

# Irinotecan

## *Irinotecan hydrochloride injection 20 mg/ml*

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### Name of Medicine

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Non-proprietary name: Irinotecan hydrochloride

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### Presentation

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Irinotecan hydrochloride injection is a sterile aqueous solution of pH 3.5, which is clear, and is colourless to pale yellow. Irinotecan hydrochloride injection also contains the ingredients sorbitol, lactic acid, and sodium hydroxide.

Each mL of irinotecan hydrochloride injection contains 20 mg irinotecan. Irinotecan hydrochloride injection is available in single-dose amber glass vials in the following package sizes: 40mg/2mL, 100mg/5mL.

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### Uses

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#### ***Actions***

Irinotecan hydrochloride is a camptothecin derivative. Camptothecins induce reversible single-strand breaks in DNA by specifically interacting with the enzyme topoisomerase I, causing the relief of torsional strain in DNA. Religation of these single-strand breaks is prevented by the binding of irinotecan hydrochloride and its active metabolite SN-38 to the topoisomerase I-DNA complex.

Irinotecan hydrochloride is cytotoxic, with the current research suggesting that this is due to topoisomerase I, DNA, and either irinotecan hydrochloride or SN-38 forming a ternary complex which interacts with replication enzymes during DNA synthesis. The result is double-strand DNA damage which cannot be efficiently repaired by Mammalian cells.

Irinotecan hydrochloride is metabolized to give the lipophilic metabolite SN-38. As an inhibitor of topoisomerase I, purified from human and rodent tumour cell lines, SN-38 is approximately 1000 times as potent as irinotecan hydrochloride. The exact contribution of SN-38 to the activity of irinotecan injection is unknown. Irinotecan hydrochloride and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. Lactone formation is promoted in an acidic pH whereas a basic pH favours the hydroxy acid anion form.

In mice bearing rodent origin cancers and in human carcinoma xenografts of various histological types, antitumour activity has been attributed to administration of irinotecan hydrochloride.

Irinotecan hydrochloride administration is associated with a cholinergic syndrome (refer to Adverse Effects) as it is a non-competitive inhibitor of acetylcholinesterase.

#### ***Pharmacokinetics***

##### **Absorption:**

Irinotecan hydrochloride plasma concentrations decline in a multi-exponential manner after intravenous infusion of irinotecan hydrochloride in humans with various cancers. There is a mean terminal elimination half-life of about 6 to 12 hours. The active metabolite SN-38 mean terminal elimination half-life is about 10 to 20 hours. The plasma terminal elimination half-life was 13.8 +/- 1.4 hours for SN-38 and 14.2 +/- 7.7

hours for irinotecan hydrochloride in a study where irinotecan hydrochloride was administered at doses of 100-750 mg/m<sup>2</sup> by intravenous infusion every three weeks for 30 minutes.

**Distribution:**

The AUC of irinotecan hydrochloride increases linearly with dose over the recommended dose range of 50 to 350 mg/m<sup>2</sup>. The AUC of SN-38 increases less than proportionally with dose. At the end of a 90-minute infusion of irinotecan hydrochloride maximum concentrations of SN-38 are generally seen within 1 hour.

Summarised in Table 1 is the pharmacokinetic parameters in patients with solid tumours for irinotecan and SN-38 following a 90-minute infusion of irinotecan hydrochloride at dose levels of 125 and 340 mg/m<sup>2</sup> as determined in two clinical studies.

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

Dose (mg/m <sup>2</sup> )	SN-38			Irinotecan				
	C <sub>max</sub> (ng/mL)	t <sub>½</sub> (hr)	AUC <sub>0-24</sub> (ng.hr/mL)	C <sub>max</sub> (ng/mL)	t <sub>½</sub> (hr)	AUC <sub>0-24</sub> (ng.hr/mL)	CL (L/hr/m <sup>2</sup> )	V <sub>area</sub> (L/m <sup>2</sup> )
340 (N = 6)	56.0 ± 28.2	21.0 <sup>2</sup> ± 4.3	474 ± 245	3392 ± 874	11.7 <sup>2</sup> ± 1.0	20604 ± 6027	13.9 ± 4.00	234 ± 69.6
125 (N = 64)	26.3 ± 11.9	10.4 <sup>1</sup> ± 3.1	229 ± 108	1660 ± 797	5.8 <sup>1</sup> ± 0.7	10200 ± 3270	13.3 ± 6.01	110 ± 48.5

C<sub>max</sub> Maximum Plasma Concentration

t<sub>½</sub> Terminal elimination half-life

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

CL Total systemic clearance

V<sub>area</sub> Volume of distribution of terminal elimination phase

<sup>1</sup> Plasma specimens collected for 24 hours following the end of the 90-minute infusion

<sup>2</sup> Plasma specimens collected for 48 hours following the end of the 90-minute infusion. These values provide a more accurate reflection of the terminal elimination half-lives of SN-38 and irinotecan hydrochloride due to the longer collection period.

Irinotecan hydrochloride and SN-38 predominantly bind to the plasma protein albumin. Irinotecan hydrochloride has been indicated to have moderate plasma protein binding by in vitro studies (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound).

**Metabolism:**

The exact mechanisms are not yet understood for the disposition of irinotecan hydrochloride in humans. Irinotecan hydrochloride is converted to the active metabolite SN-38. This reaction primarily occurs in the liver and is mediated by carboxylesterase enzymes. SN-38 is conjugated by UDP-glucuronyl transferase 1A1 to form SN-38 glucuronide, a glucuronide metabolite.

Irinotecan is oxidized by cytochrome P450 isozyme 3A4 (CYP3A4) to yield mainly 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). Both of these metabolites are relatively inactive.

**Excretion:**

The cumulative biliary and urinary excretion of irinotecan hydrochloride SN-38 and SN-38 glucuronide following administration of irinotecan hydrochloride ranged from approximately 25% (100 mg/m<sup>2</sup>) to 50% (300 mg/m<sup>2</sup>) in two patients, over a period of 48 hours. The urinary excretion of irinotecan hydrochloride was 11% to 20% of the administered dose, SN-38 <1% and SN-38 glucuronide 3%.

**Pharmacokinetics in Special Populations****Geriatric**

A lower starting dose is recommended in patients 65 years and older based on clinical toxicity experienced where irinotecan hydrochloride was administered weekly (refer to Dosage and Administration). The terminal half-life of irinotecan hydrochloride in patients who were younger than 65 years was 5.5 hours, and 6.0 hours in patients 65 years or older, in studies where irinotecan hydrochloride was administered weekly. In patients who were at least 65 years of age, dose-normalised AUC<sub>0-24</sub> for SN-38 was 11% higher than in patients younger than 65 years. There is no kinetic data on the use in elderly patients of the once-every-three-week dosage schedule.

**Paediatric**

Information is not available.

**Gender**

Irinotecan hydrochloride pharmacokinetics do not appear to be influenced by gender.

**Hepatic Insufficiency**

Patients with hepatic dysfunction have diminished irinotecan clearance while relative exposure to the active metabolite SN-38 is increased. Degree of liver impairment will affect the magnitude of these effects as measured by elevations in serum total bilirubin and transaminase concentrations (refer to Dosage and Administration).

**Renal Insufficiency**

Pharmacokinetics of irinotecan hydrochloride in the presence of renal insufficiency has not been evaluated.

**Pharmacokinetics in Combination Therapy**

In a phase I clinical study involving 26 patients with solid tumours, irinotecan hydrochloride, 5 fluorouracil (5-FU) and leucovorin (LV) were administered. The active metabolite SN-38 C<sub>max</sub> was reduced by 14% and AUC<sub>0-24</sub> was reduced by 18% when irinotecan hydrochloride was followed by 5-FU and LV administration compared with when irinotecan hydrochloride was given alone. The disposition of irinotecan hydrochloride was not substantially altered when the drugs were co-administered. Formal drug interaction studies either *in vivo* or *in vitro* to evaluate the effects on disposition of 5-FU and LV when administered with irinotecan hydrochloride have not been conducted.

