PRODUCT MONOGRAPH

Pr IRINOTECAN FOR INJECTION

Irinotecan Hydrochloride Trihydrate for Injection

20 mg/mL

USP

Antineoplastic Agent

ATC: L01XX19

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Toronto, Ontario
M1B 2K9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Solution / 20 mg/mL	Lactic acid, sorbitol and water for injection. Sodium hydroxide and/or hydrochloric acid to adjust pH

INDICATIONS AND CLINICAL USE

IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate) is indicated as a component of first-line therapy for patients with metastatic carcinoma of the colon or rectum.

IRINOTECAN FOR INJECTION is also indicated as 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 FOR INJECTION (irinotecan hydrochloride trihydrate) 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.

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 **WARNINGS AND PRECAUTIONS** – General, Geriatrics, **DOSAGE AND ADMINISTRATION, CLINICAL TRIALS**).

Pediatrics: The safety and effectiveness of irinotecan hydrochloride trihydrate in the pediatric population have not been established (see **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate) 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 the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

Co-administration of irinotecan hydrochloride trihydrate 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 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 **WARNINGS AND PRECAUTIONS** regarding potential drug- drug interactions with other CYP3A4 inhibitors and inducers.

Patients with hereditary fructose intolerance should not be given IRINOTECAN FOR INJECTION, as this product contains sorbitol.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate) 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 **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**).
- Typhlitis, ulcerative and ischemic colitis, ileus and intestinal perforation (see **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS** - Post-Market Adverse Drug Reactions).
- Severe myelosuppression with grade 3-4 neutropenia (see **WARNINGS AND PRECAUTIONS**, **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 (See **ADVERSE REACTIONS**).

General

Patients at Particular Risk:
Physicians should exercise particular caution in monitoring the effects of IRINOTECAN FOR INJECTION in patients with poor performance status. Patients with performance status of 3 or 4 should not receive IRINOTECAN 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 has not been established in patients with significant hepatic dysfunction (see **WARNINGS AND PRECAUTIONS** - Hepatic). There are known and suspected drug-drug interactions (see **CONTRAINDICATIONS** - Drug Interactions below, and **DRUG INTERACTIONS**).

Drug Interactions:

CYP3A4 Inhibitors

- Co-administration of IRINOTECAN FOR INJECTION with azole antifungals (ketoconazole, fluconazole, itraconazole) is contraindicated (see **CONTRAINDICATIONS**).
- Co-administration of irinotecan hydrochloride trihydrate 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 **DRUG INTERACTIONS**, **DOSAGE AND ADMINISTRATION**).

The appropriate starting dose of IRINOTECAN FOR INJECTION when co-administered with CYP3A4 inhibitors has not been determined.

CYP3A4 Inducers

- The co-administration of irinotecan hydrochloride trihydrate 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 **DRUG INTERACTIONS**).

The appropriate starting dose of IRINOTECAN 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 FOR INJECTION with irradiation is not recommended.

Extravasation:
IRINOTECAN 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 IV 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 **TOXICOLOGY**). Therefore, irinotecan may be able to induce chromosomal damage in human spermatozoa. For this reason, males undergoing irinotecan hydrochloride trihydrate 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 **Clinical Trial Adverse Drug 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 **Post-Market Adverse Drug Reactions**.

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 also **Drug-Drug Interactions –** Dexamethasone).

Gastrointestinal

Diarrhea:
Irinotecan hydrochloride trihydrate can induce both an early (occurring during or shortly after infusion of irinotecan hydrochloride trihydrate) and a late (generally occurring more than 24 hours after irinotecan hydrochloride trihydrate administration) form of diarrhea that appear 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 to 1.0 mg of intravenous or subcutaneous atropine should be considered (unless contraindicated) (see **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 **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 anti-diarrhea medication. Patients experiencing clinically significant (grade ≥ 2) late diarrhea, should have subsequent doses of IRINOTECAN FOR INJECTION decreased (see **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 **DRUG INTERACTIONS**) and must not be treated with irinotecan until resolution of the bowel obstruction.

Nausea and Vomiting:
IRINOTECAN FOR INJECTION is emetogenic (see **ADVERSE REACTIONS**). Pre-medication with anti-emetic agents is recommended for patients receiving IRINOTECAN 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 FOR INJECTION. Physicians should also consider providing patients with an anti-emetic regimen for subsequent use as needed.

Hematologic

Irinotecan hydrochloride trihydrate 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 FOR INJECTION should be temporarily omitted if

neutropenic fever occurs or if the absolute neutrophil count drops below 1.5 x 10^9/L. After the patient recovers to an absolute neutrophil count >1.5 x 10^9/L, subsequent doses of IRINOTECAN FOR INJECTION should be reduced depending upon the level of neutropenia observed (see **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 **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. [(10)] 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 **ACTION AND CLINICAL PHARMACOLOGY** - Pharmacokinetics).

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 **ADVERSE REACTIONS** – Hematology).

A reduced irinotecan starting dose should be considered for patients known to be homozygous for UGT1A1*28 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. As in the case with all patients, dose modification should be considered based on individual patient tolerance to treatment (see **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 **ADVERSE REACTIONS**).

The use of irinotecan hydrochloride trihydrate 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 **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 **DOSAGE AND ADMINISTRATION**).

Immune

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported (see **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.

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.

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.

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 **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.

Special Populations

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 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.

Nursing Women:
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 (see **DETAILED PHARMACOLOGY** - Pharmacokinetics).

Pediatrics:
The safety and effectiveness of irinotecan hydrochloride trihydrate in the pediatric population have not been established.

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

Monitoring and Laboratory Tests

Careful monitoring of white blood cell count with differential, hemoglobin and platelet count is recommended before each dose of IRINOTECAN FOR INJECTION. Liver function should be monitored before initiation of treatment and monthly, or as clinically indicated (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug 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 grades 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 $\geq$ 65 years than in patients < 65 years of age[(23)]. However, results from a prospective study[(16)] 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 grade 3-4 late diarrhea in patients $\geq$ 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 $\geq$ 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 $\geq$ 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 3.0% 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 **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION -** 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 tumors 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[10] (see **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. [6, 17]

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)	15.0% (6/40)
7/7	18.2% (2/11)	36.0% (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] 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. [(26)]

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 parental 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 **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 **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 **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 **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

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 5 in **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%) patients 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.

Table 1 and 2 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 1: 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 N=225		Bolus 5-FU/LV daily x 5 q 4 weeks N=219		Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	**100**	**53.3**	**100**	**45.7**	**99.6**	**45.7**
GASTROINTESTINAL						
Diarrhea						
late	84.9	22.7	69.4	13.2	83.0	31.0
grade 3	-	15.1	-	5.9	-	18.4

Adverse Event	Study 1					
	Irinotecan hydrochloride trihydrate + Bolus 5-FU/LV weekly x 4 q 6 weeks N=225		Bolus 5-FU/LV daily x 5 q 4 weeks N=219		Irinotecan hydrochloride trihydrate weekly x 4 q 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
grade 4	-	7.6	-	7.3	-	12.6
early	45.8	4.9	31.5	1.4	43.0	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	-	29.8	-	23.7	-	19.3
grade 4	-	24.0	-	42.5	-	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	-	7.1	-	14.6	-	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	-	1.8	-	0	-	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
↑ Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia[b]	43.1	-	26.5	-	46.1	-
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR						
Vasodilatation	9.3	0.9	5.0	0	9.0	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic Events[c]	9.3	-	11.4	-	5.4	-

[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 2: 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 d1&2 q 2 weeks N=145		5-FU/LV infusional d1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
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				

Adverse Event	Study 2			
	Irinotecan hydrochloride trihydrate +5-FU/LV infusional d1&2 q 2 weeks N=145		5-FU/LV infusional d1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
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 (3.0%) 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 leucopenia.

