PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION

(Irinotecan Hydrochloride Trihydrate for Injection)

Solution, 20 mg / mL, Intravenous

Manufacturer's Standard

Antineoplastic Agent

ATC: L01XX19

Fresenius Kabi Canada Ltd.

165 Galaxy Blvd, Suite 100

Toronto, ON M9W 0C8

Date of Initial Authorization:

FEB 26, 2010

Date of Revision:

SEP 08, 2022

Submission Control Number: 263348

RECENT MAJOR LABEL CHANGES

N/A

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Irinotecan Hydrochloride Trihydrate for Injection is indicated as:

- a component of first-line therapy for patients with metastatic carcinoma of the colon or rectum.
- a single agent for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-fluorouracil-based therapy.

Irinotecan Hydrochloride Trihydrate for 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.

1.1 Pediatrics

Pediatrics: The safety and effectiveness of Irinotecan Hydrochloride Trihydrate for Injection in the pediatric population have not been established (see 7 WARNINGS AND PRECAUTIONS).

1.2 Geriatrics

Geriatrics: Evidence from clinical and pharmacokinetic studies suggests that patients 65 years of age or older should be closely monitored because of a greater risk of late diarrhea in this population. Specific dosing recommendations may apply to this population depending upon the regimen used (see 7 WARNINGS AND PRECAUTIONS, General, Geriatrics; 4 DOSAGE AND ADMINISTRATION and 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

Irinotecan Hydrochloride Trihydrate for Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Co-administration of Irinotecan Hydrochloride Trihydrate for Injection with azole antifungals (ketoconazole, fluconazole, itraconazole), known CYP3A4 inhibitors, is contraindicated because this can lead to an increase in the relative exposure to the active metabolite SN-38 and can therefore possibly lead to increased toxicity.

In patients receiving concomitant Irinotecan Hydrochloride Trihydrate for Injection and ketoconazole, exposure to SN-38 was increased by approximately 110%. Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy. See 7 WARNINGS AND PRECAUTIONS regarding potential drug-drug interactions with other CYP3A4 inhibitors and inducers.

Patients with hereditary fructose intolerance should not be given Irinotecan Hydrochloride Trihydrate for Injection, as this product contains sorbitol, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Irinotecan Hydrochloride Trihydrate for Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.
- Severe early and late forms of diarrhea leading to dehydration and electrolyte imbalance (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- Typhlitis, ulcerative and ischemic colitis, ileus and intestinal perforation (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions).
- Severe myelosuppression with grade 3 - 4 neutropenia (see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS).
- Cases of bacterial, fungal and viral infections, sometimes fatal and/or life-threatening, have been reported with the use of Irinotecan Hydrochloride Trihydrate for Injection (see 8 ADVERSE REACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Recommendations common to combination and single agent Irinotecan Hydrochloride Trihydrate for Injection schedules

- Dosing of patients is not recommended with (see 7 WARNINGS AND PRECAUTIONS)
  - serum bilirubin > 35 mcmol/L, transaminase > 3 times ULN if no liver metastases, or transaminase > 5 times ULN with liver metastases
  - ECOG performance status 3 or 4
- Recommended laboratory tests (see 7 WARNINGS AND PRECAUTIONS) before/during therapy
  - white blood cell count with differential, hemoglobin and platelet count before each dose
  - liver function before initiation of treatment and monthly or as clinically indicated
- Dose reduction may be considered for patients (see 7 WARNINGS AND PRECAUTIONS)
  - aged ≥ 70 years
  - with prior pelvic/abdominal radiotherapy
  - with performance status of 2
  - with moderately elevated bilirubin levels (17 to 35 mcmol/L)
  - with Gilbert's syndrome
- Dose schedules, dose modifications and dose delay
  - patients should be carefully monitored for toxicity and assessed prior to each treatment.
  - dosage schedule and dose modifications for combination therapy are summarized in Tables 1 and 2 and for single agent therapy in Tables 3 and 4.

- dose modifications should be based on the worst preceding toxicity. Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. Patients experiencing clinically significant (defined as grade ≥ 2) diarrhea, abdominal cramping, or neutropenia on the day of treatment administration should have treatment delayed until they recover and subsequent doses should be decreased.
- a new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment related toxicity. If the patient has not recovered, consideration should be given to discontinuing therapy.
- provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. Besides the dosage modification, prompt use of oral loperamide is recommended in order to control and treat the diarrhea (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal).

4.2 Recommended Dose and Dosage Adjustment

Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose should be considered for patients known to be homozygous for UGT1A1*28 or *6 allele, as well as for those who have experienced prior hematologic toxicity with previous treatment. 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 (see 7 WARNINGS AND PRECAUTIONS, Hematologic).

Irinotecan Hydrochloride Trihydrate for Injection Combination - Agent Therapy - Dosage Schedules:

Irinotecan Hydrochloride Trihydrate for Injection should be administered as an intravenous infusion over 90 minutes. For all regimens, the dose of Leucovorin (LV) should be administered immediately after Irinotecan Hydrochloride Trihydrate for Injection, with the administration of 5-Fluorouracil (5-FU) to occur immediately after receipt of LV. The recommended regimens are shown in **Table 1**.

Table 1: Combination-Agent Dosage Schedules and Dose Modifications[a]

<table>
<tr><td rowspan="6">Regimen 1
6-wk cycle</td><td colspan="2">Irinotecan Hydrochloride Trihydrate for Injection</td><td colspan="3">125 mg/m² intravenous over 90 min once-weekly (days 1, 8, 15, 22) then 2-week rest</td></tr>
<tr><td>LV</td><td>Bolus</td><td colspan="3" rowspan="2">20 mg/m² intravenous bolus once-weekly (days 1, 8, 15, 22) then 2-week rest
500 mg/m² intravenous bolus once-weekly (days 1, 8, 15, 22) then 2-week rest</td></tr>
<tr><td>5-FU</td><td>Bolus</td></tr>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Starting Dose and Modified Dose Levels (mg/m²)</td></tr>
<tr><td>Starting Dose</td><td>Dose Level - 1</td><td>Dose Level - 2</td></tr>
<tr><td colspan="2">Irinotecan Hydrochloride Trihydrate for Injection</td><td>125</td><td>100</td><td>75</td></tr>
<tr><td>LV</td><td>Bolus</td><td>20</td><td>20</td><td>20</td></tr>
<tr><td>5-FU</td><td>Bolus</td><td>500</td><td>400</td><td>300</td></tr>
<tr><td>Regimen 2
6-wk cycle</td><td colspan="2">Irinotecan hydrochloride trihydrate</td><td colspan="3">180 mg/m² intravenous over 90 min once every 2-weeks (days 1, 15, 29) then 1-week rest</td></tr>
</table>

	LV	Infusion	200 mg/m^2 intravenous over 2 h on days 1, 2 every 2-weeks (days 1, 2, 15, 16, 29, 30) then 1-week rest		
	5-FU	Bolus Infusion[b]	400 mg/m^2 intravenous bolus immediately followed by: 600 mg/m^2 intravenous over 22 h on days 1, 2 every 2-weeks (days 1, 2, 15, 16, 29, 30) then 1-week rest		
			Starting Dose and Modified Dose Levels (mg/m^2)		
			Starting Dose	Dose Level -1	Dose Level -2
	Irinotecan Hydrochloride Trihydrate for Injection		180	150	120
	LV	Infusion	200	200	200
	5-FU	Bolus	400	320	240
	5-FU	Infusion[b]	600	480	360

[a] Dose reductions beyond dose level – 2 by decrements of ~20% may be warranted for patients continuing to experience toxicity.
[b] Infusion follows bolus administration.

Irinotecan Hydrochloride Trihydrate for Injection Combination-Agent Therapy - Dose Modifications:

Patients should be carefully monitored for toxicity and assessed prior to each treatment, especially during the first cycle of therapy. Doses of Irinotecan Hydrochloride Trihydrate for Injection and 5-FU should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose levels described in **Table 1**, subsequent doses should be adjusted as suggested in **Table 2**.

Table 2: Recommended Dose Modifications for Irinotecan Hydrochloride Trihydrate for Injection/ 5-Fluorouracil(5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥ 1.5 x 10^9/L, and the platelet count has recovered to ≥ 100 x 10^9/L, and treatment-related diarrhea is fully resolved. **Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.**

Toxicity NCI CTC grade[a] (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy[b]**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm^3) 2 (1000 to 1499/mm^3) 3 (500 to 999/mm^3) 4 (< 500/mm^3)	Maintain dose level ↓1 dose level Omit dose until resolved to ≤ grade 2 then ↓ 1 dose level Omit dose until resolved to ≤ grade 2 then ↓ 2 dose levels	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose until resolved, then ↓ 2 dose levels	↓ 2 dose levels
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2 - 3 stools/day > pretx[c]) 2 (4 - 6 stools/day > pretx) 3 (7 - 9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Delay dose until resolved to baseline then give same dose Omit dose until resolved to baseline then ↓ 1 dose level Omit dose until resolved to baseline then ↓ 1 dose level Omit dose until resolved to baseline then ↓ 2 dose levels	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
Other nonhematologic toxicities[d]		

1 2 3 4	Maintain dose level Omit dose, then ↓ 1 dose level when resolved to ≤ grade 1 Omit dose, then ↓ 1 dose level when resolved to ≤ grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤ grade 2 *For mucositis/stomatitis, decrease only 5-FU, not irinotecan hydrochloride trihydrate.*	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels *For mucositis/stomatitis, decrease only 5-FU, not irinotecan hydrochloride trihydrate.*
[a] National Cancer Institute Common Toxicity Criteria [b] Relative to the starting dose used in the previous cycle [c] Pretreatment [d] Excludes alopecia, anorexia, asthenia		

Irinotecan Hydrochloride Trihydrate for Injection Single-Agent Therapy - Dosage Schedules:

Irinotecan Hydrochloride Trihydrate for Injection should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules. Single-agent dosage regimens are shown in **Table 3**.

Table 3: Single-Agent Regimens of Irinotecan Hydrochloride Trihydrate for Injection and Dose Modifications

Weekly Regimen[a]	125 mg/m^2 intravenous over 90 min once weekly (days 1, 8, 15, 22) followed by a 2-week rest		
	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level - 1	Dose Level - 2
	125	100	75
Once-Every-3-Week Regimen[b]	350 mg/m^2 intravenous over 90 min, once weekly every 3 weeks		
	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level - 1	Dose Level - 2
	350	300	250
[a] Subsequent doses may be adjusted as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending upon individual patient tolerance. [b] Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending upon individual patient tolerance.			

Irinotecan Hydrochloride Trihydrate for Injection Single-Agent Therapy - Dose Modifications:

Patients should be carefully monitored for toxicity and doses of Irinotecan Hydrochloride Trihydrate for Injection should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose levels described in **Table 3**, subsequent doses should be adjusted as suggested in **Table 4.** The 350 mg/m^2 dose has not been evaluated in patients who are 70 years and older (see 14 CLINICAL TRIALS) and the recommended starting dose is therefore 300 mg/m^2.

Table 4: Recommended Dose Modifications for Single-Agent Schedules[a]

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥ 1.5 x 10^9/L, and the platelet count has recovered to ≥ 100 x 10^9/L, and treatment-related diarrhea is fully resolved. **Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.**			
Toxicity NCI Grade[b] (value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[c]**	
	Weekly	*Weekly*	*Once Every 3 Weeks*
No toxicity	Maintain dose level	↑ 25 mg/m² up to a maximum dose of 150 mg/m²	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm³)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm³)	↓ 25 mg/m²	Maintain dose level	Maintain dose level
3 (500 to 999/mm³)	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 25 mg/m²	↓ 50 mg/m²
4 (< 500/mm³)	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²	↓ 50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓ 50 mg/m² when resolved	↓ 50 mg/m²	↓ 50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2 - 3 stools/day > pretx[c])	Maintain dose level	Maintain dose level	Maintain dose level
2 (4 - 6 stools/day > pretx[c])	↓ 25 mg/m²	Maintain, if the only grade 2 toxicity	Maintain dose level
3 (7 - 9 stools/day > pretx[c])	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 25 mg/m², if the only grade 3 toxicity	↓ 50 mg/m²
4 (≥ 10 stools/day > pretx[c])	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²	↓ 50 mg/m²
Other non-hematologic toxicities[d]			
grade 1	Maintain dose level	Maintain dose level	Maintain dose level
grade 2	↓ 25 mg/m²	↓ 25 mg/m²	↓ 50 mg/m²
grade 3	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 25 mg/m²	↓ 50 mg/m²
grade 4	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²	↓ 50 mg/m²

[a] National Cancer Institute Common Toxicity Criteria
[b] All dose modifications should be based on the worst preceding toxicity
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

4.3 Reconstitution

Parenteral Products:

The Irinotecan Hydrochloride Trihydrate for Injection vial is for single use only. Unused portions must be discarded. Irinotecan Hydrochloride Trihydrate for Injection must be diluted prior to infusion, using 5% Dextrose Injection (preferred) or 0.9% Sodium Chloride Injection to a final concentration range of 0.12 to 3 mg/mL. Other drugs should not be added to the infusion solution.

The infusion solutions, when packaged in low-density polyethylene (LDPE) or polyvinyl chloride (PVC) containers, are physically and chemically stable for up to 28 days at controlled room temperature (15 °C to 30 °C) or at refrigerated temperatures (2 °C to 8 °C), if protected from light. If stored at room temperature (15 °C to 30 °C) but exposed to light, the infusion solutions are physically and chemically stable for 72 hours (3 days). **Freezing Irinotecan Hydrochloride Trihydrate for Injection and admixtures of Irinotecan Hydrochloride Trihydrate for Injection may result in precipitation of the drug and should be avoided. See 11 STORAGE, STABILITY AND DISPOSAL.**

4.4 Administration

Because of possible microbial contamination during dilution, it is recommended that the admixture be prepared immediately prior to use and infusion commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, or 6 hours at 15 °C to 30 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

5 OVERDOSAGE

Single doses of up to 750 mg/m^2 of irinotecan hydrochloride trihydrate have been given in some trials and there have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea. There is no known antidote for overdosage of irinotecan hydrochloride trihydrate. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications. Complete blood count (CBC), platelets, electrolytes, liver and renal function should be monitored in cases of overdosage and patients should be monitored for signs and symptoms of respiratory distress.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 5: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Intravenous	Solution: 20 mg / mL	sorbitol, lactic acid, sodium hydroxide and/or hydrochloric acid to adjust pH, water for injection

Irinotecan Hydrochloride Trihydrate for Injection is supplied as a sterile, light yellow, clear, aqueous solution. Irinotecan Hydrochloride Trihydrate for Injection is available as single-dose vials in the following package sizes:

40 mg in 2 mL of solution
100 mg in 5 mL of solution

300 mg in 15 mL of solution
500 mg in 25 mL of solution

Each mL of Irinotecan Hydrochloride Trihydrate for Injection contains 20 mg irinotecan hydrochloride trihydrate, 45 mg sorbitol, 0.9 mg lactic acid and water for injection. Sodium hydroxide and/or hydrochloric acid may be used to adjust the pH to 3 - 3.8.