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**Indications**

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Irinotecan hydrochloride is indicated for:

- First line treatment of patients with metastatic carcinoma of the colon or rectum, in combination with 5FU/Leucovorin (LV).
- Metastatic carcinoma of the colon or rectum for patients whose disease has recurred or progressed following initial therapy.

## Contraindications

Irinotecan injection is contraindicated in women who intend to become pregnant (refer to Impairment of Fertility, Carcinogenicity & Mutagenicity).

Irinotecan injection is contraindicated in patients with a known hypersensitivity to the drug or any of its excipients.

## Dosage and Administration

It is recommended that patients receive premedication with antiemetic agents. In patients experiencing cholinergic symptoms prophylactic or therapeutic atropine administration should be considered (refer to Warnings and Precautions).

### Combination Agent Therapy

#### Dosage Regimens

#### *Irinotecan injection in Combination with 5-fluorouracil (5-FU) and Leucovorin (LV)*

The recommended regimens are shown in Table 2. Irinotecan injection should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion solution). The dose of LV should be administered immediately after irinotecan injection, with the administration of 5-FU to follow immediately after the administration of LV.

**Table 2: Combination Agent Dosage Regimens & Dose Modifications<sup>1</sup>**

<b>Regimen 1</b> 6 week cycle Treatment resumes Day 43	Irinotecan injection. LV 5-FU	125mg/m <sup>2</sup> IV over 90min on day 1,8,15,22, then 2 week rest 20mg/m <sup>2</sup> IV bolus injection day 1,8,15,22, then 2 week rest 500mg/m <sup>2</sup> IV bolus injection day 1,8,15,22 then 2 week rest		
		<b>Starting dose and modified dose levels<sup>2</sup></b>		
		Starting dose (mg/m <sup>2</sup> )	Dose level -1 (mg/m <sup>2</sup> )	Dose level -2 (mg/m <sup>2</sup> )
	Irinotecan injection	125	100	75
	LV	20	20	20
	5-FU	500	400	300
<b>Regimen 2</b> 6 week cycle Treatment resumes Day 43	Irinotecan injection LV 5-FU Bolus 5-FU Infusion <sup>3</sup>	180mg/m <sup>2</sup> IV over 90min on day 1,15,29 then 1 week rest 200mg/m <sup>2</sup> IV over 2 hr on day 1,2,15,16,29,30 then 1 week rest 400mg/m <sup>2</sup> IV on day 1,2,15,16,29,30 then 1 week rest 600mg/m <sup>2</sup> over 22hr on day 1,2,15,16,29,30 then 1 week rest		
		<b>Starting dose and modified dose levels<sup>2</sup></b>		
		Starting dose (mg/m <sup>2</sup> )	Dose level -1 (mg/m <sup>2</sup> )	Dose level -2 (mg/m <sup>2</sup> )
	Irinotecan injection	180	150	120
	LV	200	200	200

	5-FU Bolus	400	320	240
	5-FU Infusion <sup>c</sup>	600	480	360

<sup>1</sup> Patients continuing to experience toxicity may be administered dose reductions beyond dose level - 2 by decrements of  $\approx 20\%$ . If patients continue to receive clinical benefits, treatment with additional courses may be continued indefinitely provided intolerable toxicity does not develop.

<sup>2</sup> Refer to Table 3

<sup>3</sup> Infusion follows bolus administration

### ***Dose Modification – Combination Agent Therapy***

Toxicity must be carefully assessed and monitored before each treatment. This is especially important during the first cycle of therapy. Individual patients may have different levels of tolerance to the treatment, the doses of irinotecan injection and 5-FU must be modified as necessary. Initial doses should be based on the values given in Table 2, with subsequent doses modified as suggested in Table 3.

All dose modifications should be based on the worst preceding toxicity.

Toxicity levels should have recovered to NCI grade 1 or less, the granulocyte count recovered to  $\geq 1.5 \times 10^9/L$ , and the platelet count recovered to  $\geq 100 \times 10^9/L$ , before a new course of therapy begins.

Before being administered the next chemotherapy dose, patients should additionally be diarrhoea free with a return to pre-treatment bowel function and have not required antidiarrhoeal medications for at least 24 hours.

1 to 2 weeks of delayed treatment should be allowed to encourage recovery from treatment-related toxicity. If the patient has not recovered after a 2 week delay, discontinuing therapy may need to be considered.

If patients continue to receive clinical benefits additional courses of irinotecan injection/5-FU/LV may be continued indefinitely, provided intolerable toxicity does not develop.

**Table 3: Recommended dose modifications during a course of therapy with the irinotecan injection /5-FU/LV combination and at the start of each subsequent course of therapy**

<b>Toxicity NCI CTC grade<sup>1</sup></b>	<b>During a Course of Therapy</b>	<b>At the Start of Subsequent Courses of Therapy<sup>2</sup></b>
<b>No toxicity</b>	Maintain dose level	Maintain dose level
<b>Diarrhoea</b>		
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 1 dose level
<b>Neutropenic fever</b>	Omit dose, until resolved then decrease by 2 dose levels.	
<b>Neutropenia</b>		
1	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Maintain dose level
3	Omit dose, until resolved to $\leq$ grade	Decrease by 1 dose level

4	2 then decrease by 1 dose level Omit dose, until resolved to ≤ grade 2 then decrease by 2 dose levels	Decrease by 2 dose levels
<b>Add other haemolytic toxicities</b>	Leucopenia or thrombocytopenia dose modifications during a course of therapy and at start of subsequent course of therapy are also based on NCI toxicity criteria and are the same as neutropenia recommended above.	
<b>Other non-haematological Toxicities<sup>3</sup></b>		
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

<sup>1</sup> Severity of adverse events based on NCI CTC (version 2.0)

<sup>2</sup> Relative to the starting dose used in the previous course

<sup>3</sup> For mucositis/stomatitis decrease only 5-FU, not irinotecan injection

## Single Agent Therapy

### Dosage Regimens

Irinotecan injection is designed to be administered as an intravenous infusion (see Preparation of Infusion solution) over 90 minutes in a recommended weekly or once-every-three-week dosage schedule as shown below in Table 4.

**Table 4: Single-Agent Regimen of irinotecan injection and Dose Modifications**

<b>Weekly regimen<sup>1</sup> Treatment 6 week cycle resumes Day 43</b>	<b>125 mg/m<sup>2</sup> IV over 90 mins day 1, 8, 15, 22 then 2 week rest</b>		
	Starting dose and modified dose levels <sup>3</sup>		
	<b>Starting dose (mg/m<sup>2</sup>)</b>	<b>Dose Level - 1 (mg/m<sup>2</sup>)</b>	<b>Dose Level - 2 (mg/m<sup>2</sup>)</b>
	125	100	75
<b>Once every three week regimen<sup>2</sup></b>	<b>350 mg/m<sup>2</sup> IV over 90 mins once every 3 weeks</b>		
	Starting dose and modified dose levels <sup>1</sup>		
	<b>Starting dose (mg/m<sup>2</sup>)</b>	<b>Dose Level - 1 (mg/m<sup>2</sup>)</b>	<b>Dose Level - 2 (mg/m<sup>2</sup>)</b>
	350	300	250

<sup>1</sup> Depending on individual patient tolerance, subsequent doses may be adjusted as high as 150 mg/m<sup>2</sup> or as low as 50 mg/m<sup>2</sup> in 25 to 50 mg/m<sup>2</sup> decrements

<sup>2</sup> Depending on individual patient tolerance, subsequent doses may be adjusted as low as 200 mg/m<sup>2</sup> in 50 mg/m<sup>2</sup> decrements

<sup>3</sup> Refer to Table 6

In patients over 65 years, with prior pelvic/abdominal radiotherapy, with a performance status of 2 or moderately increased bilirubin levels (17-34 µmol/L), a reduction in the starting dose by one dose level of irinotecan injection may be considered.

