patients with a WHO performance status of 2 the starting dose was reduced to 300 mg/m^2. Anti-emetics, atropine and loperamide were provided as supportive care and late diarrhoea persisting for greater than 24 hours despite loperamide was treated with a 7-day course of a fluoroquinolone antibiotic.

A significant survival advantage for irinotecan hydrochloride trihydrate over best supportive care or infusional fluorouracil-based therapy was demonstrated. When adjusted for baseline patient characteristics (e.g. performance status), survival among patients treated with irinotecan hydrochloride trihydrate remained significantly longer than in the control populations ($p = 0.001$ for Study 1 and $p = 0.017$ for Study 2). Clinical benefit in Study 1, as measured by pain-free survival and survival without weight loss were significantly longer for patients treated with irinotecan hydrochloride trihydrate than for patients in the best supportive care group ($p = 0.01$

and p = 0.05 respectively). The results are summarised in Table 6.

Table 6: Phase III clinical studies with the once every 3 week dosage schedule

		Study 1		**Study 2**	
		Irinotecan hydrochloride trihydrate	Best supportive care	Irinotecan hydrochloride trihydrate	fluorouracil[a]
Number of patients		189	90	127	129
Prior fluorouracil therapy (%)					
	For metastatic disease	70	63	58	68
	≤3/6 months after adjuvant[b]	27	36	38	23
	>3/6 months after adjuvant[b]	3	0	5	9
Duration of treatment (mean, months) [95% CI]		4.6 [4.2 – 5.0]	--	4.4 [3.8 – 5.0]	3.7 [3.3 – 4.1]
Median relative dose intensity (%)[c]		94	--	95	81-99
Survival (median, months) [95% CI]		9.2 [8.4 – 10.7]	6.5 [5.0 – 7.6]	10.8 [9.5 – 12.8]	8.5 [7.7 – 10.5]
1-year survival (%) [95% CI]		36.2 [29.3 – 43.1]	13.8 [6.7 – 20.9]	44.8 [36.2 – 53.4]	32.4 [24.3 – 40.5]
Progression-free survival (median, months) [95% CI]		--	--	4.2 [3.8 – 4.8]	2.9 [2.6 – 3.7]
Symptom-free survival (median, months) [95% CI]		5.9 [3.8 - 7.6]	4.1 [2.2 - 6.9]	8.1 [6.1 - 10.7]	7.0 [4.4 - 8.7]
Pain-free survival (median, months) [95% CI]		6.9 [5.8 – 8.4]	2.0 [1.8 – 5.1]	10.3 [7.8 -**]	8.5 [6.2 – 10.2]
Median survival without performance status deterioration (%) [95% CI]		5.7 [4.3 – 6.6]	3.3 [1.9 – 3.7]	6.4 [5.2 – 7.6]	5.1 [4.2 – 6.2]
Time to weight loss ≥5% (median, months) [95% CI]		6.4 [5.5 – 7.6]	4.2 [3.4 – 5.1]	8.9 [6.7 – 12.3]	7.4 [4.7 – 11.6]

[a] One of the following fluorouracil regimens was used:

(i) Leucovorin 200 mg/m^2 iv over 2 hours; followed by fluorouracil 400 mg/m^2 iv bolus; followed by fluorouracil 600 mg/m^2 continuous iv infusion over 22 hours on days 1 and 2 every 2 weeks.

(ii) fluorouracil 250-300 mg/m^2/day protracted continuous iv infusion until toxicity.

	Study 1		Study 2	
	Irinotecan hydrochloride trihydrate	Best supportive care	Irinotecan hydrochloride trihydrate	fluorouracil[a]

(iii) fluorouracil 2.6-3 g/m^2/day iv over 24 hours every week for 6 weeks with or without leucovorin 20-500 mg/m^2/day every week iv for 6 weeks with a 2 week rest between cycles

[b] Study 1 ≤6 months; Study 2 ≤3 months

[c] Relative dose intensity for irinotecan hydrochloride trihydrate based on planned dose intensity of 116.7 mg/m^2/week. Dose intensity in patients receiving fluorouracil in Study 2 varied depending upon type of regimen

** Cannot be estimated due to small sample size

In the two phase III studies, quality of life was assessed using the European Organisation on Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. In Study 1, the global quality of life scores were significantly higher for patients treated with irinotecan hydrochloride trihydrate than for those who received best supportive care (p=0.0013). In Study 2, the global quality of life scores were similar for patients who received either irinotecan hydrochloride trihydrate or infusional fluorouracil.

Other studies

A Japanese open-label, uncontrolled, late phase II study in patients with non-small-cell lung cancer enrolled a total of 153 patients. In this study, pneumonitis occurred in 6.2% (9/146) of the patients. One patient died of interstitial pneumonitis. Irinotecan hydrochloride trihydrate was given at a dose of 100 mg/m^2 intravenously once weekly. Dosage adjustments were made according to toxicity and the duration of treatment was until disease progression or unacceptable toxicity occurred (with each patient to receive at least three doses).

INDICATIONS

DBL IRINOTECAN Injection Concentrate is indicated as a component of first-line therapy for patients with metastatic carcinoma of the colon or rectum. DBL IRINOTECAN Injection Concentrate is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial therapy.

CONTRAINDICATIONS

DBL IRINOTECAN Injection Concentrate is contraindicated in patients with a known hypersensitivity to the drug or its excipients. DBL IRINOTECAN Injection Concentrate antigenicity has not been observed in clinical trials, but irinotecan hydrochloride trihydrate antigenicity occurred in tests for passive cutaneous anaphylaxis in guinea pigs and rabbits, and in tests for active systemic anaphylaxis in guinea pigs. In these tests, both animal species produced antibodies against irinotecan hydrochloride trihydrate, and some deaths occurred in guinea pigs sensitised to irinotecan hydrochloride trihydrate.

DBL IRINOTECAN Injection Concentrate is contraindicated in women who intend to become pregnant (see **PRECAUTIONS, Carcinogenicity and mutagenicity and Effects on fertility**).

DBL IRINOTECAN Injection Concentrate is contraindicated in pregnancy and lactation (see **PRECAUTIONS, Use in pregnancy** and **Use in lactation**).