7 WARNINGS AND PRECAUTIONS

General

Patients at Particular Risk:

Physicians should exercise particular caution in monitoring the effects of Irinotecan Hydrochloride Trihydrate for Injection in patients with poor performance status. Patients with performance status of 3 or 4 should not receive Irinotecan Hydrochloride Trihydrate for Injection. In patients receiving either irinotecan hydrochloride trihydrate/5-FU/LV or 5-FU/LV in clinical trials comparing these agents, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2, than in patients with a baseline performance status of 0 or 1. Close monitoring is recommended in patients who have previously received pelvic/abdominal irradiation and in the elderly as these patients may be less tolerant of the toxic effects of the drug. The use of Irinotecan Hydrochloride Trihydrate for Injection has not been established in patients with significant hepatic dysfunction (see 7 WARNINGS AND PRECAUTIONS, Hepatic). There are known and suspected drug-drug interactions (see 2 CONTRAINDICATIONS, Drug Interactions below, and 9 DRUG INTERACTIONS).

Patients with reduced UGT1A1 activity
Patients with UGT1A1*28 or *6 variants (especially if homozygous) are at increased risk of experiencing adverse events such as neutropenia and diarrhea. A reduced irinotecan starting dose should be considered for homozygous patients (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment). In addition, *28 and *6 homozygous and heterozygous patients should be closely monitored for neutropenia and diarrhea. In order to identify patients at increased risk of experiencing neutropenia and diarrhea, UGT1A1 genotyping can be useful (see 7 WARNINGS AND PRECAUTIONS, Hematologic). 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.

Drug Interactions:

CYP3A4 Inhibitors

- Co-administration of Irinotecan Hydrochloride Trihydrate for Injection with azole antifungals (ketoconazole, fluconazole, itraconazole) is contraindicated (see 2 CONTRAINDICATIONS).
- Co-administration of Irinotecan Hydrochloride Trihydrate for Injection with other CYP3A4 inhibitors [e.g., cimetidine, fluoroquinolone antibiotics (ciprofloxacin and norfloxacin in patients with compromised renal function), macrolide antibiotics (azithromycin, clarithromycin, erythromycin), atazanavir sulfate, grapefruit juice, and CYP3A4-inhibitory calcium channel blockers (verapamil, diltiazem, and nifedipine)] could lead to an increase in the relative exposure to the active metabolite

SN-38 and therefore possibly increased toxicity (see 9 DRUG INTERACTIONS and 4 DOSAGE AND ADMINISTRATION).

The appropriate starting dose of Irinotecan Hydrochloride Trihydrate for Injection when co-administered with CYP3A4 inhibitors has not been determined.

CYP3A4 Inducers

- The co-administration of Irinotecan Hydrochloride Trihydrate for Injection with CYP3A4 inducers (e.g., St. John's Wort, phenytoin, phenobarbital, carbamazepine, glucocorticoids, rifampin) leads to a reduction in the plasma concentration of the active metabolite SN-38, which could potentially lead to a reduction of efficacy (see 9 DRUG INTERACTIONS).

The appropriate starting dose of Irinotecan Hydrochloride Trihydrate for Injection when co-administered with CYP3A4 inducers has not been determined.

UGT1A1 Inhibitors

- The co-administration of atazanavir sulfate, a 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 irinotecan with a UGT1A1 inhibitor.

Irradiation Therapy:

The concurrent administration of Irinotecan Hydrochloride Trihydrate for Injection with irradiation is not recommended.

Extravasation:

Irinotecan Hydrochloride Trihydrate for Injection is administered by intravenous infusion. Care should be taken to avoid extravasation. The infusion site should be monitored for signs of inflammation or other adverse effects. If extravasation occurs, flushing the site with sterile water and/or applying ice to the area are recommended.

Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been conducted. Rats administered 2 mg/kg or 25 mg/kg irinotecan intravenously once weekly for 13 weeks and allowed to recover for 91 weeks had a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan and SN-38 were not mutagenic in bacterial *in vitro* assays (Ames assay). Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice) (see 16 NON-CLINICAL TOXICOLOGY). Therefore, irinotecan may be able to induce chromosomal damage in human spermatozoa. For this reason, males undergoing Irinotecan Hydrochloride Trihydrate for Injection treatment should discuss effective contraceptive methods with their doctors.

Cardiovascular

All thromboembolic events (includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis and vascular disorder) when considered together have been commonly

observed in patients receiving irinotecan hydrochloride trihydrate. The specific cause of these events has not been determined (see also 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions).

Myocardial ischemic events have been uncommonly observed in patients receiving irinotecan hydrochloride trihydrate. In some cases, a causal association with administration of irinotecan hydrochloride trihydrate could not be excluded (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Drug Reactions).

Driving and Operating Machinery

Patients should be warned about the potential for fatigue, dizziness or visual disturbances which may occur following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

Endocrine and Metabolism

Hyperglycemia has been reported in patients receiving irinotecan hydrochloride trihydrate. This has usually been observed in patients with a history of diabetes or evidence of glucose intolerance prior to administration of irinotecan hydrochloride trihydrate (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Dexamethasone).

Gastrointestinal

Diarrhea:

Irinotecan Hydrochloride Trihydrate for Injection can induce both an early (occurring during or shortly after infusion of Irinotecan Hydrochloride Trihydrate for Injection) and a late (generally occurring more than 24 hours after Irinotecan Hydrochloride Trihydrate for Injection administration) form of diarrhea that appears to be mediated by different mechanisms.

Early onset diarrhea is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea may be alleviated by the use of atropine. Prophylactic or therapeutic administration of 0.25 mg to 1.0 mg of intravenous or subcutaneous atropine should be considered (unless contraindicated) (see 4 DOSAGE AND ADMINISTRATION).

Late onset diarrhea can be prolonged, may lead to dehydration, electrolyte imbalance, or infection, and can be life-threatening. The mechanism of action of late onset diarrhea is unknown. All grade late onset diarrhea occurred in 80% of patients and **late diarrhea should be treated promptly with loperamide**. Patients with diarrhea should be carefully monitored, and given fluid and electrolyte replacement if they become dehydrated. Patients should be given antibiotic support (see 9 DRUG INTERACTIONS) if they develop ileus, fever, or severe neutropenia. After the first treatment, subsequent chemotherapy should be delayed until patients return to pre-treatment bowel function for at least 24 hours without need for antidiarrhea medication. Patients experiencing clinically significant (grade ≥ 2) late diarrhea should have subsequent doses of Irinotecan Hydrochloride Trihydrate for Injection decreased (see 4 DOSAGE AND ADMINISTRATION).

Management of late onset diarrhea:

At the initiation of chemotherapy, patients should be given a sufficient supply of loperamide and instructed on its appropriate use. The prompt use of oral loperamide for controlling and treating the

diarrhea is recommended and is higher than the usual dosage recommendation. Pre-treatment with loperamide before the onset of late diarrhea is not recommended. Instead, at the first episode of late-onset diarrhea (i.e., poorly formed stools or more frequent bowel movement), patients are to take 4 mg loperamide, followed by 2 mg loperamide every two hours until they are free of diarrhea for at least 12 hours. During the night, the dose of loperamide may be 4 mg administered 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.

Inflammatory Bowel Disease and/or Bowel Obstruction:

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Cases of ileus without preceding colitis have also been reported. Patients experiencing ileus should receive prompt antibiotic support (see 9 DRUG INTERACTIONS) and must not be treated with irinotecan until resolution of the bowel obstruction.

Nausea and Vomiting:

Irinotecan Hydrochloride Trihydrate for Injection is emetogenic (see 8 ADVERSE REACTIONS). Pre-medication with anti-emetic agents is recommended for patients receiving Irinotecan Hydrochloride Trihydrate for Injection. In clinical studies with the weekly dosage schedule, this pre-medication has mostly consisted of 10 mg dexamethasone given in conjunction with another type of anti-emetic agent. Anti-emetic agents should be given on the day of treatment, starting at least 30 minutes before administration of Irinotecan Hydrochloride Trihydrate for Injection. Physicians should also consider providing patients with an anti-emetic regimen for subsequent use as needed.

Hematologic

Irinotecan Hydrochloride Trihydrate for Injection commonly causes neutropenia, leukopenia, and anemia, any of which may be severe and therefore should not be used in patients with severe bone marrow failure. Therapy with Irinotecan Hydrochloride Trihydrate for Injection should be temporarily omitted if neutropenic fever occurs or if the absolute neutrophil count drops below 1.5×10^9/L. After the patient recovers to an absolute neutrophil count ≥ 1.5×10^9/L, subsequent doses of Irinotecan Hydrochloride Trihydrate for Injection should be reduced depending upon the level of neutropenia observed (see 4 DOSAGE AND ADMINISTRATION). Severe neutropenia resulting in deaths due to sepsis have been reported in patients treated with irinotecan hydrochloride trihydrate. Neutropenic complications should be managed promptly with antibiotic support (see 9 DRUG INTERACTIONS). Routine administration of colony stimulating factor is not necessary; however, physicians should consider the use of colony-stimulating factors in patients experiencing clinically significant neutropenia (≥ grade 2).

In one study, an increased risk of neutropenia was observed in patients homozygous for the UGT1A1*28 allele, who received single-agent irinotecan hydrochloride trihydrate at a dose of 350 mg/m^2. Individuals with certain genetic polymorphisms in the UGT1A1 gene (e.g., UGT1A1 *28/*28 genotype) have reduced UGT1A1 activity, which in turn increases the concentration of SN-38, the active metabolite of irinotecan (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

In patients with the UGT1A1*28 allele, treated with combination regimens that deliver doses of irinotecan hydrochloride trihydrate in the range of 100 - 180 mg/m^2, in combination with 5-FU/LV, the risk of grade 4 neutropenia was lower than in studies where irinotecan hydrochloride trihydrate was administered at doses of 300 - 350 mg/m^2 as a single agent (see 8 ADVERSE REACTIONS, Hematology).

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

A reduced irinotecan starting dose should be considered for patients known to be homozygous for UGT1A1*28 or *6 allele, as well as for those who have experienced prior hematologic toxicity with previous treatment. 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 (see 4 DOSAGE AND ADMINISTRATION).

Hepatic/Biliary/Pancreatic

Increases in serum levels of liver enzymes and bilirubin have been reported in clinical trials and in the post-market period (see 8 ADVERSE REACTIONS).

The use of Irinotecan Hydrochloride Trihydrate for Injection in patients with significant hepatic dysfunction has not been established. Irinotecan hydrochloride trihydrate was not administered to patients with serum bilirubin > 35 mcmol/L, or transaminase > 3 times the upper limit of normal if no liver metastases, or transaminase > 5 times the upper limit of normal with liver metastases (see 4 DOSAGE AND ADMINISTRATION).

In clinical trials of weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (17 - 35 mcmol/L) had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 hematologic toxicities including neutropenia than those with bilirubin levels that were less than 17 mcmol/L. Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan hydrochloride trihydrate. An association between baseline bilirubin elevations and an increased risk of late diarrhea has not been observed in studies of the weekly dosage schedule (see 4 DOSAGE AND ADMINISTRATION).

Immune

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported (see 8 ADVERSE REACTIONS).

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.

Monitoring and Laboratory Tests

Careful monitoring of white blood cell count with differential, hemoglobin and platelet count is recommended before each dose of Irinotecan Hydrochloride Trihydrate for Injection. Liver function should be monitored before initiation of treatment and monthly, or as clinically indicated (see 8 ADVERSE REACTIONS).

Neurologic

Speech disorders

There have been post-market reports of speech disorders (e.g., dysarthria, stuttering, change in voice, garbled or slurred speech, difficulty speaking) in patients treated with irinotecan. In some cases, the

speech disorder occurred in the context of other symptoms such as numbness or tingling of the tongue or mouth or symptoms attributed to cholinergic syndrome, hypersensitivity/allergy, cerebrovascular events, or intracranial neoplasia. In some cases, however, the speech disorder occurred in the absence of other symptoms and recurred with subsequent infusions of irinotecan. In most of these cases, the speech disorders occurred during or shortly after infusion of irinotecan and resolved spontaneously within minutes to hours following discontinuation of the irinotecan infusion. The cause of speech disorders in patients treated with irinotecan has not been determined.

Renal

Increases in serum creatinine or blood urea nitrogen have been observed. Rare cases of renal impairment and acute renal failure have been identified. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting and/or diarrhea, which are common and sometimes severe adverse events following irinotecan hydrochloride trihydrate treatment. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

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

Respiratory

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan hydrochloride trihydrate therapy (see 8 ADVERSE REACTIONS). 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of irinotecan in pregnant women. Irinotecan hydrochloride trihydrate has been shown to be embryotoxic in rats and rabbits at a dose of 6 mg/kg/day. It is teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6 mg/kg/day. Treatment-related changes in the fetuses included external and visceral abnormalities, skeletal variations and abnormalities. Irinotecan Hydrochloride Trihydrate for Injection may cause fetal harm when administered to a pregnant woman.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Women should undergo pregnancy tests before, during and one month after the last irinotecan dose. 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.

7.1.2 Breast-feeding

Irinotecan and its active metabolite SN-38 are present in human breast milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with irinotecan and for 7 days after the final dose.

In rats, radioactivity appeared in the milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

7.1.3 Pediatrics

The safety and effectiveness of Irinotecan Hydrochloride Trihydrate for Injection in the pediatric population have not been established.