### Patients with Impaired Hepatic Function (Single Agent)

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

**Table 5: Starting Doses in Patients with Hepatic Dysfunction - Single Agent Regimens**

Regimen	Serum ALT/AST Concentration	Serum Total Bilirubin Concentration	Starting Dose mg/m <sup>2</sup>
<b>Single - Agent Weekly</b>	≤ 5.0 x IULN	1.5 - 3.0 x IULN	60
	≤ 5.0 x IULN	3.1 - 5.0 x IULN	50
	5.1 - 20.0 x IULN	<1.5 x IULN	60
	5.1 - 20.0 x IULN	1.5 - 5.0 x IULN	40
<b>Single Agent Once Every Three Weeks</b>	-	1.5 - 3.0 x IULN	200
	-	> 3.0 x IULN	Not recommended <sup>1</sup>

<sup>1</sup> A schedule for patients with bilirubin >3.0 x IULN cannot be recommended as the safety and pharmacokinetics of irinotecan injection given once every 3 weeks have not been defined

### Dose Modifications – Single Agent Regimens

Toxicity in patients should be carefully monitored. To accommodate individual patient tolerance to treatment, doses of irinotecan injection should be modified as necessary. All dose modifications should be based on the worst preceding toxicity. Recommended dose-levels described in Table 4 and 5 and subsequent doses of irinotecan injection should be adjusted, as suggested in Table 6.

Until the toxicity has recovered to NCI grade 1 or less, the granulocyte count has recovered to ≥ 1.5x10<sup>9</sup>/L, the platelet count has recovered to ≥ 100x10<sup>9</sup>/L, and treatment-related diarrhoea is fully resolved, a new cycle of therapy should not begin. To allow recovery from treatment-related toxicity, treatment may be delayed for 1 to 2 weeks. Consideration should be given to discontinuing irinotecan injection therapy, if the patient has not recovered. Treatment with additional cycles of irinotecan injection may be continued indefinitely, provided intolerable toxicity does not develop, and as long as patients continue to experience clinical benefit.

**Table 6. Recommended dose modifications for single agent regimens**

Toxicity NCI <sup>a</sup> Grade	During a cycle of therapy	At The Start Of Subsequent Cycle Of Therapy	
	Weekly	Weekly	Once Every Three Weeks
No Toxicity	Maintain dose level	Increase by 1 dose level up to a maximum dose of 150mg/m <sup>2</sup>	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
<b>Neutropenic Fever</b>	Omit dose until resolved, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
<b>Diarrhoea</b>			
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
<b>Other Haematological toxicities</b>	Dose modifications for leucopenia, thrombocytopenia and anaemia during a cycle of therapy and at the start of subsequent cycle of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
<b>Other non-haematological toxicities</b>			
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

<sup>1</sup> Severity of adverse events based on NCI CTC (version 2.0)

## **Preparation & Administration Precautions**

Care should be taken in the handling and preparation of infusion solutions prepared from irinotecan injection as it is a potentially toxic anticancer agent. Gloves should always be used. Wash the skin immediately and thoroughly with soap and water if irinotecan solution makes contact with skin. If irinotecan injection contacts the mucous membranes, flush thoroughly with water.

### **Preparation of Infusion Solution**

Irinotecan injection must be diluted before infusion in 5% Glucose Injection (preferred) or 0.9% Sodium Chloride Injection to give a final concentration of 2.8 mg/mL. Do not add other drugs to the infusion solution.

Prior to administration and when the solutions and containers permit, parenteral drug products should be inspected visually, to check there is no particulate matter and discolouration has not occurred.

It is recommended that infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable in order to reduce microbiological hazard. If not used immediately, in-use storage times and conditions prior to use should not be longer than 24 hours at room temperature (25°C).

**Irinotecan injection is intended for single use only. Any unused portion should be discarded.**

Do not freeze irinotecan injection or admixtures of irinotecan injection or precipitation of the drug may occur.

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## **Warnings and Precautions**

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### **Administration**

Irinotecan injection 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.

### **Extravasation**

Care should be taken to avoid extravasation when administering irinotecan injection by intravenous infusion. The infusion site should be monitored for signs of inflammation. Flushing the site with sterile water and applications of ice are recommended in the case of extravasation occurring.

### **"Mayo Clinic" regimen**

The "Mayo Clinic" regimen of 5-FU/LV (administration for 4-5 consecutive days every 4 weeks) should not be used in combination with irinotecan injection; except in a well-designed clinical study. This is because of increased toxicity reports, including toxic deaths. Irinotecan injection should be used as recommended in Dosage and Administration.

### **Monitoring**

Liver function should be monitored before initiation of treatment and then monthly or as indicated clinically. White blood cell counts require careful monitoring with differential haemoglobin, and platelet counts before each dose of irinotecan injection.

### **Cardiovascular**

Rarely, thromboembolic events have been observed in patients receiving irinotecan injection. The specific cause of these events has not been determined (refer to Adverse Effects, *Cardiovascular*).

### **Cholinergic Effects**

Irinotecan injection should be used cautiously in patients with asthma or cardiovascular diseases and in patients with mechanical intestinal or urinary obstruction due to its cholinergic effects.

### **Colitis/Ileus**

Colitis cases have been reported. Some cases were complicated by bleeding ileus, ulceration and infection. Rare cases of ileus without preceding colitis have also been observed. Prompt antibiotic support should be given to patients experiencing ileus.

### **Chronic inflammatory bowel disease and/or bowel obstruction**

Patients must not be treated with irinotecan until the bowel obstruction has been resolved.

### **Diarrhoea**

Irinotecan injection can induce 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 injection) is cholinergic in nature. It is only occasionally severe and is usually transient. It may be accompanied by lacrimation, rhinitis symptoms, bradycardia, miosis, increased salivation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. If patients are experiencing cholinergic symptoms during or shortly after infusion of irinotecan injection, administration of 0.25 to 1mg of subcutaneous or intravenous atropine may be considered (unless clinically contraindicated).

Late diarrhoea (generally occurring more than 24 hours after administration of irinotecan injection) which can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life threatening. Late diarrhoea should be treated promptly with loperamide (see Warnings and Precautions, Information for Patients, for dosing recommendations for loperamide). The patient should be instructed to have loperamide readily available. Patients should be directed to begin loperamide treatment at the first episode of loose or poorly formed stools or the earliest onset of more frequent bowel movements than normally expected. In clinical trials one dosage regimen for loperamide consisted of 4mg at the first onset of late diarrhoea and then 2mg every 2 hours until the patient was diarrhoea-free for at least 12 hours. The patient may take 4mg of loperamide every 4 hours during the night. More than 48 consecutive hours treatment with loperamide at these doses may place the patient at risk of paralytic ileus. Loperamide is therefore not to be recommended used for more than 48 consecutive hours or less than 12 hours. Premedication with loperamide is not recommended.

Careful monitoring is required for patients with diarrhoea. If patients become dehydrated patients then they should be given fluid and electrolyte replacement therapy, and should be given antibiotics if they develop severe neutropenia, ileus, or fever. Subsequent chemotherapy, after the first treatment, 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. Subsequent doses of irinotecan injection should be reduced within the current cycle if NCI grade 2, 3 or 4 diarrhoea occurs (refer to Dosage and Administration).

Hospitalisation is recommended additional to the antibiotic therapy for management of the diarrhoea, in the following cases: severe diarrhoea (requiring intravenous hydration), vomiting associated with delayed (*i.e.* late) diarrhoea, diarrhoea associated with fever and diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy and in the 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 leukopenia, neutropenia, and anaemia. While serious thrombocytopenia is uncommon, these effects may be severe and therefore should not be used in patients with severe bone marrow failure (refer to Adverse Effects, Haematological).

