Front

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Barcode

hovid

VIIRI01-0 (MY)

hovid-Irinotecan Hydrochloride 20mg/mL Concentrate for Solution for Infusion

DESCRIPTION
Clear, pale yellow liquid.
Irinotecan hydrochloride can be diluted with 5% Dextrose injection or 0.9% sodium chloride to a final concentration of 0.12 mg/ml to 2.8 mg/ml which is clear, colourless liquid to clear, pale yellow liquid.

COMPOSITION
Each ml of solution contains irinotecan hydrochloride trihydrate 20 mg.
Each 2ml and 5ml vial of hovid-Irinotecan Hydrochloride for Injection 20 mg/ml contains 40 mg and 100 mg of irinotecan hydrochloride trihydrate respectively.

PHARMACODYNAMICS
Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.
In vitro, irinotecan and SN-38 were not found to be significantly recognised by the P-glycoprotein MDR, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.
Furthermore, irinotecan has a broad antitumor activity *in vivo* against murine tumour models, human xenografts, and tumors expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemia's).
Beside the antitumor activity, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

PHARMACOKINETICS
Irinotecan showed a biphasic or thriphasic elimination profile.
The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss): 157 L/m^2. The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2.5 hours, and the terminal phase half-life was 14.2 hours. The metabolite, SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the end of the infusion, at the recommended dose of 350 mg/m^2, the mean peak plasma concentrations of irinotecan and SN-38 were 7.7 µg/ml and 56 ng/ml, respectively, and the mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.
All studies have shown that irinotecan (CPT-11) and SN-38 exposure increase proportionally with CPT-11 administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.
In vitro, plasma protein binding for irinotecan and SN-38 was approximately 65% and 95% respectively.
Mass balance and metabolism studies with 14 C-labelled drug have shown that more than 50% of an intravenously administered dose of irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

Two metabolic pathways account each for at least 12% of the dose:
- Hydrolysis by carboxylesterase into active metabolite SN-38, SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose). The SN-38 glucuronite is subsequently probably hydrolysed in the intestine.
- Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity.
Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the upper normal limit. In these patients a 200 mg/m^2 irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal liver parameters.

INDICATION
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.

CONTRAINDICATIONS
- Chronic inflammatory bowel disease and/or bowel obstruction.
- History of severe hypersensitivity to irinotecan hydrochloride trihydrate or to any of the excipients.
- Lactation.
- Bilirubin >3 times the upper limit of the normal range (ULN).
- Severe bone marrow failure.
- WHO performance status> 2.
- Concomitant use with St John's Wort.
- Concomitant use with yellow fever vaccine

WARNINGS AND PRECAUTIONS
The use of irinotecan hydrochloride should be confined to units specialised 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 hydrochloride 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 antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When irinotecan hydrochloride 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 diarrhoea: Patients should be made aware of the risk of delayed diarrhoea 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 hydrochloride trihydrate. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.
Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women. If not properly treated, diarrhoea 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 antidiarrhoeal therapy must be initiated immediately.
This antidiarrhoeal treatment will be prescribed by the department where irinotecan hydrochloride trihydrate has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering irinotecan hydrochloride trihydrate when/if diarrhoea is occurring.
The currently recommended antidiarrhoeal 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 anti-diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).
In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea, in the following cases:
- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.
In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.
Haematology: Weekly monitoring of complete blood cell counts is recommended during treatment with irinotecan. 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/mm^3) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.
In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration.
There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In patients with severe diarrhoea, complete blood cell counts should be performed.
Liver impairment: Liver function tests should be performed at baseline and before each cycle.
Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to decrease of the clearance of irinotecan and thus increasing the risk of hematotoxicity in this population. Irinotecan should not be administered to patients with a bilirubin >3 times ULN.
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 diarrhoea should be hospitalised as soon as possible for treatment.
Acute cholinergic syndrome: If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (250 micrograms 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.
Respiratory disorders: 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 the 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.
Extravasation: While irinotecan is not a known vesicant, care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.
Cardiac disorders: Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy. Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).
Immunosuppresant 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.
Others: Contraceptive measures must be taken during and for at least three months after cessation of therapy.
Effects of 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.

PREGNANCY AND LACTATION
Pregnancy: There is no data from the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals. Therefore, based on results from animal studies and the mechanism of action of irinotecan, irinotecan should not be used during pregnancy unless clearly necessary.
Lactation: In lactating rats, 14C-irinotecan was detected in milk. It is not known whether irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding must be discontinued for the duration of irinotecan therapy.

DRUG INTERACTIONS
Interaction between irinotecan 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 antagonised.
Irinotecan is partly metabolized by cytochrome P450 CYP3A isoenzymes. Inducers of this system (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.
Conversely, inhibitors of this system such as ketoconazole resulted in a reduced exposure to APC and an increased exposure to SN-38.
Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided.
When co-administered with irinotecan, St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan.

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Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

Coadministration 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.

INTERACTIONS COMMON TO ALL CYTOTOXICS:
The use of anticoagulants is common due to increased risk of thrombotic events in tumoral diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required due to their narrow therapeutic index , the high intra-individual variability of blood thrombogenicity and the possibility of interaction between oral anticoagulants and anticancer chemotherapy.