7.1.4 Geriatrics

Patients greater than 65 years of age should be closely monitored because of a greater risk of late diarrhea in this population (see 14 CLINICAL TRIALS and 8 ADVERSE REACTIONS). The starting dose of Irinotecan Hydrochloride Trihydrate for Injection in patients 70 years and older for the once-every-3-week dosage schedule should be 300 mg/m^2 (see 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Gastrointestinal

Nausea, vomiting and diarrhea are common adverse events following treatment with irinotecan hydrochloride trihydrate and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of irinotecan hydrochloride trihydrate. In the clinical studies testing the every-3-week dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan hydrochloride trihydrate infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of irinotecan hydrochloride trihydrate. All grade late diarrhea occurred in approximately 80% in this patient population. For patients on the 125 mg/m^2 weekly dose, the median duration of any grade late diarrhea was 3 days. The median duration was 7 days for those patients reporting grade 3 or 4 late diarrhea on this same weekly dose.

Results from a retrospective analysis have shown that the frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥ 65 years than in patients < 65 years of age. However, results from a prospective study treating patients with metastatic colorectal cancer refractory to one 5-FU-based chemotherapeutic regimen, on a 125 mg/m^2 weekly dosage schedule (4 weeks on, 2 weeks off) did not demonstrate any statistically significant difference in the rate of treatment-emergent grades 3 - 4 late diarrhea in patients ≥ 65 years of age versus patients < 65 years of age. It should be noted, however, that a statistically significant increase in the incidence of treatment-emergent early diarrhea in patients ≥ 65 years of age versus patients < 65 years of age was found. Furthermore, a 10% reduction in median relative weekly dose intensity was required in patients ≥ 65 years versus patients < 65 years in

order to achieve tolerability. In the early Japanese trials, there is some information that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea.

Hematology

Typical adverse hematologic events of irinotecan hydrochloride trihydrate included neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia is uncommon. When evaluated in the trials of weekly administration, the frequency of grade 3 or 4 neutropenia was significantly increased in patients who had prior pelvic or abdominal irradiation. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients. Only 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients. There were no significant differences in the frequency of grade 3 and 4 neutropenia by age or gender (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment for Single-Agent and Combination- Dosage Schedules). In the early Japanese trials, there is some information that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea.

Individuals with certain polymorphs of UGT1A1, such as UGT1A1*28, may have reduced activity of this enzyme. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype).

In a single arm study of 66 patients with solid tumours or lymphomas who received irinotecan hydrochloride trihydrate as a single-agent at a dose of 350 mg/m^2 on a once every 3 weeks schedule, 3 out of 6 patients with UGT1A1 *28/*28 genotype had grade 4 neutropenia versus 3 out of 24 patients with the UGT1A1 *1/*28 genotype, and 0 out of 29 patients with the UGT1A1 *1/*1 genotype (see 7 WARNINGS AND PRECAUTIONS).

In a study which compared irinotecan hydrochloride trihydrate (100 - 125 mg/m^2) in combination with bolus 5-FU/LV (IFL regimen), oxaliplatin (85 mg/m^2) in combination with infusional 5-FU/LV (FOLFOX4 regimen) and a combination of oxaliplatin (85 mg/m^2) plus irinotecan hydrochloride trihydrate (200 mg/m^2) (IROX regimen), the incidence of grade 4 neutropenia is shown in the table below.

Rates of Grade 4 Neutropenia for UGT1A1*28 Genotype by Treatment

UGT1A1 Genotype	IFL[a] n = 109	FOLFOX4[b] n = 285	IROX[c] n = 103
6/6	6.8% (3/44)	19.4% (26/134)	9.6% (5/52)
6/7	11.1% (6/54)	22.2% (28/126)	15% (6/40)
7/7	18.2% (2/11)	36% (9/25)	54.5% (6/11)

[a] IFL: irinotecan 100 - 125 mg/m^2 followed by leucovorin 20 mg/m^2 and 5-FU 400 mg/m^2 given as a bolus on days 1, 8, 15, and 22 followed by a 2-week rest in repeated 6-week cycles.
[b] FOLFOX4: oxaliplatin 85 mg/m^2 on day 1, leucovorin 200 mg/m^2 on days 1 and 2, and 5-FU 400 mg/m^2 given as a bolus followed by 600 mg/m^2 given as a 22-hr continuous infusion on days 1 and 2 administered in repeated 2-week cycles.
[c] IROX: oxaliplatin 85 mg/m^2 followed by irinotecan 200 mg/m^2 administered on day 1 of repeated 3-week cycles.

In a study to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with irinotecan hydrochloride trihydrate and infusional 5-FU/LV at doses of 180 mg/m^2, 1 out of 22 patients with the UGT1A1 *28/*28 genotype had grade 4 neutropenia, versus 6 out of 114 patients with the UGT1A1 *1/*28 and 2 out of 114 for patients with the UGT1A1 *1/*1 genotype.

Whole Body

Asthenia, fever, and abdominal pain are generally the most common events of this type.

Cholinergic Symptoms

Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea. If these symptoms occur, they manifest during or shortly after drug infusion.

They are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are more likely to occur at higher irinotecan dose levels. The timing of the symptoms is most consistent with the occurrence of peak irinotecan serum levels during parenteral administration.

Hepatic

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

Dermatologic

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. Early effects such as dyspnea have been reported (see 7 WARNINGS AND PRECAUTIONS). In the clinical studies evaluating the weekly dosage schedule, over half the patients with dyspnea had lung metastases. The extent to which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnea in these patients is unknown.

Potentially life-threatening interstitial disease presenting with dyspnea, fever and pulmonary infiltrates (reticulonodular pattern on chest x-ray) is uncommon during irinotecan hydrochloride trihydrate therapy. Usually seen in Japanese studies, the contribution of irinotecan hydrochloride trihydrate to these events was difficult to assess because these patients also had lung tumours and some had pre-existing non-malignant pulmonary disease.

Neurologic

Insomnia and dizziness can occur, but are 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 (see 7 WARNINGS AND PRECAUTIONS).

Cardiovascular

Vasodilation (flushing) may occur during administration of irinotecan hydrochloride trihydrate. Bradycardia may also occur, but has not required intervention. These effects have been attributed to the cholinergic syndrome sometimes observed during or shortly after infusion of irinotecan hydrochloride trihydrate. All thromboembolic events, when considered together, have commonly been observed in patients receiving irinotecan hydrochloride trihydrate (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular). The specific cause of these events has not been determined.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed (see 7 WARNINGS AND PRECAUTIONS)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Combination-Agent (Irinotecan/5-FU/LV) Therapy:

A total of 955 patients with metastatic colorectal cancer received regimens of irinotecan hydrochloride trihydrate in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan hydrochloride trihydrate alone. In the two phase 3 studies, 370 patients received irinotecan hydrochloride trihydrate in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan hydrochloride trihydrate alone (see Table 1 in 4 DOSAGE AND ADMINISTRATION for recommended combination regimens).

In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received irinotecan hydrochloride trihydrate in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan hydrochloride trihydrate alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/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 from any cause within 60 days of first study treatment were reported for 15 (6.7%) patients who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone and 15 (6.7%) patients who received irinotecan hydrochloride trihydrate alone. Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan hydrochloride trihydrate alone.

In Study 1, data on hospitalization included hospitalization required as a consequence of chemotherapy-induced adverse events and hospitalizations that may have resulted from complications due to cancer or intercurrent illnesses. One hundred and thirteen (50.2%) patients of 225 who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV were hospitalized. Sixty-eight (30.2%) patients were hospitalized once, 28 (12.4%) patients were hospitalized twice and 17 (7.6%) patients were hospitalized more than two times. Ninety-nine (44.4%) patients of 223 treated with irinotecan hydrochloride trihydrate alone were hospitalized. Seventy-one (31.8%) patients were hospitalized once,

21 (9.4%) were hospitalized twice and 7 (3.1%) were hospitalized more than two times. Eighty-six (39.3%) patients of 219 treated with 5-FU/LV were hospitalized. Sixty (27.4%) patients were hospitalized once, 20 (9.1%) patients were hospitalized twice and 6 (2.7%) were hospitalized more than two times.

In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received irinotecan hydrochloride trihydrate in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-related death, which occurred in a patient who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%) patients who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

In Study 2, data on hospitalization included hospitalization required as a consequence of chemotherapy-induced adverse events. Fifty (34.5%) patients of 145 who received irinotecan hydrochloride trihydrate in combination with 5-FU/LV were hospitalized. Thirty-five (24.1%) patients were hospitalized once, 8 (5.5%) patients were hospitalized twice and 7 (4.8%) patients were hospitalized more than two times. Twenty-nine (20.3%) patients of 143 treated with 5-FU/LV were hospitalized. Twenty-one (14.7%) patients were hospitalized once, 6 (4.2%) patients were hospitalized twice and 2 (1.4%) patients were hospitalized more than two times.

The most clinically significant adverse events (all grades 1 - 4) for patients receiving irinotecan hydrochloride trihydrate based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, 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 weekly irinotecan hydrochloride trihydrate/5-FU/LV than with monthly administration of 5-FU/LV.

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

Table 6: Study 1 - Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	**Study 1**					
	Irinotecan hydrochloride trihydrate + Bolus 5-FU/LV weekly x 4 q 6 weeks		**Bolus 5-FU/LV daily x 5 q 4 weeks**		**Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks**	
	n = 225		**n = 219**		**n = 223**	
	Grades 1 - 4	**Grades 3 & 4**	**Grades 1 - 4**	**Grades 3 & 4**	**Grades 1 - 4**	**Grades 3 & 4**
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea						
late	84.9	22.7	69.4	13.2	83	31
grade 3	--	15.1	--	5.9	--	18.4
grade 4	--	7.6	--	7.3	--	12.6
early	45.8	4.9	31.5	1.4	43	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4

Adverse Event	Study 1					
	Irinotecan hydrochloride trihydrate + Bolus 5-FU/LV weekly x 4 q 6 weeks		Bolus 5-FU/LV daily x 5 q 4 weeks		Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks	
	n = 225		n = 219		n = 223	
	Grades 1 - 4	Grades 3 & 4	Grades 1 - 4	Grades 3 & 4	Grades 1 - 4	Grades 3 & 4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96	2.6	98.6	2.7	96	1.7
Neutropenic infection	--	1.8	--	0	--	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
↑ Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia[b]	43.1	--	26.5	--	46.1	--
RESPIRATORY						
Dyspnea	27.6	6.3	16	0.5	22	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR						
Vasodilatation	9.3	0.9	5	0	9	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic Events[c]	9.3	--	11.4	--	5.4	--

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

[b] Complete hair loss = Grade 2

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

Note: Combination toxicities (gastrointestinal and cardiovascular syndromes) may occur simultaneously and both contribute to the toxicity profile

Table 7: Study 2 - Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 2			
	Irinotecan hydrochloride trihydrate +5-FU/LV infusional D 1&2 q 2 weeks n = 145		5-FU/LV infusional D 1&2 q 2 weeks n = 143	
	Grades 1 - 4	Grades 3 & 4	Grades 1 - 4	Grades 3 & 4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea				
late	72.4	14.4	44.8	6.3
grade 3	--	10.3	--	4.2
grade 4	--	4.1	--	2.1
Cholinergic syndrome[b]	28.3	1.4	0.7	0
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40	4.1	28.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	--	36.4	--	12.7
grade 4	--	9.8	--	0.7
Leukopenia	81.3	17.4	42	3.5
Anemia	97.2	2.1	90.9	2.1
Neutropenic fever	--	3.4	--	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	--	2.1	--	0
BODY AS A WHOLE				
Asthenia	57.9	9	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC & NUTRITIONAL				
↑ Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia[c]	56.6	--	16.8	--
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0
CARDIOVASCULAR				
Hypotension	3.4	1.4	0.7	0
Thromboembolic Events[d]	11.7	--	5.6	--

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

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

[c] Complete hair loss = Grade 2

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

Note: Combination toxicities (gastrointestinal and cardiovascular syndromes) may occur simultaneously and both contribute to the toxicity profile

Single - Agent Therapy:

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with irinotecan hydrochloride trihydrate.

Seventeen of the patients died within 30 days of the administration of irinotecan hydrochloride trihydrate. In five cases (1.6%, 5/304), the deaths were potentially drug-related. These five patients experienced a constellation of medical events that included known effects of irinotecan hydrochloride trihydrate. One of these patients died of neutropenic sepsis without fever. Neutropenic fever, defined as NCI grade 4 neutropenia and grade 2 or greater fever, occurred in nine (3%) other patients. These patients recovered with supportive care. Thirteen (4.3%) patients discontinued irinotecan hydrochloride trihydrate treatment because of medical events.

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

Adjustments in the dose of irinotecan hydrochloride trihydrate were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The first dose of at least one cycle of irinotecan hydrochloride trihydrate was reduced for 67% of patients who began the studies at the 125 mg/m^2 starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125 mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia.

The adverse events in Table 8 are based on the experience of the 304 patients enrolled in the three studies.

Table 8: Adverse Events Occurring in > 10% of 304 Patients with Previously Treated Metastatic Carcinoma of the Colon or Rectum[a]

Body System & Event	% of Patients Reporting	
	NCI Grades 1 - 4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)*	87.8	30.6
7-9 stools/day (grade 3)	--	(16.4)
≥10 stools/day (grade 4)	--	(14.1)
Nausea	86.2	16.8
Vomiting	66.8	12.5
Anorexia	54.9	5.9
Diarrhea (early)†	50.7	7.9
Constipation	29.9	2
Flatulence	12.2	0
Stomatitis	11.8	0.7
Dyspepsia	10.5	0
HEMATOLOGIC		
Leukopenia	63.2	28
Anemia	60.5	6.9
Neutropenia	53.9	26.3
0.5 to < 1 x 10^9/L (grade 3)	--	(14.8)
< 0.5 x 10^9/L (grade 4)	--	(11.5)
WHOLE BODY		
Asthenia	75.7	12.2
Abdominal Cramping/Pain	56.9	16.4
Fever	45.4	0.7
Pain	23.7	2.3
Headache	16.8	0.7
Back Pain	14.5	1.6
Chills	13.8	0.3
Minor Infection‡	14.5	0
Edema	10.2	1.3
Abdominal Enlargement	10.2	0.3
METABOLIC & NUTRITIONAL		
↓Body Weight	30.3	0.7
Dehydration	14.8	4.3
↑Alkaline Phosphatase	13.2	3.9
↑SGOT	10.5	1.3
DERMATOLOGIC		
Alopecia	60.5	NA§
Sweating	16.4	0
Rash	12.8	0.7
RESPIRATORY		
Dyspnea	22	3.6
↑Coughing	17.4	0.3
Rhinitis	15.5	0
NEUROLOGIC		
Insomnia	19.4	0
Dizziness	14.8	
CARDIOVASCULAR		
Vasodilation (Flushing)	11.2	0

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

* Occurring > 24 hours after administration of irinotecan hydrochloride trihydrate

† Occurring ≤ 24 hours after administration of irinotecan hydrochloride trihydrate

‡ Primarily upper respiratory infections

§ Not applicable; complete hair loss = NCI grade 2

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan hydrochloride trihydrate, 129 received 5-FU, and 90 received best supportive care.