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

Table 3: 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	2.0
Flatulence	12.2	0
Stomatitis	11.8	0.7
Dyspepsia	10.5	0
HEMATOLOGIC		
Leukopenia	63.2	28.0
Anemia	60.5	6.9
Neutropenia	53.9	26.3
0.5 to<1.0 x $l0^9$/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	22.0	3.6
↑Coughing	17.4	0.3
Rhinitis	15.5	0

Body System & Event	% of Patients Reporting	
	NCI Grades 1–4	NCI Grades 3 & 4
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.

The following table lists the grade 3 and 4 adverse events reported in the 535 patients enrolled in the two studies (V301 and V302) evaluating the once-every-3-week dosage schedule.

Table 4: Percent of Patients experiencing Grade 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	22.0	10.9
Vomiting	13.8	7.8	14.2	4.7
Nausea	13.8	3.3	11.0	3.9
Abdominal Pain	13.8	15.6	8.7	7.8
Constipation	9.5	7.8	7.9	6.2

Adverse Event	Study V301		Study V302	
	Irinotecan hydrochloride trihydrate n=189	BSC* n=90	Irinotecan hydrochloride trihydrate n=127	5-FU† n=129
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 & NUTRITIONAL				
Hepatic‡	8.5	6.7	8.7	6.2
DERMATOLOGIC				
Hand & 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 iv over 2 hr; followed by 5-FU, 400 mg/m^2 iv bolus; followed by 5-FU, 600 mg/m^2 continuous iv infusion over 22 hr on days 1 and 2 every 2 wk. (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous iv infusion until toxicity. (3) 5-FU, 2 to 3 g/m^2/day iv over 24 hr every wk for 6 wk with or without leucovorin, 20 to 500 mg/m^2/day every wk iv 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.

Post-Market Adverse Drug Reactions

The following events have been identified during post-marketing 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 **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 **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 **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 **WARNINGS AND PRECAUTIONS).**

Speech disorders have been reported in patients treated with irinotecan (see **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.

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 **ACTION AND CLINCIAL PHARMACOLOGY** Pharmacokinetics). Pharmacokinetic drug-drug and drug-herbal interactions have been shown (table below). 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.

Drug-Drug Interactions:

Pharmacokinetic Interactions

	Ref[a]	Effect	Clinical Comment
CYP3A4 inhibitors			**Potential for increased toxicity**
Azole antifungals			
Ketoconazole	CT	SN-38 ~ 110% increased,	
Fluconazole, itraconazole	T	APC ~ 90% decreased	See CONTRAINDICATIONS
Cimetidine	T		
Fluoroquinolone antibiotics			
Ciprofloxacin, norfloxacin	T		
Macrolide antibiotics			
Azithromycin, clarithromycin, erythromycin	T		See WARNINGS AND PRECAUTIONS
Calcium channel blockers			
Diltiazem, verapamil, nifedipine	T		
Grapefruit juice	T		
Atazanavir sulfate	T	See Atazanavir Product Monograph and below	
CYP3A4 inducers			**Potential for decreased efficacy**
Anticonvulsants			
Carbamazepine	CT,C	Irinotecan decreased ~ 60%,	
Phenobarbital, phenytoin		SN-38 decreased ~ 75%	
St John's Wort	C	SN-38 decreased ~40%	See WARNINGS AND PRECAUTIONS and Drug-Herb Interactions below
Glucocorticoids			
Dexamethasone	T		
Rifampin	T		

[a] Level of Evidence; 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. Co-administration of azole antifungals and irinotecan is contraindicated and patients should discontinue ketoconazole at least 1 week prior to starting irinotecan hydrochloride trihydrate therapy (see **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 **WARNINGS AND PRECAUTIONS**).

Pharmacodynamic Interactions

Antineoplastic agents: Adverse events due to IRINOTECAN FOR INJECTION, such as myelosuppression and diarrhea, would be expected to be enhanced by combination with other anti-neoplastic agents having similar adverse effects.

Laxatives: It would be expected that laxative use during IRINOTECAN FOR INJECTION 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 FOR INJECTION. The physician may wish to withhold diuretics during IRINOTECAN FOR INJECTION 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 anti-emetic 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.

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 (see **WARNINGS AND PRECAUTIONS**).

Laboratory-Test Interactions:

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

DOSAGE AND ADMINISTRATION

Recommendations common to combination and single agent IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate for injection) schedules

- Dosing of patients is not recommended with (see **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 **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 **WARNINGS AND PRECAUTIONS**)
  - aged ≥ 70 years
  - with prior pelvic/abdominal radiotherapy
  - with performance status of 2
  - with moderately elevated bilirubin levels (17-35 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 5 and 6 and for single agent therapy in Tables 7 and 8
  - dose modifications should be based on the worst preceding toxicity. Patients should return to pre-treatment bowel function without requiring anti-diarrhea 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 **WARNINGS AND PRECAUTIONS**, Gastrointestinal).

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 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 (see **WARNINGS AND PRECAUTIONS**, Hematologic).

IRINOTECAN FOR INJECTION Combination-Agent Therapy - Dosage Schedules:

IRINOTECAN 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 FOR INJECTION, with the administration of 5-Fluorouracil (5-FU) to occur immediately after receipt of LV. The recommended regimens are shown in Table 5.

Table 5: Combination-Agent Dosage Schedules & Dose Modifications[a]

Regimen 1 6-wk cycle	IRINOTECAN FOR INJECTION	125 mg/m^2 IV over 90 min once-weekly (days 1,8,15,22) then 2-week rest		
	LV Bolus	20 mg/m^2 IV bolus once-weekly (days 1,8,15,22) then 2-week rest		
	5-FU Bolus	500 mg/m^2 IV bolus once-weekly (days 1,8,15,22) then 2-week rest		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level-1	Dose Level-2
	IRINOTECAN FOR INJECTION	125	100	75
	LV Bolus	20	20	20
	5-FU Bolus	500	400	300
Regimen 2 6-wk cycle	IRINOTECAN FOR INJECTION	180 mg/m^2 IV over 90 min once every 2-weeks (days 1,15,29) then 1-week rest		
	LV Infusion	200 mg/m^2 IV over 2 h on days 1,2 every 2-weeks (days 1,2,15,16,29,30)		

	5-FU Bolus Infusion[b]	then 1-week rest 400 mg/m^2 IV bolus immediately followed by 600 mg/m^2 IV over 22 h on days 1, 2 every 2-weeks (days 1, 2, 15, 16, 29, 30) then 1-week rest

	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level-1	Dose Level-2
IRINOTECAN 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 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 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 5, Combination-Agent Dosage Schedules & Dose Modifications, subsequent doses should be adjusted as suggested in Table 6, Recommended Dose Modifications for Combination Schedules.

