1.7 Product Information

1.7.1 Summary of Product Characteristics (SmPC) (Enclosed)

Summary Of Product Characteristics

IRINOTECAN INJECTION 40mg/2ml & 100mg/5ml

1) Name of The Medicinal Product:

Irinotecan Injection 40mg/2ml & 100mg/5ml

2) Qualitative & Quantitative Composition:

Each ml contains,

Irinotecan Hydrochloride Trihydrate USP….20mg
Water for Injection……Q.S

3) Pharmaceutical Form:

A light yellow coloured clear solution

Clinical Particulars:

4.1) Therapeutic Indications:

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.

Irinotecan Hydrochloride in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing RAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy.

Irinotecan Hydrochloride 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 Hydrochloride in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

4.2) Posology & Method of Administration:

Posology

For adults only

Irinotecan Hydrochloride solution for infusion should be infused into a peripheral or central vein.

Recommended Dosage

<u>In Monotherapy (for Previously Treated Patient)</u>

The recommended dosage of Irinotecan Hydrochloride is 350 mg/m^2 administered as an intravenous infusion over a 30- to 90- minute period every three weeks.

<u>In Combination Therapy (for Previously Untreated Patient)</u>

Safety and efficacy of Irinotecan Hydrochloride in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule.

- Irinotecan Hydrochloride plus 5FU/FA in Every 2 Weeks Schedule

The recommended dose of Irinotecan Hydrochloride 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 this medicinal product.

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

Treatment Duration

Treatment with Irinotecan Hydrochloride 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 Hydrochloride. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased and therefore the risk of hepatotoxicity 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 ULN, the recommended dosage of Irinotecan Hydrochloride is 350 mg/m^2.
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan Hydrochloride is 200 mg/m^2.
- Patients with bilirubin beyond to 3 times the ULN should not be treated with Irinotecan Hydrochloride. No data are available in patients with hepatic impairment treated by Irinotecan Hydrochloride in combination.

Patients with Impaired Renal Function

Irinotecan Hydrochloride 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.

Paediatric Population

The safety and efficacy of Irinotecan Hydrochloride in children have not yet been established. No data are available.

Method of Administration

Precautions to be taken before handling or administering the medicinal product.

Preparation for the infusion solution:

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe. Irinotecan Hydrochloride Injection 20mg/ml is intended for single use only and any unused portion should be discarded. Irinotecan Hydrochloride Injection should be diluted in 5% Dextrose Injection or 0.9% Sodium Chloride Injection, to a final concentration range of 0.12 to 2.8 mg/ml. in most clinical trials, Irinotecan Hydrochloride Injection was administered in 250mL to 500 ml of 5% Dextrose Injection. The solution is physically and chemically stable for 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, and stored at a refrigerated temperatures (approximately 2° to 8°C, 36°to 46°F) and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, is not recommended due to low and specific incidence of visible particulates. Freezing Irinotecan Hydrochloride Injection and admixtures of Irinotecan Hydrochloride Injection may result in precipitation of the drugs and should be avoided. The Irinotecan Hydrochloride Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of the possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of the admixtures prepared with the 5% Dextrose Injection, or Sodium Chloride Injection, the solution should be used within 6 hours if kept at room temperature. If reconstitution and dilutions are performed under strict aseptic conditions (e.g. on Laminar Air Flow Bench) Irinotecan Hydrochloride Injection solution be used (Infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36°to 46°F). Other drugs should not be added to the infusion solution. Parental dug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution or container permit.

4.3) Contraindications:

- Chronic inflammatory bowel disease and/or bowel obstruction.
- Hypersensitivity to the active substance(s) or to any of the excipients listed.
- Breast-feeding.
- 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.
- Live attenuated vaccines.

For additional contraindications of cetuximab or bevacizumab or capecitabine, refer to the product information for these medicinal products.

