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Irinotecan Hydrochloride Trihydrate

VIIRI02-0 (PHIL)

Irinovid

20 mg/mL Concentrate for Solution for I.V. Infusion

Antineoplastic

FORMULATION

Each mL of solution contains Irinotecan Hydrochloride Trihydrate 20mg.

Each 2mL and 5mL vial of Irinovid contains 40mg and 100mg of Irinotecan Hydrochloride Trihydrate respectively.

DESCRIPTION

Pale yellow, clear, aqueous solution.

PHARMACODYNAMICS

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.

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. 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. 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.

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. 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).

INDICATION

Irinotecan hydrochloride is indicated for the treatment in 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.
- Irinotecan in combination with cetuximab is indicated for the treatment of patients with metastatic colorectal cancer (KRAS wild-type) with expression of epidermal growth factor receptor (EGFR), who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy.
- Irinotecan in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.
- Irinotecan in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

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 (immediate need for 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 using the three 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 i.e. diarrhoea may occur more than 24 hours after the administration of Irinotecan at any stage before the next administration. 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 liquid containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately.

Appropriate arrangement must be made to ensure that the clinician who administers Irinotecan will also prescribe the anti-diarrhoeal treatment. 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 institution 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 must 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 of drug administration.

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 signs and symptoms such as sweating, abdominal cramping, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated.

These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more frequently with higher irinotecan doses.

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.

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.

Chronic inflammatory bowel disease and/or bowel obstruction: Patients must not be treated with irinotecan until resolution of the bowel obstruction.

Neurologic: Dizziness has been observed and may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Renal function: Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhoea. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Irradiation therapy: Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in treating patients with extensive prior irradiation (e.g. > 25% of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan). Dosing adjustment may apply to this population.

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 immuno-compromised 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: Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's Wort) of CYP3A4 may alter the metabolism of irinotecan and should be avoided.

PREGNANCY AND LACTATION

Women of child-bearing potential/Contraception in males and females: Women of childbearing potential and men have to use effective contraception during and up to 1 month and 3 months after treatment respectively.

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: 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.

Fertility: There are no human data on the effect of irinotecan on fertility. In animals adverse effects of irinotecan on the fertility of offspring has been documented.

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.

Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. 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.

Co-administration of ketoconazole results in a decrease in the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

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.

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.
  - There is no evidence that the safety profile of irinotecan is influenced by cetuximab or vice versa.
  - There is no demonstrated significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38. However, this does not preclude any increase of toxicities due to their pharmacological properties.

MAIN SIDE/ ADVERSE EFFECTS

Infections and infestations
Common: Infection

Blood and lymphatic system disorders
Very common: Neutropenia, anaemia
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

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

For adults only. After dilution Irinotecan hydrochloride solution for infusion should be infused into a peripheral or central vein. Treatment with irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Recommended dosage

- ***In monotherapy (for previously treated patient)***
  The recommended dosage of irinotecan hydrochloride trihydrate is 350 mg/m^2 administered as an intravenous infusion over a 30-90 minute period every three weeks.
- ***In combination therapy (for previously untreated patient)***
  - Irinotecan plus 5FU/FA in every 2 weeks schedule.
    The recommended dose of 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.
  - For the posology and method of administration of concomitant cetuximab, refer to the product information for cetuximab. Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.
  - For the posology and method of administration of bevacizumab, refer to the bevacizumab summary of product characteristics.
  - For the posology and method of administration of capecitabine combination, refer to the appropriate sections in the capecitabine summary of product characteristics.

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 diarrhoea is fully resolved.

At the start of a subsequent infusion of therapy, the dose of Irinotecan hydrochloride, 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 hydrochloride trihydrate 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 cetuximab.

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. Refer also to the recommendations for dose modifications in combination regimen given in the summary of product characteristics for capecitabine.

Patients with impaired hepatic function:
In patients with hepatic dysfunction, the following starting doses are recommended:

Table 1: Starting Doses in Patients with Hepatic Dysfunction: *Single-agent Weekly Regimen*

Serum Total Bilirubin Concentration	Serum ALT/AST Concentration	Starting Dose, mg/m^2
1.5-3.0 x IULN	≤ 5,0 x IULN	60
3.1-5.0 x IULN	≤ 5,0 x IULN	50
<1.5 x IULN	5.1-20.0 x IULN	60
1.5-5.0 x IULN	5.1-20.0 x IULN	40

Table 2: Starting Doses in Patients with Hepatic Dysfunction: *Single-agent Once-Every-3-Week Regimen*

Serum Total Bilirubin Concentration	Starting Dos, mg/m^2
1.5-3.0 x IULN	200
>3.0 x IULN	Not Recommended[a]

[a] The safety and pharmacokinetics of irinotecan given once-every-3-weeks have not been defined in patients with bilirubin >3.0 x institutional upper limit of normal (IULN) and this schedule cannot be recommended in these patients.

Patients with impaired renal function: Studies in this population have not been conducted. Therefore, caution should be undertaken in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis.

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.

Paediatric: The effectiveness of irinotecan in paediatric patients has not been established. Hence, use in children is not recommended.

Directions for reconstitution: As with any other injectable drugs, the irinotecan solution must be prepared aseptically.

If any precipitate is observed in the vials or after dilution, 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 bottle containing either 0.9% sodium chloride solution or 5% glucose solution. The infusion should then be thoroughly mixed by manual rotation.

Shelf-life of reconstituted solution: Irinotecan hydrochloride solution is physically and chemically stable with infusion solutions (0.9% (w/v) sodium chloride solution and 5% (w/v) glucose solution) for up to 28 days when stored in LDPE or PVC containers at 5°C or at 30°C and protected from light. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days.

It is recommended, however, that in order to reduce microbiological hazard, the infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Caution for Usage: For single use only.

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

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

Storage: Store at temperatures not exceeding 30°C. Protect from light and freezing.

Availability: 1 x 2 ml vial (40 mg/ 2ml), 1 x 5 ml vial (100 mg/ 5ml)

Registration Number: DR-XY46926

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Manufactured for: **HOVID Bhd.**
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