For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Irinotecan Hydrochloride Injection USP

IRINOTEL

SAFETY WARNINGS

Irinotecan Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. Irinotecan Injection can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of Irinotecan may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper peristalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine. Late diarrhea (generally occurring more than 24 hours after administration of Irinotecan can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated or antibiotic therapy if they develop ileus, fever, or severe. Administration of Irinotecan should be interrupted and subsequent doses reduced if severe diarrhea occurs. Severe myelosuppression may occur.

DESCRIPTION

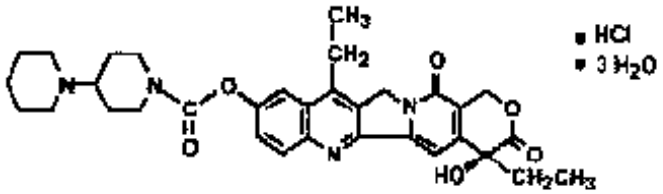
Irinotecan is a semisynthetic derivative of the plant alkaloid camptothecin extracted from the Chinese tree *Camptotheca accuminata*. It inhibits topoisomerase I function by binding to the topoisomerase I / DNA-cleavable complex.

COMPOSITION

Each mL contains:

Irinotecan Hydrochloride Trihydrate	20.0 mg
Sorbitol USNF	45.0 mg
Lactic Acid USP	0.9 mg
Water for injection USP	q.s.

CHEMICAL STRUCTURE



Irinotecan Hydrochloride

Irinotecan hydrochloride is a pale yellow-to-yellow crystalline powder. Chemically it is (***(S)***-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1**H** pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. It is slightly soluble in water and organic solvents. It has an empirical formula of $C_{33}H_{38}N_4O_6.HCl.3H_2O$ and a molecular weight of 677.19.

PHARMACOLOGY

Pharmaco-therapeutic class: cytostatic topoisomerase I inhibitor
(L: antineoplastic and immunomodulating agent)

Mechanism of action

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

PHARMACOKINETICS

Absorption and distribution

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

Over the 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. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism and excretion

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 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in special populations

Geriatric: The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥ 65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥ 65 years of age were observed. Although dose-normalized AUC0-24 for SN-38 in patients ≥ 65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant.

Gender**:** The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Race**:** The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

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.

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

CLINICAL STUDIES

<u>In monotherapy</u>
Clinical Phase II/III were performed in more than 980 patients in the every 3-week dosage schedule with metastatic colorectal cancer who failed a previous 5-FU regimen. The efficacy of irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

In Phase II studies, performed on 455 patients in every 3 week dosage schedule, the progression free survival at 6 months was 30% and the median survival was 9 months. The median time to progression was 18 weeks. In addition, non-comparative Phase II studies were performed in 304 patients treated with a weekly schedule regimen, at a dose of 125 mg/m^2 administered as an intravenous infusion over 90 minutes for 4 consecutive weeks followed by 2 weeks rest. In these studies, the median time to progression was 17 weeks and median to survival was 10 months. A similar safety profile has been observed in the weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m^2, compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

<u>In combination therapy</u>
A Phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of irinotecan at 180 mg/m^2 once every 2 weeks is followed by infusion with FA (200 mg/m^2 over a 2-hour intravenous infusion) and 5-FU (400 mg/m^2) as an intravenous bolus, followed by 600 mg/m^2 over a 22-hour intravenous infusion). On day 2, FA and 5-FU are administered at the same doses and schedules. In the weekly schedule, the administration

of irinotecan at 80 mg/m^2 is followed by infusion with FA (500 mg/m^2 over a 2-hour intravenous infusion) and then by 5-FU (2300 mg/m^2 over a 24-hour intravenous infusion) over 6 weeks.

In the weekly schedule, the incidence of severe diarrhea was 44.4% in patients treated with irinotecan in combination with 5-FU/FA and 25.6% in patients treated with 5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm^3) was 5.8% in patients treated with irinotecan in combination with 5-FU/FA and in 2.4% in patients treated with 5-FU/FA alone. In addition, median time to definitive performance status deterioration was significantly longer in irinotecan combination group than in 5-FU/FA alone group (p=0.046). Quality of life was assessed in this Phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the irinotecan groups. The evolution of the Global Health Status/Quality of life was slightly better in irinotecan combination group, although not significant, showing that efficacy of irinotecan in combination could be reached without affecting the quality of life.

