In combination therapy
Severe diarrhoea was observed in 13.1% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have a severe diarrhoea.
Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically *(Clostridium difficile)*.
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 below 1,000 cells/mm³ including 7.6% with a neutrophil count <500 cells/mm³.
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.
Anaemia was reported in about 58.7% of patients (8% with haemoglobin <8 g/dl and 0.9% with haemoglobin <6.5 g/dl).
Thrombocytopenia (<100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets 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 below 1,000 cells/mm³ including 2.7% with a neutrophil count <500 cells/mm³.

Total recovery was usually reached within 7 to 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 one case.
Anaemia was reported in 97.2% of patients (2.1% with haemoglobin <8 g/dl).
Thrombocytopenia (<100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm³) has been observed.
One case of peripheral autoimmune thrombocytopenia has been reported in the post-marketing experience.

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 diarrhoea 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.

Respiratory disorders
Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnoea have been reported.

Skin and subcutaneous tissue disorders
Alopecia was very common and reversible.

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

Nervous system disorders
Paresthesia has been reported.

OVERDOSAGE
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 diarrhoea. There is no known antidote for Irinotecan. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

CLINICAL PHARMACOLOGY
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.

Pharmacodynamics
Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan. The precise contribution of SN-38 to the activity of *RINOWEL* is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.
Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.
Pharmacokinetics
After intravenous infusion of irinotecan in humans, irinotecan 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. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium. 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. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m^2 determined in reported studies in patients with solid tumors are summarized in Table:

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

Dose (mg/m^2)	Irinotecan					SN-38		
	Cmax (ng/mL)	AUC0–24 (ng·h/mL)	t1/2 (h)	Vz (L/m^2)	CL (L/h/m^2)	Cmax (ng/mL)	AUC0–24 (ng·h/mL)	t1/2 (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8* ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4* ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7† ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0† ±4.3

Cmax - Maximum plasma concentration
AUC0–24 - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
t1/2 - Terminal elimination half-life
Vz - 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.

Distribution
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
Irinotecan 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 can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC) do not inhibit cytochrome P-450 isozymes. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). 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 with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*.
Excretion
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).
Effect of Age
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. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan.
Effect of Gender
The pharmacokinetics of irinotecan do not appear to be influenced by gender.
Effect of Race
The influence of race on the pharmacokinetics of irinotecan has not been evaluated.
Effect of Hepatic Impairment
Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made.
Effect of Renal Impairment
The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, caution should be undertaken in patients with impaired renal function. RINOWEL is not recommended for use in patients on dialysis.
Drug Interactions
Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the pharmacokinetics of irinotecan.

INCOMPATIBILITIES
None known.
This medicinal product must not be mixed with other medicinal products.

STORAGE
Store protected from light, at a temperature not exceeding 25°C

HANDLING, PREPARATION AND DISPOSAL
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 the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.
Preparation for the intravenous infusion administration:
As with any other injectable drugs, the Irinotecan solution must be prepared aseptically.
If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents.
RINOWEL Injection must be diluted prior to infusion. Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250ml to 500ml infusion bag or bottle containing either 5% dextrose solution (preferred) or 0.9% sodium chloride injection, to a final concentration range of 0.12 to 2.8mg/ml. The infusion should then be thoroughly mixed by manual rotation.
The reconstituted solution should be used within 4 hours if kept at room temperature. When reconstituted with 5% Dextrose Injection, the reconstituted solution can be used within 24 hours if refrigerated at 2°-8°C (36°-46°F) but freezing should be avoided.
Irinotecan 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.

Disposal:
All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.
Any unused product or waste material should be disposed of in accordance with local requirements.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Irinotecan has moderate influence on the ability to drive and use machines.
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.

PRESENTATION
RINOWEL is presented in 2 strengths, 40 mg/2 ml and 100 mg/5 ml supplied in sterile, single use vial of 2ml & 5ml respectively.

REFERENCES:

Pack Insert of Camptosar of Pfizer.
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Alison Brayfield, ed. (2014). Martindale: The Complete Drug Reference (38th ed.). London: Pharmaceutical Press.
Polovich, M.,White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and Biotherapy guideline and recommendations for practice (2nd. ed) Pittsburgh, PA: Oncology Nursing Society.

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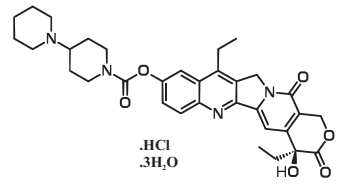
For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Irinotecan Hydrochloride Injection IP
RINOWEL®
Rx only

WARNING
RINOWEL 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. RINOWEL 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 RINOWEL) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis 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 RINOWEL) 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 neutropenia. Administration of RINOWEL should be interrupted and subsequent doses reduced if severe diarrhea occurs.
Severe myelosuppression may occur.