Table 6: Recommended Dose Modifications for IRINOTECAN FOR INJECTION /5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedule

Patients should return to pre-treatment bowel function without requiring anti-diarrhea 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 FOR INJECTION*	Maintain dose level Maintain dose level ↓1 dose level ↓ 2 dose levels *For mucositis/ stomatitis decrease only 5-FU not IRINOTECAN FOR INJECTION*

[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 FOR INJECTION Single-Agent Therapy - Dosage Schedules:
IRINOTECAN 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 7.

Table 7: Single-Agent Regimens of IRINOTECAN FOR INJECTION and Dose Modifications

Weekly Regimen[a]	125 mg/m^2 IV 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 125	Dose Level-1 100	Dose Level-2 75
Once-Every-3-Week Regimen[b]	350 mg/m^2 IV over 90 min, once weekly every 3 weeks[c]		
	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose 350	Dose Level-1 300	Dose Level-2 250

[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 FOR INJECTION Single-Agent Therapy - Dose Modifications:
Patients should be carefully monitored for toxicity and doses of IRINOTECAN FOR INJECTION should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in Table 7, Single-Agent Regimens of IRINOTECAN FOR INJECTION and Dose-Modifications, subsequent doses should be adjusted as suggested in Table 8, Recommended Dose Modifications for Single-Agent Schedules. The 350 mg/m^2 dose has not been evaluated in patients who are 70 years and older (see **CLINICAL TRIALS**) and the recommended starting dose is therefore 300 mg/m^2.

Table 8: Recommended Dose Modifications for Single-Agent Schedules[a]

Patients should return to pre-treatment bowel function without requiring anti-diarrhea 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 Week*
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3) 2 (1000 to 1499/mm^3) 3 (500 to 999/mm^3) 4 (< 500/mm^3)	 Maintain dose level ↓ 25 mg/m^2 Omit dose, then ↓ 25 mg/m^2 when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m^2 when resolved to ≤ grade 2	 Maintain dose level Maintain dose level ↓ 25 mg/m^2 ↓ 50 mg/m^2	 Maintain dose level Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea 1 (2-3 stools/day > pretx[c]) 2 (4-6 stools/day > pretx[c]) 3 (7-9 stools/day > pretx[c]) 4 (≥10 stools/day> pretx[c])	 Maintain dose level ↓ 25 mg/m^2 Omit dose, then ↓ 25 mg/m^2 when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m^2 when resolved to ≤ grade 2	 Maintain dose level Maintain, if the only grade 2 toxicity ↓ 25 mg/m^2, if the only grade 3 toxicity ↓ 50 mg/m^2	 Maintain dose level Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
Other non-hematologic toxicities [d] grade 1 grade 2 grade 3 grade 4	 Maintain dose level ↓ 25 mg/m^2 Omit dose, then ↓ 25 mg/m^2 when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m^2 when resolved to ≤ grade 2	 Maintain dose level ↓ 25 mg/m^2 ↓ 25 mg/m^2 ↓ 50 mg/m^2	 Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2 ↓ 50 mg/m^2

[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

Administration

Parenteral Products:
The IRINOTECAN FOR INJECTION vial is for single use only. Unused portions must be discarded. IRINOTECAN 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 3.0 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 to 30°C) or at refrigerated temperatures (2 to 8°C), if protected from light. If stored at room temperature (15 to 30°C) but exposed to light, the infusion solutions are physically and chemically stable for 72 hours (3 days). **Freezing IRINOTECAN FOR INJECTION and admixtures of IRINOTECAN FOR INJECTION may result in precipitation of the drug and should be avoided**.

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 to 8°C, or 6 hours at 15 to 30ºC, 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.

OVERDOSAGE

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

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 FOR INJECTION. 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action:

IRINOTECAN FOR INJECTION (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.

Pharmacokinetics:

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

Table 9: Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

	125 mg/m^2 (n=64)		**340 mg/m^2 (n=6)**	
	Irinotecan	SN-38	Irinotecan	SN-38
C_{max} (ng/mL)	1,660 ± 797	26.3 ± 11.9	3,392 ± 874	56.0 ± 28.2
AUC $_{0-24}$ (ng•hr/mL)	10,200 ± 3,270	229 ± 108	20,604 ± 6,027	474 ± 245
$t_{½}$ (hr)	5.8* ± 0.7	10.4* ± 3.1	11.7† ± 1.0	21.0† ± 4.3
V_{area} (L/m^2)	110 ± 48.5	-	234 ± 69.6	-
CL (L/hr/m^2)	13.3 ± 6.01	-	13.9 ± 4.00	-

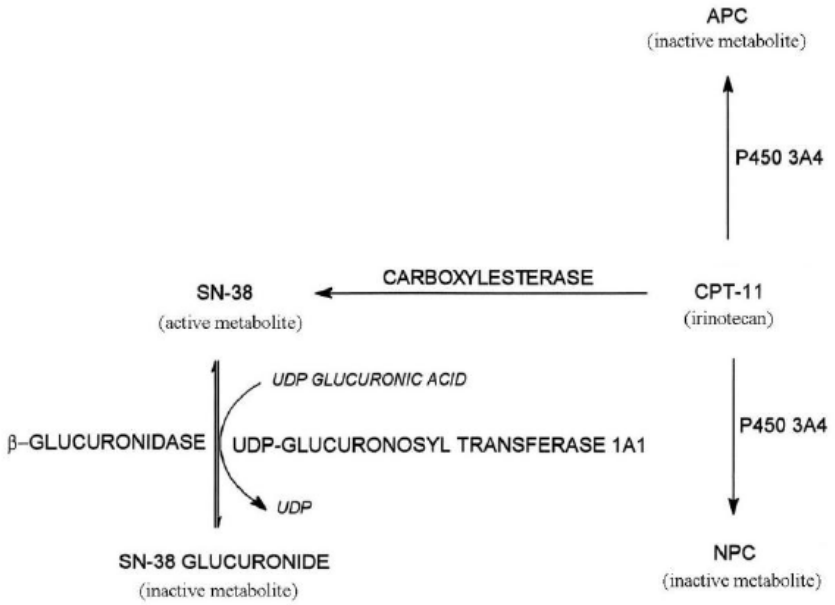
C_{max} Maximum plasma concentration
AUC_{0-24} Area under plasma concentration-time curve from 0 to 24 hours after end of infusion
$t_{½}$: Terminal elimination half-life
V_{area}: Volume of distribution of terminal elimination phase
CL: Total systemic clearance
* Plasma specimens collected for 24 hours following the end of the 90-minute infusion
† 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) [(10)] (See WARNINGS AND PRECAUTIONS – Hematologic and 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-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin) and the minor metabolite, NPC (7-ethyl-10-(4 amino-1 piperidino)carbonyloxycamptothecin). See diagram below.



In one pharmacokinetic study of patients administered a starting dose of irinotecan 125mg/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 (6.0 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, 1.0% 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 **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

Special Populations and Conditions

Renal Insufficiency:
The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been formally 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 **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Gender:
There is no clinically important gender influence on the pharmacokinetics of irinotecan; the influence of race has not been studied.