Eleven (3.5%) patients treated with irinotecan hydrochloride trihydrate died within 30 days of treatment. In three cases (1%, 3/316), the deaths were potentially related to irinotecan hydrochloride trihydrate treatment and were attributed to neutropenic infection, grade 4 diarrhea and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Fifty-five percent (295/535) of patients were hospitalized at least once due to serious adverse events: 60% (188/316) of patients received irinotecan hydrochloride trihydrate, 63% (57/90) received best supportive care, and 39% (50/129) received 5-FU-based therapy. Eight percent (25/316) of patients treated with irinotecan hydrochloride trihydrate and 7% (9/129) treated with 5-FU-based therapy discontinued treatment due to adverse events.

Table 9 lists the grades 3 and 4 adverse events reported in the 535 patients enrolled in the two studies (V301 and V302) evaluating the once-every-three-week dosage schedule.

Table 9: Percent (%) of Patients Experiencing Grades 3 & 4 Adverse Events in Comparative Studies of Once-Every-3-Week Irinotecan Hydrochloride Trihydrate Therapy[a]

Adverse Event	Study V301		Study V302	
	Irinotecan hydrochloride trihydrate n = 189	BSC* n = 90	Irinotecan hydrochloride trihydrate n = 127	5-FU† n = 129
TOTAL Grade 3/4 Adverse Events	79.4	66.7	69.3	54.3
GASTROINTESTINAL				
Diarrhea	21.7	5.6	22	10.9
Vomiting	13.8	7.8	14.2	4.7
Nausea	13.8	3.3	11	3.9
Abdominal Pain	13.8	15.6	8.7	7.8
Constipation	9.5	7.8	7.9	6.2
Anorexia	5.3	6.7	5.5	3.9
Mucositis	1.6	1.1	2.4	5.4
HEMATOLOGIC				
Leukopenia/Neutropenia	22.2	0	14.2	2.3
Anemia	7.4	6.7	6.3	3.1
Hemorrhage	5.3	3.3	0.8	3.1
Thrombocytopenia	1.1	0	3.9	1.6
Infection				
without grade 3/4 neutropenia	8.5	3.3	0.8	3.9
with grade 3/4 neutropenia	1.1	0	1.6	0
Fever				
without grade 3/4 neutropenia	2.1	1.1	1.6	0
with grade 3/4 neutropenia	2.1	0	3.9	1.6
BODY AS A WHOLE				
Pain	18.5	22.2	16.5	13.2
Asthenia	14.8	18.9	13.4	11.6
CHOLINERGIC SYNDROME	12.2	0	1.6	0
METABOLIC and NUTRITIONAL				
Hepatic‡	8.5	6.7	8.7	6.2
DERMATOLOGIC				

Adverse Event	Study V301		Study V302	
	Irinotecan hydrochloride trihydrate n = 189	BSC* n = 90	Irinotecan hydrochloride trihydrate n = 127	5-FU† n = 129
Hand and Foot syndrome	1.6	0	0.8	4.7
Cutaneous signs§				3.1
RESPIRATORY¶	10.1	7.8	4.7	7
NEUROLOGIC**	12.2	13.3	8.7	3.9
CARDIOVASCULAR††	8.5	3.3	3.9	1.6
OTHER‡‡	31.7	27.8	11.8	14

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

* BSC = best supportive care

† One of the following 5-FU regimens were used: (1) Leucovorin, 200 mg/m^2 intravenous over 2 hr; followed by 5-FU, 400 mg/m^2 intravenous bolus; followed by 5-FU, 600 mg/m^2 continuous intravenous infusion over 22 hr on days 1 and 2 every 2 wk. (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous intravenous infusion until toxicity. (3) 5-FU, 2 to 3 g/m^2/day intravenous over 24 hr every wk for 6 wk with or without leucovorin, 20 to 500 mg/m^2/day every wk intravenous for 6 wk with 2-wk rest between cycles.

‡ Hepatic includes events such as ascites and jaundice.

§ Cutaneous signs include events such as rash.

¶ Respiratory includes events such as dyspnea and cough.

** Neurologic includes events such as somnolence.

†† Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction.

‡‡ Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The clinical trial adverse reaction pediatric data is not available.

8.3 Less Common Clinical Trial Adverse Reactions

The less common clinical trial adverse reaction data is not available.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

The less common clinical trial adverse reaction pediatric data is not available.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

The clinical trial abnormal laboratory findings data is not available.

Post-Market Findings

The post-market abnormal laboratory findings data is not available.

8.5 Post-Market Adverse Reactions

The following events have been identified during postmarketing use of irinotecan hydrochloride trihydrate in clinical practice.

Infrequent cases of colitis, including typhlitis, ulcerative and ischemic colitis, have been observed. This can be complicated by ileus or what was described as toxic megacolon, ulceration, bleeding, obstruction, and infection. Rare cases of intestinal perforation have been reported. Cases of ileus

without preceding colitis have also been observed. Patients experiencing ileus should receive prompt antibiotic support (see 7 WARNINGS AND PRECAUTIONS). Hiccups have also been reported.

Rare cases of hyponatremia mostly related to diarrhea and vomiting have been reported.

Increases in serum levels of transaminases (i.e., AST and ALT), GGT and bilirubin in the absence of progressive liver metastasis have been observed; rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting, or sepsis (see 7 WARNINGS AND PRECAUTIONS).

Early effects such as muscular contraction or cramps and paresthesia have been reported.

Severe pulmonary events are infrequent. Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnea have been reported (see 7 WARNINGS AND PRECAUTIONS).

Myocardial ischemic events, with some cases resulting in fatality, have been observed in patients treated with irinotecan hydrochloride trihydrate, the majority of whom had underlying cardiac disease, other known risk factors for cardiac disease and/or were treated with other concomitant cytotoxic chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

Speech disorders have been reported in patients treated with irinotecan (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

Cases of bacterial, fungal and viral infections, sometimes fatal and/or life-threatening, have been reported with the use of irinotecan hydrochloride trihydrate, mostly in combination with other chemotherapeutic and/or immunosuppressant agents.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Irinotecan hydrochloride trihydrate is metabolized by carboxyl esterase to an active metabolite, SN-38, and oxidized by CYP3A4 to two relatively inactive metabolites (APC and NPC). SN-38 is glucuronidated to an inactive conjugate (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). Pharmacokinetic drug-drug and drug-herbal interactions have been shown (**Table 10**). These have most often been attributed to inhibition or induction of CYP3A4, though multiple mechanisms have been suggested to contribute to the interactions (induction/inhibition of carboxyl esterase, UDP-glucuronyl transferase 1A1, and drug transporters).

In vitro drug interaction studies reveal that the metabolism of irinotecan to its active metabolite SN-38 by carboxylesterase enzymes is not inhibited by 5-fluorouracil (5-FU). Data from a phase 1 clinical study involving irinotecan hydrochloride trihydrate, 5-FU, and leucovorin (LV) in 26 patients with solid tumours indicate that the disposition of irinotecan and its active metabolite SN-38 are not substantially altered when the drugs are co-administered. *In vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

Irinotecan and active metabolite SN-38 are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1). Co-administration of

irinotecan with inhibitors of CYP3A4 [e.g., cimetidine, macrolide antibiotics (azithromycin, clarithromycin, erythromycin), azole antifungals (fluconazole, ketoconazole, itraconazole), grapefruit juice, CYP3A4-inhibitory calcium channel blockers such as verapamil, diltiazem, and nifedipine] and/or UGT1A1 may result in significantly increased systemic exposure to irinotecan and the active metabolite SN-38 and potential toxicity.

This interaction has been documented in cancer patients with the co-administration of irinotecan hydrochloride trihydrate and ketoconazole, a potent enzyme inhibitor, where the relative exposure to the CYP3A4-mediated metabolite APC was reduced by 87%, whereas the relative exposure to the active metabolite SN-38 increased by 100%.

Physicians should take this into consideration when administering irinotecan with these drugs.

Exposure to fluoroquinolones such as ciprofloxacin or norfloxacin may be increased in patients with compromised renal function due to dehydration or colorectal cancer complications. In these circumstances, co-administration of irinotecan hydrochloride trihydrate and CYP3A4-inhibitory fluoroquinolone antibiotics could potentially lead to increased SN-38 exposure and enhanced toxicity.

Similarly, co-administration of irinotecan hydrochloride trihydrate with CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, glucocorticoids, St. John's Wort) leads to reduction in plasma levels of the active metabolite SN-38, which may have a deleterious impact on treatment outcome. This interaction has been documented in cancer patients with the co-administration of irinotecan hydrochloride trihydrate with St. John's Wort and with the co-administration of irinotecan hydrochloride trihydrate with phenytoin.

The prescribing information of concomitant medications should also be consulted to identify potential interactions.

9.3 Drug-Behavioural Interactions

Drug-Behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Table 10 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
CYP3A4 inhibitors			**Potential for increased toxicity**
Azole antifungals			
ketoconazole	CT	SN-38 ~ 110% increased, APC ~ 90% decreased	See 2 CONTRAINDICATIONS
fluconazole, itraconazole	T		
Cimetidine	T		See 7 WARNINGS AND PRECAUTIONS
Fluoroquinolone antibiotics:			
ciprofloxacin, norfloxacin	T		
Macrolide antibiotics:			
azithromycin,	T		
clarithromycin,			

[Proper/Common name]	Source of Evidence	Effect	Clinical Comment
erythromycin			
Calcium channel blockers:			
diltiazem, verapamil, nefedipine	T		
Grapefruit juice	T		
Atazanavir sulfate	T	See Atazanavir Product Monograph and below	
CYP3A4 inducers			**Potential for decreased efficacy**
Anticonvulsants:			See 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS, 9.6 Drug – Herb Interactions
carbamazepine, phenobarbital, phenytoin	CT, C	Irinotecan decreased ~ 60% SN-38 decreased ~ 75%	
St John's Wort	C	SN-38 decreased ~ 40%	
Glucocorticoids:			
dexamethasone	T		
Rifampin	T		

Legend: C = Case Study, CT = Clinical Trial, T= Theoretical

Appropriate starting dose for patients taking drugs shown or anticipated to alter the kinetics of irinotecan hydrochloride trihydrate has not been formally defined. Coadministration of azole antifungals and irinotecan is contraindicated and patients should discontinue ketoconazole at least 1 week prior to starting irinotecan hydrochloride trihydrate therapy (see 2 CONTRAINDICATIONS). Patients should not drink grapefruit juice during treatment. Consideration should be given to starting or substituting to non-enzyme inducing anticonvulsants at least one week prior to initiation of irinotecan hydrochloride trihydrate therapy in patients requiring anticonvulsant treatment. 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 drugs (see 7 WARNINGS AND PRECAUTIONS).

Pharmacodynamic Interactions:

Antineoplastic agents: Adverse events due to irinotecan hydrochloride trihydrate, such as myelosuppression and diarrhea, would be expected to be enhanced by combination with other antineoplastic agents having similar adverse effects.

Laxatives: It would be expected that laxative use during irinotecan hydrochloride trihydrate therapy may worsen the incidence or severity of diarrhea.

Diuretics: The use of diuretics should be carefully monitored because of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by irinotecan hydrochloride trihydrate. The physician may wish to withhold diuretics during irinotecan hydrochloride trihydrate dosing, and certainly during periods of active vomiting or diarrhea.

Dexamethasone: Lymphocytopenia has been reported in patients receiving irinotecan hydrochloride trihydrate. It is possible that the administration of dexamethasone as an anti-emetic prophylaxis may

have enhanced the likelihood of this effect. However, in these reports, serious opportunistic infections were not observed and no complications were specifically attributed to lymphocytopenia.

Hyperglycemia has been reported in patients receiving irinotecan hydrochloride trihydrate. This has usually 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 dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

Prochlorperazine: The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4 of 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 of 80 patients). However, the 8.5% incidence of akathisia is within the range reported for use of prochlorperazine when given as premedication for other chemotherapies.

Neuromuscular blocking agents: Interaction between irinotecan hydrochloride trihydrate 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.

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the $AUC_{0\text{-last}}$ of irinotecan and its active metabolite SN-38. Results from a phase III clinical trial reported a small increase in diarrhea and leukopenia adverse events in the patients treated with IFL + AVASTIN when compared to patients treated with IFL alone. Patients who develop severe diarrhea, leukopenia or neutropenia with AVASTIN and irinotecan combination therapy should have irinotecan dose modifications as specified.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

St. John's Wort: Exposure to the active metabolite SN-38 is reduced by approximately 40% in patients taking concomitant St. John's Wort and irinotecan hydrochloride trihydrate. St. John's Wort should be discontinued at least 1 week prior to the first cycle of Irinotecan Hydrochloride Trihydrate for Injection (see 7 WARNINGS AND PRECAUTIONS).

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Irinotecan hydrochloride trihydrate is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata.* Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active

metabolite SN-38 bind to the topoisomerase I - DNA complex and prevent religation of these single-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38, which is formed from irinotecan primarily by liver carboxylesterase enzymes. The SN-38 metabolite is approximately 1000 times more potent than irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines. The precise contribution of SN-38 to the activity of irinotecan hydrochloride trihydrate in humans has not been completely defined. Both irinotecan 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.

10.2 Pharmacodynamics

This information is not available.

10.3 Pharmacokinetics

After intravenous infusion of irinotecan hydrochloride trihydrate in humans, irinotecan plasma levels decline in a multiexponential manner. A summary of mean irinotecan and SN-38 pharmacokinetic parameters in patients with metastatic carcinoma of the colon and rectum (dosed at 125 mg/m^2 or 340 mg/m^2) is shown in **Table 11**.