- **Concomitant use contraindicated**
  - *Yellow fever vaccine:* risk of fatal generalised reaction to vaccines
- **Concomitant use not recommended**
  - *Live attenuated vaccines (except yellow fever):* risk of systemic, possible fatal disease (eg-infections). This risk is increased in subjects who are already immunosuppressed by their underlying disease
    Use an inactivated vaccine where this exists (poliomyelitis)
  - *Phenytoin:* Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement due to increased hepatic metabolism by phenytoin
- **Concomitant use to take into consideration**
  - *Ciclosporine, Tacrolimus:* Excessive immunosuppression with risk of lymphoproliferation

MAIN SIDE/ADVERSE EFFECTS

The most common, dose-limiting adverse reactions of irinotecan are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.
The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, sweating, myosis and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan. These symptoms disappear after atropine administration.
Very commonly severe transient acute cholinergic syndrome was observed.

After monotherapy,
Infections and infestations
Common: Infection

Blood and lymphatic system disorders
Very Common: Neutropenia, anemia
Common: Thrombocytopenia, febrile neutropenia

Metabolism and nutrition disorders
Very Common: Decreased appetite

Nervous System Disorders
Very Common: Cholinergic syndrome

Gastrointestinal Disorders
Very Common: Diarrhoea, vomiting, nausea, abdominal pain
Common: Constipation

Skin and subcutaneous tissue disorders
Very common: Alopecia (reversible)

General disorders and administration site conditions
Very common: Mucosal inflammation, pyrexia, asthenia

Investigations
Common: Blood creatinine increased, transaminases (SGPT and SGOT) increased, bilirubin increased, blood alkaline phosphatase increased

After combination therapy,
In combination with cetuximab, additional reported adverse reactions were those expected with cetuximab (such as acneform rash).
In patients treated with capecitabine in combination with irinotecan, the adverse reactions reported in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: Very common, all grade adverse drug reactions: thrombosis/embolism; Common, all grade adverse drug reactions: hypersensitivity reaction, cardiac ischemia/infarction; Common, grade 3 and grade 4 adverse drug reactions: febrile neutropenia.
In patients treated with capecitabine in combination with irinotecan and bevacizumab, the grade 3 and grade 4 adverse reactions reported in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: Common, grade 3 and grade 4 adverse drug reactions: neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction.
Grade 3 hypertension was the principal significant risk involved with the addition of bevacizumab to bolus irinotecan/5-FU/FA. In addition, there was a small increase in the grade 3/4 chemotherapy adverse events of diarrhoea and leukopenia with this regimen compared to patients receiving bolus irinotecan/5-FU/FA alone.

Combination therapy (180 mg/m^2 every 2 weeks schedule)

Infections and infestations
Common: Infection

Blood and lymphatic system disorders
Very Common: Neutropenia, thrombocytopenia, anemia
Common: Febrile neutropenia

Metabolism and nutrition disorders
Very Common: Decreased appetite

Nervous System Disorders
Very Common: Cholinergic Syndrome

Gastrointestinal Disorders
Very Common: Diarrhoea, Vomiting, Nausea,
Common: Constipation, Abdominal Pain

Skin and subcutaneous tissue disorders
Very common: Alopecia (reversible)

General disorders and administration site conditions
Very common: Mucosal Inflammation, asthenia
Common: Pyrexia

Investigations
Very common: Transaminases (SGPT and SGOT) increased, Bilirubin increased, Blood alkaline phosphatase increased

OVERDOSE AND TREATMENT

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.

DOSAGE AND ADMINISTRATION

Recommended Dose
In monotherapy (for previously treated patient): The recommended dosage 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 in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule:

• hovid Irinotecan plus 5FU/FA in every 2 weeks schedule
The recommended dose of hovid-Irinotecan is 180 mg/m^2 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
hovid-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 diarrhoea 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 hovid Irinotecan and/or 5FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (grade 4)),
- non-haematological toxicity (grade 3-4).

Recommendations for dose modifications of cetuximab when administered in combination with irinotecan must be followed according to the product information for this medicinal product.
In combination with capecitabine for patients 65 years of age or more, a reduction of the starting dose of capecitabine to 800 mg/m^2 twice daily is recommended according to the summary of product characteristics for capecitabine.

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

Special populations
Patients with impaired hepatic function: In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (ULN)) in patients with performance status ≤ 2, should determine the starting dose of irinotecan. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased and therefore the risk of hematotoxicity is increased. Thus, weekly 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.
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 intense surveillance.

Direction for reconstitution
hovid-Irinotecan Injection must be diluted prior to infusion. hovid-Irinotecan can be diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. The instruction on dilution and final concentration is as follow:
hovid-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.
Withdraw the required amount of solution from the vials and then dilute with 250 ml of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. The infusion solution should then be thoroughly mixed by manual rotation. It should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.
If the solution is diluted with 0.9% Sodium Chloride Injection, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C (ambient light). If the solution is diluted with 5% Dextrose Injection, chemical and physical in-use stability has been demonstrated for 24 hours at 25°C (ambient light) or 48 hours at 2°C to 8°C (protected from light). From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.
Inspect visually prior to use. Only clear solutions without particles should be used.
The medicinal product is for single use only. Any unused infusion solution should be discarded.

Caution for Usage

- As with other antineoplastic agents, irinotecan must be prepared and handled with caution. The use of protective goggles, protection masks and sterile single-use 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.
- Disposal: All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.
- Do not admix with other medications.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30˚C. Protect from light and freezing.

Presentation/Packing: 1 x 2 ml vial (40 mg/2 ml)
1 x 5 ml vial (100 mg/5 ml)

Product Registration Holder:
HOVID Bhd.
121, Jalan Tunku Abdul Rahman (Jalan Kuala Kangsar),
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