Irnocam®

Irinotecan Hydrochloride

FORMS AND PRESENTATION
Irnocam® 40: Solution for injection, 1 vial.
Irnocam® 100: Solution for injection, 1 vial.
COMPOSITION
Each 1 ml contains irinotecan hydrochloride 20mg.
Irnocam® 40: Each vial of 2 ml contains 40 mg Irinotecan hydrochloride, trihydrate (40mg/2ml).
Irnocam® 100: Each vial of 5 ml contains 100 mg Irinotecan hydrochloride, trihydrate (100mg/5ml)
Excipients: Sorbitol, Lactic acid, Sodium hydroxide, Hydrochloric acid.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic Group: other antineoplastic agents
ATC Code: L01XX19
Mechanism of action
Irinotecan is a semisynthetic derivative of Camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of type I DNA topoisomerase. It is metabolized by carboxylesterases in most tissues, thus yielding SN-38, which was found to be more active than Irinotecan on purified type I topoisomerase and more cytotoxic than Irinotecan against several human and murine tumour lines. Inhibition of type I DNA topoisomerase by Irinotecan or SN-38 induces lesions in the single-stranded DNA, and these lesions block DNA replication fork and are responsible for the cytotoxicity. This cytotoxic effect was found to be time dependent and S-phase specific.
In vitro, Irinotecan and SN-38 are not significantly recognized by P-glycoprotein (MDR), and Irinotecan has a cytotoxic activity against cell lines resistant to Doxorubicin and Vinblastine.
In addition to the antitumor effect of Irinotecan, the most relevant pharmacological effect of Irinotecan is the inhibition of acetylcholinesterase.
Pharmacokinetic properties
Absorption
At the end of the infusion, with 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 of pharmacokinetic parameters is generally observed for SN-38.
Distribution
All studies have shown that the exposure to Irinotecan (CPT-11) or SN-38 increases proportionally with the CPT-11 dose administered; their pharmacokinetic behaviours are independent of the number or previous cycles and of the administration schedule.
Binding of plasma proteins to Irinotecan and SN-38 in vitro was approximately 65% and 95%, respectively.
Biotransformation
Mass balance and metabolic studies conducted with the drug labelled with C-14 revealed that more than 50% of the dose of Irinotecan administered intravenously is excreted as unchanged drug, 33% is eliminated by the stool, especially in the bile, and 22 % through the urine.
Two metabolic pathways are responsible for at least 12% of the dose:
• Hydrolysis mediated by carboxylesterases yielding the active metabolite SN-38, which is eliminated primarily by glucuronidation and still excreted by the renal and biliary routes (less than 0.5% of the dose of Irinotecan). It is likely that the SN-38-glucuronide is subsequently hydrolyzed in the intestines.
• Oxidation promoted by the CYP3A enzymes, resulting in the opening of the outer ring of piperidine with formation of the aminopentanoic acid derivative (PCA) and of the primary amine derivative (NPC).
In the plasma, the main entity is unchanged Irinotecan, followed by APC, SN-38-glucuronide and SN-38. Only the SN-38 has a significant cytotoxic effect.
Irinotecan clearance decreases by about 40% in patients with bilirubinemia between 1.5 and 3 times above the upper normal limit. In these patients, a dose of 200 mg/m^2 Irinotecan leads to a plasma exposure to the drug comparable to that observed with 350 mg/m^2 in cancer patients with normal liver parameters.
Elimination
In a phase I study in 60 patients on a dosage regimen with an intravenous infusion of 30 minutes with 100 to 750 mg/m^2, once every three weeks, Irinotecan showed biphasic or triphasic elimination. Mean plasma clearance was 15 l/h/m^2 and volume of distribution at steady state (Vdss) had a value of 157 l/m^2. The mean plasma half-life of the first phase of the three phase model was 12 minutes, that of the second phase was 2.5 hours, and the terminal phase half-life was 14.2 hours. The SN-38 showed biphasic elimination with a mean elimination half-life in the terminal phase of 13.8 hours.
INDICATIONS
Irnocam® is indicated for the treatment of patients with advanced colorectal cancer:
• In combination with 5-fluorouracil (5-FU) and folinic acid (FA) in patients not having undergone previous chemotherapy for advanced cancer.
• As a single agent in patients who have not been successful with an established treatment regimen containing 5-FU.
Irnocam® 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 have not received prior treatment for metastatic disease or after failure of a cytotoxic therapy that included Irinotecan .
Irnocam® in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated as first-line treatment for patients with colon or rectum metastatic carcinoma.
Irnocam® in combination with a Capecitabine with or without Bevacizumab is indicated as first-line treatment for patients with metastatic colorectal carcinoma.
CONTRAINDICATIONS
• Chronic inflammatory bowel disease and/or bowel obstruction.
• History of severe hypersensitivity reactions to Irinotecan hydrochloride or to any of the excipients.
• Lactation.
• Bilirubin > 3 times the upper limit of the normal range.
• Severe bone marrow failure.
• WHO performance status > 2.
• Concomitant use with St John's Wort.
PRECAUTIONS
The use of Irinotecan should be restricted to units specialized in the administration of cytotoxic chemotherapy and 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, in the following cases Irinotecan should be prescribed only after consideration of the expected benefits in relation to the possible therapeutic risks:
• in patients with a risk factor, particularly those with a WHO performance status = 2.
• in the few rare cases where it is considered likely that the patients will not be aware of the recommendations for the control of adverse effects (immediate need for prolonged anti-diarrhoeal treatment combined with a high fluid intake at the onset of late diarrhoea). Careful supervision in hospital is recommended for these patients.