PRECAUTIONS

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

Irinotecan will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:

- in patients presenting a risk factor, particularly those with a WHO performance status = 2.
- in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

Extravasation. DBL IRINOTECAN Injection Concentrate is administered by intravenous infusion.

Care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and application of ice are recommended.

Mayo Clinic Regimen. Except in a well-designed clinical study, DBL IRINOTECAN Injection Concentrate should not be used in combination with the "Mayo Clinic" regimen of fluorouracil/LV (administration for 4-5 consecutive days every 4 weeks; refer to Table 3) because of reports of increased toxicity, including toxic deaths. DBL IRINOTECAN Injection Concentrate should be used as recommended in **DOSAGE AND ADMINISTRATION**.

Immunosuppressant Effects/Increased Susceptibility to Infections: Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including irinotecan, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Cardiovascular. Thromboembolic events including angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis and vascular disorder have been observed rarely in patients receiving irinotecan hydrochloride trihydrate. The specific cause of these events has not been determined.

Diarrhoea and its Management

Irinotecan hydrochloride trihydrate can induce both an early and a late form of diarrhoea that appear to be mediated by different mechanisms. Both forms of diarrhoea may be severe.

Early diarrhoea (occurring during or shortly after infusion of irinotecan hydrochloride trihydrate) 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, bradycardia and intestinal hyperperistalsis that can cause abdominal cramping. Administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing cholinergic symptoms occurring

during or shortly after infusion of irinotecan hydrochloride trihydrate. Patients ≥65 years of age should be closely monitored due to a greater risk of early diarrhoea observed in this population.

Late diarrhoea (generally occurring more than 24 hours after administration of irinotecan hydrochloride trihydrate) can be prolonged, may lead to dehydration, electrolyte imbalance or infection and can be life-threatening. Late diarrhoea should be treated promptly with loperamide. Patients should be instructed to have loperamide readily available and begin treatment at the first episode of poorly formed or loose stools, or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials consisted of 4 mg at the first onset of late diarrhoea, and then 2 mg every 2 hours until the patient was diarrhoea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours. Premedication with loperamide is not recommended.

Patients with diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated and should be given antibiotics if they develop ileus, fever or severe neutropenia. After the first treatment, subsequent chemotherapy should be delayed until patients are diarrhoea-free (return to pre-treatment bowel function) for at least 24 hours without the need for antidiarrhoea medication. If NCI grade 2, 3 or 4 diarrhoea occurs, subsequent doses of irinotecan hydrochloride trihydrate should be reduced within the current cycle (see **DOSAGE AND ADMINISTRATION**).

In addition to antibiotic treatment, hospitalization is recommended for management of the diarrhoea, in the following cases: diarrhoea associated with fever, server diarrhoea (requiring intravenous hydration), patients with vomiting associated with delayed (*i.e.*, late) diarrhoea and diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy and in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea).

Haematology

Irinotecan commonly causes neutropenia, leucopenia and anaemia, any of which may be

severe and therefore should not be used in patients with severe bone marrow failure (refer to **ADVERSE EFFECTS**, **Haematological**). Serious thrombocytopenia is uncommon.

Neutropenia: Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan hydrochloride trihydrate. Neutropenic complications should be managed promptly with antibiotic support. Therapy with irinotecan hydrochloride trihydrate should be temporarily omitted if neutropenic fever occurs or if the absolute neutrophil count drops below 1.5 x 10^9/L. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1.5 x 10^9/L. After the patient recovers, subsequent doses of irinotecan hydrochloride trihydrate should be reduced depending upon the level of neutropenia observed (see **DOSAGE AND ADMINISTRATION**). Routine administration of a colony-stimulating factor (CSF) is not necessary but physicians may consider CSF use in individual patients experiencing problems related to neutropenia.

Colitis/Ileus*:* Cases of colitis have been reported. In some cases, colitis was complicated by ulceration, bleeding, ileus and infection. Cases of ileus without preceding colitis have also been reported. Patients experiencing ileus should receive prompt antibiotic support.

Chronic inflammatory bowel disease and/or bowel obstruction: Patients must not be treated with irinotecan hydrochloride trihydrate until resolution of the bowel obstruction.

Patients with Reduced UGT1A1 Activity: Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which mediates the conjugation of the active metabolite SN-38 (see **Pharmacokinetics, *Metabolism***) is encoded by the UGT1A1 gene. This gene is highly polymorphic resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1*28 variant allele are. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced enzyme activity and increased systemic exposure to SN-38. Higher plasma concentrations of SN-38 are observed in individuals who are homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype) compared to patients who have one or two wild-type alleles.

Another specific polymorphism of UGT1A1 gene (that reduces the activity of this enzyme) is a missense mutation known as UGT1A1*6 variant.

Patients with UGT1A1*28 or *6 variants (especially if homozygous) are at increased risk of experiencing adverse events such as neutropenia and diarrhoea. A reduced irinotecan starting dose should be considered for homozygous patients. In addition, *28 and *6 homozygous and heterozygous patients should be closely monitored for neutropenia and diarrhoea.

The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on individual patient tolerance to treatment.

In order to identify patients at increased risk of experiencing neutropenia and diarrhoea, UGT1A1 genotyping can be useful. More in detail, UGT1A1*28 genotyping can be useful in Caucasians, Africans and Latinos, UGT1A1*6 in East-Asians and combined UGT1A1*28 and *6 in Chinese and Japanese, since these are the populations in which these variants are more prevalent.

Use with caution in the following circumstances

Patients at particular risk. Physicians should exercise particular caution in monitoring the effects of irinotecan hydrochloride trihydrate in patients with poor performance status, in elderly patients and in patients who have previously received pelvic/abdominal irradiation (refer to **ADVERSE EFFECTS**). Patients with poor performance status are at increased risk of irinotecan-related adverse events. In patients receiving either irinotecan hydrochloride trihydrate/fluorouracil/LV or fluorouracil/LV in clinical trials comparing these agents, higher rates of hospitalisation, 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 of 0 or 1. Patients with performance status of 3 or 4 should not receive irinotecan hydrochloride trihydrate.

Impaired renal function. Studies in patients with impaired renal function have not been conducted (refer to **PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics in Special Populations**). Therefore, caution should be undertaken in patients with impaired renal function.

Irinotecan is not recommended for use in patients on dialysis.

