Irinox

Irinotecan Hydrochloride

COMPOSITION
Irinox 40 Injection: Each 2 ml contains Irinotecan Hydrochloride USP 40 mg.
Irinox 100 Injection: Each 5 ml contains Irinotecan Hydrochloride USP 100 mg.

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.

Pharmacokinetics
Absorption
T_{max} is 1 h (active metabolite). C_{max} and AUC 0-24 are 1,660 ng/mL and 10,200 ngoh/mL, respectively, for Irinotecan 125 mg/m^2 , and 3,392 ng/mL and 20,604 ngoh/mL, respectively, for Irinotecan 340 mg/m^2

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.

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).

INDICATIONS
* Irinotecan Injection is indicated as a component of first-line therapy in combination with 5-Fluorouracil (5-FU) and Leucovorin (LV) for patients with metastatic carcinoma of the colon or rectum.
* Irinotecan is 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

Combination-Agent Dosage Regimens & Dose Modificationsa

Regimen 1 6-wk cycle with bolus 5-FU (next cycle begins on day 43)	Irinotecan LV 5-FU	125 mg/m^2 IV over 90 min, d 1,8,15,22 20 mg/m^2 IV bolus, d 1,8,15,22 500 mg/m^2 IV bolus, d 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level-1	Dose Level-2
	Irinotecan LV 5-FU	125 20 500	100 20 400	75 20 300
Regimen 2 6-wk cycle with infusional 5-FU (next cycle begins on day 43)	Irinotecan LV 5-FU Bolus 5-FU Infusion	180 mg/m^2 IV over 90 min, d 1,15,29 200 mg/m^2 IV over 2 h, d 1,2,15,16,29,30 400 mg/m^2 IV bolus, d 1,2,15,16,29,30 600 mg/m^2 IV over 22 h, d1,2,15,16,29,30		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level-2
	Irinotecan LV 5-FU Bolus 5-FU Infusion	180 200 400 600	150 200 320 480	120 200 240 360

Single-Agent Regimens of Irinotecan and Dose Modifications

Weekly Regimen	125 mg/m^2 IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen	350 mg/m^2 IV over 90 min, once every 3 wks		
	Starting Dose & Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

Premedication Regimen
It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of Dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT3 blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of Irinotecan.

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 must be diluted prior to infusion. Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, 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.
The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing Irinotecan and admixtures of Irinotecan may result in precipitation of the drug and should be avoided.

The Irinotecan Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on Laminar Air Flow bench), Irinotecan Injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

CONTRAINDICATIONS
Irinotecan Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients

WARNINGS AND PRECAUTIONS
Diarrhea and Cholinergic Reactions
Early diarrhea (occurring during or shortly after infusion of Irinotecan) 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.

Myelosuppression
Deaths due to sepsis following severe neutropenia have been reported in patients treated with Irinotecan.
Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with Irinotecan.

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 Irinotecan treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
Irinotecan can cause fetal harm when administered to a pregnant woman.

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.

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 Irinotecan in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg.

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. Irinotecan 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.

ADVERSE EFFECTS
Common adverse reactions (>30%) observed in combination therapy clinical studies are: Nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

PHARMACEUTICAL INFORMATION
Storage Condition
Store the vial in original carton at 15°C to 30°C, away from light. Keep out of the reach of children.

Presentation & Packaging
Irinox 40 Injection: Each commercial box contains 1 vial of 2 ml Irinotecan Hydrochloride injection (20 mg/ml).
Irinox 100 Injection: Each commercial box contains 1 vial of 5 ml Irinotecan Hydrochloride injection (20 mg/ml).

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Manufactured By
BEACON
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Mymensingh, Bangladesh