When Irinotecan is used in monotherapy, it is usually prescribed using the three week dosage schedule. However, a weekly-dosage schedule may be considered in patients who 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 five days after the infusion of Irinotecan. Patients should quickly inform their physician of the occurrence of diarrhoea and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who have had previous abdominal/pelvic radiotherapy, those with baseline hyperleukocytosis and those with performance status ≥ 2 and women. If not appropriately treated, the 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 adequate anti-diarrhoeal therapy must be initiated immediately. Appropriate arrangements 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 the diarrhoea can be treated as soon as it occurs. In addition, they must inform their physician, or the institution where Irinotecan was administered, when/if diarrhoea has occurred.
The anti-diarrhoeal treatment currently recommended consists of high doses of Loperamide (4 mg at the start, followed by 2 mg every 2 hours). This treatment should be continued for 12 hours after the last liquid stool and must not be modified. In no event shall Loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, and the treatment should last at least 12 hours.
In addition to the anti-diarrhoeal treatment, a broad spectrum prophylactic antibiotic should be administered when the diarrhoea is associated with severe neutropenia (neutrophil count <500 cells/mm^3).
In addition to the antibiotic treatment, hospitalization is recommended for the control of diarrhoea in the following cases:
• Diarrhoea associated with fever,
• Severe diarrhoea (requiring intravenous hydration),
• Diarrhoea persisting beyond 48 hours after initiation of treatment with high doses of Loperamide.
Loperamide should not be administered prophylactically, even in patients who have had delayed diarrhoea during previous administrations of the medicinal product.
If the patient has experienced severe diarrhoea, a dose reduction is recommended in subsequent cycles.
Haematology
During Irinotecan treatment, weekly monitoring of complete blood cell counts is recommended. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38°C and neutrophil count ≤1000 cells/mm^3) should be urgently treated in hospital with broad-spectrum intravenous antibiotics.
A dose reduction for subsequent administration is recommended in patients who have experienced severe haematological events. There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In these patients, a complete blood cell count should be taken.
Patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity.
The metabolite, SN-38 is detoxified by UGT1A1 (Uridine diphosphate glucuronosyl transferase 1A1) to SN-38 glucuronide. Individuals with a congenital deficiency of UGT1A1 (Crigler-Najjar syndrome type 1 and type 2 or individuals who are homozygous for the UGT1A1*28 allele [Gilbert's syndrome]) are at increased risk of toxicity from Irinotecan. A reduced initial dose should be considered for these patients.
Impaired hepatic function
Liver function tests must be performed at baseline and prior to each cycle of drug administration.
Weekly monitoring of complete blood counts should be conducted in patients with bilirubin values ranging from 1.5 to 3 times the ULN due to decreased clearance of Irinotecan and thus increased risk of haematotoxicity in this population. For patients with a bilirubin > 3 times the ULN.
Nausea and vomiting
Prophylactic treatment with an antiemetic before each administration of Irinotecan is recommended. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalized for treatment as soon as possible.
Acute cholinergic syndrome
If acute cholinergic syndrome appears (defined as early diarrhoea and certain other signs and symptoms such as sweating, abdominal cramps, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated.
Caution should be exercised in the treatment of patients with asthma. If the patient experiences an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent administration of Irinotecan.
Respiratory diseases
During therapy with Irinotecan, conditions with pulmonary infiltrates indicating the occurrence of interstitial lung disease have been uncommon. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicinal products, radiotherapy and cell growth factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during therapy with Irinotecan.
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 minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)
Immunosuppressant 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.
Elderly
Due to a greater frequency of decreased biological functions, e.g., of the hepatic function in elderly patients, dose adjustment of Irinotecan in this population should require more caution.
Chronic inflammatory bowel disease and/or bowel obstruction
Patients must not be treated with Irinotecan until the bowel obstruction is resolved.
Patients with impaired renal function
Studies have not been conducted in this patient group.
Others
- Since the medicine contains sorbitol, it is not suitable for patients with hereditary fructose intolerance. 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 with sepsis.
- Contraceptive measures must be taken during and for at least three months after the 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 Cytochrome P450 3A4 (CYP3A4) may alter the metabolism of Irinotecan and should be avoided.
Effects on ability to drive and use machines
Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of Irnocam® and advised not to drive or operate machinery if these symptoms occur.
FERTILITY, PREGNANCY AND LACTATION
Pregnancy
There is no information on the use of Irinotecan in pregnant women. Irinotecan has been

shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan should not be used during pregnancy.

