IRINOTECAN THYMOORGAN®

Irinotecan hydrochloride trihydrate

WARNINGS

IRINOTECAN THYMOORGAN 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 THYMOORGAN can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms ofdiarrheamay be severe. Early diarrhea (occurring during or shortly after infusion of IRINOTECAN THYMOORGAN) 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 (see PRECAUTIONS). Late diarrhea (generally occurring more than 24 hours after administration of IRINOTECAN THYMOORGAN) 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 (see WARNINGS). Administration of IRINOTECAN THYMOORGAN should be interrupted and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND ADMINISTRATION). Severe myelosuppression may occur (see WARNINGS).

COMPOSITION

Active ingredient: Irinotecan hydrochloride trihydrate.

ACTION

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

The intensity of the major toxicities encountered with Irinotecan (e.g., leukoneutropenia and diarrhea) are related to the exposure (AUC) to parent drug and metabolite SN-38. Significant correlations were observed between hematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhea intensity and both Irinotecan hydrochloride and metabolite SN-38 AUC values in monotherapy.

INDICATIONS

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

- In combination with 5-fluorouracil 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.

ADMINISTRATION AND DOSAGE

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.

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/m² 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 (5FU) and folinic acid (FA) have been assessed with the following schedule: Irinotecan plus 5FU/FA in every 2 weeks schedule. The recommended dose of Irinotecan is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30- to 90- minute period, followed by infusion with folinic acid and 5-fluorouracil.

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 a subsequent infusion of therapy, the dose of Irinotecan, and 5FU 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 5FU 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 hematotoxicity 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/m².
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan is 200 mg/m².
- 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:

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 the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution come into contact with the mucous membranes, wash immediately with water.

Preparation for 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. Aseptically withdraw the required amount of Irinotecan solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottles, containing either 0.9% sodium chloride solution or 5% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

Disposal

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

CONTRAINDICATIONS

Irinotecan is contraindicated in patients with:

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

WARNINGS AND PRECAUTIONS

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 weighted 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 patient 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 discharge 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/mm³). In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhea in the following cases: diarrhea associated with fever, severe diarrhea (requiring intravenous hydration), 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 experienced severe diarrhea, a reduction in dose is recommended for subsequent cycles.

Nausea and vomiting: A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhea should be hospitalised 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: 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. Febrile neutropenia (temperature > 38°C and neutrophil count <1,000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics. 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 a bilirubin > 3 times the ULN.

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.

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.

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

SIDE EFFECTS

Gastrointestinal:

- 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% of patients 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).
- Dehydratation: Episodes of dehydration commonly associated with diarrhea and/or vomiting have been reported. Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydratation 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 withantiplatelet antibodies has been reported in the post-marketing experience. Thrombocytopenia (decrease in the number of platelets) and anemia (decrease in the number of red blood cells) may also occur.

Transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase, bilirubin or creatinine have been observed. Other side effects: A very few patients who become dehydrated as a result of diarrhea, vomiting or infection may have kidney problems, low blood pressure or cardio-circulatory failure. Other side effects may occur, but the patient do not need to contact his physician unless they become troublesome: hair loss, fatigue, allergic skin reactions, stomach ache, muscular cramps, constipation, inflammation at the injection site, abdominal pain, inflammation of the lining of the mouth. There have been very rare post marketing reports of transient speech disorders associated with Irinotecan infusions. Interstitial pneumonia and pneumonitis presenting as pulmonary infiltrates have rarely been observed. Mild allergic reactions although uncommon and rare anaphylactoid reactions (allergic reactions) have been reported. Rare cases of hypokalemia (low potassium concentration in the blood) mostly related with diarrhea and vomiting have been reported.

In the weekly schedule, the incidence of severe diarrhea was 44.4% in patients treated with Irinotecan in combination with 5FU/FA and 25.6% in patients treated with 5FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm^3) was 5.8% in patients treated with Irinotecan in combination with 5FU/FA and in 2.4% in patients treated with 5FU/FA alone. In addition, median time to definitive performance status deterioration was significantly longer in Irinotecan combination group than in 5FU/FA alone group (p=0.046).

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, lachrimation 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.
- 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.
- Nervous system disorders: There have been very rare post marketing reports of transient speech disorders associated with Irinotecan infusions.

DRUG INTERACTIONS

Interaction 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-depolarizing drugs may be antagonized.

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 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 below 25°C, away from light.

The Irinotecan 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), Irinotecan solution should be used (infusion completed) within 12 hours, at room temperature or within 24 hours, if stored at 2-8°C after the first breakage.

PRESENTATIONS

Vials

IRINOTECAN THYMOORGAN 40 mg:
Irinotecan hydrochloride trihydrate 40 mg/ Vial (2 ml)
IRINOTECAN THYMOORGAN 100 mg:
Irinotecan hydrochloride trihydrate 100 mg/ Vial (5 ml)
Excipients: Sorbitol, Lactic acid, Hydrochloric acid, Sodium hydroxide, Water for injection.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

THYMOORGAN Pharmazie GmbH

Manufactured by:
Thymoorgan Pharmazie GmbH, Germany
For:
Hikma Pharmaceuticals, Amman - Jordan

Keep medicament out of the reach of children

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