STORAGE AND STABILITY

Store at controlled room temperature (15 to 30°C). Protect from light. The product is available in an amber glass vial that is packaged in plastic blister to protect from breakage. It is recommended that the vial (and plastic blister) remain in the carton until time of use. The IRINOTECAN FOR INJECTION vial should be inspected for damage and visible signs of leaks

before removing the plastic blister. If there are signs of breakage or leakage from the vial, do not open the plastic blister. Incinerate the unopened package.

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 FOR INJECTION. Preparation of IRINOTECAN FOR INJECTION should be done in a vertical laminar flow hood. The use of gloves, safety glasses and protective clothing is recommended. If IRINOTECAN FOR INJECTION solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If IRINOTECAN FOR INJECTION contacts the mucous membranes, flush thoroughly with water. All waste material that has come in contact with IRINOTECAN FOR INJECTION should be properly segregated, sealed and incinerated.

DOSAGE FORMS, COMPOSITION AND PACKAGING

IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate for injection) is supplied as a sterile, pale yellow, clear, aqueous solution. IRINOTECAN FOR INJECTION is available as single use vials in the following package sizes:

500 mg in 25 mL of solution

Each mL of IRINOTECAN 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 3.0 - 3.8.

The rubber stoppers used in the vials are latex free.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

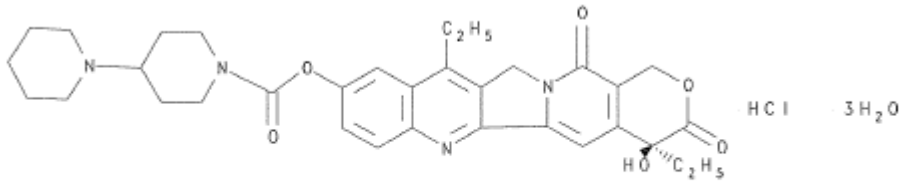
Drug Substance

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-1H-pyrano[3',4':6,7]-indolizino[1,2-*b*] quinolin-9-yl ester, monohydrochloride, trihydrate, (*S*)-

Empirical Formula: $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

Structural Formula:



CPT-11

Molecular Weight: 677.2

Description: Pale yellow to light yellow crystalline powder. The partition coefficient in an acidic medium (pH < 6) was 0.03; in a basic medium (pH> 9) was 0.05.

Solubility: It is freely soluble in DMSO and sparingly soluble in water. It is very slightly soluble in acetone and isopropanol, and practically insoluble in dichloromethane, diethyl ether, ethyl acetate and *n*-heptane.

CLINICAL TRIALS

Irinotecan hydrochloride trihydrate has been studied in clinical trials as a combination therapy with 5-FU and LV and as a single agent (see **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. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In Study 2, 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. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever, or if ileus developed.

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 10.

Table 10: 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**
Number of Patients	231	226	226	198	187
Demographics and Treatment Administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance Status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary Tumour (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35

	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**
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	39	21	18	35	22
Response Rate[b] (%)	($p<0.0001$)[c]			($p<0.005$)[c]	
Median Time to Tumour Progression[d]	7	4.3	4.2	6.7	4.4
(months)	($p=0.004$)[d]			($p<0.001$)[d]	
Median Survival	14.8	12.6	12	17.4	14.1
(months)	($p<0.05$)[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

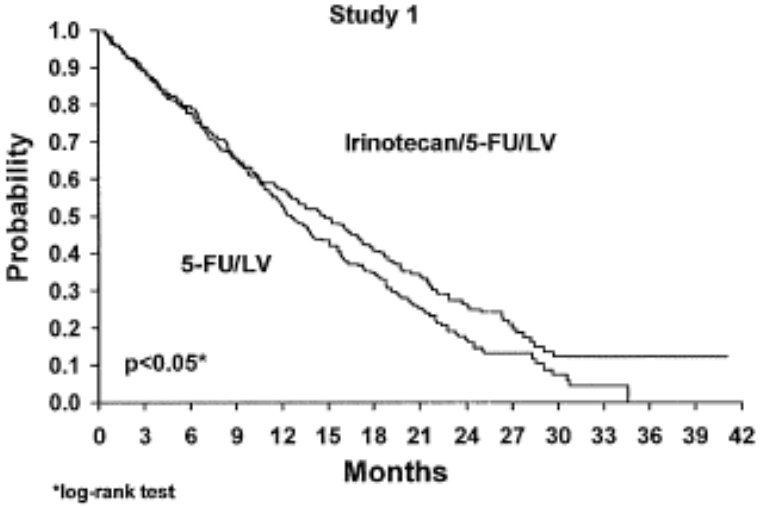
[c] Chi-square test

[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).

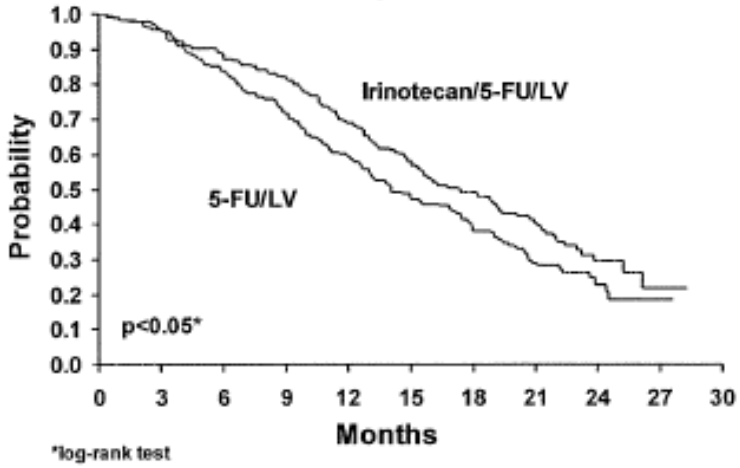
Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan hydrochloride trihydrate/5 FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

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



*log-rank test

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



*log-rank test

Figure 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)