4.4) Special Warnings & Precautions for Use:

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 antidiarrheal 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 Hydrochloride 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. 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 hyperleukocytosis, 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 antidiarrheal therapy must be initiated immediately. This

antidiarrheal treatment will be prescribed by the department where Irinotecan Hydrochloride has been administered. After discharge from the hospital, the patients should obtain the prescribed medicinal products 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 when/if diarrhoea 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 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

In clinical studies, the frequency of NCI CTC Grade 3 and 4 neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more have also had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL.

Weekly monitoring of complete blood cell counts is recommended during Irinotecan Hydrochloride 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 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 the ULN, due to decrease of the clearance of irinotecan and thus increasing the risk of hepatotoxicity in this population. For patients with a bilirubin > 3 times the ULN.

Nausea and Vomiting

A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan Hydrochloride. 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 Hydrochloride.

Respiratory Disorders

Interstitial lung disease presenting as lung infiltration is uncommon during irinotecan therapy. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumo-toxic medicinal products, 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 Hydrochloride should be cautious in this population.

Chronic Inflammatory Bowel Disease and/or Bowel Obstruction

Patients must not be treated with Irinotecan Hydrochloride until resolution of the bowel obstruction.

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 minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia).

Vascular Disorders

Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, and arterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Others

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

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.

Contraception in Women of Childbearing Potential/Men:

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan.

Breast-feeding

Due to the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of Irinotecan Hydrochloride therapy.

This medicine contains sorbitol. Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with HFI. Medicines (containing fructose) given intravenously may have life-threatening effects in individuals with HFI and should not be administered in this population unless there is an overwhelming clinical need, and no alternatives are available.

A detailed history about HFI symptoms has to be taken of each patient prior to being given this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per dose, essentially 'sodium-free'.

4.5) Interaction with Other Medicinal Products & Other Forms of Interaction:

Concomitant Use Contraindicated

Saint John's Wort: Decrease in the active metabolite of irinotecan, SN-38, plasma levels. In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m^2 was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations were observed. As a result, St. John's Wort should not be administered with irinotecan.

Live Attenuated Vaccines (e.g., Yellow Fever Vaccine): Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant Use Not Recommended

Concurrent administration of irinotecan with a strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided:

Strong CYP3A4 and/or UGT1A1 Inducing Medicinal Products: (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin or apalutamide):

Risk of reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. Several studies have shown that concomitant administration of CYP3A4-inducing anticonvulsant medicinal products leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant medicinal products were reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of CYP3A4 enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites. Additionally, with phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products.

Strong CYP3A4 Inhibitors: (e.g., ketoconazole, itraconazole, voriconazole, posaconazole, protease inhibitors, clarithromycin, erythromycin, telithromycin):

A study has shown that the co-administration of ketoconazole resulted 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.

UGT1A1 Inhibitors: (e.g., atazanavir, ketoconazole, regorafenib)

Risk to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration if the combination is unavoidable.

Other CYP3A4 Inhibitors: (e.g., crizotinib, idelalisib)

Risk of increase in irinotecan toxicity, due to a decrease in irinotecan metabolism by crizotinib or idelalisib.

Caution for Use

Vitamin K Antagonists: Increased risk of haemorrhage and thrombotic events in tumoral diseases. If vitamin K antagonist are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Concomitant Use to Take into Consideration

Immunodepressant Agents: (e.g., cyclosporine, tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Neuromuscular Blocking Agents: Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan Hydrochloride has anticholinesterase activity, medicinal products with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medicinal products may be antagonised.

Other Combinations

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

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no 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.

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

Antineoplastic Agents (Including Flucytosine as a Prodrug for 5-fluorouracil): Adverse effects of irinotecan, such as myelosuppression, may be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

4.6) Fertility, Pregnancy & Lactation:

Contraception

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan.

Pregnancy

There are limited 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 Hydrochloride should not be used during pregnancy unless clearly necessary.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

Breast-feeding

The available data are limited but suggested that irinotecan and its metabolite are excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of Irinotecan Hydrochloride therapy.