INDICATIONS

Irinotecan is indicated for the treatment of patients with advanced colorectal cancer:

- In combination with 5-flurouracil and folinic acid in patients without prior chemotherapy for advanced disease.
- As a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

CONTRAINDICATIONS

Irinotecan is contraindicated in patients with:

- A chronic inflammatory bowel disease and/or a bowel obstruction (see PRECAUTIONS AND WARNINGS).
- A history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of Irinotecan.
- In pregnant or breast-feeding women.
- In patients with bilirubin >3 times the ULN (see PRECAUTIONS AND WARNINGS).
- In patients with a severe bone marrow failure.
- In patients presenting a risk factor, particularly those with a WHO performance status >2.

ADVERSE EFFECTS

The adverse reactions considered to be possibly or probably related to the administration of irinotecan have been reported from 765 patients at the recommended dose of 350 mg/m^2 in monotherapy and from 145 patients treated by irinotecan treated in combination with 5-FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m^2.

Gastrointestinal disorders:

• Delayed diarrhea

Diarrhea (occurring more than 24 hours after administration) is a dose-limiting toxicity of irinotecan. In monotherapy severe diarrhea was observed in 20% of patients who follow recommendations for the management of diarrhea. Of the evaluable cycles, 14% have a severe diarrhea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.

In combination therapy severe diarrhea was observed in 13.1% who follow recommendations for the management of diarrhea. Of the evaluable cycles, 3.9% have a severe diarrhea. Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (Clostridium difficile).

• Nausea and vomiting
In monotherapy, nausea and vomiting were severe in approximately 10% of patients treated with antiemetics. In combination therapy a lower incidence of nausea and vomiting was observed (2.1% and 2.8% of patients, respectively).

• Dehydration
Episodes of dehydration commonly associated with diarrhea and/or vomiting have been reported. Infrequent cases or renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting.

•Other gastrointestinal events
Constipation relative to irinotecan and/or loperamide has been observed; in monotherapy, in less than 10% of patients and in combination therapy in 3.4% of patients. Infrequent cases of intestinal obstruction, ileus, or gastrointestinal hemorrhage and rare cases of colitis were reported. Rare cases of intestinal perforation were reported. Other mild effects include anorexia, abdominal pain and mucositis.

Blood disorders:
• Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

• In monotherapy, neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count <1,000 cells/mm^3 including 7.6% with a neutrophil count <500 cells/mm^3. Total recovery was usually reached by day 22. Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles. Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles) and resulted in death in 2 cases. Anemia was reported in about 58.7% of patients (8% with hemoglobin <8 g/dL and 0.9% with hemoglobin <6.5 g/dL). Thrombocytopenia (<100,000 cells/mm^3) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelet count <50,000 cells/mm^3 and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.

• In combination therapy, neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm^3) in 9.8% of patients. Of the evaluable cycles, 67.3% had a neutrophil count <1,000 cells/mm^3 including 2.7% with a neutrophil count <500 cells/mm^3. Total recovery was usually reached within 7-8 days. Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles. Infectious episodes occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles) and resulted in death in 1 case. Anemia was reported in about 97.2% of patients (2.1% with hemoglobin <8 g/dL). Thrombocytopenia (<100,000 cells/mm^3) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm^3) has been observed. Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who

experienced sepsis. One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

General disorders and infusion site reactions:

Acute cholinergic syndrome: Severe transient acute cholinergic syndrome was observed in 9% of patients treated in monotherapy and in 1.4% of patients treated in combination therapy. The main symptoms were defined as early diarrhea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan. These symptoms disappear after atropine administration. Asthenia was severe in less than 10% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy. The causal relationship to irinotecan has not been clearly established. Fever in the absence of infection, and without concomitant severe neutropenia, occurred in 12% of patients treated in monotherapy and in 6.2% of patients treated in combination therapy. Mild infusion site reactions have been reported although uncommonly.