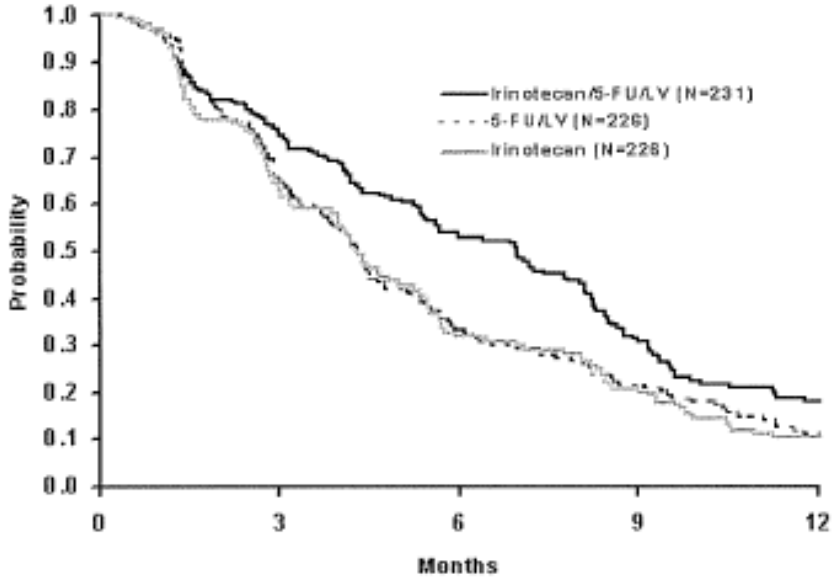
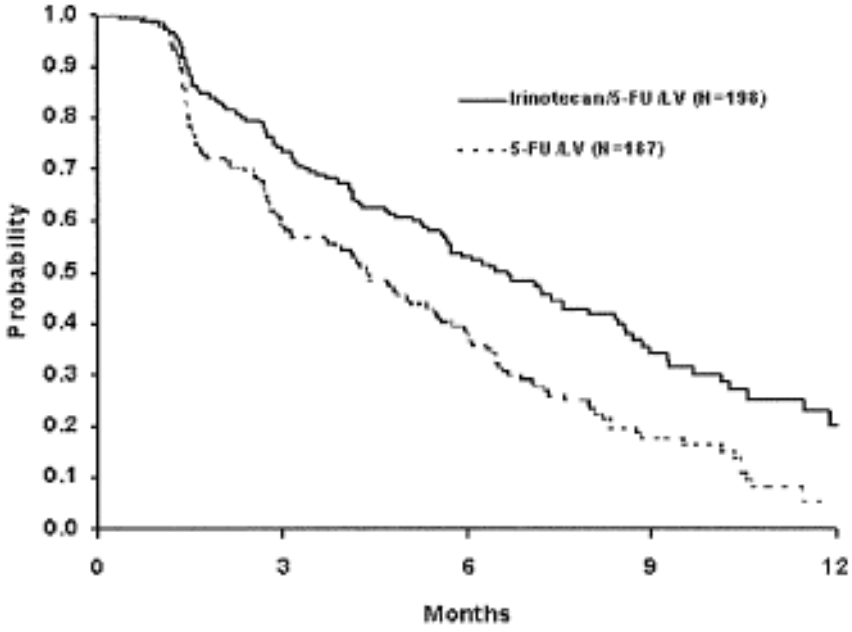


Figure 4 Time to Tumour Progression (Study 2)



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 questionnaire. Over the first 30-32 weeks of treatment, the return of questionnaire at the scheduled assessments was 76-82% for irinotecan hydrochloride trihydrate/5-FU/LV, and 77-97% 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 46-61% for irinotecan hydrochloride trihydrate/5-FU/LV and 46-60% 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 observation 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/5-FU/LV than those treated with 5-FU/LV alone (11.2 months versus 9.9 months; log rank p=.046). The impact of the side effects of irinotecan hydrochloride trihydrate with/without in combination of 5-FU/LV on the quality of life of patients were not addressed in this questionnaire.

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. All of the patients had a performance status (PS) of 0 to 2, with the majority at 0 or 1. 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 15.0% (95% confidence interval (CI), 10.0 to 20.1%). 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:
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.

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 11 below:

Table 11: 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]	2.0[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 were derived from two questions about the patient's sense of general well being in the past week. The results are summarized in the table below based on patients' worst post-baseline scores.

Table 12: 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.

DETAILED PHARMACOLOGY

Pharmacodynamics:

General:

Both irinotecan and SN-38 inhibited isolated topoisomerase I enzyme, and both were active in cell-based cytotoxicity and DNA damage assays. However, the activity of irinotecan correlated with its conversion to SN-38. In systems where the metabolic conversion of irinotecan to SN-38 is slow, the potency of SN-38 was markedly higher than that of irinotecan. Cell killing *in vitro* by both irinotecan and SN-38 was strongly dependent on exposure time, which is expected for agents with an S-phase-specific mechanism of action. Multi drug-resistant tumour models *in vivo* showed minimal cross-resistance to camptothecin analogs, including irinotecan. Irinotecan was highly active in tumour-bearing mice by intravenous, intraperitoneal, oral or subcutaneous routes. Divided-dose schedules (e.g. three doses given every fourth day) were superior to single-dose administration. Multiple-cycle, protracted regimens by intravenous, oral, or subcutaneous routes were especially effective.

The efficacy of irinotecan was studied in a panel of seven transplantation-established human carcinoma xenografts. Tumours were implanted SC into athymic mice and therapy was initiated when tumours had reached 100-300 mm^3. Tumour growth inhibition $\geq$ 90% was achieved against MX-1 mammary carcinoma and St-15 gastric adenocarcinoma when irinotecan was given IV on a Days 1, 5, 9 schedule, and against MX-1 Co-4 colon adenocarcinoma, and QG-56 squamous-cell lung carcinoma when drug was administered PO three times separated by four days. Complete remissions were noted in 100% of MX-1 carcinoma-bearing mice treated IV at 200 mg/kg or PO at 400 mg/kg (total dose). Significant growth inhibition was also noted in mice bearing SC-6 gastric adenocarcinoma. Minimal activity was noted in mice bearing MKN-28 and MKN-45 gastric adenocarcinomas. Three-dose intermittent IV administration was superior to one-dose IV administration. The activity of irinotecan compared favourably with that of doxorubicin, cisplatin, and mitomycin tested concurrently.

Emetic Effects:
The emetic effects of irinotecan and its metabolites U-101503, SN-38 and piperidinopiperidine (PP) side chain were studied after single-dose IV administration to Beagle dogs. The dosing regimens were irinotecan, 20 to 40 mg/kg (eight dogs); SN-38, 11.6 to 23.3 mg/kg (four dogs); and PP, 5 to 9.9 mg/kg (four dogs). Dogs were observed for 9 days after dosing. At 20 mg/kg of irinotecan, five of six dogs showed emesis within 1 to 2 minutes of drug administration. During the 9-day observation period, anorexia, diarrhea, and soft feces were observed in all dogs, with some dogs exhibiting symptoms by 7 days after irinotecan administration. At 40 mg/kg of irinotecan, emesis was induced in 1 minute, and the two dogs died 3 and 6 minutes later. When SN-38 (11.6 mg/kg) and PP (50 mg/kg) were administered to the dogs, no emesis or nausea was noted.

Gastrointestinal Effects:
Gastrointestinal motility in mice was slightly suppressed at a dose of 24 mg/kg and strongly suppressed at a dose of 80 mg/kg of irinotecan in surviving mice (five of ten mice died). No effects were observed at doses of up to 8 mg/kg.

At doses of 24 mg/kg or higher, irinotecan inhibited gastric emptying rate in rats. At a dose of 80 mg/kg, gastric secretion in rats was inhibited. Increased gastric and intestinal motility were observed in anesthetized dogs at doses of 0.24 to 2.4 mg/kg of irinotecan.