### **Hepatic Insufficiency**

The clearance of irinotecan is decreased in patients with hyperbilirubinemia, and therefore the risk of haematotoxicity is increased (refer to Pharmacokinetics).

The use of irinotecan given as a single agent on the once-every-three-weeks schedule has not been established in patients with a serum total bilirubin concentration of  $> 3.0 \times$  institutional upper limit of normal (IULN). In clinical trials of the single agent weekly dosage schedule, patients had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia if they had modest elevations in total baseline serum total bilirubin levels (17-34  $\mu\text{mol/L}$ ) versus those patients with bilirubin levels that were less than 17  $\mu\text{mol/L}$  (50% versus 18%;  $p < 0.001$ ) (refer to Pharmacokinetics Special Populations and Dosage and Administration).

Patients may be at greater risk of myelosuppression when receiving therapy with irinotecan if they have deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome.

### **Hypersensitivity**

Severe anaphylactic and anaphylactoid reactions have been observed due to hypersensitivity reactions.

### **Immunosuppressant Effects/Increased Susceptibility to Infections**

Avoid live vaccines in patients receiving irinotecan. Administration of chemotherapeutic agents such as irinotecan injection may immunocompromise patients. If immunocompromised patients are administered live or live-attenuated vaccines, they may become seriously or fatally infected. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

### **Impaired renal function**

Caution is advised in administering irinotecan to patients with impaired renal function as studies have not been conducted in this patient population (refer to Pharmacokinetics, *Pharmacokinetics in Special Populations*). Irinotecan is not recommended for use in patients on dialysis.

### **Irradiation therapy**

Concurrent administration of irinotecan with irradiation therapy has not been adequately studied and is not recommended. Patients are at increased risk of severe myelosuppression following the administration of irinotecan injection if they have previously received pelvic/abdominal irradiation.

### **Nausea and vomiting**

Physicians should consider providing an antiemetic regimen (e.g., prochlorperazine) for patients with subsequent irinotecan use. The majority of patients in clinical studies of the weekly dosage schedule received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT<sub>3</sub> blocker (e.g., ondansetron or granisetron). It is recommended that patients receive premedication with antiemetic agents, as irinotecan is emetogenic. Antiemetic agents should be started at least 30 minutes before administration of irinotecan injection on the day of treatment.

Patients need to be hospitalised as soon as possible for treatment if they have vomiting associated with delayed (i.e. late) diarrhoea.

### **Neutropenia**

Deaths in patients due to sepsis following severe myelosuppression when treated with irinotecan injection have been reported.

Neutropenic complications should be managed immediately with antibiotic support. If the absolute neutrophil count drops below  $1.5 \times 10^9/\text{L}$  or neutropenic fever occurs, therapy with irinotecan injection should be temporarily stopped. The granulocyte count should have recovered to  $\geq 1.5 \times 10^9/\text{L}$  before beginning a new cycle of therapy. After recovery by the patient, subsequent doses of irinotecan injection should be reduced depending upon the level of neutropenia observed (see Dosage and Administration).

A colony-stimulating factor (CSF) may be considered by physicians in individual patients with significant neutropenia, however routine administration of this is not necessary.

### **Patients with poor performance status**

There is an increased risk of irinotecan-related adverse events in patients with poor performance status. Physicians should be particularly cautious in monitoring the effects of irinotecan injection in patients with poor performance status including the elderly and in patients who had previously received pelvic/abdominal irradiation (see Adverse Effects). In patients receiving either irinotecan injection/5-FU/LV or 5-FU/LV in clinical trials comparing these agents, higher rates of neutropenic fever, hospitalisation, first-cycle treatment discontinuation, thromboembolism 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 injection.

### **Respiratory**

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Interstitial pulmonary disease can be fatal. Pre-existing lung disease, colony stimulating factors, radiation therapy and use of pneumotoxic drugs are risk factors possibly associated with the development of interstitial pulmonary disease. Close monitoring for respiratory symptoms before and during irinotecan therapy is important in patients with risk factors.

### **Others**

This product is unsuitable in hereditary fructose intolerance as it contains sorbitol.

### **Advice for Patients**

Patients should be advised of the expected toxic effects of irinotecan injection, particularly of gastrointestinal complications such as vomiting, nausea, diarrhoea, abdominal cramping and infection.

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

## ***Pregnancy***

Category D. There are no adequate and well-controlled studies of irinotecan hydrochloride in pregnant women. Irinotecan injection may cause foetal harm when administered to a pregnant woman. Clinical studies show administration of 6 mg/kg/day intravenous irinotecan hydrochloride to rabbits (about one-half the recommended human weekly starting dose on a  $\text{mg}/\text{m}^2$  basis) and rats (AUC about 0.2 times the corresponding values in patients administered 125  $\text{mg}/\text{m}^2$ ) during the period of organogenesis, is embryotoxic. This is seen as decreased numbers of live fetuses and as increased post-implantation loss. Irinotecan hydrochloride administered at doses greater than 1.2 mg/kg/day (AUC about 1/40th the corresponding values in patients administered 125  $\text{mg}/\text{m}^2$ ) was teratogenic in rats, and teratogenic in rabbits at 6.0 mg/kg/day. These teratogenic effects included a variety of external, visceral, and skeletal abnormalities.

While receiving treatment with irinotecan injection, women of childbearing potential should be advised to avoid becoming pregnant. The patient should be apprised of the potential hazard to the foetus if the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug,

## ***Use in Lactation***

It is recommended that breastfeeding be discontinued when receiving therapy with irinotecan injection as many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants. Clinical studies revealed that radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabelled irinotecan hydrochloride. It was concentrated up to 65-fold relative to plasma concentrations at 4 hours post administration.

## ***Use in Children***

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

## ***Impairment of Fertility, Carcinogenicity & Mutagenicity***

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

There was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas in rats administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan hydrochloride once per week for 13 weeks (AUC about 1.3 times the values of patients administered 125 mg/m<sup>2</sup>) and then allowed to recover for 91 weeks. Long-term carcinogenicity studies with irinotecan hydrochloride were not conducted.

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

## ***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 hydrochloride, and advised not to drive or operate machinery if these symptoms occur (refer to Warnings and Precautions).

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## **Adverse Effects**

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### ***Combination Therapy***

In the two phase III studies, a total of 955 patients with metastatic colorectal cancer received irinotecan hydrochloride alone, irinotecan hydrochloride combined with 5-FU/LV or 5-FU/LV alone. 223 patients received irinotecan hydrochloride alone, 370 patients received irinotecan hydrochloride in combination with 5-FU/LV and 362 patients received 5-FU/LV alone.

Fifty-nine (6.1%) patients died within 30 days of study treatment: 13 (5.8%) received irinotecan hydrochloride alone, 27 (7.3%) received irinotecan hydrochloride in combination with 5-FU/LV, and 19 (5.3%) received 5-FU/LV alone. Deaths that may have been related to treatment occurred in 2 (0.9%)

patients who received irinotecan hydrochloride alone (2 neutropenic fever), 3 (0.7%) patients who received irinotecan hydrochloride combined with 5-FU/LV (2 neutropenic fever/sepsis, 1 treatment toxicity), and 3 (0.7%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown). Deaths within 60 days of study treatment were reported for 15 (6.7%) patients who received irinotecan hydrochloride alone, 18 (4.9%) patients who received irinotecan hydrochloride in combination with 5-FU/LV, and 18 (5.0%) patients who received 5-FU/LV alone.