Respiratory disorders: Interstitial pneumonia and pneumonitis presenting as pulmonary infiltrates have rarely been observed. Early effects such as dyspnea have been reported.

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

Skin and subcutaneous tissue disorders: Alopecia was very common and reversible. Mild cutaneous reactions have been reported although uncommonly.

Immune system disorders: Mild allergic reactions although uncommon and rare anaphylactoid reactions have been reported.

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

Laboratory tests: In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2%, 8.1% and 1.8% of the patients, respectively, in the absence of progressive liver metastasis. Transient and mild to moderate increases in serum levels of creatinine have been observed in 7.3% of the patients.

In combination therapy transient serum levels (Grades 1 and 2) of either ALT, AST, alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis. Transient Grade 3 was observed in 0%, 0%, 0% and 1% of the patients, respectively. No Grade 4 was observed.

Transient increase of amylase and occasionally transient increase of lipase have been very rarely reported. Rare cases of hypokalemia mostly related with diarrhea and vomiting have been reported.

Other reactions:

Cardiac disorders:

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

Gastrointestinal disorders:
Infrequent cases of intestinal obstruction, ileus, megacolon, or gastrointestinal hemorrhage, and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis were reported. In some cases, colitis was complicated by ulceration, bleeding, ileus, or infection. Cases of ileus without preceding colitis have also been reported. Rare cases of intestinal perforation werereported.

Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypovolemia:
There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities.

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting, or sepsis.

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

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

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

Respiratory, thoracic and mediastinal disorders:
Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnea have been reported. Hiccups have also been reported.

Investigations:
Rare cases of hyponatremia mostly related with diarrhea and vomiting have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been very rarely reported.

DRUG INTERACTIONS

CYP3A4 and/or UGT1A1 inhibitors

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 and/or UGT1A1 may result in increased systemic exposure to irinotecan and the active metabolite SN-38. Physicians should take this into consideration when administering irinotecan with these drugs.

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

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

CYP3A4 inducers

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

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

Other interactions

Neuromuscular blocking agents: Interactions between irinotecan hydrochloride 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-depolarising drugs may be antagonized.

Antineoplastic agents: The adverse effects of irinotecan, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

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

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

Laxatives: Laxative use during therapy with irinotecan is expected to worsen the incidence or severity of diarrhea.

Diuretics: Dehydration secondary to vomiting and/or diarrhea may be induced by irinotecan. The physician may wish to withhold diuretics during dosing with irinotecan and during periods of active vomiting or diarrhea.

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

PRECAUTIONS AND WARNINGS

The use of irinotecan should be confined to units specialized in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy. Given the nature and incidence of adverse events, irinotecan will only be prescribed in the following cases after the expected benefits have been weighed against the possible therapeutic risks:

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

When irinotecan is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

Delayed diarrhea: Patients should be made aware of the risk of delayed diarrhea occurring more than 24 hours after the administration of irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately. Patients with an increased risk of diarrhea are those who had previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women. If not properly treated, diarrhea can be life threatening, especially if the patient is concomitantly neutropenic. As soon as the first liquid stool occurs, the patients should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrheal therapy must be initiated immediately. The antidiarrheal treatment will be prescribed by the department where irinotecan has been administered. After discharged from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhea as soon as it occurs. In addition, they must inform their physician or the department administering irinotecan when/if diarrhea is occurring. The currently recommended antidiarrheal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours. In addition to the antidiarrheal treatment, a prophylactic broad-spectrum antibiotic should be given; when diarrhea is associated with severe neutropenia (neutrophils count < 500 cells/mm^3). In addition to the antibiotic treatment, hospitalization is recommended for management of the diarrhea in the following cases: diarrhea associated with fever, severe diarrhea (requiring intravenous hydration), patients with vomiting associated with delayed (i.e., late) diarrhea and diarrhea persisting beyond 48 hours following the initiation of high-dose loperamide therapy. Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhea at previous cycles. In patients who experience severe diarrhea, a reduction in dose is recommended for subsequent cycles.

Nausea and vomiting: Irinotecan is emetogenic. Nausea and vomiting can be severe and usually occurs during or shortly after infusion of irinotecan. It is recommended that patients receive pre-

medication with antiemetic agents. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhea should be hospitalized as soon as possible for treatment.