Fertility

There are no human data on the effect of irinotecan on fertility. In animal's adverse effects of irinotecan on the fertility of offspring has been documented.

Prior to starting to take Irinotecan Hydrochloride consider advising patients on the preservation of gametes.

4.7) Effects on Ability to Drive & Use Machines:

Irinotecan Hydrochloride has moderate influence on the 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 Irinotecan Hydrochloride and advised not to drive or operate machinery if these symptoms occur.

4.8) Undesirable Effects:

Monotherapy

The following adverse reactions considered to be possibly or probably related to the administration of irinotecan hydrochloride have been reported from 765 patients at the recommended dose of 350 mg/m^2 in monotherapy. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Adverse Reactions Reported with Irinotecan hydrochloride in Monotherapy (350 mg/m^2 every 3 weeks schedule)

System Organ Class	Frequency	Adverse Effect
Infections & Infestations	Common	Infection

Blood & Lymphatic System Disorders	Very Common	Neutropenia
	Very Common	Anemia
	Common	Thrombocytopenia
	Common	Febrile Neutropenia
Metabolism & Nutrition Disorders	Very Common	Decreased Appetite
Nervous System Disorders	Very Common	Cholinergic Syndrome
Gastrointestinal Disorders	Very Common	Diarrhea
	Very Common	Vomiting
	Very Common	Nausea
	Very Common	Abdominal Pain
	Common	Constipation
Skin And Subcutaneous Tissue Disorders	Very Common	Alopecia (Reversible)
General Disorders & Administration Site Conditions	Very Common	Mucosal Inflammation
	Very Common	Pyrexia
	Very Common	Asthenia
Investigations	Common	Blood Creatinine Increased
	Common	Transaminases (ALT And AST) Increased
	Common	Blood Bilirubin Increased
	Common	Blood Alkaline Phosphatase Increased

Combination therapy

Adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan 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, myocardial ischaemia/infarction; Common, Grade 3 and Grade 4 adverse drug reactions: febrile neutropenia.

Adverse Reactions Reported with Irinotecan hydrochloride in Combination Therapy (180 mg/m^2 Every 2 Weeks Schedule)		
System	**Frequency**	**Adverse Effect**
Infections & Infestations	Common	Infection
Blood & Lymphatic System Disorders	Very Common	Thrombocytopenia
	Very Common	Neutropenia
	Very Common	Anemia
	Common	Febrile Neutropenia

Metabolism & Nutrition Disorders	Very Common	Decreased Appetite
Nervous System Disorders	Very Common	Cholinergic Syndrome
Gastrointestinal Disorders	Very Common	Diarrhea
	Very Common	Vomiting
	Very Common	Nausea
	Common	Abdominal Pain
	Common	Constipation
Skin & Subcutaneous Tissue Disorders	Very Common	Alopecia (Reversible)
General Disorders & Administration Site Conditions	Very Common	Mucosal Inflammation
	Very Common	Asthenia
	Common	Pyrexia
Investigations	Very Common	Transaminases (ALT And AST) Increased
	Very Common	Blood Bilirubin Increased
	Very Common	Blood Alkaline Phosphatase Increased

Post-marketing surveillance

Frequencies from post-marketing surveillance are not known (cannot be estimated from available data).

System	Adverse Effects
Infections & Infestations	Pseudomembranous Colitis One of Which Has Been Documented Bacteriologically (*Clostridium Difficile*) Sepsis Fungal Infections* & Viral Infections†
Blood & Lymphatic System Disorders	Thrombocytopenia With Antiplatelet Antibodies
Immune System Disorders	Hypersensitivity Anaphylactic Reaction
Metabolism & Nutrition Disorders	Dehydration (Due to Diarrhea & Vomiting) Hypovolemia
Nervous System Disorders	Speech Disorder Generally Transient in Nature, In Some Cases, The Event Was Attributed to The Cholinergic Syndrome Observed During or Shortly After Infusion of Irinotecan Paranesthesia Muscular Contractions Involuntary
Cardiac Disorders	Hypertension (During or After Infusion) Cardio Circulatory Failure‡
Vascular Disorders	Hypotension‡
Respiratory, Thoracic & Mediastinal	Interstitial Lung Disease Presenting as Lung Infiltration Is Uncommon