Discontinuations due to adverse events were reported for 26 (11.7%) patients who received irinotecan hydrochloride alone, 26 (7.0%) patients who received irinotecan hydrochloride in combination with 5-FU, and 15 (4.1%) patients who received 5-FU/LV 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<sup>1</sup>**

Adverse Event	Study 1			Study 2	
	Irinotecan HCl n=223 <sup>b</sup>	5-FU/LV n=219 <sup>b</sup>	Irinotecan HCl 5-FU/LV n=225 <sup>b</sup>	5-FU/LV n=143 <sup>c</sup>	Irinotecan HCl 5-FU/LV n=145 <sup>c</sup>
Total Grade 3/4 Adverse Events	45.7	45.7	53.3	39.2	72.4
<b>CARDIOVASCULAR</b>					
Vasodilatation	0	0	0.9	-	-
Hypotension	1.7	0.5	1.3	0	1.4
Thrombophlebitis	1.8	3.2	2.7	-	-
Pulmonary embolus	0.4	1.4	2.7	-	-
Myocardial infarction	0.4	0	1.3	-	-
<b>DERMATOLOGICAL</b>					
Exfoliative dermatitis	0	0.5	0	-	-
Rash	0.4	0.9	0	-	-
Hand and foot syndrome	-	-	-	0.7	0.7
Cutaneous signs	-	-	-	0	0.7
<b>GASTROINTESTINAL</b>					
Diarrhoea					
- late	31.0	13.2	22.7	6.3	14.5
- grade 3	18.4	5.9	15.1	4.2	10.3
- grade 4	12.6	7.3	7.6	2.1	4.1
- early	6.7	1.4	4.9	-	-
Nausea	16.1	8.2	15.6	3.5	2.1
Abdominal pain	13.0	11.5	14.6	0.7	2.1
Vomiting	12.1	4.1	9.7	2.8	3.5
Anorexia	7.2	3.7	5.8	0.7	2.1
Constipation	0.4	1.8	3.1	1.4	0.7
Mucositis	2.2	16.9	2.2	2.8	4.1

<b>HAEMATOLOGICAL</b>					
Neutropenia	31.0	66.7	53.8	13.4	46.2
- grade 3	19.3	23.7	29.8	12.7	36.4
- grade 4	12.1	42.5	24.0	0.7	9.8
Leucopenia	21.5	23.3	37.8	3.5	17.4
Anaemia	4.5	5.5	8.4	2.1	2.1
Neutropenic fever	5.8	14.6	7.1	0.7	3.4
Thrombocytopenia	1.7	2.7	2.6	0	0
Neutropenic infection	2.2	0	1.8	0	2.1
<b>METABOLIC &amp; NUTRITIONAL</b>					
Increased Bilirubin	7.2	8.2	7.1	10.6	3.5
<b>RESPIRATORY</b>					
Dyspnea	2.2	0.5	6.3	0	1.4
Cough	0.4	0	1.3	-	-
Pneumonia	1.3	1	2.7	-	-
<b>NEUROLOGICAL</b>					
Dizziness	1.8	0	1.3	-	-
Somnolence	1.3	1.8	1.8	-	-
Confusion	0	0	1.8	-	-
<b>BODY AS A WHOLE</b>					
Asthenia	13.9	11.9	19.5	4.2	9.0
Pain	2.2	3.6	3.1	8.4	9.7
Fever	0.4	3.6	1.7	0.7	0.7
Infection	0.4	1.4	0	3.5	7.6

<sup>1</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>2</sup> Number of patients in the as-treated population for each group

<sup>3</sup> Number of patients treated in the de Gramont regimen (B2/C2 treatment arms of Table 3)

Alopecia, diarrhoea, neutropenia, nausea and vomiting were the most clinically significant adverse events for patients receiving irinotecan hydrochloride-based therapy. Diarrhoea, neutropenia, neutropenic fever and mucositis were the most clinically significant adverse events for patients receiving 5-FU/LV therapy. Grade 4 neutropenia, neutropenic fever (defined as  $\geq$  grade 2 fever and grade 4 neutropenia) and mucositis were observed less often with irinotecan hydrochloride/5-FU/LV than with administration of 5-FU/LV in Study 1.

### **Single Agent Therapy**

304 patients with metastatic carcinoma of the colon or rectum were treated in phase II trials with the once weekly dosage schedule for irinotecan injection as single agent therapy as well as 316 patients treated with the once-every-3-week dosage schedule and over 1100 patients with a variety of tumour types treated in Japan. Throughout these clinical studies, generally the types of toxicities observed were similar.

Medical events caused the discontinuation of irinotecan injection treatment in 8% of patients treated with the once-every-3-week dosage schedule and 4.3% of patients treated with the weekly dosage schedule.

Deaths occurred in seventeen of the 304 patients treated with the weekly dosage schedule within 30 days of the administration of irinotecan injection. In five of these cases (1.6%), the deaths were potentially drug-related. Deaths occurred in eleven patients treated with irinotecan hydrochloride in the once-every-three-week dosage schedule within 30 days of treatment. In three cases (1%), the deaths were potentially related to treatment with irinotecan hydrochloride. The main causes of the deaths that were potentially related to treatment with irinotecan injection were; neutropenic infection, asthenia and Grade 4 diarrhoea.

Table 8 below shows the frequency of the most common adverse events reported from the single agent second line studies. Additional information on adverse events follows the Table.

**Table 8: Adverse events reported from the second line single agent therapy in 304 patients<sup>1</sup>**

<i>Event</i>	<b>3 weekly dosage schedule (NCI Grade 3 &amp; 4 only)</b>		<b>Weekly dosage schedule</b>	
	<b>Study 1 (%)</b>	<b>Study 2 (%)</b>	<b>% NCI Grade 3 &amp; 4</b>	<b>% of Patients</b>
<b>DERMATOLOGICAL</b>				
Alopecia	N/A <sub>5</sub>	N/A <sub>5</sub>	N/A <sub>5</sub>	60.5
Sweating	-	-	0	16.4
Rash	1.6	0.8	0.7	12.8
<b>GASTROINTESTINAL</b>				
Diarrhoea (late)	21.7	22	30.6	87.8
Nausea	13.8	11	16.8	86.2
Vomiting	13.8	14.2	12.5	66.8
Abdominal cramping/pain	13.8	8.7	16.4	56.9
Anorexia	5.3	5.5	5.9	54.9
Diarrhoea (early)	12.2	1.6	7.9	50.7
Constipation	9.5	7.9	2	29.9
Flatulence	--	--	--	12.2
Stomatitis	--	--	0.7	11.8
Dyspepsia	--	--	--	10.5
<b>HAEMATOLOGICAL</b>				
Leucopenia <sup>2</sup>	22.2	14.2	28	63.2
Anaemia	7.4	6.3	6.9	60.5
Neutropenia <sup>2</sup>	22.2	14.2	26.3	53.9
Thrombocytopenia	1.1	3.9	--	--
<b>METABOLIC &amp; NUTRITIONAL</b>				
Weight reduction			0.7	30.3
Dehydration			4.3	14.8

Increased alkaline phosphatase			3.9	13.2
Increased SGOT			1.3	10.5
<b>RESPIRATORY</b>				
Dyspnoea			3.6	22
Increased coughing			0.3	17.4
Rhinitis			0	15.5
<b>BODY AS A WHOLE</b>				
Asthenia	14.8	13.4	12.2	75.7
Fever	--	--	0.7	45.4
Pain	18.5 <sup>3</sup>	16.5 <sup>4</sup>	2.3	23.7
Headache	--	--	0.7	16.8
Back pain	--	--	1.6	14.5
Chills	--	--	0.3	13.8
Minor infections	--	--	0	14.5
Oedema	--	--	1.3	10.2
Abdominal enlargement	--	--	0.3	10.2

<sup>1</sup> Severity of adverse events based on NCI CTC (version 1.0)

<sup>2</sup> Combined results for leucopenia/neutropenia are presented for the once-every-3-week dosage schedule

<sup>3</sup> In this study, 22.2% of patients treated with best supportive care experienced NCI Grade 3/4 pain

<sup>4</sup> In this study, 13.2% of patients treated with infusional 5-FU experienced NCI Grade 3/4 pain

<sup>5</sup> Complete hair loss = NCI grade 2

## **Overview of Adverse Events**

### **Body as a Whole**

Abdominal pain, asthenia and fever are generally the most common events of this type.