Fertility

Women of fertile age receiving Irinotecan should inform the treating physician immediately should pregnancy occur. Contraceptive measures must be taken by women of fertile age and also by male patients during and for at least three months after treatment. In animals adverse effects of irinotecan on the fertility of offspring has been documented.

Breast-feeding

14C-Irinotecan has been detected in the milk of lactating rats. It is not known whether Irinotecan is excreted in human milk. Breastfeeding must be discontinued during treatment with Irinotecan due to the potential for adverse effects in breast-feeding infants.

DRUG INTERACTIONS

Interaction between Irinotecan and neuromuscular blocking agents cannot be ruled out. Irinotecan is an anticholinesterase, and medicines which have anticholinesterase activity may prolong the neuromuscular blocking effects of Suxamethonium and antagonise the neuromuscular blockade of non-depolarising agents.

Several studies have shown that concomitant administration of cytochrome P450 3A (CYP3A) inducers as anticonvulsant drugs (e.g., Carbamazepine, Phenobarbital or Phenytoin) leads to a reduced exposure to Irinotecan, SN-38 and SN-38 glucuronide, and to reduced pharmacodynamic effects.

The effects of such anticonvulsant drugs were reflected by a decrease in the AUC of SN-38 and SN-38G by 50% or more. In addition, the induction of CYP3A enzymes enhances both glucuronidation and biliary excretion, and these effects may play an important role in reducing exposure to Irinotecan and its metabolites.

A study has shown that the co-administration of Ketoconazole resulted in a decrease in the AUC of the principal oxidative metabolite 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 concomitantly taking drugs known to inhibit (e.g. Ketoconazole) or induce (e.g. Carbamazepine, Phenobarbital, Phenytoin, Rifampicin) drug metabolism by CYP3A4.

Concomitant administration of Irinotecan with an inhibitor/inducer of this metabolic pathway can alter the metabolism of Irinotecan and should be avoided.

Coadministration of 5-FU/FA in the combination regimen does not change the pharmacokinetics of Irinotecan.

There is no evidence that the safety profile of Irinotecan is influenced by Cetuximab or vice versa.

Concentrations of SN-38 were on average 33 % higher in patients receiving Irinotecan/5-FU/FA in combination with Bevacizumab, compared with those receiving Irinotecan/5-FU/FA alone. Due to high inter-patient variability and to limited sampling size, it is uncertain whether the increase in SN-38 levels observed was due to Bevacizumab. There was a small increase in diarrhoea and leukocytopenia adverse events. More dose reductions of Irinotecan were reported in patients receiving Irinotecan/5-FU/FA in combination with Bevacizumab.

Patients who develop severe diarrhoea, leukocytopenia or neutropenia with a combination of Bevacizumab and Irinotecan should have Irinotecan dose modifications.

Atazanavir sulphate: 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 cytotoxic:

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.

Concomitant use to take into consideration

- Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation.

ADVERSE EFFECTS

Undesirable effects are presented in order of decreasing seriousness within each frequency class.

Very common: ≥ 1/10

• Neutropenia (reversible and not cumulative), Anaemia, Thrombocytopenia (in case of combination therapy), Infectious episodes (with monotherapy).
• Severe delayed diarrhea, Severe nausea and vomiting (with monotherapy).
• Alopecia (reversible).
• Fever in the absence of infection and without concomitant severe neutropenia (with monotherapy).
• During combination therapy, transient serum levels (grade 1 and 2) of either ALT, AST, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis.

Common: ≥ 1/100 to < 1/10

• Febrile neutropenia, Infectious episodes (with combination therapy), Infectious episodes associated with severe neutropenia resulting in death in 3 cases, Thrombocytopenia (with monotherapy).
• Severe nausea and vomiting (with combination therapy), Episodes of dehydration (associated with diarrhoea and/or vomiting), Constipation related to Irinotecan and/or Loperamide.
• Severe transient acute cholinergic syndrome (the main symptoms were early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, miosis, lacrimation and increased salivation), Asthenia, Fever in the absence of infection and without concomitant severe neutropenia with combination therapy.
• In monotherapy, transient and mild to moderate increases in serum levels of either ALT, AST, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis, Transient, mild to moderate increases in serum levels of creatinine, During combination therapy, transient grade 3 serum levels of bilirubin.