Table 11: Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Solid Tumours

	125 mg/m^2 (n = 64)		**340 mg/m^2 (n = 6)**	
	Irinotecan	SN-38	Irinotecan	SN-38
C_{max} (ng/mL)	1660 (± 797)	26.3 (± 11.9)	3392 (± 874)	56 (± 28.2)
AUC_{0-24} (ng•hr/mL)	10200 (± 3270)	229 (± 108)	20604 (± 6027)	474 (± 245)
$t_{1/2}$(hr)	5.8* (± 0.7)	10.4* (± 3.1)	11.7 $^{\uparrow}$ (± 1)	21$^{\uparrow}$ (± 4.3)
V_{area}(L/m^2)	110 (± 48.5)	--	234 (± 69.6)	--
CL (L/hr/m^2)	13.3 (± 6.01)	--	13.9 (± 4)	--

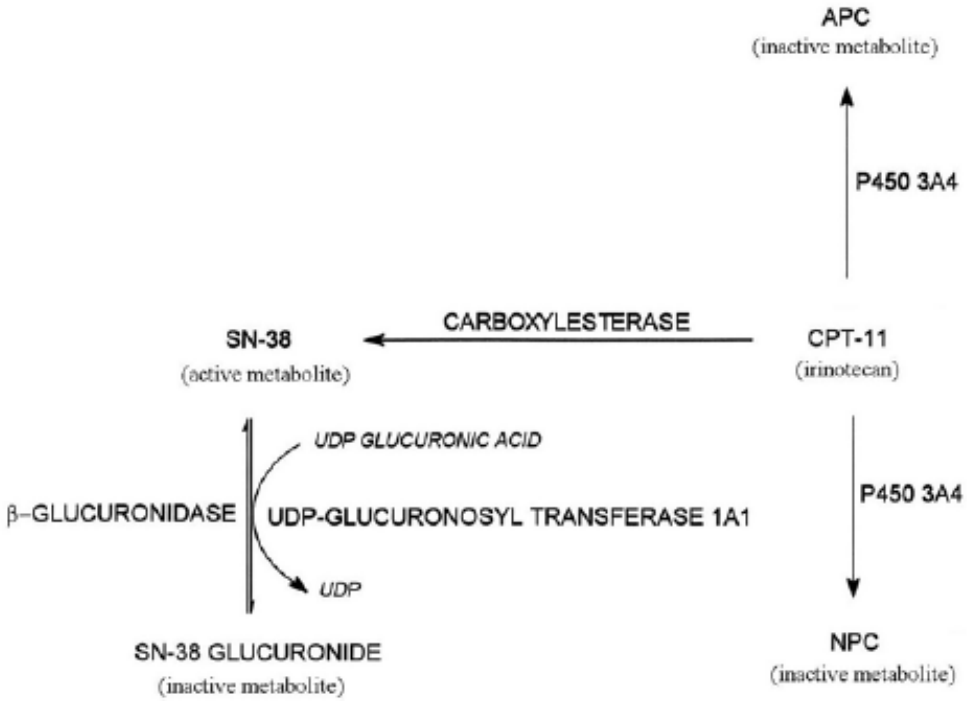
C_{max}:	Maximum plasma concentration
AUC_{0-24}	Area under plasma concentration-time curve from 0 to 24 hours after end of infusion
$t_{1/2}$:	Terminal elimination half-life
V_{area}:	Volume of distribution of terminal elimination phase
CL:	Total systemic clearance
*:	Plasma specimens collected for 24 hours following the end of the 90-minute infusion
$^{\uparrow}$:	Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose. The AUC of SN-38 increases less than proportionally with dose. Irinotecan exhibits moderate plasma protein binding (30 to 68% bound). SN-38 is approximately 95% bound to human plasma proteins, mainly albumin.

The complete disposition of irinotecan in humans has not been fully elucidated. Irinotecan (CPT-11) is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan (CPT-11) can also undergo CYP3A4-mediated oxidative metabolism to several pharmacologically inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. UGT1A1 enzyme activity is reduced in individuals with certain genetic polymorphisms, such as UGT1A1*28. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also known as UGT1A1 7/7).

In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2) on a once-every-3-week schedule, patients homozygous for the UGT1A1*28 allele (UGT1A1 7/7) had higher systemic exposures to SN-38 than those who were homozygous for the wild-type UGT1A1 allele (UGT1A1 *1/*1) (see 7 WARNINGS AND PRECAUTIONS, Hematologic and 8 ADVERSE REACTIONS, Hematology). The urinary excretion of irinotecan (11 to 20%), SN-38 (< 1%), and SN-38 glucuronide (3%) is low.

Irinotecan is oxidized by cytochrome P450 isozyme 3A4 (CYP3A4) to yield two relatively inactive metabolites, APC (7-ethyl-l0-[4-N-(5-aminopentanoic acid)-l-piperidino]- carbonyloxycamptothecin) and the minor metabolite, NPC (7-ethyl-l0-(4 amino-1-piperidino)carbonyloxycamptothecin). See diagram below.



In one pharmacokinetic study of patients administered a starting dose of irinotecan 125 mg/m^2, the terminal half-life of irinotecan was statistically significantly longer in patients who were 65 years or older compared to patients younger than 65 years (6 hours versus 5.5 hours, respectively). Dose-normalized AUC_{0-24} was 14.8% higher, C_{max} was 11.3% higher and clearance was 17.5% lower in patients 65 years and older compared with patients younger than 65 years. Also, dose normalized AUC_{0-24} of SN-38 was 11.2% higher in subjects age 65 years and over compared to subjects less than 65 years, but this result was not statistically significant.

In a different pharmacokinetic study that was prospectively designed to investigate the effect of age on irinotecan toxicity, no statistically significant differences in irinotecan pharmacokinetics were seen in patients ≥ 65 years compared to those < 65 years administered a single 125 mg/m^2 irinotecan dose. Irinotecan C_{max} and AUC_{0-24} were, respectively, 0.7% and 0.3% lower in patients ≥ 65 years compared to patients who were < 65 years. Values for SN-38 C_{max} and AUC_{0-24} were, respectively, 1.8% lower and 0.8% higher in patients > 65 years compared to patients < 65 years and values for SN-38 glucuronide C_{max} and AUC_{0-24} were, respectively, 1% and 3.1% lower in patients ≥ 65 years compared to patients who were < 65 years.

The reason for the conflicting results between the two pharmacokinetic results is not known. Clinically, however, particular caution should be exercised when administering irinotecan to elderly patients as these patients may be less tolerant of the toxic effects of the drug (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

Special Populations and Conditions

- **Sex:** There is no clinically important gender influence on the pharmacokinetics of irinotecan.
- **Ethnic Origin:** The influence of race has not been studied.
- **Hepatic Insufficiency**: Irinotecan 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 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).
- **Renal Insufficiency:** The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been formally studied.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15 °C to 30 °C). Protect from light and freezing. Irinotecan Hydrochloride Trihydrate for Injection is available in an amber glass vial that is packaged in a carton. It is recommended that the vial remain in the carton until time of use. The Irinotecan Hydrochloride Trihydrate for Injection glass vial should be inspected for damage and visible signs of leakage before opening the carton. If there are signs of breakage or leakage from the vial, do not open the carton. Incinerate the unopened package.

12 SPECIAL HANDLING INSTRUCTIONS

As with other potentially toxic anti-cancer agents, care should be exercised in the handling and preparation of infusion solutions containing Irinotecan Hydrochloride Trihydrate for Injection. Preparation of Irinotecan Hydrochloride Trihydrate for Injection should be done in a vertical laminar flow hood. The use of gloves, safety glasses and protective clothing is recommended. If Irinotecan Hydrochloride Trihydrate for Injection solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Irinotecan Hydrochloride Trihydrate for Injection contacts the mucous membranes, flush thoroughly with water. All waste material that has come in contact with irinotecan hydrochloride trihydrate should be properly segregated, sealed and incinerated.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

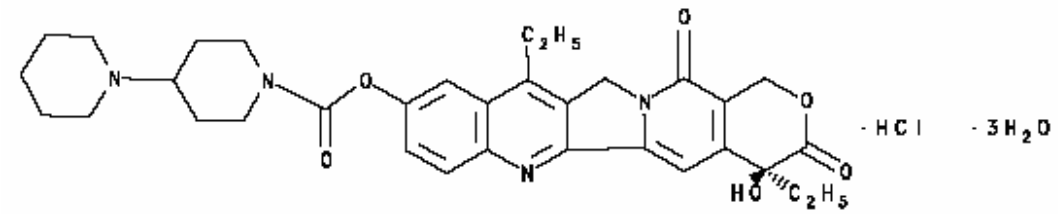
Drug Substance

Proper name: Irinotecan hydrochloride trihydrate

Chemical name: [1,4'-Bipiperidine]-1'-carboxylic acid, 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, monohydrochloride, trihydrate, (*S*)-

Molecular formula and molecular mass**:** $C_{33}H_{38}N_4O_6 \bullet HCl \bullet 3H_2O$; 677.19 g/mol

Structural formula:



CPT-11

Physicochemical properties:

Description: Pale yellow to yellow crystalline powder which melts at 256.5 °C with decomposition. The partition coefficient in an acidic medium (pH < 6) was 0.03; in a basic medium (pH > 9) was 0.05.

Solubility: It is soluble in water but sparingly soluble in organic solvents.

Specific Rotation: $[\alpha]^{20}_{D}$ +67.7° as per Merck Index

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Irinotecan hydrochloride trihydrate has been studied in clinical trials as a combination therapy with 5-FU and LV and as a single agent (see 4 DOSAGE AND ADMINISTRATION). Weekly and once-every-2-week dosage schedules were used for the combination-agent treatment. Weekly and once-every-3-week dosage schedules were used for the single-agent studies. Clinical studies of combination and single-agent uses are described below.

First-line Treatment of Metastatic Colorectal Cancer:

Two phase 3, randomized, controlled, multicentre, multinational clinical trials support the use of irinotecan hydrochloride trihydrate in combination with 5-FU/LV as a first-line treatment for patients with metastatic carcinoma of the colon or rectum. In both studies, these combinations of irinotecan hydrochloride trihydrate with 5-FU and LV were compared with 5-FU/LV alone.

- Study 1 compared combination irinotecan hydrochloride trihydrate/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan hydrochloride trihydrate-alone treatment arm given on a weekly schedule was also included.
- Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan hydrochloride trihydrate. A 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) < 500/mm^3, even in the absence of fever or diarrhea.

In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever, or if ileus developed.

Table 12: Summary of patient demographics for clinical trials in First-line Treatment of Metastatic Colorectal Cancer

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (Female / Male (%))
1	Phase 3, randomized, controlled, multicentre, multinational	Irinotecan hydrochloride trihydrate + Bolus 5-FU/LV weekly x 4 q 6 weeks	231	62 (25-85)	34/65
		Bolus 5-FU/LV daily x 5 q 4 weeks	226	61 (19-85)	45/54
		Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks	226	61 (30-87)	35/64
2	Phase 3, randomized, controlled, multicentre, multinational	Irinotecan hydrochloride trihydrate + Infusional 5-FU/LV	198	62 (27-75)	33/67
		Infusional 5-FU/LV	187	59 (24-75)	47/53

Recurrent or Progressive Metastatic Colorectal Cancer:

Weekly Dosage Schedule:

Data from three single-agent studies, involving a total of 304 patients, support the use of irinotecan hydrochloride trihydrate in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. In each study, irinotecan hydrochloride trihydrate was administered in repeated 6-week cycles as a once weekly dose for 4 weeks, followed by a 2-week rest period. In these trials, the starting doses of irinotecan hydrochloride trihydrate were 100, 125 or 150 mg/m^2.

Across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed for an overall response rate of 15% (95% confidence interval (CI), 10 to 20.1%).

Table 13: Summary of patient demographics for clinical trials in Recurrent or Progressive Metastatic Colorectal Cancer - Weekly Dosage Schedule

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)[1]	Mean age (Range)	Sex
1	Single agent study	Irinotecan hydrochloride trihydrate – administered intravenously as a once weekly dose of 100 mg/m^2 for 4 weeks, followed by a 2-week rest period.	Unknown	Unknown	Female and male patients (respective percentage unknown)
2	Single agent study	Irinotecan hydrochloride trihydrate – administered intravenously as a once weekly dose of 125 mg/m^2 for 4 weeks, followed by a 2-week rest period.	193	Unknown	Female and male patients (respective percentage unknown)
3	Single agent study	Irinotecan hydrochloride trihydrate – administered intravenously as a once weekly dose of 150 mg/m^2 for 4 weeks, followed by a 2-week rest period.	Unknown	Unknown	Female and male patients (respective percentage unknown)

[1]Total subjects across all three studies: 304

Once-Every-3-Week Dosage Schedule:

Two phase 3, multicentre, randomized, clinical studies support the use of irinotecan hydrochloride trihydrate in patients with metastatic colorectal cancer whose disease has progressed following prior 5-FU therapy. Second-line irinotecan hydrochloride trihydrate plus best supportive care was compared with best supportive care alone in the first study (V301) and with infusional 5-FU-based therapy in the second study (V302). The primary endpoint in both studies was survival. A total of 535 patients were randomized in 94 centres in Europe, the Middle East, and South Africa. Irinotecan hydrochloride trihydrate was administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m^2 for patients who were 70 years and older, or who had a WHO performance status of 2. The highest total dose permitted was 700 mg.

Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Antiemetics, atropine, and loperamide were provided as needed. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients were to be followed every 3 to 6 weeks for 1 year.

Table 14: Summary of patient demographics for clinical trials in Recurrent or Progressive Metastatic Colorectal Cancer - Once-Every-3-Week Dosage Schedule

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)[1]	Mean age (Range)
V301	Phase 3, multicentre, randomized	Second-line Irinotecan hydrochloride trihydrate plus best supportive care compared with best supportive care alone: Irinotecan hydrochloride trihydrate administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. Irinotecan hydrochloride trihydrate administered intravenously at a starting dose of 300 mg/m^2 over 90 minutes once every 3 weeks.	535	 Unknown 70 and older
V302	Phase 3, multicentre, randomized	Second-line Irinotecan hydrochloride trihydrate plus best supportive care compared with infusional 5-FU-based therapy: Irinotecan hydrochloride trihydrate administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. Irinotecan hydrochloride trihydrate administered intravenously at a starting dose of 300 mg/m^2 over 90 minutes once every 3 weeks.	535	 Unknown 70 and older

14.2 Study Results

First-line Treatment of Metastatic Colorectal Cancer

In both studies, the combination of irinotecan hydrochloride trihydrate/5-FU/LV therapy resulted in significant improvement in objective tumour response rates, time to tumour progression (TTP) and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan hydrochloride trihydrate containing regimens in the control arms. Fifty six percent (56%) of patients in Study 1, who received 5-FU/LV therapy were treated with irinotecan hydrochloride trihydrate as second-line therapy and thirty four percent (34%) of patients in Study 2, who received 5-FU/LV were treated with irinotecan hydrochloride trihydrate as second-line therapy. Patient characteristics and major efficacy results are shown in **Table 15**.