### **Cardiovascular**

Patients receiving irinotecan injection have rarely experienced 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. The specific cause of these events has not been determined.

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

Vasodilation (flushing) may occur during administration of irinotecan injection.

### **Cholinergic Symptoms**

These symptoms are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are more likely to occur at higher doses. Patients may have cholinergic symptoms of diaphoresis rhinitis, flushing and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhoea, increased salivation, lacrimation, and miosis. These symptoms will manifest during or shortly after drug infusion as during parenteral administration, if they should occur and peak irinotecan hydrochloride serum levels are most consistent with the occurrence of the symptoms.

### **Dermatologic**

Alopecia and rashes have been reported during treatment with irinotecan injection. Rashes did not result in discontinuation of treatment.

### **Gastrointestinal**

Among those patients treated at the 125 mg/m<sup>2</sup> 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 or 4 late diarrhoea was significantly greater in patients 65 years or older (39.8% versus 23.4%, p=0.0025). Diarrhoea, nausea, and vomiting are common adverse events and can be severe following treatment with irinotecan injection.

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 for treating these events.

Administration of irinotecan injection has been observed to be associated with colonic ulceration, and sometimes with gastrointestinal bleeding.

### **Haematology**

Neutropenia, leucopenia (including lymphocytopenia), and anaemia are commonly seen in patients administered irinotecan injection. Serious thrombocytopenia is uncommon. One death due to neutropenic sepsis without fever was judged to be potentially drug-related (0.3%, 1/304) in clinical studies with the single agent weekly dosage schedule. Blood transfusions were given to 9.9% of patients. 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 (48.1% versus 24.1%, p=0.0356), in the trials of single agent weekly administration. In these same studies, patients with baseline serum total bilirubin levels of 17 µmol/L or more also had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 17 µmol/L (50% versus 17.7%, p<0.001).

### **Hepatic**

NCI grade 3 or 4 liver enzyme abnormalities were seen in less than 10% of patients in the clinical studies with the single agent weekly dosage schedule. These events usually occur in patients with known hepatic metastases. Hepatic events, such as jaundice of NCI Grade 3/4 severity and ascites occurred in 8.5% of patients in one study and 8.7% of patients in another for the once-every-3-week dosage schedule.

### **Metabolic and Nutritional**

Diarrhoea, nausea and vomiting caused the dehydration observed in 14.8% of patients in clinical studies.

### **Neurological**

In clinical trials of the single agent weekly dosage schedule, insomnia and dizziness were observed in 19.4% and 14.8% respectively of patients studied. These events were not usually considered to be directly related to the administration of irinotecan injection. Orthostatic hypotension in patients with dehydration may sometimes cause the symptom of dizziness.

## **Renal**

Serum creatinine increase or blood urea nitrogen increase are generally attributable to complications of infection or to dehydration related to nausea, vomiting or diarrhoea or complications of infection. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

## **Respiratory**

Lung metastases were found in over half the patients with dyspnoea in the clinical studies evaluating the single agent weekly dosage schedule. It is unknown the extent to which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnoea in these patients. Severe pulmonary events are infrequent. Respiratory events, such as dyspnoea and cough of NCI Grade 3/4 severity, for the once-every-three-week dosage schedule, 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 early Japanese studies a small percentage of patients. Irinotecan hydrochloride's contribution to these preliminary events was difficult to assess because these patients also had some pre-existing nonmalignant pulmonary disease and some had lung tumours. Clinical studies in the USA, as a result of these observations, enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

## **Other**

Observed in 1-10% of patients in clinical trials were other NCI grade 3 or 4 drug-related adverse events; including mucositis, bilirubinaemia and hypovolaemia. NCI grade 3 or 4 rectal disorder: gastrointestinal monilia, hypokalaemia, hypomagnesaemia, increased GGTP, malaise, sepsis and abnormal gait were observed in fewer than 1% of patients.

## **Post-marketing Surveillance**

*Cardiac disorders:* Following irinotecan therapy, myocardial ischaemic events have occurred predominantly in patients with; underlying cardiac disease, previous cytotoxic chemotherapy and other known risk factors associated for cardiac disease.

*Gastrointestinal Disorders:* Infrequent cases of megacolon, gastrointestinal haemorrhage or intestinal obstruction were reported, and rare cases of colitis, including typhlitis (ileocecal syndrome), ischemic and ulcerative colitis were reported. Colitis was complicated by ulceration bleeding, ileus or infection in some cases. Cases of ileus without preceding colitis have also been reported. Intestinal perforation have been reported in rare cases.

*Hypovolemia:* Infrequent cases of hypotension, renal insufficiency or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis. In patients who become infected and/or volume depleted from severe vomiting or diarrhoea, there have been rare cases of renal impairment and acute renal failure.

*Immune System Disorders:* Severe anaphylactic or anaphylactoid hypersensitivity reactions have been reported.

*Investigational:* Hyponatremia related with diarrhoea and vomiting have been reported in rare cases. Very rarely reported were 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.

*Musculoskeletal and connective tissue disorders:* Muscular contraction or cramps and paresthesia have been reported.

*Respiratory thoracic and mediastinal disorders:* During irinotecan therapy, interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon. Dyspnoea and hiccups have been reported (refer to Warnings and Precautions).

*Nervous system disorders:* While generally transient in nature, speech disorders have been observed in patients treated with irinotecan. The event in some cases was attributed during or after infusion of irinotecan and attributed to cholinergic syndrome.

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## Interactions

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**Anticonvulsants:** CYP3A-inducing anticonvulsant drugs (e.g. carbamazepine, phenobarbital or phenytoin) lead to reduced exposure to SN-38 if administered concurrently with irinotecan. In patients requiring anticonvulsant treatment, consideration should be given to starting or substituting non-enzyme-inducing anticonvulsants at least one week prior to initiation of irinotecan therapy.

**Antineoplastic agents:** Other antineoplastic agents having similar adverse effects would be expected to exacerbate the adverse effects of irinotecan injection, such as myelosuppression and diarrhoea.

**Atazanavir sulphate:** When co-administering Atazanavir sulphate and irinotecan hydrochloride, physicians should take into consideration that coadministration of atazanavir sulfate, which is a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to the irinotecan metabolite SN-38.

**Dexamethasone:** Irinotecan injection clinical trials have reported lymphocytopenia in patients. However, the administration of dexamethasone as a prophylactic antiemetic may have enhanced the chances of this effect occurring. Serious opportunistic infections have not been observed and no complications have specifically been attributed to lymphocytopenia.

Dexamethasone given as antiemetic prophylaxis with irinotecan injection probably contributed to the hyperglycaemia reported in some patients. Hyperglycemia was usually reported in patients with evidence of glucose intolerance prior to administration of irinotecan injection or with a history of diabetes mellitus.

**Diuretics:** During periods of active vomiting or diarrhoea the physician may consider withholding diuretics due to the risk of dehydration secondary to vomiting and/or diarrhoea induced by irinotecan injection.

**Ketoconazole:** Ketoconazole should not be administered during irinotecan therapy and should be discontinued at least 1 week prior to starting irinotecan administration. Concomitant ketoconazole causes irinotecan clearance to be greatly reduced in patients causing increased exposure to the active metabolite SN-38.

**Laxatives:** The effect on incidence or severity of diarrhoea with concomitant laxative use has not been studied, but it is expected that it would be worsened during therapy with irinotecan injection.