Pharmacokinetics:

Absorption:
Single-dose pharmacokinetics of irinotecan, irinotecan-derived SN-38 and SN-38 sodium have been studied in rats (1-40 mg/kg), mice (10-40 mg/kg) and beagle dogs (10 mg/kg). In rats, clearance exceeded hepatic plasma flow at 2 mg/kg (3.34 versus 1.95 L/hr/kg) but fell to 1.42 L/hr/kg at 40 mg/kg, suggesting saturable metabolism or excretion. The area under the plasma concentration-time curve (AUC) of irinotecan increased 47-fold over the 20-fold increase in dose from 2 to 40 mg/kg. The AUC of SN-38 derived from intravenous irinotecan increased 5-fold over a 20-fold increase in dose. Thus, exposure of rats to irinotecan increases at a greater-than-dose-proportional rate; yet, the ability to deliver SN-38 increases at a less-than-dose-proportional rate over the dose range of 2 to 40 mg/kg. In mice, the plasma clearance of irinotecan at 10 mg/kg was 3.38 L/hr/kg, and was approximately equal to estimated hepatic plasma flow (3 L/hr/kg). Clearance decreased with dose to 1.82 L/hr/kg at 40 mg/kg. In dogs, irinotecan clearance (0.24 L/hr/kg) and exposure to SN-38 were much lower than for rats or mice at an equivalent dose.

Distribution:
The disposition of camptothecin-labelled [^{14}C]irinotecan and [^{14}C]SN-38 and piperidinopiperidine-labelled [^{14}C]irinotecan has been studied in rats. Kidney, adrenals, thyroid, lung, pancreas, pituitary, and liver were exposed to the highest levels of radiolabel following a single 10 mg/kg dose of camptothecin-labelled irinotecan. Radioactivity related to [^{14}C]irinotecan crossed the placenta of pregnant rats and was also observed in the milk of lactating rats. Radioactivity in all fetal tissues was below detectable levels at 48 hours post-dose. Milk concentrations dropped from 45 mcg-eq/mL at 5 minutes to 0.05 mcg-eq/mL at 24 hours post- dose. Fractional human plasma protein binding was 30% to 43% (irinotecan) and 92% to 96% (SN-38) with human serum albumin as the major protein to which binding occurs. Rat blood cell binding ratios were 29% at 5 minutes and 76.7% at 72 hours after dosing [^{14}C]irinotecan, whereas no binding was observed after dosing [^{14}C]SN-38.

Biotransformation:
Irinotecan was metabolized by rats, mice, dogs and human tissues to the active metabolite SN-38. At approximately equal doses of 10 mg/kg, ratios of AUCs of SN-38 to irinotecan was greatest in the mouse followed (in order) by rat, man, and dog. In rats, SN-38 was conjugated with glucuronic acid. No evidence for induction or inhibition of cytochrome P450 by irinotecan has been observed. Hepatic esterases are presumed to be the major enzymes involved in SN-38 formation. Metabolism was limited in the rat, with irinotecan accounting for 55% of the biliary/fecal excreted drug-related material and SN-38 and SN-38 glucuronide accounting for 22% and 9% respectively. Extensive metabolism was observed in the dog with less than 6% of the total dose recovered in feces as irinotecan and SN-38. Biliary/fecal elimination accounted for more than 60% of the administered dose in both rats and dogs.

Excretion:
The primary route of elimination for both rats and dogs was biliary via feces, accounting for 67% to 77% of the administered dose. Urinary excretion accounted for 22% to 27% of the dose. The excretion of radioactivity over 0 to 72 hours after single intravenous administration of

[^{14}C]irinotecan to rats averaged 25% and 73% of the administered dose in the urine and feces, respectively. When [^{14}C]irinotecan (PP label) was administered, 41% and 55% of the administered dose was excreted in the urine and feces, respectively. Within 48 hours after intraduodenal injection of bile from a [^{14}C]irinotecan-doses donor rat, 13% and 5% of the dose were recycled and excreted into bile and urine, respectively.

TOXICOLOGY

Acute Toxicity				
Species/ Strain	**No./Sex**	**Route**	**LD_{50} (mg/kg)**	
			Male	**Female**
Mouse/Slc:ddY	70M, 70F	IV	134.1	132.4
	80M, 80F	PO	1044.7	1212.6
Rat/Crj:CD	60M, 60F	IV	83.6	85.1
	80M, 80F	PO	866.9	1026.5
Dog/beagle	4M, 4F	IV	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	70M 70F	0, 0.032, 0.16, 0.8, 4, 20 Adriacin = 0.8	IV	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	54M	0, 20 Adriacin = 0.4	IV	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)	150M 150F	0, 0.0064, 0.032, 0.16, 0.8, 4	IV	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	90M 90F	0, 20 SN-38= 0.019, 0.093, 0.464, 2.32, 11.6	IV	4 wks	4 wks for SN-38 at 11.6 only	SN-38 at 11.6 mg/kg/day resulted in unequivocal toxologic 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	12M	0.6, 2.5, 10 CPT= 2.5	IV	14 day	--	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	18F	Oral = 0, 6.25, 18.75, 25 IV = 2.5, 7.5	Oral IV	5 day	8 day	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) correlated with AUCs. Lethality/severe toxicity occurred at doses of 7.5 mg/kg/day IV and 18.75 and 25.0 mg/kg/day oral. Primary target tissues were bone marrow, intestinal tract and lymphoid tissues.
Dog/beagle	12M 12F	0, 0.1, 0.4, 1.6	IV	28 day	--	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	12M	0, 0.1, 0.4, 1.6	IV	13 wks	--	Histopathological changes seen in thymus, lymph nodes, spleen,

Species/ Strain	No./Sex	Dose (mg/kg/day)	Route	Duration	Recovery Period	Results/Observations
	12F					trachea, lungs, intestinal tract and skin. No-effect level was less than 0.1 mg/kg/day.
Dog/beagle	12M 12F	0, 0.01, 0.1, 1	IV	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	12F	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	IV	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.

Reproduction and Teratology

Type of Study	Species/ Strain	Number/Sex	IV Doses (mg/kg/day)	Results/Observations
Fertility (Segment I)	Rat/Slc:SD	100M/100F	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 6.0 mg/kg/day.
Embyrotoxicity (Segment II)	Rat/Slc:SD Rabbit/JW-NIBS	96F 64F	0, 0.24, 1.2, 6 0, 0.06, 0.6, 6.0	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	100F	0, 0.24, 1.20, 6.0	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.

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	IP, 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.

Carcinogenicity:

Long-term carcinogenicity studies with irinotecan were not conducted. However rats were administered IV 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.

Local Tolerance:

Local tolerance of irinotecan was satisfactory when given to rabbits by the IM route, instilled in the eye, or applied to intact and abraded skin. The IM 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.

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PART III: CONSUMER INFORMATION

[Pr] IRINOTECAN FOR INJECTION
Irinotecan Hydrochloride Trihydrate for Injection

This leaflet is part III of a three-part "Product Monograph" published when IRINOTECAN FOR INJECTION was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about IRINOTECAN FOR INJECTION. Contact your physician or pharmacist if you have any questions about the drug.

This leaflet provides some useful information about your medicine. Please read it carefully before you start your treatment with IRINOTECAN FOR INJECTION.

It is important to remember that other physicians, pharmacists or nurses with whom you come into contact may not be fully familiar with your condition or with all of the side effects of the treatments that you will be receiving. For this reason, it is important that you keep this information with you and share it with your family doctor, home-care nurse, emergency room physician, or other medical personnel who may be assisting you.

ABOUT THIS MEDICATION

What the medication is used for:
IRINOTECAN FOR INJECTION (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.

What it does:
IRINOTECAN FOR INJECTION, like most chemotherapy agents, 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.