DESCRIPTION
RINOWEL Injection (Irinotecan hydrochloride injection IP) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.
RINOWEL is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two 2 strengths, 40 mg/2 ml and 100 mg/5 ml
Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, IP and 0.9 mg of lactic acid, IP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. *RINOWEL* is intended for dilution with 5% Dextrose Injection, IP (D5W) or 0.9% Sodium Chloride Injection, IP prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, IP.
Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as Camptotheca acuminata or is chemically synthesized.
The chemical name is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. Its structural formula is as follows:



Irinotecan Hydrochloride
Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6.HCl.3H_2O$ and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

COMPOSITION
Each ml of **RINOWEL** contains

Irinotecan Hydrochloride Trihydrate IP	20 mg
Sorbitol IP	45 mg
Lactic Acid IP	0.9 mg
Water for Injection IP	q.s.
Sodium Hydroxide IP/Hydrochloric Acid IP	To adjust pH

INDICATIONS AND USAGE
RINOWEL Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. RINOWEL is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

DOSAGE AND ADMINISTRATION
For adults only.
Irinotecan solution for infusion should be infused into a peripheral or central vein.

Recommended dosage
In Colorectal cancer used alone:
Regimen 1 (weekly) - Irinotecan 125 mg/m^2 I.V. Infusion over 90 minutes on days 1,8,15 and 22 then 2 week rest. Depending on the toxicity the dose of Irinotecan can be gradually modified to 100 or 75 mg/m^2.
Regimen 2 (every 3 weeks) - Irinotecan 350 mg/m^2 I.V. Infusion over 90 minutes once every 3 weeks. Depending on the toxicity the dose of Irinotecan can be gradually modified to 300 or 250 mg/m^2.

In Colorectal cancer in combination with 5- Fluorouracil (5FU) and Leucovorin (LV):
Regimen 1 - 6 week cycle with Bolus 5FU/ LV - Irinotecan 125 mg/m^2 I.V. Infusion over 90 minutes on days 1,8,15 and 22 + LV 20 mg/m^2 I.V Bolus on days 1,8,15 and 22 + 5FU 500 mg/m^2 I.V. Bolus on days 1,8,15 and 22. The next cycle will begin on day 43. Depending on the toxicity the dose of Irinotecan & 5FU can be gradually modified to 100+400 mg/m^2 or 75+300 mg/m^2 respectively or by decrements of 20%without altering the dose of LV.
Regimen 2 - 6 week cycle with Infusional 5FU/ LV - Irinotecan 180 mg/m^2 I.V. Infusion over 90 minutes on days 1,15 and 29 + LV 200 mg/m^2 I.V Infusion over 2 hours on days 1,2,15,16,29 and 30 + 5FU 400 mg/m^2 I.V. Bolus on days 1,2,15,16,29 and 30 followed by 5FU 600 mg/m^2 I.V. Infusion over 22 hours on days 1,2,15,16,29 & 30. The next cycle will begin on day 43. Depending on the toxicity the dose of Irinotecan, 5FU Bolus & 5FU Infusion can be gradually modified to 150+320+480 mg/m^2 or 120+240+360 mg/m^2 respectively or by decrements of 20% without altering the dose of LV.
Dosage adjustments - In any of the dosage regimen, dosing for patients with Bilirubin >2 mg/dL can not be recommended because of insufficient safety information in such patients. A new cycle of therapy should not begin for 1 to 2 weeks until the granulocyte count or neutropenia has recovered to ≥1500/mm^3, the platelet count has recovered to ≥100,000/mm^3 and treatment related neutropenic fever & diarrhea has fully resolved and recovery of all other adverse events to grade 0 or 1 NCI-CTC. If the patient has not recovered after a 2 week delay, therapy should be discontinued.
Premedication - It is recommended that patients receive premedication with antiemetic agents e.g. Ondansetron or Granisetron alongwith 10 mg Dexamethasone starting at least 30 minutes before starting treatment. Prophylactic Atropine treatment should be considered to alleviate cholinergic symptoms.

