COMPOSITION

Irita Injection: Each vial contains Irinotecan Hydrochloride USP 40 mg/2ml Injection.

Irita-100 Injection: Each vial Contains Irinotecan Hydrochloride USP 100mg/5ml Injection.

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

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.

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

Colorectal cancer combination regimen 1: Irinotecan 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8,15, 22 with LV 20 mg/m^2 intravenous bolus infusion on days 1, 8, 15, 22 followed by 5-FU intravenous bolus infusion on days 1, 8, 15, 22 every 6 weeks.

Colorectal cancer combination regimen 2: Irinotecan 180 mg/m^2 intravenous infusion over 90 minutes on days 1, 15, 29 with LV 200 mg/m^2 intravenous infusion over 2 hours on days 1, 2, 15, 16, 29, 30 followed by 5-FU 400 mg/m^2 intravenous bolus infusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30.

Colorectal cancer single agent regimen 1: Irinotecan 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8, 15, 22 then 2-week rest.

Colorectal cancer single agent regimen 2: Irinotecan 350 mg/m^2 intravenous infusion over 90 minutes on day 1 every 3 weeks.

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 Infusion Solution

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^o to 8^{o}C, 36^o to 46^{o}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

Irita

Irinotecan Hydrochloride USP

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admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2^o to 8^{o}C, 36^o to 46^{o}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^o to 8^{o}C, 36^o to 46^{o}F).

Side 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.

CONTRAINDICATIONS

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

Precaution

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 hyper peristalsis 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. 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. Grade 3-4 late diarrhea occurred in 23-31% of patients receiving weekly dosing.

Myelosuppression: Deaths due to sepsis following severe neutropenia have been reported in patients treated with Irinotecan. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. Manage febrile neutropenia promptly with antibiotic support.

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

Pregnancy category D. 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. It is not non weather this drug excreted in human male.

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/m^2.

Renal Impairment

The influence of renal impairment on the of Irino tecan 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.

Storage

Store the vial in original carton between 15^o C - 30^o C, away from light. Keep out of the reach of children.

Presentation & Packaging

Irita Injection: Each box contains 1 vial of 2 ml Irinotecan Hydrochloride USP injection (40 mg).

Irita-100 Injection: Each box contains 1 vial of 5 ml Irinotecan Hydrochloride USP injection (100 mg).