When it should not be used:
Do not use IRINOTECAN FOR INJECTION if:

- you are allergic to the product or any of its ingredients (see below);
- you have hereditary fructose intolerance.

IRINOTECAN FOR INJECTION should not be used with certain antifungals (e.g. ketoconazole, fluconazole, itraconazole).

What the medicinal ingredient is:
Each mL of IRINOTECAN FOR INJECTION contains 20 mg of irinotecan hydrochloride trihydrate.

What the important nonmedicinal ingredients are:
IRINOTECAN FOR INJECTION also contains sorbitol and lactic acid, and may contain sodium hydroxide and/or hydrochloric acid (used to adjust the pH).

What dosage forms it comes in:
IRINOTECAN FOR INJECTION (irinotecan hydrochloride trihydrate for injection) is supplied as a sterile, clear pale yellow solution, in single use vials.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
IRINOTECAN FOR INJECTION should be given under the supervision of a doctor who is experienced in the use of anti-cancer drugs. Serious side effects with the use of IRINOTECAN FOR INJECTION include:

- Severe early and late forms of diarrhea that can be life-threatening as they may lead to dehydration (fluid loss) and electrolyte (salt) imbalance.
- 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).
- Decreased production of blood cells resulting in neutropenia (low blood level of immune cells).
- Cases of bacterial, fungal and viral infections, sometimes fatal and/or life-threatening.

BEFORE you use IRINOTECAN FOR INJECTION talk to your doctor or pharmacist if any of the following applies to you:

- If you have low blood cell counts due to a decreased ability of the bone marrow to produce blood cells.
- If you have liver or lung disease.
- If you have a heart disease, recent heart attack or irregular heartbeat.
- If you are taking other drugs (including laxatives, diuretics/fluid pills) or have been previously treated with IRINOTECAN FOR INJECTION or other anti-cancer drugs.
- If you are taking antibiotics, antifungals (e.g. ketoconazole), heart medications (calcium channel blockers), anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine), atazanavir sulfate (an anti-HIV medication), or natural health products (e.g. St. John's Wort).
- If you have diarrhea, constipation, or trouble eating and drinking.
- If there is any possibility that you may become pregnant, ask your physician about using birth control to prevent pregnancy during your treatment with IRINOTECAN FOR INJECTION. Tell your physician right away if you become pregnant during treatment. IRINOTECAN FOR INJECTION can be harmful to an unborn child.
- If you have been nursing, you should stop before starting treatment with IRINOTECAN FOR INJECTION. Ask your baby's physician to recommend a formula that would be best for your baby.

- If you wish to have a baby in the future.
- If you have colitis (bowel inflammation) / ileus (lack of bowel movement).
- If you are undergoing or have previously undergone radiation treatment.
- If you have diabetes.

Men undergoing treatment with irinotecan should discuss effective contraceptive methods with their doctor.

Before you use IRINOTECAN FOR INJECTION, talk to your physician to understand what kind of tests will be needed before and during treatment. Your doctor 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 physician determine your condition before and during treatment.

Will I be able to work?
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.

Will I be able to drive and use machines?
Many of the side effects of IRINOTECAN FOR INJECTION such as fatigue and changes in vision could affect your ability to drive and operate machinery. Pay attention to how you are affected by the medication and avoid driving, using machines or doing any other activity that would require you to be alert or have accurate vision.

What happens after treatment?
After you have completed all your chemotherapy treatments, your doctor will check you regularly to make sure the cancer has not returned.

Other warnings you should know about:

Female Patients:
• If you are pregnant, or still able to get pregnant and/or breast-feed, there are specific risks you must discuss with your healthcare professional.
• Avoid becoming pregnant while taking IRINOTECAN FOR INJECTION. It may harm your unborn child or make you lose the pregnancy. You should use effective methods of birth control while taking IRINOTECAN FOR INJECTION. If you do become pregnant while taking IRINOTECAN FOR INJECTION, tell your doctor right away.
• **For women who can get pregnant:** a pregnancy test should be done: before you start to take IRINOTECAN FOR INJECTION; regularly while you are taking it; and one month after taking your last dose. You should use effective methods of birth control while taking IRINOTECAN FOR INJECTION and for 6 months after you take your last dose of IRINOTECAN FOR INJECTION.
• IRINOTECAN FOR INJECTION may pass into breast milk. Do not breast-feed while you are taking IRINOTECAN FOR INJECTION and for 1 week after taking your last dose of IRINOTECAN FOR INJECTION. If you are planning to breastfeed, tell your doctor.

Male Patients:
• Use a condom when having sexual intercourse with a woman (even if she is pregnant). The condom must be used while you are taking IRINOTECAN FOR INJECTION, and for 3 months after you take your last dose of IRINOTECAN FOR INJECTION.
• Your female partner must also use an effective method of birth control.
• Do not donate sperm while taking IRINOTECAN FOR INJECTION and for 3 months after stopping IRINOTECAN FOR INJECTION.

INTERACTIONS WITH THIS MEDICATION

Some drugs (prescription and over-the-counter), herbal medicines and foods can increase the severity of side effects caused by IRINOTECAN FOR INJECTION or can decrease the efficacy of IRINOTECAN FOR INJECTION.

Talk to your doctor about these or any other medications you take before you start treatment with IRINOTECAN FOR INJECTION:
- antibiotics (e.g. ciprofloxacin, norfloxacin, clarithromycin, erythromycin, azithromycin, rifampin);
- antifungals (e.g. ketoconazole, fluconazole, itraconazole); heart medications (e.g. calcium channel blockers, such as verapamil, diltiazem, nifedipine);
- anticonvulsant (antiepileptic) drugs (e.g. phenytoin, phenobarbital and carbamazepine).
- atazanavir sulfate (an anti-HIV medication)

Some herbal medicines/supplements, such as St. John's Wort, could potentially make IRINOTECAN FOR INJECTION less effective in treating your cancer. Talk to your doctor about any herbal medicine/supplement you are taking.

Do not drink grapefruit juice when on IRINOTECAN FOR INJECTION.

PROPER USE OF THIS MEDICATION

Usual dose:
Your physician will determine 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 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 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 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.

It is very important to always go to your medical or laboratory appointments, as indicated by your physician or nurse.

How is IRINOTECAN FOR INJECTION given?
You receive IRINOTECAN FOR INJECTION through a vein in the arm ("intravenously" or "IV"), usually in the hospital, outpatient department or clinic. To administer IRINOTECAN FOR INJECTION, your physician or nurse 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 physician 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 FOR INJECTION. However, you may get other medicines before or after IRINOTECAN 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 FOR INJECTION, one at a time.

Overdose:

In case of overdose, you may experience increased side effects. If you suspect an overdose, talk to your doctor or nurse immediately, or contact the nearest hospital emergency room or poison control centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, IRINOTECAN FOR INJECTION may cause side effects. Everyone reacts differently to chemotherapy and not all people will experience every side effect.

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 cells count normally increases and new cells grow back. After your chemotherapy is completely finished, your hair will begin to grow back.