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

Hepatic insufficiency. In patients with hyperbilirubinaemia, the clearance of irinotecan is decreased and therefore the risk of haematotoxicity is increased (refer to **PHARMACOLOGY, Pharmacokinetics**, **Pharmacokinetics in Special Populations**).

The use of irinotecan hydrochloride trihydrate in patients with a serum bilirubin concentration of >3.0 x institutional upper limit of normal (IULN) given as a single agent on the once every 3 weeks schedule has not been established. In clinical trials of the single agent weekly dosage schedule, it has been noted that patients with even modest elevations in total baseline serum bilirubin levels (17-34 µmol/L) had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 17 µmol/L (50% versus 18%; p<0.001) (refer to **PHARMACOLOGY, Pharmacokinetics in Special Populations** and **DOSAGE AND ADMINISTRATION**). Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with irinotecan hydrochloride trihydrate.

Cholinergic Effects. Irinotecan hydrochloride trihydrate has cholinergic effects and should be used with caution in patients with asthma or cardiovascular diseases, and in patients with mechanical intestinal or urinary obstruction.

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

Before administration

Monitoring. Careful monitoring of the white blood cell count with differential, haemoglobin and platelet count is recommended before each dose of irinotecan hydrochloride trihydrate. Liver function should be monitored before initiation of treatment and monthly or as clinically indicated.

Nausea and vomiting. Irinotecan hydrochloride trihydrate is emetogenic. It is recommended that patients receive premedication with anti-emetic agents. In clinical studies with the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of anti-emetic agent, such as a 5-HT_3 blocker (e.g. ondansetron or granisetron). Anti-emetic agents should be given on the day of treatment, starting at least 30 minutes before administration of DBL IRINOTECAN Injection Concentrate. Physicians should also consider providing patients with an anti-emetic regimen (e.g., prochlorperazine) for subsequent use as needed. Patients with vomiting associated with delayed (*i.e.* late) diarrhoea should be hospitalized as soon as possible for treatment.

Advice to patients. Patients should be advised of the expected toxic effects of irinotecan hydrochloride trihydrate, particularly of gastrointestinal complications such as nausea, vomiting, abdominal cramping, diarrhoea and infection. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhoea (generally occurring more than 24 hours after administration of irinotecan hydrochloride trihydrate) at the first episode of poorly formed or loose stools, or the earliest onset of bowel movements more frequent than normally expected for the patient (see **PRECAUTIONS**, **Diarrhoea and its Management)**.

Patients should be advised to consult their physician if any of the following occur after treatment with DBL IRINOTECAN Injection Concentrate: diarrhoea for the first time; inability to control diarrhoea within 24 hours; vomiting; fever or evidence of infection; symptoms of dehydration, such as faintness, light-headedness or dizziness; bloody or black stools; inability to take fluids by mouth due to nausea or vomiting. Patients should also be alerted to the possibility of alopecia. Laxatives should be avoided (see **Interactions with other medicines**) and patients should contact their physician to discuss any laxative use.

Others

As this product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Carcinogenicity and mutagenicity and Impairment of Fertility

Long-term carcinogenicity studies with irinotecan hydrochloride trihydrate were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan hydrochloride trihydrate once per week for 13 weeks (AUC about 1.3 times the values of patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Irinotecan hydrochloride trihydrate was clastogenic both *in vitro* (Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). Neither irinotecan hydrochloride trihydrate or SN-38 was mutagenic in the *in vitro* Ames assay.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan hydrochloride trihydrate in doses of up to 6 mg/kg/day to rats. Atrophy of male reproductive organs was observed after multiple daily irinotecan hydrochloride trihydrate doses both in rodents at 20 mg/kg (AUC approximately the same value as in patients administered 125 mg/m^2 weekly) and dogs at 0.4 mg/kg (AUC about 1/15th the value in patients administered 125 mg/m^2 weekly).

Use in pregnancy (Category D[†])

There are no adequate and well-controlled studies of irinotecan in pregnant women. Irinotecan hydrochloride trihydrate may cause foetal harm when administered to a pregnant woman. Administration of 6 mg/kg/day intravenous irinotecan hydrochloride trihydrate to rats (AUC about 0.2 times the corresponding values in patients administered 125 mg/m^2) and rabbits (about one-half the recommended human weekly starting dose on a mg/m^2 basis) during the period of organogenesis, is embryotoxic as characterised by increased post-implantation loss and decreased numbers of live foetuses. Irinotecan hydrochloride trihydrate was teratogenic in rats at doses greater than 1.2 mg/kg/day (AUC about 1/40th the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6.0 mg/kg/day. Teratogenic effects included

[†] *Category D: Drugs which have caused, are suspected to cause or may be expected to cause, an increase incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

a variety of external, visceral, and skeletal abnormalities.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan.

Use in lactation

The available data are limited to one patient only. Irinotecan and its active metabolite SN-38 were measured in the milk of one lactating patient. The effect on newborn/infants is unknown. Because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with irinotecan.

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabelled irinotecan hydrochloride trihydrate and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. Irinotecan hydrochloride trihydrate has been shown to impair learning ability and cause a delay in postnatal development in rats.

Use in children

The safety and effectiveness of irinotecan hydrochloride trihydrate in children have not been established.

Use in elderly

Physicians should exercise particular caution in monitoring the effects of irinotecan hydrochloride trihydrate in elderly patients. A reduction in the starting dose of DBL IRINOTECAN Injection Concentrate may be considered for patients over 65 years of age (see **DOSAGE AND ADMINISTRATION**).

Interactions with other medicines

CYP3A4 and/or UGT1A1 Inhibitors. Irinotecan and its active metabolite SN-38 are metabolised via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) (see **PHARMACOLOGY**, **Pharmacokinetics**). Coadministration of irinotecan with inhibitors of CYP3A4 and/or UGT1A1 may result in increased systemic exposure to irinotecan and the active metabolite SN-38. Physicians should take this into consideration when administering irinotecan with these drugs.

Neuromuscular blocking agents. Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since irinotecan has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing drugs may be antagonized.

Antineoplastic agents. The adverse effects of irinotecan hydrochloride trihydrate, such as myelosuppression and diarrhoea, would be expected to be exacerbated by other antineoplastic agents having similar adverse events.