Uncommon: ≥ 1/1,000 to < 1/100

• Renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who had had sepsis.
• Moderate allergy reactions.
• Interstitial pulmonary disease presenting as pulmonary infiltrates, Early effects such as dyspnoea.
• Pseudomembranous colitis (one case has been documented bacteriologically: Clostridium difficile), Renal insufficiency, hypotension or cardio-circulatory failure as a consequence of dehydration associated with diarrhoea and/or vomiting, Intestinal obstruction, paralytic ileus, or gastrointestinal haemorrhage.
• Moderate skin reaction.
• Infusion site reactions.

Rare: ≥ 1/10,000 to < 1/1,000

• Anaphylactic/ Anaphylactoid reactions.
• Hypertension during or following the infusion.
• Colitis, including typhlitis, ischaemic and ulcerative colitis, Intestinal perforation, Other mild effects include anorexia, abdominal pain and mucositis, Symptomatic or asymptomatic pancreatitis.
• Early effects such as muscular contraction or cramps and paraesthesia.
• Hypokalemia, Hyponatremia.

Very rare: < 1/10,000

• One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.
• Tumour lysis syndrome.
• Transient speech disorder.
• Increases of amylase and/or lipase.

Unknown (cannot be calculated from the available data)

• Fungal infections, Viral infections.

DOSAGE AND ADMINISTRATION

For adults only. The diluted infusion solution of Irinotecan should be infused into a peripheral or central vein.

Recommended posology

Irinotecan doses mentioned in this summary of product characteristics refer to mg of Irinotecan hydrochloride.

In monotherapy (in patients previously treated)

The recommended dose of Irinotecan is 350 mg/m^2 administered in the form of intravenous infusion over a period of 30 to 90 minutes, every three weeks.

In combination therapy (in patients not previously treated)

The safety and effectiveness of Irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) were evaluated as per the following schedule.

• Irinotecan hydrochloride plus 5-FU/FA, every 2 weeks.

The recommended dose of Irinotecan is 180 mg/m^2 administered once every 2 weeks, in the form of intravenous infusion, over a period of 30 to 90 minutes, followed by an infusion of FA and 5-FU.

For the dosage and mode of administration of concomitant Cetuximab, see the prescribing information for this medicinal product. Irinotecan should not be given before an hour after the end of the infusion of Cetuximab.

For the dosage and mode of administration of Bevacizumab, see the respective Summary of Product Characteristics.

For the dosage and mode of administration of Capecitabine used in combination see the appropriate sections of the Summary of Product Characteristics.

Dose adjustments

Irinotecan should be administered after an appropriate recovery from all adverse events of grade 0 or 1 according to the National Cancer Institute - Common Toxicity Criteria (NCI-CTC) scale and when treatment–related diarrhoea is fully resolved.

At the beginning of subsequent administration of infusion therapy, the dose of Irinotecan and 5-FU, where applicable, should be reduced according to the worst degree of adverse effects observed over the previous administration. The treatment should be delayed for 1-2 weeks to allow recovery from adverse effects associated with treatment.

In the presence of the following adverse effects, the dose should be reduced by 15 to 20% in relation to Irinotecan and/or 5-FU, where applicable:

• haematological toxicity (grade 4 neutropenia, febrile neutropenia [grade 3-4 neutropenia and grade 2-4 fever], thrombocytopenia and leucopoenia [grade 4]),
• non- haematological toxicity (grade 3-4).

Recommendations for Cetuximab dose modification should be followed when administered in combination with Irinotecan, according to the prescribing information for that medicinal product.

Refer to the Summary of Product Characteristics of Bevacizumab for dose modifications of this medicinal product when administered in combination with Irinotecan/5-FU/FA.

If used in combination with Capecitabine on patients aged 65 years or more, it is recommended to make an initial dose reduction of Capecitabine to 800 mg/m^2 twice daily, according to the Summary of Product Characteristics of Capecitabine. See also the recommendations for dose changes in the combination regimen indicated in the Summary of Product Characteristics of Capecitabine.

Duration of the treatment

The treatment with Irinotecan should be continued until there is objective disease progression or unacceptable toxicity

Method of administration

Precautions to be taken before handling or administering the medicinal product

As with other antineoplastic agents, Irnocam® must be prepared and handled with caution. The use of glasses, mask and gloves is required.

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

Preparation for the intravenous infusion administration

As with any other injectable medicinal products, the Irnocam® 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 Irnocam® 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.

OVERDOSAGE

There have been reports of overdose, with 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 treatment should be initiated to prevent dehydration due to diarrhoea and to treat any infectious complications.

STORAGE CONDITIONS

Store below 30°C.

Store in the original package in order to protect from light.

It is recommended, 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 °C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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