Other, more rare, side effects could be heart attack, stroke or blood clot (thromboembolism). The kinds of side effects, how often they occur, and how bad they may be, could be related to the dose of chemotherapy, or the regimen used. If you are having a problem with side effects, call your doctor or nurse. They can suggest medicines or other ways to prevent or relieve your discomfort.

Tell your physician, oncology pharmacist or nurse 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 physician may give you a medicine to relieve these symptoms. You may also get medicine before or after future treatments to prevent these symptoms.

Tell your physician, oncology pharmacist or nurse right away if any of the following occur *any time after receiving IRINOTECAN FOR INJECTION*:
- Diarrhea for the first time during your treatment.
- Black or bloody stools.
- Symptoms of dehydration (fluid loss), such as lightheadedness, dizziness, or fainting. Your skin may appear flushed, dry, and pale; you may not urinate very much; you may feel irritable or confused. If you are having diarrhea or are vomiting often, you may become dehydrated.
- Shortness of breath along with fluid build-up (for example, swelling in the ankles).
- Fever over 38°C (100°F), or other signs of infection.
- Difficulty speaking, change in voice and/or tingling or numbness of the mouth or tongue.
- You cannot take liquids by mouth due to nausea or vomiting, have been vomiting for more than 12 hours, or are still having nausea or vomiting although you've taken medicine to control it.
- You cannot get the diarrhea under control within 24 hours.
- You have taken loperamide for 24 hours and still have diarrhea.
- You bleed or bruise easily.
- You have a new skin rash or itching.
- You have pain where IRINOTECAN FOR INJECTION was injected.

DIARRHEA
Diarrhea is a common side effect of the chemotherapy you are receiving. IRINOTECAN FOR INJECTION can cause both an early and late form of diarrhea. Early diarrhea occurs during or shortly after you have been given IRINOTECAN FOR INJECTION. Late diarrhea occurs more than 24 hours and can start up to several days after you have been given IRINOTECAN FOR INJECTION. Whilst 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 doctor, oncology pharmacist or nurse 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. The above recommended dosage to treat your diarrhea is higher than the usual dosage of loperamide. 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 needs particular attention. In this circumstance, vomiting can prevent you from taking fluids lost due to diarrhea. As a result, you could be in danger of serious dehydration that could result in severe complications or death. Should diarrhea and vomiting persist together for more than 12 hours, you will need evaluation for intravenous fluid replacement since you are unlikely to improve on your own.

Diarrhea in association with fever also needs particular attention. The fever may be a sign of infection that could result in severe complications or death. If you have a fever in association with diarrhea, you will need prompt evaluation for intravenous antibiotic therapy.

Diarrhea lasting for more than 24 hours while using loperamide is also a concern, even if you do not have nausea, vomiting, or fever. Prolonged diarrhea can put you at risk for dehydration or infection and may require that you receive intravenous fluids and antibiotics. If you have diarrhea lasting for 24 hours, you will need evaluation. Depending upon the circumstances, your physician may request that you begin to take an antibiotic for several days in order to prevent infection that could be seen in association with the diarrhea. Alternatively, your physician may wish to have you seen in the clinic or emergency room.

NAUSEA AND VOMITING

The amount of nausea and vomiting varies widely from person to person. Some 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. As noted above, vomiting can become quite severe, and you can lose body fluid for which you may need intravenous fluids or hospitalization. In addition, vomiting may make it difficult for you to take medications (such as loperamide for diarrhea).

Your physician 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, you should contact your physician or seek help at the emergency room.

OTHER BOWEL PROBLEMS

Cases of colitis, which may be accompanied by abdominal pain and/or presence of blood in the stools, have been observed. Rarely ileus has also been reported. If you experience either of these, please consult your physician.

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.

Infections and infestations such as bacterial, fungal and viral infections have been observed during IRINOTECAN FOR INJECTION treatment. If you experience any of the signs of infections above during or after your treatment with

IRINOTECAN FOR INJECTION, notify your health care professional immediately.

Your physician may prescribe oral antibiotics to help prevent infection during chemotherapy. Your physician may also give you a medicine to help increase the number of your white blood cells. If there is evidence of an infection, your physician may need to admit you to the hospital for a short period of time to receive intravenous antibiotics.

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 CLOT

Although these types of serious medical conditions are uncommon during IRINOTECAN FOR INJECTION therapy, they may occur both in patients with known risk factors for heart disease 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 angina 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).

You should seek medical attention immediately if you experience any of these symptoms.

ANEMIA

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 physician or nurse. Your physician may give you medicine to treat anemia that is caused by chemotherapy. Do not start taking iron tablets on your own - they may not work for anemia caused by chemotherapy medicines and can make your nausea worse.

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, housework 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. However, 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 observed during or immediately following irinotecan hydrochloride trihydrate treatment. In most cases, these symptoms improved within minutes to hours after finishing irinotecan hydrochloride trihydrate 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 FOR INJECTION, notify your health care professional immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your physician or pharmacist or nurse	
	Only if severe	In all cases
Common		
Diarrhea with nausea and/or vomiting[1]		✓
Diarrhea lasting more than 24 hours[1]		✓
Diarrhea with fever[1]		✓
Vomiting for more than 12 hours[2]		✓
Dehydration manifest by lightheadedness, dizziness, or fainting; dry, flushed or pale		✓

skin; irritability or confusion[3]		
Fever, chills or sweating, sore throat or coughing, redness or swelling around cut, wound or a catheter site, burning feeling when you urinate[4]		✓
Uncommon		
Black or bloody stool[5]		✓
Bruising, small red hemorrhages into the skin, failure of cuts to stop bleeding or blood in stool		✓
Chest Pain in association with shortness of breath and sensation of fullness/ heaviness[6]		✓
Sudden loss of vision, difficulty speaking, loss of muscular function or loss of sensation on one side of your body[7]		✓
Swelling in one of your legs, arm or neck[8]	✓	
Rare		
Progressively increasing shortness of breath	✓	
Very rare		
Allergic Reaction (skin rash/ swelling/difficulty breathing)	✓	

1 See section entitled "DIARRHEA" above.
2 See section entitled "NAUSEA AND VOMITING" above.
3 See signs of dehydration under the section entitled "Tell your physician, oncology pharmacist or nurse right away if any of the following occur any time after receiving IRINOTECAN FOR INJECTION" above.
4 See section entitled "INFECTION" above.
5 See section entitled "Tell your physician, oncology pharmacist or nurse right away if any of the following occur any time after receiving IRINOTECAN FOR INJECTION" above.
6 See symptoms of heart attack under section entitled "HEART ATTACKS, STROKES, OR BLOOD CLOT" above.
7 See symptoms of stroke under section entitled "HEART ATTACKS, STROKES, OR BLOOD CLOT" above.
8 See symptoms of a blood clot (thromboembolism) under section entitled "HEART ATTACKS, STROKES, OR BLOOD CLOT" above.

This is not a complete list of side effects. For any unexpected effects while taking IRINOTECAN FOR INJECTION, contact your physician or pharmacist.

HOW TO STORE IT

Store IRINOTECAN FOR INJECTION at room temperature (15 to 30°C). Protect from light. It is recommended that the vial (and plastic blister) remain in the carton until time of use.

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.

MORE INFORMATION

If you want more information about IRINOTECAN FOR INJECTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); or by contacting Teva Canada Limited by:

Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

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