Anticonvulsants. Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to SN-38. Consideration should be given to starting or substituting non-enzyme–inducing anticonvulsants at least one week prior to initiation of irinotecan therapy in patients requiring anticonvulsant treatment.

Ketoconazole. Irinotecan clearance is greatly reduced in patients receiving concomitant ketoconazole, leading to increased exposure to the active metabolite SN-38. Ketoconazole should be discontinued at least 1 week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

St. John's Wort (Hypericum perforatum). Exposure to the active metabolite SN-38 is reduced in patients taking concomitant St. John's Wort. St John's Wort should be discontinued at least 1 week prior to the first cycle of irinotecan, and should not be administered during irinotecan therapy.

Atazanavir sulfate. Co-administration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these medicines.

Dexamethasone. Lymphocytopenia has been reported in patients receiving irinotecan hydrochloride trihydrate and it is possible that the administration of dexamethasone as anti-emetic 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 the lymphocytopenia.

Hyperglycaemia has also been reported in patients receiving irinotecan hydrochloride trihydrate. Usually this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan hydrochloride trihydrate. It is probable that the administration of dexamethasone contributed to hyperglycaemia in some patients.

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

Laxatives. It would be expected that the incidence or severity of diarrhoea would be worsened by laxative use during therapy with irinotecan hydrochloride trihydrate, but this has not been studied.

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

Bevacizumab. Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38.

Effects on Laboratory Tests

There are no known interactions between irinotecan hydrochloride trihydrate and laboratory tests.

Effects on Ability to Drive and Use Machines

The effect of irinotecan on the ability to drive or use machinery has not been evaluated. However, patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

ADVERSE EFFECTS

Combination Therapy in First Line Treatment of Metastatic Colorectal Cancer

In the two phase III studies, a total of 955 patients with metastatic colorectal cancer received irinotecan hydrochloride trihydrate in combination with fluorouracil/LV, fluorouracil/LV alone, or irinotecan hydrochloride trihydrate alone (see Table 3, **CLINICAL TRIALS**). In these studies, 370 patients received irinotecan hydrochloride trihydrate in combination with fluorouracil/LV, 362 patients received fluorouracil/LV alone, and 223 patients received irinotecan hydrochloride trihydrate alone.

Fifty-nine (6.1%) patients died within 30 days of last study treatment: 27 (7.3%) received irinotecan hydrochloride trihydrate in combination with fluorouracil/LV, 19 (5.3%) received fluorouracil/LV alone, and 13 (5.8%) received irinotecan hydrochloride trihydrate alone. Deaths potentially related to treatment occurred in 3 (0.7%) patients who received irinotecan hydrochloride trihydrate in combination with fluorouracil/LV (2 neutropenic fever/sepsis, 1 treatment toxicity), 3 (0.7%) patients who received fluorouracil/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan hydrochloride trihydrate alone (2 neutropenic fever). Deaths within 60 days of study treatment were reported for 18 (4.9%) patients who received irinotecan hydrochloride trihydrate in combination with fluorouracil/LV, 18 (5.0%) patients who received fluorouracil/LV alone and 15 (6.7%) patients who received irinotecan hydrochloride trihydrate alone. Discontinuations due to adverse events were reported for 26 (7.0%) patients who received

irinotecan hydrochloride trihydrate in combination with fluorouracil/LV, 15 (4.1%) patients who received fluorouracil/LV alone, and 26 (11.7%) patients who received irinotecan hydrochloride trihydrate alone.

Table 7 lists the grade 3 and 4 clinically relevant adverse events reported in the combination treatment arms of the two phase III studies.

Table 7: Percent (%) of Patients Experiencing Clinically Relevant Grade 3 & 4 Adverse Events in Phase III Studies of Combination Therapies[a]

	Adverse Event			**Study 1**			**Study 2**	
				Irinotecan HCl fluorouracil/LV N=225[b]	**fluorouracil/LV N=219**[b]	**Irinotecan HCl N=223**[b]	**Irinotecan HCl fluorouracil/LV N=145**[c]	**fluorouracil/LV N=143**[c]
	TOTAL Grade 3/4 Adverse Events			53.3	45.7	45.7	72.4	39.2
GASTROINTESTINAL								
	Diarrhoea							
		late		22.7	13.2	31.0	14.4	6.3
			grade 3	15.1	5.9	18.4	10.3	4.2
		early	grade 4	7.6	7.3	12.6	4.1	2.1
				4.9	1.4	6.7	--	--
	Nausea			15.6	8.2	16.1	2.1	3.5
	Abdominal pain			14.6	11.5	13.0	2.1	0.7
	Vomiting			9.7	4.1	12.1	3.5	2.8
	Anorexia			5.8	3.7	7.2	2.1	0.7
	Constipation			3.1	1.8	0.4	0.7	1.4
	Mucositis			2.2	16.9	2.2	4.1	2.8
HAEMATOLOGICAL								
	Neutropenia			53.8	66.7	31.0	46.2	13.4
			grade 3	29.8	23.7	19.3	36.4	12.7
			grade 4	24.0	42.5	12.1	9.8	0.7

Adverse Event	Study 1			Study 2	
	Irinotecan HCl fluorouracil/ LV N=225[b]	fluorouracil/LV N=219[b]	Irinotecan HCl N=223[b]	Irinotecan HCl fluorouracil/LV N=145[c]	fluorouracil/LV N=143[c]
Leucopenia	37.8	23.3	21.5	17.4	3.5
Anaemia	8.4	5.5	4.5	2.1	2.1
Neutropenic fever	7.1	14.6	5.8	3.4	0.7
Thrombocytopenia	2.6	2.7	1.7	0	0
Neutropenic infection	1.8	0	2.2	2.1	0
BODY AS A WHOLE					
Asthenia	19.5	11.9	13.9	9.0	4.2
Pain	3.1	3.6	2.2	9.7	8.4
Fever	1.7	3.6	0.4	0.7	0.7
Infection	0	1.4	0.4	7.6	3.5
METABOLIC & NUTRITIONAL					
Increased bilirubin	7.1	8.2	7.2	3.5	10.6
DERMATOLOGICAL					
Exfoliative dermatitis	0	0.5	0	--	--
Rash	0	0.9	0.4	--	--
Hand & foot syndrome	--	--	--	0.7	0.7
Cutaneous signs	--	--	--	0.7	0
RESPIRATORY					
Dyspnoea	6.3	0.5	2.2	1.4	0
Cough	1.3	0	0.4	--	--
Pneumonia	2.7	1.0	1.3	--	--
NEUROLOGICAL					
Dizziness	1.3	0	1.8	--	--
Somnolence	1.8	1.8	1.3	--	--
Confusion	1.8	0	0	--	--
CARDIOVASCULAR					