Table 15: Combination Dosage Schedule - Study Results

	Study 1			Study 2	
	Irinotecan hydrochloride trihydrate + Bolus 5-FU/LV weekly x 4 q 6 weeks	**Bolus 5-FU/LV daily x 5 q 4 weeks**	**Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks**	**Irinotecan hydrochloride trihydrate + Infusional 5-FU/LV**	**Infusional 5-FU/LV**
Performance Status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary Tumour (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median Time from Diagnosis to Randomization (months, range)	1.9 (0 - 161)	1.7 (0 - 203)	1.8 (0.1 - 185)	4.5 (0 - 88)	2.7 (0 - 104)
Prior Adjuvant 5-FU Therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median Duration of Study Treatment[a] (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)[a]					
Irinotecan	72	--	75	87	--
5-FU	71	86	--	86	93
Efficacy Results					
Confirmed Objective Tumour Response Rate[b] (%)	39	21	18	35	22
	($p < 0.0001$)[c]			($p < 0.005$)[c]	
Median Time to Tumour Progression[d] (months)	7	4.3	4.2	6.7	4.4
	($p = 0.004$)[d]			($p < 0.001$)[d]	
Median Survival (months)	14.8	12.6	12	17.4	14.1
	($p < 0.05$)[d]			($p < 0.05$)[d]	

[a] Study 1: n=225 (irinotecan hydrochloride trihydrate/5-FU/LV), n=219 (5-FU/LV), n=223 (irinotecan hydrochloride trihydrate)
Study 2: n=199 (irinotecan hydrochloride trihydrate/5-FU/LV), n=186 (5-FU/LV)
[b] Confirmed ≥4 to 6 weeks after first evidence of objective response
[c] Chi-square test
[d] Log-rank test

Improvement was noted with irinotecan hydrochloride trihydrate-based combination therapy relative to 5-FU/LV when response rates and time to tumour progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities).

Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan hydrochloride trihydrate/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 1 Survival First-Line Irinotecan / 5-FU/LV vs 5-FU/LV

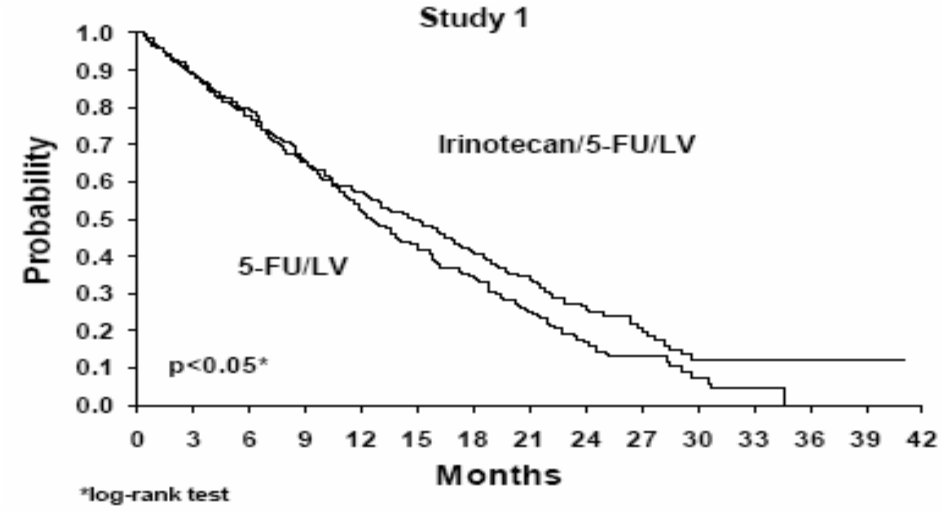
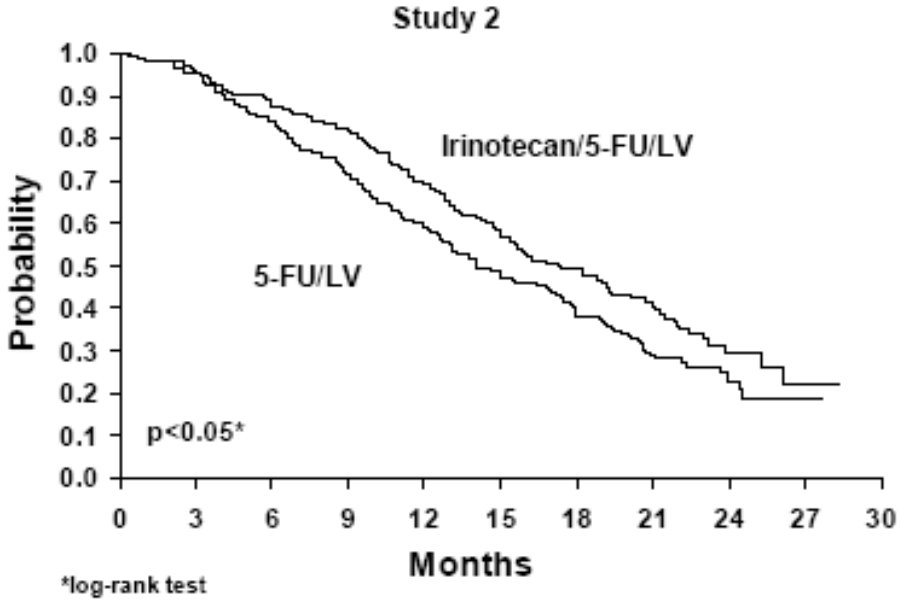


Figure 2 Survival First-Line Irinotecan / 5-FU/LV vs 5-FU/LV



Figures 3 and 4 illustrate the Kaplan-Meier Time to Tumour Progression curves for comparison of irinotecan hydrochloride trihydrate/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 3 Time to Tumour Progression (Study 1)

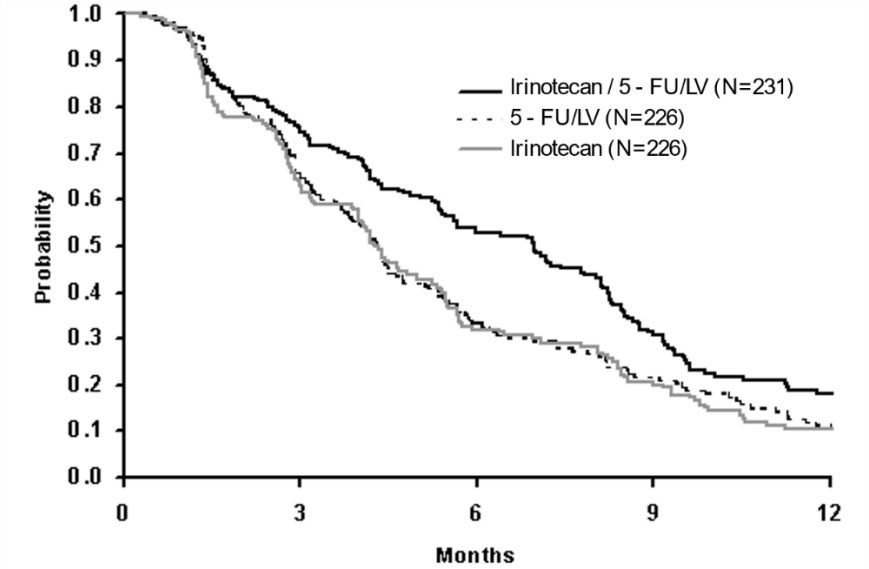
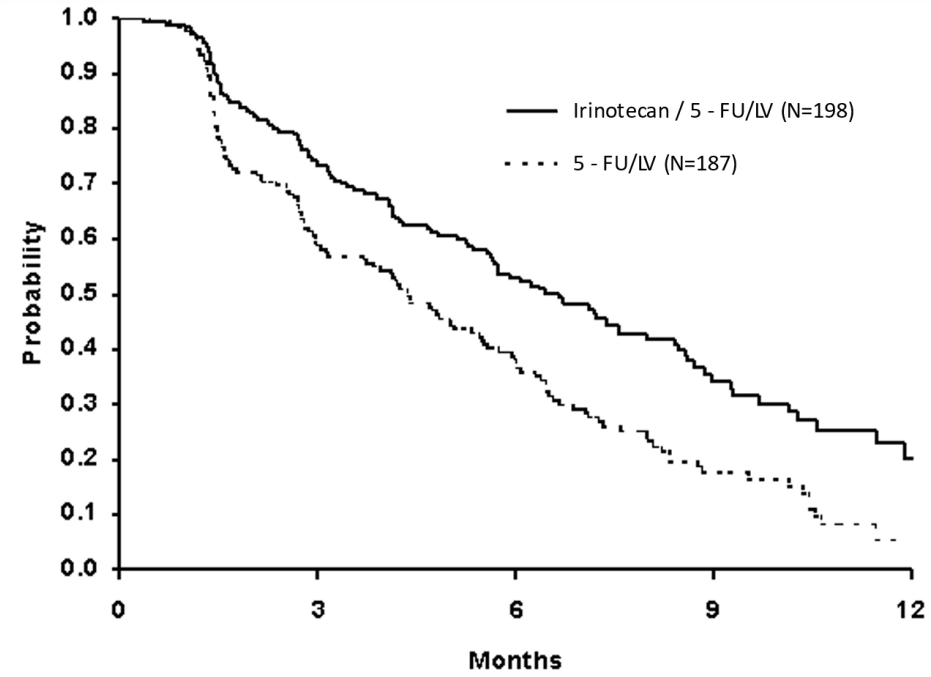


Figure 4 Time to Tumour Progression (Study 2)



Cox regression modeling was used to evaluate the effect of treatment with irinotecan hydrochloride trihydrate/5-FU/LV versus 5-FU/LV alone on time to tumour progression and survival in the context of prespecified patient baseline characteristics. The most predictive factors for improved survival with the irinotecan hydrochloride trihydrate/5FU/LV combination therapy were: normal serum lactate dehydrogenase (LDH) and better performance status.

In Study 1, treatment with combination irinotecan hydrochloride trihydrate/5-FU/LV was associated with a 36% lower risk of tumour progression and a 20% lower risk of death relative to treatment with 5-FU/LV. In Study 2, treatment with irinotecan hydrochloride trihydrate/5-FU/LV was associated with 42% lower risk of tumour progression and a 23% lower risk of death relative to treatment with 5-FU/LV.

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both first line therapy studies. At the beginning of the treatment in Study 1, there was close to one hundred percent (99%) return of the filled questionnaires. Over the first 30 to 32 weeks of treatment, the return of questionnaire at the scheduled assessments was 76 % - 82% for irinotecan hydrochloride trihydrate/5-FU/LV, and 77% to 97% for those treated with 5-FU/LV alone. In Study 2, there was an 83% return of the questionnaires at baseline whereas during the first 28 weeks the return was 46% to 61% for irinotecan hydrochloride trihydrate/5-FU/LV and 46% to 60% for 5-FU/LV alone.

In Study 1, the pain, role functioning, and global health status/QOL scales were prospectively selected to test treatment effect by the analysis of variance for repeated measurements. Data imputation method as suggested by Zwinderman was adopted in the presence of missing data during follow-up, which was due to withdrawal of patients. On the basis of the performed analysis, there were no significant differences between the group treated with irinotecan hydrochloride trihydrate/5-FU/LV and the group given 5-FU/LV in any of the three items analyzed. However, when analyzing worst scores, mean changes in pain and role functioning were significantly better for patients receiving irinotecan hydrochloride trihydrate/5-FU/LV than those treated with 5-FU/LV. It was also observed that increases in mean scores for appetite loss were less prominent with irinotecan hydrochloride trihydrate/5-FU/LV relative to 5-FU/LV alone. Similar findings were apparent in Study 2.

The repeated-measurement analysis conducted on global health status/QOL showed no statistically significant treatment effect although the evolution of the global health status scale tended to be better with irinotecan-containing combination treatment. In the presence of missing data due to patient withdrawal, both last observations carried forward (LOCF) and the mean of the worst scores of progressive patients were used as imputation methods.

A difference was found in favour of irinotecan hydrochloride trihydrate/5-FU/LV therapy in assessment of time to definitive deterioration of global health status scale from baseline. In this analysis, times to either 5% or a 20% decrement in global health status were statistically improved with irinotecan hydrochloride trihydrate/5-FU/LV (log rank p = 0.03 and 0.04, respectively). When similarly analyzing the time to 10% or 30% declines in global health status, the differences were close to significant (log rank p = 0.06 in both cases). The median time to performance status deterioration was significantly longer with patients treated with irinotecan hydrochloride trihydrate/5-FU/LV than those treated with 5-FU/LV alone (11.2 months versus 9.9 months; log rank p = 0.046). The impact of the side effects of irinotecan hydrochloride trihydrate with/without combination of 5-FU/LV on the quality of life of patients was not addressed in this questionnaire.

Recurrent or Progressive Metastatic Colorectal Cancer:

Weekly Dosage Schedule:

All of the patients had a performance status (PS) of 0 to 2, with the majority at 0 or 1. The majority of responses were observed within the first two cycles of therapy. The median duration of response for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months). An additional 53.4% (103/193) of the patients treated at a starting dose of 125 mg/m^2 achieved a best response of stable disease by formal response criteria.

Response to irinotecan hydrochloride trihydrate was seen in both males and females of all ages. These patients responded to irinotecan hydrochloride trihydrate regardless of whether prior 5-FU had been given as adjuvant therapy or for metastatic disease. Patients with cancer of the colon or rectum responded to the drug, and these responses occurred both in patients with single and multiple metastatic sites.

The Kaplan-Meier estimate of median survival time for patients on the 125 mg/m^2 starting dose was 8.9 months (range, 0.3 to 33.4 months). The majority of patients treated with irinotecan hydrochloride trihydrate had an increase in, or stabilization of body weight, and an improvement or maintenance of performance status. Among responding patients with tumour-related symptoms, the majority experienced amelioration of these symptoms during irinotecan hydrochloride trihydrate treatment.