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

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category D
RINOWEL can cause fetal harm when administered to a pregnant woman. Radioactivity related to 14C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan Cmax and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Intravenous administration of irinotecan 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose produced an irinotecan Cmax and AUC of about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2. In rabbits, the embryotoxic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. In separate studies in rats, this dose produced an irinotecan Cmax and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2. In rabbits, the teratogenic dose was about one-half the recommended human weekly starting 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. There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with RINOWEL.
Nursing Mothers
Radioactivity appeared in rat 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. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from RINOWEL, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use
The effectiveness of irinotecan in pediatric patients has not been established.
Geriatric Use
Patients greater than 65 years of age should be closely monitored because of a greater risk of early and late diarrhea in this population. The starting dose of RINOWEL in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg/m^2.
Renal Impairment
The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, use caution in patients with impaired renal function. RINOWEL is not recommended for use in patients on dialysis.
Hepatic Impairment
Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. Therefore, use caution when administering RINOWEL to patients with hepatic impairment. The tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made.

CONTRAINDICATIONS

RINOWEL Injection is contraindicated in:
·Hypersensitivity to the active substance or to any of the excipients.
·Chronic inflammatory bowel disease and/or bowel obstruction.
·Pregnancy and lactation.
·Bilirubin > 3 times the upper limit of the normal range.
·Severe bone marrow failure.
·WHO performance status > 2.
·Concomitant use with St John's Wort.
·Contraindications for other medicinal products also apply, when combined with Irinotecan.

WARNINGS AND PRECAUTIONS

Diarrhea and Cholinergic Reactions
Early diarrhea (occurring during or shortly after infusion of RINOWEL) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic symptoms may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). These symptoms are expected to occur more frequently with higher irinotecan doses.
Avoid diuretics or laxatives in patients with diarrhea.
Myelosuppression
Deaths due to sepsis following severe neutropenia have been reported in patients treated with RINOWEL. Manage febrile neutropenia promptly with antibiotic support. Hold RINOWEL if neutropenic fever occurs or if the absolute neutrophil count drops <1000/mm^3. After recovery to an absolute neutrophil count =1000/mm^3, subsequent doses of RINOWEL should be reduced.
Patients With Reduced UGT1A1 Activity
Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of RINOWEL treatment.
Hypersensitivity
Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue RINOWEL if anaphylactic reaction occurs.
Renal Impairment/Renal Failure
Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.
Pulmonary Toxicity
Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan (in combination and as monotherapy). Risk factors 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 RINOWEL therapy. In Japanese studies, a reticulonodular pattern on chest x-ray was observed in a small percentage of patients. New or progressive, dyspnea, cough, and fever should prompt interruption of chemotherapy, pending diagnostic evaluation. If IPD is diagnosed, RINOWEL and other chemotherapy should be discontinued and appropriate treatment instituted as needed.
Toxicity of the 5 Day Regimen
Outside of a well-designed clinical study, RINOWEL Injection should not be used in combination with a regimen of 5-FU/LV administered for 4–5 consecutive days every 4 weeks because of reports of increased toxicity, including toxic deaths.
Increased Toxicity in Patients with Performance Status 2
In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, 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.
Embryofetal Toxicity
RINOWEL can cause fetal harm when administered to a pregnant woman. Irinotecan was embryotoxic in rats and rabbits at doses significantly lower than those administered to humans on a mg/m^2 basis. In rats, at exposures approximately 0.2 times those achieved in humans at the 125 mg/m^2 dose, irinotecan was embryotoxic and resulted in decreased learning ability and female fetal body weight in surviving pups; the drug was teratogenic at lower exposures (approximately 0.025 times the AUC in humans at the 125 mg/m^2 dose). There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with RINOWEL.
Patients with Hepatic Impairment
The use of RINOWEL in patients with significant hepatic impairment has not been established.

DRUG INTERACTIONS

5-Fluorouracil (5-FU) and Leucovorin (LV)
In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU) and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the Cmax and AUC0–24 of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was used in the combination trials and is recommended. Formal *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.
Strong CYP3A4 Inducers
Exposure to irinotecan or its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital, carbamazepine, or St. John's wort. The appropriate starting dose for patients taking these or other strong inducers such as rifampin and rifabutin has not been defined. Consider substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of RINOWEL therapy. Do not administer strong CYP3A4 inducers with RINOWEL unless there are no therapeutic alternatives.
Strong CYP3A4 or UGT1A1 Inhibitors
Irinotecan and its active metabolite, SN-38, are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), respectively. Patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Coadministration of RINOWEL with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting RINOWEL therapy. Do not administer strong CYP3A4 or UGT1A1 inhibitors with RINOWEL unless there are no therapeutic alternatives.