Adverse Event	Study 1			Study 2	
	Irinotecan HCl fluorouracil/LV N=225[b]	fluorouracil/LV N=219[b]	Irinotecan HCl N=223[b]	Irinotecan HCl fluorouracil/LV N=145[c]	fluorouracil/LV N=143[c]
Vasodilation	0.9	0	0	--	--
Hypotension	1.3	0.5	1.7	1.4	0
Thrombophlebitis	2.7	3.2	1.8	--	--
Pulmonary embolus	2.7	1.4	0.4	--	--
Myocardial infarction	1.3	0	0.4	--	--

[a] Severity of adverse events based on National Cancer Institute's Common Toxicity Criteria (NCI CTC) (version 1.0)

[b] Number of patients in the as-treated population for each group

[c] Number of patients treated in the de Gramont regimen (B2/C2 treatment arms of *Table 3*)

The most clinically significant adverse events for patients receiving irinotecan hydrochloride trihydrate-based therapy were diarrhoea, nausea, vomiting, neutropenia, and alopecia (complete hair loss = Grade 2). The most clinically significant adverse events for patients receiving fluorouracil/LV therapy were diarrhoea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as ≥grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with irinotecan hydrochloride trihydrate/fluorouracil/LV than with administration of fluorouracil/LV.

There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*. In combination with cetuximab additional reported undesirable effects were those expected with cetuximab (such as acneiform rash).

Single Agent Therapy in Recurrent or Progressive Metastatic Colorectal Cancer

Information on adverse effects for irinotecan hydrochloride trihydrate as single agent therapy is available from 304 patients with metastatic carcinoma of the colon or rectum treated in phase II trials with the once weekly dosage schedule, 316 patients treated with the once-every-3-week dosage schedule and over 1100 patients with a variety of tumour types treated in Japan. In

general the types of toxicities observed were similar. 4.3% of patients treated with the weekly dosage schedule and 8% of patients treated with the once-every-3-week dosage schedule discontinued treatment with irinotecan hydrochloride trihydrate because of medical events. Seventeen of the 304 patients treated with the weekly dosage schedule died within 30 days of the administration of irinotecan hydrochloride trihydrate and in five cases (1.6%), the deaths were potentially drug-related. Eleven patients treated with irinotecan hydrochloride trihydrate in the once-every-3-week dosage schedule died within 30 days of treatment and in three cases (1%), the deaths were potentially related to treatment with irinotecan hydrochloride trihydrate. The main causes of the deaths potentially related to treatment were neutropenic infection, Grade 4 diarrhoea and asthenia.

The frequency of the most common adverse events reported from the single agent second line studies is presented in Table 8 below. Additional information on adverse events follows the table, organised by body system category.

Table 8: Adverse events reported from the second line single agent therapy in 304 patients[a]

	Weekly dosage schedule		**3 weekly dosage schedule (NCI Grade 3 & 4 only)**	
Event	*% of Patients*	*% NCI Grade 3 & 4*	*Study 1 (%)*	*Study 2 (%)*
GASTROINTESTINAL				
Diarrhoea (late)	87.8	30.6	21.7	22.0
Nausea	86.2	16.8	13.8	11.0
Vomiting	66.8	12.5	13.8	14.2
Abdominal cramping/pain	56.9	16.4	13.8	8.7
Anorexia	54.9	5.9	5.3	5.5
Diarrhoea (early)	50.7	7.9	12.2	1.6
Constipation	29.9	2.0	9.5	7.9
Flatulence	12.2	--	--	--
Stomatitis	11.8	0.7	--	--
Dyspepsia	10.5	--	--	--
HAEMATOLOGICAL				

	Weekly dosage schedule		3 weekly dosage schedule (NCI Grade 3 & 4 only)	
Event	*% of Patients*	*% NCI Grade 3 & 4*	*Study 1 (%)*	*Study 2 (%)*
Leucopenia[b]	63.2	28.0	22.2	14.2
Anaemia	60.5	6.9	7.4	6.3
Neutropenia[b]	53.9	26.3	22.2	14.2
Thrombocytopenia	--	--	1.1	3.9
BODY AS A WHOLE				
Asthenia	75.7	12.2	14.8	13.4
Fever	45.4	0.7	--	--
Pain	23.7	2.3	18.5[c]	16.5[d]
Headache	16.8	0.7	--	--
Back pain	14.5	1.6	--	--
Chills	13.8	0.3	--	--
Minor infection	14.5	0	--	--
Oedema	10.2	1.3	--	--
Abdominal enlargement	10.2	0.3	--	--
METABOLIC AND NUTRITIONAL				
Weight reduction	30.3	0.7		
Dehydration	14.8	4.3		
Increased alkaline phosphatase	13.2	3.9		
Increased SGOT	10.5	1.3		
DERMATOLOGICAL				
Alopecia	60.5	Not applicable[e]	Not applicable[e]	Not applicable[e]
Sweating	16.4	0	--	--
Rash	12.8	0.7	1.6	0.8
RESPIRATORY				
Dyspnoea	22.0	3.6		
Increased coughing	17.4	0.3		
Rhinitis	15.5	0		

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

	Weekly dosage schedule		**3 weekly dosage schedule (NCI Grade 3 & 4 only)**	
Event	*% of Patients*	*% NCI Grade 3 & 4*	*Study 1 (%)*	*Study 2 (%)*

[b] Combined results for leucopenia/neutropenia are presented for the once-every-3-week dosage schedule

[c] In this study, 22.2% of patients treated with best supportive care experienced NCI Grade 3/4 pain

[d] In this study, 13.2% of patients treated with infusional fluorouracil experienced NCI Grade 3/4 pain

[e] Complete hair loss = NCI grade 2

Gastrointestinal

Nausea, vomiting and diarrhoea are common adverse events following treatment with irinotecan hydrochloride trihydrate and can be severe. Among those patients treated at the 125 mg/m^2 single agent weekly dose, the median duration of any grade of late diarrhoea was 3 days, and for grade 3 or 4 late diarrhoea was 7 days. The frequency of grade 3 and 4 late diarrhoea was significantly greater in patients 65 years or older (39.8% versus 23.4%, p=0.0025).