Once-Every-3-Week Dosage Schedule:

The data indicate a statistically significant survival advantage for irinotecan hydrochloride trihydrate over best supportive care or infusional 5-FU-based therapy ($p = 0.001$ and $p = 0.035$, respectively). The benefit appears early and is sustained during follow up. One-year survivals are 36% vs 14% (irinotecan hydrochloride trihydrate vs supportive care) and 45% vs 32% (irinotecan hydrochloride trihydrate vs infusional 5-FU). Median survivals are 9.2 months vs 6.5 months (irinotecan hydrochloride trihydrate vs supportive care) and 10.8 months vs 8.5 months (irinotecan hydrochloride trihydrate vs infusional 5-FU). Median survival and 1-year survival for the patients receiving the once-every-3-week dosage regimen of irinotecan hydrochloride trihydrate in these phase 3 studies were similar to those seen in phase 2 studies of patients on the weekly regimen of second-line irinotecan hydrochloride trihydrate therapy developed in North America.

Multiple regression analyses were performed to assess the influence of baseline patient characteristics (e.g., performance status) on survival. When adjusted for these characteristics, survival among patients treated with irinotecan hydrochloride trihydrate remained significantly longer than in the control populations ($p = 0.001$ for V301 and $p = 0.017$ for V302).

Surrogate efficacy endpoints are summarized in Table 16 below:

Table 16: Once-Every-3-Week Dosage Schedule Study Results

	V301		V302	
	Irinotecan hydrochloride trihydrate	**Supportive care**	**Irinotecan hydrochloride trihydrate**	**5-FU**
Median survival without PS deterioration (months)	5.7[1]	3.3[1]	6.4	5.1
Median survival without weight loss > 5% (months)	6.4[2]	4.2[2]	8.9	7.4
Median symptom-free survival (months)	5.9	4.1	8.1	7
Median pain-free survival (months)	6.9[3]	2[3]	10.3	8.5
Median progression free survival (months)	-	-	4.2[4]	2.9[4]
Tumour response CR+PR+SD/PD	-	-	64%/36%[5]	44%/56%[5]

[1] p = 0.0001; [2] p = 0.018; [3] p = 0.003 [4] p = 0.03; [5] p = 0.002

PS: performance status; CR: complete response; PR: partial responses; SD: stable diseases; PD: progressive diseases

All surrogate endpoints show an advantage for irinotecan hydrochloride trihydrate groups. In study V301, these differences were statistically significant for: survival without PS deterioration, survival without weight loss, and pain-free survival. In Study V302, these differences were significant for progression-free survival and tumour response.

In the two randomized studies of second line therapy for metastatic colorectal cancer, the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C-30) instrument was utilized. At each visit, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have trouble taking a long walk?" (Yes or No). The answers from 30 questions were converted into 15 subscales, that were scored 0 to 100. The global health status was derived from two questions about the patient's sense of general well being in the past week. The results are summarized in Table 17 based on patients' worst post-baseline scores.

Table 17: EORTC QLQ-C30: Mean Worst Post-Baseline Score* (Data from Two Randomized Studies for Second Line Therapy)

QLQ- C30 Subscale	Study 1			Study 2		
	Irinotecan hydrochloride trihydrate	BSC†	p-value	Irinotecan hydrochloride trihydrate	5-FU	p-value
Global Health Status	47	37	0.03	53	52	0.9
Functional Scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite Loss	37	57	0.001	35	38	0.9
Pain Assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial Impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

† Best supportive care

* For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Species/ Strain	No./Sex	Route	LD_{50} (mg/kg)	
			Male	Female
Mouse/Slc:ddY	70 M, 70 F	intravenous	134.1	132.4
	80 M, 80 F	oral	1044.7	1212.6
Rat/Crj:CD	60 M, 60F	intravenous	83.6	85.1
	80 M, 80 F	oral	866.9	1026.5
Dog/beagle	4 M, 4 F	intravenous	40 - 80	40 - 80

Acute toxicity in rodents consists of tremors, convulsions, respiratory distress, and death. The acute toxicity of irinotecan after a single oral dose was 8- to 10-fold less than for a single intravenous dose.

Repeated-dose toxicity studies showed that irinotecan caused vomiting, anorexia, alopecia, diarrhea, soft stools, anemia, leukopenia, and thrombocytopenia. Irinotecan has an effect on tissues with high proliferative activity such as bone marrow, thymus gland, spleen, lymph nodes and testes.

Long-Term Toxicity

Species/ Strain	No./Sex	Dose (mg/kg/day)	Route	Duration	Recovery Period	Results/Observations
Rat/strain unspecified	70 M 70 F	0, 0.032, 0.16, 0.8, 4, 20 Adriacin = 0.8	intravenous	1 mo	--	Toxic changes observed in bone marrow, thymus, spleen & lymph nodes. Toxic effects of Adriacin (0.8 mg/kg/day) were more potent than with 20 mg/kg/day irinotecan. The safety of irinotecan was at least 25X higher than for Adriacin. No-effect dose was estimated to be 0.8 mg/kg/day.
Rat/Crj:CD	54 M	0, 20 Adriacin = 0.4	intravenous	28 day	0, 2, and 4 wks	Toxic signs included salivation, ↑ body wt gain, ↑ food consumption, anemia, ↑ lymphocytes and serum protein. Toxicity also seen in stomach, kidney and testes. Most of the changes induced by irinotecan were reversible during the 4 wk recovery period. Recovery from toxicity was poorer with Adriacin, and was irreversible in the kidney and testes.
Rat/Crj:CD (SD)	150 M 150 F	0, 0.0064, 0.032, 0.16, 0.8, 4	intravenous	6 mo	1 mo	At doses of 4 mg/kg/day similar changes were noted as in the 28 day studies. No-effect dose was 0.16 mg/kg/day for males and 0.8 mg/kg/day for females.
Rat/Crj: CD (SD) BR	90 M 90 F	0, 20 SN-38 = 0.019, 0.093, 0.464, 2.32, 11.6	intravenous	4 wks	4 wks for SN-38 at 11.6 only	SN-38 at 11.6 mg/kg/day resulted in unequivocal toxicologic changes that were similar to, but generally less marked than for rats given 20 mg/kg/day of irinotecan. The no-effect level for SN-38 was considered to be 2.32 mg/kg/day.
Dog/beagle	12 M	0.6, 2.5, 10 CPT = 2.5	intravenous	14 days	--	Toxic changes observed in tissues & organs which are active in division and proliferation. The safety of irinotecan was about 4X greater than that of CPT. The no-effect dose of irinotecan was estimated to be 0.6 mg/kg/day.
Dog/beagle	18 F	Oral = 0, 6.25, 18.75, 25 intravenous = 2.5, 7.5	oral intravenous	5 days	8 days	Comparable toxicity with either route of administration. No indication that oral route was irritating to the GI tract. Absorption by the oral route was rapid with significant plasma levels at the lowest dose. Toxicity (either route)

Species/ Strain	No./Sex	Dose (mg/kg/day)	Route	Duration	Recovery Period	Results/Observations
						correlated with AUCs. Lethality/ severe toxicity occurred at doses of 7.5 mg/kg/day intravenous and 18.75 and 25 mg/kg/day oral. Primary target tissues were bone marrow, intestinal tract and lymphoid tissues.
Dog/beagle	12 M 12 F	0, 0.1, 0.4, 1.6	intravenous	28 days	--	Toxic changes were more prominent in the male dogs. Organs affected included spleen, thymus, liver, mesenteric lymph nodes and testes. Also noted were decreases in white cells, lymphocytes, and total protein. No-effect dose was estimated to be 0.1 mg/kg/day.
Dog/beagle	12 M 12 F	0, 0.1, 0.4, 1.6	intravenous	13 wks	--	Histopathological changes seen in thymus, lymph nodes, spleen, trachea, lungs, intestinal tract and skin. No-effect level was less than 0.1 mg/kg/day.
Dog/beagle	12 M 12 F	0, 0.01, 0.1, 1	intravenous	26 wks	--	Treatment-related changes for both sexes included skin discolouration, alopecia, atrophy of the thymus, soft stools, anemia and ↑ in total serum protein. No-effect level considered to be 0.01 mg/kg/day.
Dog/beagle	12 F	A: 20 mg/kg once every 2 wks B: 10 mg/kg/day, 1 day/wk for 2 wks C: 4 mg/kg/day for 5 consecutive days for 2 wks	intravenous	6 wk-dose regimen	--	Vomiting, soft stools, diarrhea and anorexia noted in each dose regimen. Hematological changes included ↑ in leukocytes and platelets. Severity of toxic changes greatest with consecutive daily dosing (Grp C), followed by Grp A and then by Grp B.

Carcinogenicity: Long-term carcinogenicity studies with irinotecan were not conducted. However, rats were administered intravenous doses of 2 mg/kg or 25 mg/kg once per week for 13 weeks, followed by a 91- week observation period. There was a significant linear dose-related incidence in combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Genotoxicity:

Mutagenicity

Type of Study	Species	Concentration Range	Results
Reverse Mutation Assay *(in vitro)*	*S. typhimurium, E. coli*	156 - 5000 mcg/plate, U-101503: 31 - 1000 mcg/plate	Irinotecan and SN-38 were not mutagenic in the Ames assay with or without metabolic activation up to the maximum concentrations.
Chromosomal Aberration Test *(in vitro)*	Chinese hamster cell line D-6	1.56 - 200 mcg/mL, U-101503 = 0.0016 – 20 mcg/mL	Irinotecan and SN-38 produced significant increases in the number of chromosomal aberrations both with and without metabolic activation.
Micronucleus Test *(in vivo)*	Mouse	intraperitoneal, 2.5 - 200 mg/kg	Irinotecan produced a significant and dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells.

Reproductive and Developmental Toxicology:

Reproduction and Teratology

Type of Study	Species/ Strain	Number/Sex	Intravenous Doses (mg/kg/day)	Results/Observations
Fertility (Segment I)	Rat/Slc:SD	100 M/100 F	0, 0.24, 1.2, 6	No significant effects on fertility or general reproductive performance observed in doses up to 6 mg/kg/day. Conclude that no-effect dose for general toxicity to male and female rats is 0.24 mg/kg/day; for fertility of males and females is 1.2 mg/kg/day; & for development of fetuses is 6 mg/kg/day.
Embryo-toxicity (Segment II)	Rat/Slc: SD Rabbit/JW-NIBS	96 F 64 F	0, 0.24, 1.2, 6 0, 0.06, 0.6, 6	Teratogenic at 6 mg/kg/day in rats and rabbits. In the rat, no-effect doses were 1.2 and 0.24 mg/kg/day for maternal toxicity and fetal development toxicity respectively. In the rabbit, no-effect doses were 0.6 and 0.06 mg/kg/day for maternal toxicity and fetal development toxicity respectively.
Peri-, Postnatal (Segment III)	Rat/Slc: SD	100 F	0, 0.24, 1.2, 6	No significant differences in morphological changes observed between control and irinotecan groups in F_2 fetuses. No-effect dose for maternal animals and offspring was 1.2 mg/kg/day.

Local Tolerance: Local tolerance of irinotecan was satisfactory when given to rabbits by the intramuscular route, instilled in the eye, or applied to intact and abraded skin. The intramuscular irritation of irinotecan in the rabbit at a dose of 20 mg/site was less than that for 5 mg/site of doxorubicin.

Antigenicity Potential: Irinotecan did not demonstrate antigenicity in mice but had antigenic potential in guinea pigs and rabbits. SN-38 did not demonstrate antigenicity in either mice or guinea pigs. The active systemic anaphylactic assay (ASA), enzyme-linked immunosorbent assay (ELISA) and passive cutaneous anaphylaxis (PCA) showed positive reactions to the piperidinopiperidine side-chain.

17 SUPPORTING PRODUCT MONOGRAPHS

1. Camptosar® (Solution, 20 mg/mL), submission control number 257414, Product Monograph, Pfizer Canada ULC. (February 17, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION

(Irinotecan Hydrochloride Trihydrate for Injection)

Read this carefully before you start taking **IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION**.

Serious Warnings and Precautions

IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION should be given under the supervision of a healthcare professional who is experienced in the use of chemotherapy drugs.

Serious side effects with the use of IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION include:

- **Diarrhea:** Severe early and late forms of diarrhea that can be life-threatening as they may lead to dehydration (fluid loss) and electrolyte (salt) imbalance.
- **Gut problems (inflammation and blockage):** Bowel inflammation (typhlitis and colitis), lack of bowel movement (ileus), or a hole in the wall of the small intestine or large bowel (intestinal perforation).
- **Infections:** Decreased production of white blood cells resulting in neutropenia (low blood level of immune cells). Cases of bacterial, fungal and viral infections, sometimes fatal and/or life-threatening

What is IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION used for?

IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION is a chemotherapy drug (drug used to treat cancer), used:

- in combination with other drugs to treat cancers of the colon and rectum that have spread to other areas of the body;
- alone to treat cancers of the colon and rectum that have spread to other areas of the body and were not able to be treated effectively with 5-fluorouracil-based therapy.

How does IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION work?

IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, like most chemotherapy drugs, works by killing rapidly dividing cells, such as cancer cells. In some cancers, chemotherapy can be used to reduce tumour size, or stop them from growing.

What are the ingredients in IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION?

Medicinal ingredients: irinotecan hydrochloride

Non-medicinal ingredients: sorbitol, lactic acid, sodium hydroxide and/or hydrochloric acid to adjust pH, water for injection

IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION comes in the following dosage forms:

solution, 20 mg / mL

Do not use IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION if:

- you are allergic to irinotecan hydrochloride or any of the non-medicinal ingredients in IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION (see **What are the ingredients in IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION?**);
- you have hereditary fructose intolerance. Sorbitol is a non-medicinal ingredient in IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION.
- you are taking medicine to treat a fungal infection, such as ketoconazole, fluconazole, itraconazole.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. Talk about any health conditions or problems you may have, including if you:

- have low blood cell counts due to a decreased ability of the bone marrow to produce blood cells.
- have liver or lung problems.
- have a heart disease, have had a recent heart attack or have an irregular heartbeat.
- are taking other drugs (including laxatives, diuretics/fluid pills) or have been previously treated with IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION or other chemotherapy drugs.
- have diarrhea, constipation, or trouble eating and drinking.
- have colitis (bowel inflammation) / ileus (lack of bowel movement).
- are undergoing or have previously undergone radiation treatment.
- have diabetes.