Acute cholinergic syndrome. If acute cholinergic syndrome appears (defined as early diarrhea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated. Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan.

Hematology: Irinotecan 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. Serious thrombocytopenia is uncommon. Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of irinotecan. The concurrent administration with irradiation has not been adequately studied and is not recommended. Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. There were no significant differences in the frequency of Grade 3 and 4 neutropenia by age.

Neutropenic fever (concurrent NCI Grade 4 neutropenia and ≥ Grade 2 fever) occurred in fewer than 10% of patients in clinical studies; however, deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. Therapy with irinotecan should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below $1000/mm^3$.

Weekly monitoring of complete blood cell counts is recommended during irinotecan treatment. Patients should be aware of the risk of neutropenia and the significance of fever. In patients who experienced severe hematological events, a dose reduction is recommended for subsequent administration. There is an increased risk of infections and hematological toxicity in patients with severe diarrhea. In patients with severe diarrhea, complete blood cell counts should be performed.

Liver impairment: Liver function tests should be performed at baseline and before each cycle. In patients with hyperbilirubinemia, the clearance of irinotecan hydrochloride is decreased and therefore the risk of hematotoxicity is increased. Thus, frequent monitoring of complete blood counts should be conducted in this patient population. Irinotecan should not be used in patients with bilirubin >3 times the ULN.

Patients with reduced UGT1A1 activity: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form the inactive glucuronide metabolite SN-38G. This glucuronidation reaction is mediated primarily by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which is encoded by the UGT1A1 gene. The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1 28

ariant allele. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced enzyme activity and increased systemic exposure to SN-38. Higher plasma concentrations of SN-38 are observed in individuals who are homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype) versus patients who have one or two wild-type alleles.

Data from a meta-analysis of nine studies involving a total of 821 patients indicate that individuals with Crigler-Najjar syndrome (types 1 and 2) or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of hematological toxicity (Grades 3 and 4) following administration of irinotecan at moderate or high doses (>150 mg/m^2). A relationship between UGT1A1 genotype and the occurrence of irinotecan induced diarrhea was not established.

Patients who are homoyzygous (UGT1A1*6/*6 or UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients.

Patients known to be homozygous for UGT1A1*28 should be administered the normally indicated irinotecan starting dose. However, these patients should be monitored for hematologic toxicities. A reduced irinotecan starting dose should be considered for patients who have experienced prior hematologic toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on individual patient tolerance to treatment.

Hypersensitivity reactions: Hypersensitivity reactions, including severe anaphylactic/anaphylactoid reactions, have been reported.

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

Respiratory: NCI Grade 3 or 4 dyspnea has been observed. The extent to which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnea is unknown. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had pre-existing non-malignant pulmonary disease.

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

Elderly: Due to the greater frequency of decreased biological functions, in particular hepatic

function, in elderly patients, dose selection with irinotecan should be cautious in this population.

Patients with bowel obstruction: Patients must not be treated with irinotecan until resolution of the bowel obstruction.

Patients with impaired renal function: Studies in this population have not been conducted.

Driving: Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur.

Others: Since this medicine contains sorbitol, it is unsuitable in hereditary fructose intolerance. 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. Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Neither irinotecan nor SN-38 was not mutagenic in the *in vitro* Ames assay. However, in the *in vitro* Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration–dependent manner. Additionally, in the *in vivo* mouse micronucleus assay, a single intraperitoneal dose of irinotecan over the dosage range of 2.5 to 200 mg/kg caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m^2).

Radioactivity related to 14C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3rd and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6 mg/kg/day (about one-half the

recommended weekly human dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

Pregnancy and Lactation

Pregnancy
Irinotecan is teratogenic in rats and rabbits. Irinotecan may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of irinotecan in pregnant women.

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

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

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

Lactation
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. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with irinotecan.

DOSAGE AND ADMINISTRATION

Strictly follow the recommended dosage unless directed otherwise by the physician.

Dosage

For adults only

- In monotherapy (for previously treated patient):

The recommended dosage of irinotecan is 350 mg/m^2 administered as an intravenous infusion over a 30- to 90-minute period every three weeks.