Abdominal pain and cramping are associated with early-onset diarrhoea (diarrhoea which occurs within 24 hours of drug administration). In studies it has been found that atropine is useful in ameliorating these events. Colonic ulceration, sometimes with gastrointestinal bleeding, ileus and infection, has been observed in association with administration of irinotecan hydrochloride trihydrate.

Haematological

Irinotecan hydrochloride trihydrate commonly causes neutropenia, leucopenia (including lymphocytopenia) and anaemia. Serious thrombocytopenia is uncommon. In clinical studies with the single agent weekly dosage schedule, one death due to neutropenic sepsis without fever was judged to be potentially drug-related (0.3%, 1/304). Blood transfusions were given to 9.9% of patients. When evaluated in the trials of single agent weekly administration, the frequency of grade 3 or 4 neutropenia was significantly higher in patients who had received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48.1% versus 24.1%, p=0.0356). In these same studies, patients with total baseline serum bilirubin levels of 17 µmol/L 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 17 µmol/L (50% versus 17.7%, p<0.001).

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 diarrhoea. 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 more likely to occur at higher doses. The timing of the symptoms is most consistent with the occurrence of peak irinotecan hydrochloride trihydrate serum levels during parenteral administration.

Metabolic and nutritional

Hepatic. For the once-every-3-week dosage schedule, hepatic events, such as ascites and jaundice of NCI Grade 3/4 severity occurred in 8.5% of patients in one study and 8.7% of patients in another study. In the clinical studies evaluating the single agent 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. The dehydration observed in 14.8% of patients in these studies was as a consequence of diarrhoea, nausea and vomiting. Increases in serum creatinine or blood urea nitrogen, generally attributable to complications of infection or to dehydration related to nausea, vomiting or diarrhoea have been observed.

Renal. There have been cases of acute renal failure. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Dermatological

Alopecia has been reported during treatment with irinotecan hydrochloride trihydrate. Rashes have also been reported but did not result in discontinuation of treatment.

Respiratory

Severe pulmonary events are infrequent. Over half the patients with dyspnoea in the clinical studies evaluating the single agent weekly dosage schedule had lung metastases; the extent to

which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnoea in these patients is unknown. For the once-every-3-week dosage schedule, respiratory events, such as dyspnoea and cough of NCI Grade 3/4 severity occurred in 10.1% of patients in one study and 4.7% of patients in another study.

A potentially life-threatening pulmonary syndrome, consisting of dyspnoea, fever and a reticulonodular pattern on chest x-ray was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan hydrochloride trihydrate to these preliminary events was difficult to assess because these patients also had lung tumours and some had pre-existing nonmalignant pulmonary disease. As a result of these observations, however, clinical studies in the USA enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

Neurological

Insomnia and dizziness were observed in 19.4% and 14.8% respectively of patients studied in clinical trials of the single agent weekly dosage schedule but were not usually considered to be directly related to the administration of irinotecan hydrochloride trihydrate. Dizziness may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Cardiovascular

Vasodilation (flushing) may occur during administration of irinotecan hydrochloride trihydrate. Irinotecan hydrochloride trihydrate has anti-cholinesterase activity. As such, there are possible cardiovascular effects due to its administration. These include sudden death, blackout and bradycardia. Patients should be monitored for cholinergic effects during administration of irinotecan hydrochloride trihydrate, and atropine should be readily available for treatment of these effects. There were no cases of sudden death reported in the Phase II clinical studies of the single agent weekly dosage schedule involving 304 patients. In these studies, two patients (0.7%) suffered syncope and one patient (0.3%) suffered bradycardia.

Thromboembolic events including 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 and vascular disorder have been observed rarely in patients receiving irinotecan hydrochloride trihydrate. The specific cause of these events has not been determined.

Other

Other NCI grade 3 or 4 drug-related adverse events observed in 1-10% of patients in clinical trials included mucositis, bilirubinaemia and hypovolaemia. In fewer than 1% of patients, NCI grade 3 or 4 rectal disorder, gastrointestinal monilia, hypokalaemia, hypomagnesaemia, increased GGTP, malaise, sepsis urinary tract infection, breast pain and abnormal gait were observed.

Post-marketing Surveillance

Gastrointestinal disorders. Infrequent cases of intestinal obstruction, ileus, megacolon or gastrointestinal hemorrhagic and rare cases of colitis, including typhlitis (ileocecal syndrome), ischaemic and ulcerative colitis have been reported. In some cases, colitis was complicated by ulceration, bleeding, ileus or infection. Cases of ileus without preceding colitis have also been reported. Rare cases of intestinal perforation have been reported. Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypovolaemia. There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities. Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Infections and infestations. Bacterial, fungal and viral infections have been reported.

Immune system disorders. Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have also been reported.

Investigations. Rare cases of hyponatraemia mostly related with diarrhoea and vomiting have been reported. Transient and mild to moderate increases in serum levels of transaminases (*i.e.* AST and ALT) in the absence of progressive liver metastasis, transient increase of amylase

and occasionally transient increase of lipase have been very rarely reported.

Musculoskeletal and connective tissue disorders. Early effects such as muscular contraction or cramps and paresthesia have been reported.

Nervous System Disorders. Speech disorders, generally transient in nature, have been reported in patients treated with irinotecan; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Respiratory disorders. Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnea have been reported (refer to **PRECAUTIONS**).

Cardiac disorders. Myocardial ischemic events have been observed following irinotecan therapy predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease or previous cytotoxic chemotherapy.

Renal and cardiovascular disorders. Infrequent cases of renal insufficiency including acute renal failure, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis (see **PRECAUTIONS**).

Other. Hiccups have been reported.

DOSAGE AND ADMINISTRATION

It is recommended that patients receive premedication with anti-emetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms (see **PRECAUTIONS**).

Combination Therapy in First Line Treatment of Metastatic Colorectal Cancer

DBL IRINOTECAN Injection Concentrate should be administered as an intravenous infusion (IV) over 90 minutes (see **Preparation of Infusion Solution**). For all regimens, the dose of LV

should be administered immediately after DBL IRINOTECAN Injection Concentrate, with the administration of fluorouracil to follow immediately after the administration of LV. The recommended regimens are shown in Table 9.