Irinotecan has anticholinesterase activity which may prolong the neuromuscular blocking effects of Suxamethonium and other neuromuscular blocking agents

Patients who have previously received pelvic/ abdominal irradiation are at increased risk of severe myelosuppression following administration of Irinotecan.

Co-administration of Dexamethasone as antiemetic prophylaxis with Irinotecan increases the incidence of lymphocytopenia as well as hyperglycaemia.

Co-administration of Prochloperazine as antiemetic premedication with Irinotecan increases the incidence of akathisia.

Concomitant use of diuretics with Irinotecan should be used with caution in view of the potential risk of dehydration secondary to vomiting and diarrhea caused by Irinotecan.

ADVERSE REACTIONS

The following 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/m² in monotherapy, and from 145 patients treated by irinotecan in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².
The most serious and/or most frequently occurring adverse events of irinotecan, both in monotherapy and in combination therapy, were gastrointestinal (diarrhoea, nausea, vomiting constipation), haematological (neutropenia, anaemia, thrombocytopenia), fever, asthenia, Acute Cholinergic Syndrome, infections and alopecia.
The frequencies in the following table are defined using the convention: very common (= 1/10); common (= 1/100 to <1/10); uncommon (= 1/1,000 to 1/100); rare (=1/10,000 to 1/1,000); very rare (<1/10,000).

Further details are given after this table.

MedDRA System Organ Classes	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)
Gastrointestinal Disorders					
Monotherapy	- Diarrhoea[1] - Abdominal pain - Severe nausea - Severe vomiting	- Mucositis - Constipation[2]	- Pseudo-membranous colitis - Intestinal obstruction - Ileus - Gastrointestinal haemorrhage	- Colitis[3] - Intestinal perforation	
Combination Therapy	- Diarrhoea[1] - Abdominal pain - Mucositis	- Severe nausea - Severe vomiting - Constipation[2]	- Pseudo-membranous colitis - Intestinal obstruction - Ileus - Gastrointestinal haemorrhage	- Colitis[3] - Intestinal perforation	
Blood and Lymphatic System Disorders					
Monotherapy	- Neutropenia - Anaemia	- Neutropenia with fever - Thrombocytopenia			
Combination Therapy	- Neutropenia - Anaemia - Thrombocytopenia	- Neutropenia with fever			Autoimmune Thrombocytopenia
General Disorders and Administration Site Conditions					
Monotherapy	- Fever[4]	- Acute Cholinergic Syndrome - Severe asthenia	- Infusion Site Reactions		
Combination Therapy		- Acute Cholinergic Syndrome - Severe asthenia - Fever[4]			
Infections and Infestations					
Monotherapy	- Infectious Episodes[5]				
Combination Therapy		- Infectious Episodes[5]			
Metabolism and Nutrition Disorders					
Monotherapy	- Dehydration[6]	- Anorexia			
Combination Therapy	- Dehydration[6] - Anorexia				
Vascular Disorders					
Monotherapy			- Hypotension[7] - Cardio-circulatory failure[7]	- Hypertension	
Combination Therapy					
Renal and urinary disorders					
Monotherapy			- Renal insufficiency[7]		
Combination Therapy					
Respiratory, Thoracic and Mediastinal Disorders					
Monotherapy	- Dyspnoea		- Interstitial pulmonary disease		
Combination Therapy		- Dyspnoea			
Skin and Subcutaneous Tissue Disorders					
Monotherapy	- Alopecia		- Cutaneous reactions		
Combination					
Immune System Disorders					
Monotherapy			- Allergic reactions	- Anaphylactic reactions	
Combination Therapy					
Investigations					
Monotherapy		- Serum transaminases increase - Serum alkaline phosphatase increase - Serum bilirubin increase - Serum creatinine increase			
Combination Therapy	- Serum SGOT increase (Grades 1 and 2) - Serum SGPT increase (Grades 1 and 2) - Serum alkaline phosphatase increase (Grades 1 and 2) - Serum bilirubin increase (Grades 1 and 2)	- Serum bilirubin increase (Grade 3)		- Hypokalemia - Hyponatremia	- Amylase and/or lipase increase
Nervous System Disorders					
Monotherapy					- Transient speech disorders
Combination Therapy					

[1] Can be severe, delayed and associated with fever.
[2] Associated with irinotecan and/or loperamide
[3] Including typhlitis, and ischemic or ulcerative colitis.
[4] Fever, in the absence of infection and severe neutropenia.
[5] With or without severe neutropenia.
[6] Commonly associated with diarrhoea and/or vomiting.
[7] Due to dehydration associated with diarrhoea and/or vomiting, or sepsis.

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