Disorders	During Irinotecan Therapy; Early Effects Such as Dyspnea Have Been Reported. Dyspnea & Hiccups
Gastrointestinal Disorders	Intestinal Obstruction Ileus: Cases of Ileus Without Preceding Colitis Have Also Been Reported Megacolon Gastrointestinal Hemorrhage Colitis: In Some Cases, Colitis Was Complicated by Ulceration, Bleeding, Ileus, or Infection. Typhlitis Colitis Ischemic & Colitis Ulcerative Symptomatic or Asymptomatic Pancreatic Enzymes Increased Intestinal Perforation
Hepatobiliary Disorders	Steatohepatitis & Hepatic Steatosis
Skin & Subcutaneous Tissue Disorders	Skin Reaction
Musculoskeletal & Connective Tissue Disorders	Cramps

*e.g., Pneumocystis Jiroveci pneumonia, bronchopulmonary aspergillosis, systemic candida.
†e.g., Herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis.
‡Infrequent cases of renal insufficiency, hypotension or cardio circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

4.9) Overdose:

Symptoms

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.

Management

There is no known antidote for Irinotecan Hydrochloride. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5) Pharmacological Properties:

5.1) Pharmacodynamic Properties:

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 (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinomas) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemias).

Beside the antitumor activity of Irinotecan Hydrochloride, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

5.2) Pharmacokinetic Properties:

Absorption

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.

Distribution

The phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m^2 every three weeks, the volume of distribution at steady state (Vss): 157 L/m^2.

In vitro, plasma protein binding for irinotecan and SN-38 was approximately 65% and 95%, respectively.

Biotransformation

Mass balance and metabolism studies with 14C-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 glucuronide 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.

Elimination

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m^2 every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/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. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours.

Irinotecan clearance is decreased by about 40% in patients with bilirubinaemia 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.

Linearity/Non-Linearity

A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three-compartment model were like those observed in phase I studies. 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.

Pharmacokinetic/Pharmacodynamic Relationship(s)

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

5.3) Preclinical Safety Data

Irinotecan and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice.

However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m^2 (which is less than half the human recommended dose), no treatment related tumours were reported 91 weeks after the end of treatment.

Single and repeated dose toxicity studies with Irinotecan Hydrochloride have been carried out in mice, rats, and dogs. The main toxic effects were seen in the haematopoietic and lymphatic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Alopecia was also observed in the dog.

The severity of these effects was dose-related and reversible.

Reproduction

Irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born to treated animals with external abnormalities showed a decrease in fertility. This was not seen in morphologically normal pups. In pregnant rats there was a decrease in placental weight and in the offspring a decrease in fetal viability and increase in behavioural abnormalities

6) Pharmaceutical Particulars:

6.1) List of Excipients:

Sorbitol IP/BP/USP

Latic Acid IP/BP/USP

Latic Acid IP/BP/USP

Sodium Hydroxide IP/BP/USP

Water for Injection IP/BP/USP

6.2) Incompatibilities:

None known.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3) Shelf Life:

24 Months

6.4) Special Precautions for Storage:

Store below 25°C. Protect from light. Do not freeze. It is recommended that unopened vial should remain in the carton until the time of use.

6.5) Nature & Contents of Container:

Irinotecan for Injection is available in amber single-use vial containing Irinotecan Hydrochloride 40mg/100mg.

6.6) Special Precautions for Disposal & Other Handling:

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

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

Disposal:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7) Marketing Authorisation Holder:

Naprod Lifesciences Pvt. Ltd

8) Marketing Authorisation Number(s):

03982/3320/NMR/2017

9) Date of First Authorisation/Renewal of Authorization:

01/08/2018

10) Date of Revision of The Text

N/A