Table 9: Combination Agent Dosage Regimens & Dose Modifications[a]

Regimen 1 6 week cycle Treatment resumes Day 43	Irinotecan hydrochloride trihydrate	125 mg/m^2 IV over 90 min on day 1, 8, 15, 22 then 2 wk rest		
	LV	20 mg/m^2 IV bolus injection day 1, 8, 15, 22 then 2 wk rest		
	fluorouracil	500 mg/m^2 IV bolus injection day 1, 8, 15, 22 then 2 wk rest		
		Starting dose and modified dose levels[b]		
		Starting dose (mg/m^2)	Dose level –1 (mg/m^2)	Dose Level –2 (mg/m^2)
	Irinotecan hydrochloride trihydrate	125	100	75
	LV	20	20	20
	fluorouracil	500	400	300
Regimen 2 6 week cycle Treatment resumes Day 43	Irinotecan hydrochloride trihydrate	180 mg/m^2 IV over 90 min on day 1, 15, 29 then 1 wk rest		
	LV	200 mg/m^2 IV over 2 h on day 1, 2, 15, 16, 29, 30 then 1 wk rest		
	fluorouracil Bolus	400 mg/m^2 IV on day 1, 2, 15, 16, 29, 30 then 1 wk rest		
	fluorouracil Infusion[c]	600 mg/m^2 IV over 22 h on day 1, 2, 15, 16, 29, 30 then 1 wk rest		
		Starting dose and modified dose levels[b]		
		Starting dose (mg/m^2)	Dose level –1 (mg/m^2)	Dose level –2 (mg/m^2)
	Irinotecan hydrochloride trihydrate	180	150	120
	LV	200	200	200

	fluorouracil Bolus	400	320	240
	fluorouracil Infusion[c]	600	480	360

[a] Dose reductions beyond dose level –2 by decrements of ~20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

[b] Refer to *Table 10*

[c] Infusion follows bolus administration

Dosing for patients with bilirubin >34 mmol/L cannot be recommended since such patients were not included in clinical trials.

Irinotecan in combination with Cetuximab

For dosage and administration of concomitant cetuximab, refer to the full prescribing information for cetuximab. Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Dose Modifications

Patients should be carefully monitored for toxicity and assessed prior to each treatment, especially during the first cycle of therapy. Doses of DBL IRINOTECAN Injection Concentrate and fluorouracil should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose levels described in Table 9, subsequent doses should be adjusted as suggested in Table 10, which shows the recommended dose modifications for combination schedules. All dose modifications should be based on the worst preceding toxicity. Patients should be diarrhoea free (return to pre-treatment bowel function) without requiring antidiarrhoeal medications for at least 24 hours before receiving the next chemotherapy administration.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less, the granulocyte count has recovered to $\geq 1.5 \times 10^9$/L, the platelet count has recovered to $\geq 100 \times 10^9$/L and treatment-related diarrhoea is fully resolved. Treatment should be delayed for 1 to 2 weeks to allow recovery from treatment-related toxicity. If the patient has not recovered after a 2 week delay, consideration should be given to discontinuing therapy. Provided intolerable

toxicity does not develop, treatment with additional cycles of DBL IRINOTECAN Injection Concentrate /fluorouracil/LV may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 10: Recommended dose modifications during a cycle of therapy with the DBL IRINOTECAN Injection Concentrate/fluorouracil/LV combination and at the start of each subsequent cycle of therapy:

	Toxicity NCI CTC grade[a]	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy[b]**
No toxicity		Maintain dose level	Maintain dose level
Neutropenia			
	1	Maintain dose level	Maintain dose level
	2	Decrease by 1 dose level	Maintain dose level
	3	Omit dose until resolved to ≤grade 2, then decrease by 1 dose level	Decrease by 1 dose level
	4	Omit dose until resolved to ≤grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels
Neutropenic fever		Omit dose until resolved, then decrease by 2 dose levels	
Other haematological toxicities		Dose modifications for leucopenia 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.	
Diarrhoea			
	1	Delay dose until resolved to baseline, then give same dose	Maintain dose level
	2	Omit dose until resolved to baseline, then decrease by 1 dose level	Maintain dose level
	3	Omit dose until resolved to baseline, then decrease by 1 dose level	Decrease by 1 dose level
	4	Omit dose until resolved to baseline, then decrease by 2 dose levels	Decrease by 2 dose levels
Other non-haematological Toxicities[c]			

	1	Maintain dose level	Maintain dose level
	2	Omit dose until resolved to ≤grade 1, then decrease by 1 dose level	Maintain dose level
	3	Omit dose until resolved to ≤grade 2, then decrease by 1 dose level	Decrease by 1 dose level
	4	Omit dose until resolved to ≤grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels

[a] Severity of adverse events based on NCI CTC (version 2.0)

[b] Relative to the starting dose used in the previous cycle

[c] For mucositis/stomatitis decrease only fluorouracil, not DBL IRINOTECAN Injection Concentrate

Single Agent Therapy in Recurrent or Progressive Metastatic Colorectal Cancer

DBL IRINOTECAN Injection Concentrate should be administered as an intravenous infusion (see **Preparation of Infusion Solution**) over 90 minutes in a recommended weekly or once every 3 week dosage schedule as shown below in Table 11.

Table 11: Single-Agent Regimens of DBL IRINOTECAN Injection Concentrate and Dose Modifications

Weekly Regimen[a] 6 week cycle Treatment resumes Day 43	125 mg/m^2 IV over 90 mins day 1, 8, 15, 22 then 2 week rest		
	Starting dose and modified dose levels[c]		
	Starting Dose (mg/m^2)	Dose Level –1 (mg/m^2)	Dose Level –2 (mg/m^2)
	125	100	75
Once every 3 week regimen[b]	350 mg/m^2 IV over 90 mins once every 3 weeks		
	Starting dose and modified dose levels[c]		
	Starting Dose (mg/m^2)	Dose Level –1 (mg/m^2)	Dose Level –2 (mg/m^2)
	350	300	250

[a] Subsequent doses may be adjusted as high as 150 mg/m^2 or as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending on individual patient tolerance

[b] Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending on individual patient tolerance

[c] Refer to *Table 13*

A reduction in the starting dose by one level of DBL IRINOTECAN Injection Concentrate may be considered for patients with any of the following circumstances: over 65 years, prior pelvic/abdominal radiotherapy, performance status of 2 or moderately increased bilirubin levels (17 - 34 µmol/L). Dosing for patients with bilirubin >34 mmol/L cannot be recommended since such patients were not included in clinical trials.