Other warnings you should know about:

Serious Side Effects: IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION can cause the following serious side effects:

- **Diarrhea:** Diarrhea is a common side effect of the chemotherapy you are receiving. IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION can cause both an early and late form of diarrhea. Early diarrhea occurs during or shortly after you have been given IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. Late diarrhea occurs more than 24 hours and can start up to several days after you have been given IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. While both forms can be severe, late diarrhea can become severe, quite quickly, and can result in loss of body fluid requiring hospitalization or lead to infection. For this reason,

it is important that you pay careful attention to each bowel movement and use the medications provided by your healthcare professional to control diarrhea symptoms.

You have diarrhea if your stools are soft, loose or watery, increased in number or it is hard to control your bowel due to urgency to go to the toilet. Loperamide is a medicine to help control the severity of diarrhea. You should begin to take loperamide immediately at the earliest sign of a loose stool or the earliest onset of bowel movements more frequent than you would normally expect. However, never take loperamide to prevent diarrhea.

You should take the loperamide as follows: 4 mg (2 tablets) at the first onset of loose stools or diarrhea and then 2 mg (1 tablet) every 2 hours until you have been without diarrhea for at least 12 hours. During the night, you may take 4 mg (2 tablets) of loperamide every 4 hours. In addition, you should try to drink lots of clear liquids (e.g. water, apple juice, broth, sports drinks, non-fizzy soft drinks) in order to prevent dehydration. You should not use loperamide for more than 48 consecutive hours.

Diarrhea associated with nausea and/or vomiting: Vomiting can prevent you from replacing fluids lost due to diarrhea. As a result, you could be in danger of serious dehydration that could result in severe complications or death. If you have diarrhea and vomiting together for more than 12 hours, talk to your healthcare professional right away.

Diarrhea in association with fever: The fever may be a sign of infection that could result in severe complications or death. If you have a diarrhea and a fever, talk to your healthcare professional right away.

Diarrhea lasting for more than 24 hours (while using loperamide): Prolonged diarrhea, even without nausea, vomiting or fever, can put you at risk for dehydration or infection. If you have diarrhea lasting for 24 hours, talk to your healthcare professional right away.

- **Nausea and Vomiting:** The amount of nausea and vomiting varies widely from person to person. Some people have mild nausea and vomiting, while others may have severe nausea and vomiting for a short time after treatment. Nausea and vomiting may start right after a chemotherapy treatment or several hours later and may last several days. Vomiting can become quite severe, and you can lose body fluid which can cause you to become dehydrated. Vomiting can also make it difficult for you to take medications (such as loperamide for diarrhea). Your healthcare professional can give you medicine to prevent nausea or reduce its severity. Here are some tips that may help reduce nausea.
    - Eat small meals or snacks throughout the day instead of 2 or 3 large meals.
    - Eat foods that are cold or at room temperature.
    - Cut out foods that are fried, spicy, fatty or sweet.
    - Stay away from odours that may bother you such as cooking smells, cigarette smoke, car exhaust or perfume.
    - Sit upright in a chair after eating – don't lie flat for at least 2 hours.
    - Wear loose-fitting clothes, especially around the waist.

- You can also try drinking clear fluids (water, diluted soft drinks, apple juice, and broth) or sucking on popsicles, ice chips, mints, or sour candy (but avoid sour candy if you have mouth sores).
- Eat something light a few hours before your chemotherapy treatment.

If these suggestions and the medications you are taking do not work, or if nausea and vomiting become so severe you cannot take anti-nausea or other medications, talk to your healthcare professional right away or go to your nearest emergency room.

- **Gut Problems (inflammation and blockage):** Cases of colitis (inflammation of the intestines) and ileus (lack of bowel movements) have been reported in people taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION.
- **Infection: A** week or two after a chemotherapy cycle, your white blood cell count may be low. This is the most dangerous time for getting an infection. White blood cells defend your body against infections. When there are very few white blood cells, there may not be enough to fight off an infection. It's important to know the signs of infection so that you can get treatment before the infection becomes serious. The signs of infection include:
  - fever over 38 °C (100 °F)
  - chills or sweating
  - sore throat or coughing
  - redness or swelling around a cut, wound or a catheter site
  - a burning feeling when you urinate
  - unusual vaginal itching or discharge

  Talk to your healthcare professional right away if you have any signs of infection.

  Your healthcare professional may prescribe oral antibiotics to help prevent infection during chemotherapy. They may also give you a medicine to help increase the number of your white blood cells. The following tips can help you prevent infections:
  - Wash your hands often. Use lotion afterwards to prevent your skin from becoming dry and cracked.
  - Bathe or shower every 1 to 2 days.
  - Be careful not to cut yourself when you use a knife, scissors, razor or other sharp objects.
  - Stay away from people who are sick.
  - Have someone else clean cat litter boxes, birdcages or fish tanks.
  - Eat well-balanced meals.
- **Heart Attacks, Strokes or Blood Clots:** These types of serious heart and blood problems have happened in people taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. They may happen both in patients with known risk factors for heart problems or blood clots and in patients without known risk factors for these conditions. These conditions can be life-threatening or fatal. The signs of heart attacks, strokes or blood clot include:
  - Worsening of pre-existing chest pain.

- New onset of chest pains and/or shortness of breath.
- Sudden loss of vision, difficulty speaking, or loss of muscular function or loss of sensation on one side of your body.
- Swelling in one of your legs (this may be evidence of a blood clot in the legs that could put you at risk for more serious complications).
- If you have a central venous catheter and you develop swelling in the arm or neck on the side of the catheter (possible evidence of a blood clot).

Get immediate medical help if you experience any of these symptoms.

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects.

Anemia (low levels of red blood cells): Chemotherapy medicines affect the bone marrow, which is where red blood cells are formed. Red blood cells carry oxygen to the muscles and other tissues in your body. When there are too few red blood cells, your muscles, and other body tissues can't get enough oxygen to do their work, and you feel exhausted. If your red blood cell count drops very low, you may also feel weak or dizzy, or may have shortness of breath. These are all symptoms of anemia. If you have these symptoms, tell your healthcare professional.

Fatigue: Feeling tired - or fatigued - is one of the most common side effects of chemotherapy. Many other factors such as stress, diet, sleeping patterns, and your age can also cause fatigue. For some, fatigue may start to improve 2 to 3 months after you complete your chemotherapy treatments. Here's how you can help reduce fatigue.

- Plan your activities. Allow rest between periods of activity.
- List all of the things you have to do, and number them in order of importance. Only do the things on your list that must get done. Leave the other tasks for another day.
- Ask family and friends to help you with driving, house-work or other tasks. For example, ask your friend to pick up a few things for you the next time they go to the supermarket.
- Eat a well-balanced diet.
- Do light exercise regularly.

Hair loss: Hair loss is common in chemotherapy. The hair loss is temporary, and your hair usually starts to grow back within 2 or 3 months after you've finished your treatments. Many survivors suggest getting a wig before you start chemotherapy treatment. That way, your stylist can match your current hair color and set- it in the same style. While wigs can be expensive, there are organizations such as The Canadian Cancer Society that provide wigs free of charge. In addition to wigs, some people like to wear stylish hats, scarves, or turbans to cover their head.

Speech Disorders: Speech disorders such as difficulty speaking, stuttering and/or slurred speech, sometimes occurring with tingling or numbness of the mouth or tongue, have been seen during or immediately following IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION treatment. In most cases, these symptoms improved within minutes to hours after finishing IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION treatment. If you experience any difficulty speaking, change in voice and/or tingling or numbness of the mouth or tongue during or after your treatment with IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, tell your healthcare professional right away.

Female Patients:

- You should not get pregnant while taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 6 months after your last dose. It may harm your unborn baby or make you lose the pregnancy. If you get pregnant while taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, tell your healthcare professional right away.
- If you are a woman who is able to get pregnant a pregnancy test should be done: before you start to take IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION; regularly while you are taking it; and one month after taking your last dose.
- You must use an effective method of birth control while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 6 months after you take your last dose.
- IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION may pass into breast milk. Do not breastfeed while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 1 week after your last dose. If you are planning to breastfeed, talk to your healthcare professional about other ways to feed your baby while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION.

Male Patients:

- You must not father a child while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 3 months after your last dose.
- Use a condom when having sexual intercourse with your female partner, even if she is pregnant. You must continue to use condoms while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, and for 3 months after your last dose.
- Your female partner must also use an effective method of birth control while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 3 months after your last dose. If your female partner gets pregnant while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION talk to your healthcare professional right away.
- Do not donate sperm while taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and for 3 months after your last dose.

Blood Tests and Monitoring: Before you use IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, talk to your healthcare professional to understand what kind of tests will be needed before, during and after treatment. It is very important to go to all the medical appointments that your healthcare professional has scheduled for you. Your healthcare professional will order blood tests to check your blood count (white blood cells, red blood cells, and platelets), heart and liver function, X-rays or other tests. These tests will help your healthcare professional determine your condition before you start taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION and while you are taking it.

After you have completed all your chemotherapy treatments, your healthcare professional will check you regularly to make sure the cancer has not returned.

Working During IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION Treatment: Some people work full time, while others work part time or wait until their chemotherapy treatments are finished before returning to work. It depends on the type of job you have and the side effects you experience.

Driving and Using Machines: Many of the side effects of IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION such as fatigue, dizziness, and changes in vision can affect your ability to drive and

operate machinery. Give yourself time after you have been given IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION to see how you feel before driving a vehicle or using machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION:

- antibiotics used to treat bacterial infections, such as ciprofloxacin, norfloxacin, clarithromycin, erythromycin, azithromycin, rifampin
- medicines used to treat fungal infections, such as ketoconazole, fluconazole, itraconazole
- medicines used to treat heart problems called "calcium channel blockers", such as verapamil, diltiazem, nifedipine
- medicines used to prevent seizures, such as phenytoin, phenobarbital, carbamazepine
- atazanavir sulfate, a medicine used to treat HIV infection
- cimetidine, a medicine used to treat ulcers
- dexamethasone, a medicine used to treat certain types of swelling or allergies
- St. John's Wort, an herbal medicine used to treat depression
- grapefruit juice. Do not drink grapefruit juice, eat grapefruit or consume any products that contain grapefruit or grapefruit juice while you are taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION.

How to take IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION:

Usual dose:

Your healthcare professional will decide on your dose and the length of your treatment based on your treatment goals, the medicines you receive, and how your body responds to those medicines.

Chemotherapy is usually given in cycles that include rest periods between treatments. The rest periods give your body a chance to build healthy new cells and regain your strength before your next treatment. You may receive one dose of IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION every week for four weeks (on Day 1, 8, 15, 22 of the cycle) followed by a 2-week rest. Or, you may receive IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION once every 2 weeks (on Day 1, 15, 29 of the cycle) followed by a 1-week rest. Or, you may receive IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION once every 3 weeks. Your treatment cycle will depend on your medical condition and the other chemotherapy medicines you are getting. Do not skip doses or make changes in your treatment on your own.

How is IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION given?

You will be given IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION through a vein in the arm ("intravenously" or "IV"), usually in the hospital, outpatient department or clinic. To administer IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, your healthcare professional will insert a thin needle or plastic tube (IV) in a vein, which allows fluid to drip into your vein from a plastic bag.

If you are getting many treatments over several weeks or months, for your convenience, your healthcare professional may insert a catheter (thin tube) or port into a large vein in your body that is

placed there as long as it is needed. Medicines get injected through the catheter or port rather than directly into a vein.

It usually takes about 90 minutes to inject IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. However, you may get other medicines before or after IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, so your entire treatment may last longer. If you are getting a medicine to prevent nausea, you will probably take that medicine first. Then you will get the rest of your IV medicines, including IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, one at a time.

Overdose:

If you think you, or a person you are caring for, have been given too much IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION?

These are not all the possible side effects you may have when taking IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION. If you experience any side effects not listed here, tell your healthcare professional.

Chemotherapy medicines work by killing the fastest growing cells in the body, which include cancer cells and some normal cells. Normal cells that grow very rapidly are in your bone marrow, lining of the mouth, stomach, and hair follicles. Since these fast-growing cells can be affected by chemotherapy medicines, this can lead to side effects such as diarrhea. The most common side effects are: low white cell count (increasing the risk of infection), low red cell count (anemia), nausea and vomiting, and hair loss. These side effects usually disappear after treatment ends. Before your next cycle of chemotherapy, your white blood cell count normally increases and new cells grow back. After your chemotherapy is completely finished, your hair will begin to grow back.

Tell your healthcare professional right away if you feel any of the following symptoms *during your treatment or a few hours after treatment*:

- Runny nose, watery eyes, more saliva in your mouth.
- Diarrhea and/or stomach cramps.
- Nausea or vomiting.
- Sweating.
- Flushing (your face and neck may feel hot and look red).
- Visual disturbances.
- Pain or burning during the injection.

Don’t wait until your treatment is finished. Your healthcare professional may give you a medicine to relieve these symptoms. You may also get medicine before or after future treatments to prevent these symptoms.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Diarrhea, Nausea and Vomiting: • Diarrhea for the first time during your treatment • Diarrhea with nausea and/or vomiting • Diarrhea lasting more than 24 hours • Diarrhea with fever • Vomiting for more than 12 hours		√	
Dehydration: light-headedness, dizziness, or fainting; dry, flushed or pale skin; irritability or confusion, urinating less often		√	
Infections: fever, chills or sweating, sore throat or coughing, redness or swelling around cut, wound or a catheter site, burning feeling when you urinate		√	
UNCOMMON			
Gut problems (inflammation, blockage): black or bloody stool, abdominal pain, inability to pass gas or stool		√	
Low levels of blood platelets: bruising, small red haemorrhages into the skin, failure of cuts to stop bleeding or blood in stool		√	
Heart Attack: chest pain, shortness of breath, and sensation of fullness/ heaviness in the chest		√	
Stroke: sudden loss of vision, difficulty speaking, loss of muscular function or loss of sensation on one side of your body		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Blood Clot: swelling, warmth and redness in a vein of one of your legs, arm or neck		√	
RARE			
Progressively increasing shortness of breath		√	
VERY RARE			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION will be stored by your healthcare professional.

If you want more information about IRINOTECAN HYDROCHLORIDE TRIHYDRATE FOR INJECTION:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.fresenius-kabi.com/en-ca/), or by calling 1-877-821-7724.

This leaflet was prepared by:

Fresenius Kabi Canada Ltd.

165 Galaxy Blvd, Suite 100

Toronto, ON M9W 0C8

Last revised: September 08, 2022