**Neuromuscular blocking agents:** Drugs with anticholinesterase activity, such as irinotecan, may cause the neuromuscular blockade of non-depolarizing drugs to be antagonized and may prolong the neuromuscular blocking effects of suxamethonium. Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out.

**Prochlorperazine:** In clinical trials of the single agent weekly dosage schedule, the incidence of akathisia was less when prochlorperazine was administered on separate days (1.3%, 1/80 patients) to irinotecan injection than when these drugs were given on the same day (8.5%, 4/47 patients). This 8.5% incidence of akathisia, when given as a premedication for other chemotherapies, is within the range reported for use of prochlorperazine.

**St. John's Wort (*Hypericum perforatum*):** Concomitant St. John's Wort with irinotecan reduces exposure to the active metabolite SN-38 in patients. St. John's Wort should not be administered during irinotecan therapy and should be discontinued at least 1 week prior to the first cycle of irinotecan.

**Drug-Laboratory Test Interactions:**

There are no known interactions between irinotecan injection and laboratory tests.

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## Overdosage

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At approximately twice the recommended therapeutic dose, there have been reports of overdosage which may be fatal. The adverse events experienced were similar to those reported with the recommended dosage regimens at single doses up to 750 mg/m<sup>2</sup>. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea.

Respiratory and cardiovascular function will need to be supported in cases of overdose. Dehydration due to diarrhoea and any infectious complications must have immediate maximum supportive care.

There is no known antidote for overdosage of irinotecan injection.

Contact the National Poisons Information Centre (telephone 0800 POISON or 0800 764 766) for advice on the management of an overdose.

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## Pharmaceutical Precautions

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Store at or below 25°C. Protect from light. It is recommended that the unopened vial should remain in the carton until the time of use. Irinotecan injection is intended for single use only. Any unused portion should be discarded.

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## Medicine Classification

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Prescription Medicine

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## Further Information

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Irinotecan hydrochloride is a pale yellow to yellow crystalline powder which is slightly soluble in organic solvents and water.

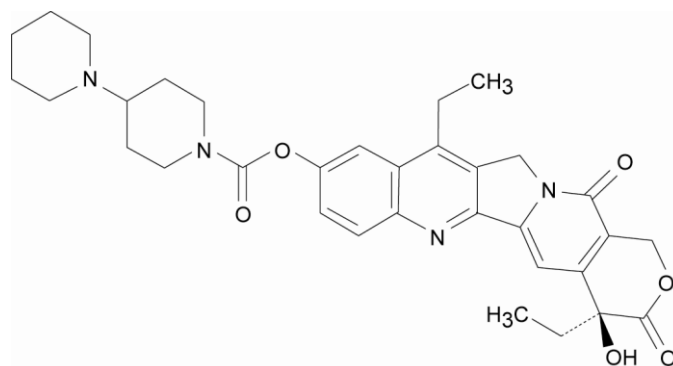
Irinotecan hydrochloride is a semi-synthetic derivative of an alkaloid extract from plants such as *Camptotheca acuminata* called camptothecin.

Irinotecan hydrochloride injection is a topoisomerase I inhibitor class antineoplastic agent.

Empirical formula: C<sub>33</sub>H<sub>38</sub>N<sub>4</sub>O<sub>6</sub>.HCl.3H<sub>2</sub>O

Chemical name: [1,4'-Bipiperidine]-1'-carboxylic acid (4S)—4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl ester hydrochloride trihydrate

Molecular weight: 677.18.



## CLINICAL TRIALS

Irinotecan injection has been studied in clinical trials as a first-line agent in metastatic colorectal cancer in combination with 5-FU and LV and as a single agent used after failure of initial therapy. Irinotecan injection used in combination treatment had weekly and once every 2 week schedules. Irinotecan injection as the single agent was administered weekly and once every 3 weeks in the study. Patients with a WHO performance status of 3 or 4 have not been studied in clinical trials (refer to Table 9).

**Table 9: WHO scale for 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 randomized, controlled, open label, multinational phase III clinical trials support the use of irinotecan injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. The dosing regimens of these studies are given in Table 10.

**Table 10: 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	125mg/m <sup>2</sup> irinotecan HCl IV infusion over 90 mins. Treatment was administered once weekly for four weeks with treatment resuming on Day 43.	N/A

B1	Irinotecan HCl LV 5-FU	125mg/m <sup>2</sup> irinotecan HCl IV infusion over 90 mins followed immediately by 20mg/m <sup>2</sup> LV administered as an IV bolus injection and then 500mg/m <sup>2</sup> 5-FU as an IV bolus injection. Treatment was administered once weekly for four weeks with treatment resuming on Day 43 (Saltz regimen) <sup>1</sup>	80mg/m <sup>2</sup> IV infusion over 90 mins of irinotecan HCl plus a 500mg/m <sup>2</sup> LV IV infusion over 2 hours followed immediately by an 2300mg/m <sup>2</sup> 5-FU IV infusion over 24 hours. Treatment was administered once weekly for six weeks with treatment resuming on Day 50 (AIO regimen) <sup>1</sup>
B2	Irinotecan HCl LV 5-FU	N/A	180mg/m <sup>2</sup> IV infusion over 90 mins of irinotecan HCl on day 1, plus one hour later a 200mg/m <sup>2</sup> LV IV infusion over 2 hours followed immediately by a 400mg/m <sup>2</sup> 5-FU IV bolus injection and a 600mg/m <sup>2</sup> 5-FU IV infusion over 22 hours on days 1 and 2. Treatment was administered every 2 weeks (de Gramont regimen) <sup>1</sup>
C1	LV 5-FU	20mg/m <sup>2</sup> LV administered as an IV bolus injection followed immediately by 425 mg/m <sup>2</sup> 5-FU as an IV bolus injection. Treatment was given for 5 consecutive days with the treatment repeating on Day 29 (Mayo Clinic regimen) <sup>1</sup>	500mg/m <sup>2</sup> LV IV infusion over 2 hours followed immediately by a 2600 mg/m <sup>2</sup> 5-FU IV infusion over 24 hours. Administration was weekly for 6 weeks with treatment resuming on Day 50 (AIO regimen) <sup>1</sup>
C2	LV 5-FU	N/A	200mg/m <sup>2</sup> LV IV infusion over 2 hours followed immediately by a 400mg/m <sup>2</sup> 5-FU IV bolus injection and a 600mg/m <sup>2</sup> 5-FU IV infusion over 22 hours on days 1 and 2. Treatment was administered every 2 weeks (de Gramont regimen) <sup>1</sup>

<sup>1</sup> Based on the Saltz, Mayo Clinic, de Gramont and Association of Medical Oncology of the German Cancer Society (AIO) dosing regimens.

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

In both studies, objective tumour response rate, time to tumour progression (TPP), and survival with the combination of irinotecan hydrochloride/5-FU/LV therapy when compared with 5-FU/LV alone were significantly improved. 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 11.