Patients with Impaired Hepatic Function (Single Agent)

In patients with hepatic dysfunction, the following starting doses are recommended:

Table 12: Starting Doses in Patients with Hepatic Dysfunction – Single Agent Regimens

Regimen	Serum Total Bilirubin Concentration	Serum ALT/AST Concentration	Starting Dose, mg/m^2
Single – Agent Weekly	1.5–3.0 x IULN	≤5.0 x IULN	60
	3.1–5.0 x IULN	≤5.0 x IULN	50
	<1.5 x IULN	5.1–20.0 x IULN	60
	1.5–5.0 x IULN	5.1–20.0 x IULN	40
Single Agent Once Every 3 Weeks	1.5–3.0 x IULN	-	200
	>3.0 x IULN	-	Not recommended[a]

[a] The safety and pharmacokinetics of IRINOTECAN given once every 3 weeks have not been defined in patients with bilirubin >3.0 x IULN and this schedule cannot be recommended in these patients.

Dose Modifications

Patients should be carefully monitored for toxicity and doses of DBL IRINOTECAN Injection Concentrate should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in Table 11 and 12, subsequent doses of DBL IRINOTECAN Injection Concentrate should be adjusted as suggested in Table 13. All dose modifications should be based on the worst preceding toxicity.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less, the granulocyte count has recovered to $\geq 1.5 \times 10^9$/L, the platelet count has recovered to $\geq 100 \times 10^9$/L and treatment-related diarrhoea is fully resolved. Treatment may be delayed for 1 to 2 weeks to allow recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing DBL IRINOTECAN Injection Concentrate therapy. Provided intolerable toxicity does not develop, treatment with additional cycles of DBL IRINOTECAN Injection Concentrate may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 13: Recommended dose modifications during a cycle of therapy with the weekly dosage schedule and at the start of each subsequent cycle of therapy with both dosage schedules

Toxicity NCI[a] Grade	**During a cycle of therapy**	**At the start of subsequent cycles of therapy**	
	Weekly	Weekly	Once every 3 weeks
No toxicity	Maintain dose level	Increase by 1 dose level up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Maintain dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Neutropenic fever	Omit dose until resolved, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Other haematological toxicities	Dose modifications for leucopenia, thrombocytopenia and anaemia 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		

Toxicity NCI[a] Grade		**During a cycle of therapy**	**At the start of subsequent cycles of therapy**	
		Weekly	Weekly	Once every 3 weeks
		neutropenia above.		
Diarrhoea				
	1	Maintain dose level	Maintain dose level	Maintain dose level
	2	Decrease by 1 dose level	Maintain dose level	Maintain dose level
	3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
	4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Other non-haematological toxicities				
	1	Maintain dose level	Maintain dose level	Maintain dose level
	2	Decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
	3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
	4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level

[a] Severity of adverse events based on NCI CTC (version 2.0)

Preparation and Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from DBL IRINOTECAN Injection Concentrate. The use of gloves is recommended. If a solution of DBL IRINOTECAN Injection Concentrate contacts the skin, wash the skin immediately and thoroughly with soap and water. If DBL

IRINOTECAN Injection Concentrate contacts the mucous membranes, flush thoroughly with water.

DBL IRINOTECAN Injection Concentrate contains no antimicrobial agent. It is for single use in one patient only. Discard any residue.

Preparation of Infusion Solution

The vial should be inspected for damage and visible signs of leaks. If damaged, incinerate the unopened package.

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe. If particulate matter is seen, do not use the contents.

DBL IRINOTECAN Injection Concentrate must be diluted prior to infusion. DBL IRINOTECAN Injection Concentrate should be diluted in 5% Glucose Injection (preferred) or 0.9% Sodium Chloride Injection to a final concentration range of 0.12 to 2.8 mg/mL. Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

Solutions diluted in 0.9% Sodium Chloride Injection in infusion bags are physically and chemically stable for up to 24 hours at 25°C when exposed to light, and up to 7 days when stored refrigerated (2 to 8°C) in the dark. Refrigeration of admixtures using 0.9% sodium chloride injection is not recommended due to a low and sporadic incidence of visible particles. Solutions diluted in 5% Glucose Injection in infusion bags are physically and chemically stable for 48 hours at 25°C when exposed to light, and to 7 days when stored refrigerated (2 to 8°C) in the dark. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2° to 8°C for not more than 24 hours.

Do not freeze admixtures of DBL IRINOTECAN Injection Concentrate as this may result in precipitation of the drug.

Pharmaceutical Precautions

The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good technique for handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling DBL IRINOTECAN Injection Concentrate should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow containment system). The work surface should be protected by disposable plastic backed absorbent paper.
- All items used for administration of cleaning, including gloves, should be placed in high-risk, waste-disposal bags for high temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- Accidental contact with the eyes or skin should be treated immediately. Copious lavage with water is appropriate treatment for contact with the eyes, whereas water or soap and water, or sodium bicarbonate solution may be used on the skin; medical attention should be sought.

OVERDOSAGE

Symptoms

In humans, at single doses up to 750 mg/m^2, adverse events were similar to those reported with the recommended dosage regimens. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse effects reported were severe neutropenia and severe diarrhoea.

Treatment

There is no known antidote for overdosage of irinotecan hydrochloride trihydrate. Support respiratory and cardiovascular function. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

PRESENTATION

DBL IRINOTECAN Injection Concentrate is supplied in single use, amber glass vials containing 20 mg/mL of irinotecan hydrochloride trihydrate.

Product	**Pack Size**
40 mg/2 mL	1 vial
100 mg/5 mL	1 vial
500 mg/25 mL	1 vial

STORAGE

Store below 30°C. Protect from light.

MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited

Warning (based on the Ministry of Public Health's Announcement)

This drug may cause serious harm, should be used under the supervision of a physician.