- In combination therapy (for previously untreated patient):

Safety and efficacy of irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) have been assessed with the following schedule: irinotecan plus 5-FU/FA in every 2 weeks schedule. The recommended dose of irinotecan is 180 mg/m^2 administered once every 2 weeks as an intravenous infusion over 30- to 90-minute period, followed by infusion with FA and 5-FU.

Dosage adjustments
Irinotecan should be administered after appropriate recovery of all adverse events to Grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-

related diarrhea is fully resolved.

At the start of subsequent infusion of therapy, the dose of irinotecan, and 5-FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events. With the following adverse events a dose reduction of 15% to 20% should be applied for irinotecan and/or 5-FU when applicable: hematological toxicity (neutropenia Grade 4, febrile neutropenia (neutropenia Grade 3-4 and fever Grade 2-4), thrombocytopenia and leucopenia (Grade 4), non-hematological toxicity (Grade 3-4).

Treatment duration
Treatment with irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations

Elderly
No specific pharmacokinetic studies have been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. This population should require more intensive surveillance.

Patients with impaired hepatic function:
In monotherapy: in patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased and therefore the risk of hematoxicity is increased. Thus, frequent monitoring of complete blood counts should be conducted in this patient population.
- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of irinotecan is 350 mg/m^2.
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of irinotecan is 200 mg/m^2.
- Patients with bilirubin beyond to 3 times the ULN should not be treated with irinotecan).

No data are available in patients with hepatic impairment treated by irinotecan in combination.

Patients with impaired renal function:
Irinotecan is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted.

Preparation and handling:
As with other antineoplastic agents, irinotecan must be prepared and handled with caution. The use of glasses, mask and gloves is required. If irinotecan solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water.

If irinotecan solution or infusion solution comes into contact with the mucous membranes, wash immediately with water.

Preparation for intravenous infusion administration:
Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe. Irinotecan Injection 20 mg/ml is intended for single use only and any unused portion should be discarded.

Irinotecan Injection must be diluted prior to infusion. Irinotecan Injection should be diluted in 5 % Dextrose Injection, (preferred) or 0.9 % Sodium Chloride Injection, to a final concentration range of 0.12 mg/ml to 2.8 mg/ml. Other drugs should not be added to the infusion solution.

Administration
Irinotecan solution for infusion should be infused into a peripheral or central vein. Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

OVERDOSE:
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 irinotecan. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

STORAGE:
Store at temperature between 15-30ºC. Protect from light. Do not freeze. The vials should remain in the carton until the time of use. Physical and chemical stability is maintained for 24 hours at room temperature and in ambient fluorescent lighting after reconstitution. The solution should be used immediately after reconstitution, as it contains no antibacterial preservative. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), the solution should be used (infusion completed) within 24 hours, if stored at 2°C-8°C after the first breakage. Keep medicine out of the reach of children. Physical admixture with other drugs is not recommended. Visually inspect for particulate matter, precipitation, or discoloration prior to use.

INCOMPATIBILITIES:
This medicinal product must not be mixed with other medicinal products except those mentioned in this package insert.

HANDLING AND DISPOSAL:
Irinotecan is a potent chemotherapeutic anti cancer agent. All standard procedures applicable for proper handling of anticancer agents should be considered.

- Irinotecan should be handled only by persons conversant with standard practices of handling and disposal of anticancer agents. The use of gloves is recommended.
- In case, irinotecan comes in contact with skin or mucosa, wash the skin or mucosa thoroughly with soap and water.

All materials used for dilution and administration should be disposed of according to hospital standard procedure applicable to cytotoxic agents.

PRESENTATION:
IRINOTEL, a sterile, light yellow clear aqueous solution, is available as 2-ml and 5-ml injection containing 40 mg and 100 mg of Irinotecan HCl trihydrate respectively at a concentration of 20 mg/ml.

IRINOTEL is packed as 2 ml and 5 ml fill volumes in 6 ml USP type I, amber color, tubular glass vial, stoppered with 20 mm flurotec elastomeric closure (fluoropolymer coated, chlorobutyl elastomeric closure) and 20 mm aluminum flipoff seal.

MANUFACTURER INFORMATION:

Manufactured in India by:
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