**Table 11: Combination therapy in first line treatment of metastatic colorectal cancer: Study Results**

	Study 1	Study 1	Study 1	Study 2	Study 2
	Bolus 5-FU/LV	Irinotecan	Irinotecan + bolus 5-FU/LV	Infusional 5 FU/LV	Irinotecan + Infusional 5 FU/LV
Number of patients	226	226	231	187	198
<b>Demographics and Treatment Administration</b>					
Female/Male (%)	45/54	35/64	34/65	47/53	33/67
Median Age in years (range)	61 (19-85)	61 (30-87)	62 (25-85)	59 (24-75)	62 (27-75)
Performance Status (%) <sup>1</sup>					
0	41	46	39	51	51
1	45	46	46	41	42
2	13	8	15	8	7
Median Time from Diagnosis to Randomisation (months, range)	1.7 (0-203)	1.8 (0.1-185)	1.9 (0-161)	2.7 (0-104)	4.5 (0-88)
Median Duration of Study Treatment (months)	4.1	3.9	5.5	4.5	5.6
Median Primary Tumour (%)					
Colon	85	84	81	65	55
Rectum	14	15	17	35	45
Median Relative Dose Intensity (%)					
Irinotecan	--	75	72	--	87
5-FU	86	--	71	93	86
Prior Adjuvant 5-FU Therapy (%)					
No	92	90	89	76	74
Yes	8	10	11	24	26
<b>Efficacy Results</b>					
Confirmed Objective Tumour Response Rate <sup>2</sup> (%) [95%CI]	21 [16-27]	18 [13-24]	39 [33-46]	22 [16-29]	35 [28-42]
Median Time to Tumour Progression (months) [95%CI]	4.3 [3.7-4.6]	4.2 [3.9-5.0]	7 [5.4-8.0]	4.4 [3.2-5.5]	6.7 [5.7-8.0]
Median Survival (months) [95% CI]	12.6 [11.1-14.6]	12 [11.3-13.5]	14.8 [12.3-17.1]	14.1 [12.6-17.4]	17.4 [15.2-20.2]

<sup>1</sup> Refer to Table 9 : WHO Scale for performance status.

<sup>2</sup> Confirmed ≥ 4 to 6 weeks after first evidence of objective response

Irinotecan hydrochloride-based combination therapy, relative to 5-FU/LV alone was noted to have improved response rates and time to tumour progression which were examined across all demographic and disease-related sub-groups (as categorized by age, gender, performance status, ethnic origin, time from diagnosis of cancer, extent of organ involvement with cancer, prior adjuvant therapy and baseline laboratory abnormalities).

The European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both studies. There was no statistical evidence that there were significant differences between irinotecan hydrochloride/5-FU/LV combination and 5-FU/LV alone with regard to QOL improvement, however descriptive evidence suggested a general trend favouring QOL improvement or less-worsening in favour of the irinotecan hydrochloride combination regimen.

### Single Agent Treatment in Recurrent or Progressive Metastatic Colorectal Cancer After 5-FU Based Treatment

#### Weekly Dosage Schedule

In the United States three multicentre, open-label, phase II studies were conducted in a total of 304 patients. These studies utilised repeated courses of irinotecan injection with once weekly treatment for 4 consecutive weeks, followed by a two week rest period. These studies were evaluated in patients with metastatic colorectal cancer that recurred or progressed following a prior 5-FU based chemotherapeutic regimen with particular focus on tumour response rate and toxicity with irinotecan injection. Starting doses of irinotecan injection in these trials were 100, 125 or 150 mg/m<sup>2</sup>. These 150 mg/m<sup>2</sup> doses proved to be poorly tolerated due to unacceptably high rates of grade 4 febrile neutropenia and late diarrhoea. The results of the individual studies are shown in Table 12.

**Table 12. Phase II clinical studies with the once weekly dosage schedule**

	Study			
	A	B	C <sup>1</sup>	C <sup>1</sup>
Number of Patients	48	90	102	64
Dose (mg/m <sup>2</sup> /wk x 4)	125 <sup>2</sup>	125	100	125
Prior 5-FU therapy (%)				
Classification unknown	2.1	12.2	2.9	0
Duration of treatment (median, months)	5.4	3.5	3.3	3.9
For metastatic disease	81.3	65.5	67.7	73.4
≤ 6 months after adjuvant	14.6	6.7	27.5	26.6
> 6 months after adjuvant	2.1	15.6	2.0	0
Objective response rate (%) <sup>3</sup> [95%CI]	20.8 [9.3-32.3]	13.3 [6.3-20.4]	8.8 [3.3-14.3]	14.1 [5.5-22.6]
Time to response (median, months)	2.6	1.5	2.8	2.8
Response duration (median, months)	6.4	5.9	6.4	5.6
Median relative dose intensity (%) <sup>4</sup>	74	67	81	73

<sup>1</sup> The initial dose in Study C was 125 mg/m<sup>2</sup> but was reduced to 100 mg/m<sup>2</sup> 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.

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

<sup>3</sup> There were 2 complete responses and 38 partial responses

- <sup>4</sup> Relative dose intensity for irinotecan injection based on planned dose intensity of 100, 83.3 and 66.7 mg/m<sup>2</sup>/wk corresponding with 150, 125 and 100 mg/m<sup>2</sup> starting doses respectively

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, across the studies. A somewhat greater percentage of patients who were treated with the 125 mg/m<sup>2</sup> starting dose (53.4%; 103/193) than with the 100 mg/m<sup>2</sup> starting dose (39.2%; 40/102) had stable disease during therapy, consistent with the results in Study C.

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

Whether or not patients had responded to prior 5-FU based treatment did not affect response rates with irinotecan injection given for metastatic disease. Patients who had received irradiation to the pelvis previously responded to irinotecan injection at approximately the same rate as those who had not previously received irradiation.

### ***Once-Every-Three-Week Dosage Schedule***

Two phase III, randomized, multicentre, studies were conducted in patients with metastatic colorectal cancer whose disease had recurred or progressed following 5-FU therapy (n=535) with a three weekly dosage regimen. The primary endpoint in both studies was survival, but parameters of clinical benefit and quality of life were also assessed. Best supportive care was compared with second-line irinotecan hydrochloride in one study and with infusional 5-FU based therapy in the second study.

350 mg/m<sup>2</sup> of irinotecan was infused intravenously as a starting dose increasing up to a maximum total dose of 700 mg over 90 minutes. The starting dose was reduced to 300 mg/m<sup>2</sup> for patients 70 years or older and for patients with a WHO performance status of 2. Supportive care was provided on the form of antiemetics, atropine and loperamide and late diarrhoea persisting for greater than 24 hours despite loperamide was treated with a course of a fluoroquinolone antibiotic for 7-days.

Irinotecan hydrochloride has a significant advantage over best supportive care or infusional 5-FU-based therapy. Survival among patients treated with irinotecan hydrochloride remained significantly longer than in the control populations (p=0.001 for Study 1 and p=0.017 for Study 2) when adjusted for baseline patient characteristics (e.g. performance status). Clinical benefit in Study 1 were significantly longer for patients treated with irinotecan hydrochloride than for patients in the best supportive care group (p0.01 and p0.05 respectively). This was measured by pain-free survival and survival without weight loss. The results are summarised in Table 13.

**Table 13. Phase III clinical studies with a Once-Every-Three-Week Dosage Schedule:**

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

- <sup>1</sup> One of the following 5-FU regimens was used:
- Leucovorin 200mg/m<sup>2</sup> iv over 2 hours; followed by 5-FU 400mg/m<sup>2</sup> iv bolus; followed by 5-FU 600mg/m<sup>2</sup> continuous iv infusion over 22 hours on days 1 and 2 every 2 weeks.
  - 5-FU 250-300mg/m<sup>2</sup>/day protracted continuous iv infusion until toxicity
  - 5-FU 2.6-3g/m<sup>2</sup>/day iv over 24 hours every week for 6 weeks with or without leucovorin 20-500mg/m<sup>2</sup>/day every week iv for 6 weeks with a 2 week rest between cycles

<sup>2</sup> Study 1 - 6 months; Study 2 ≤ 3 months

<sup>3</sup> Dose intensity in patients receiving 5-FU in Study 2 varied depending upon the type of regime. Relative dose intensity for irinotecan hydrochloride based on planned dose intensity of 116.7mg/m<sup>2</sup>/week.

\*\* Small sample size prevent estimation

In Study 1, with irinotecan hydrochloride, patients treated had significantly higher global quality of life scores for than for those who received best supportive care (p=0.0013). In Study 2, for patients who received either irinotecan hydrochloride or infusional 5-FU, the global quality of life scores were similar. Quality of life was assessed using the European Organisation on Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in the two phase III studies.

### ***Other Studies***

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

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