Package Insert

IRICAN 40 & 100

Irinotecan Hydrochloride Trihydrate Injection

20 mg/ml, 2 ml and 5 ml

Name and strength of active ingredient

Each ml contains:

Irinotecan Hydrochloride Trihydrate	20 mg
Water for Injections Ph. Eur.	Q.S.

Product Description

A pale yellow clear solution. When examined under suitable conditions of visibility it should be practically free from particles.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Other Antineoplastic agents

Mechanism of action

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 tumor cell lines. The inhibition of DNA topoisomerase I by Irinotecan or SN38 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 recognized 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 tumor 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 leukaemia's).
Beside the antitumour activity of Irinotecan, the most relevant pharmacological effect is the inhibition of acetylcholinesterase.

Pharmacokinetic properties

In a phase I study in 60 patients with a dosage regimen of a 30 minute intravenous infusion of 100 to 750 mg/m² every three weeks, Irinotecan showed a biphasic or tri phasic elimination profile. The mean plasma clearance was 15 L/h/m² and the volume of distribution at steady state (Vss): 157 L/m². The mean plasma half-life of the first phase of the tri phasic 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. At the end of the infusion, at the recommended dose of 350 mg/m², 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 inter individual variability in pharmacokinetic parameters is generally observed for SN-38.

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 similar to those observed in phase I studies. All studies have shown that Irinotecan (CPT11) and SN-38 exposure increase proportionally with CPT11 administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.

In vitro, plasma protein binding for Irinotecan and SN-38 was approximately 65 % and 95 % respectively.
Mass balance and metabolism studies with 14 C-labeled drug have shown that more than 50% of an intravenously administered dose of Irinotecan is excreted as unchanged drug, with 33% in the faeces mainly via the bile and 22% in urine.

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

Unchanged Irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN38. Only SN-38 has significant cytotoxic activity.
Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the ULN. In these patients a 200 mg/m² Irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters.

Indication/Usage

Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml 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 Trihydrate Injection 20 mg/ml in combination with Cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR) expressing, KRAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of Irinotecan including cytotoxic therapy.

Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml 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 Trihydrate Injection 20 mg/ml in combination with Capecitabine with or without Bevacizumab is indicated for first – line treatment of patients with metastatic colorectal carcinoma.

Posology and method of administration

Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml is indicated in adults. After dilution Irinotecan Hydrochloride Trihydrate Injection should be infused into a peripheral or central vein.

Recommended dosage

In monotherapy (for previously treated patient)

The recommended dosage of Irinotecan Hydrochloride Trihydrate Injection is 350 mg/m² administered as an intravenous infusion over a 30 to 90 minute period every three weeks.

In combination therapy (for previously untreated patient)

Safety and efficacy of Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule:

Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml plus 5FU/FA in every 2 weeks schedule. The recommended dose of Irinotecan Hydrochloride Trihydrate Injection is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

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 product of characteristics.
For the posology and method of administration of Capecitabine combination, please refer to the appropriate sections in the Capecitabine summary of product characteristics.

Dosage adjustments

Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml 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 Trihydrate Injection, 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 Injection 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.
Refer to the Bevacizumab summary product of characteristics for dose modifications of Bevacizumab when administered in combination with Irinotecan Hydrochloride Trihydrate Injection /5FU/FA.
In combination with Capecitabine for patients 65 years of age or more, a reduction of the starting dose of Capecitabine to 800 mg/m2 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 Trihydrate Injection 20 mg/ml 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 Trihydrate Injection. In these patients with hyper bilirubinemia and prothrombin time greater than 50%, the clearance of Irinotecan is decreased and therefore the risk of hematotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of Irinotecan Hydrochloride Trihydrate Injection is 350 mg/m²,
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan Hydrochloride Trihydrate Injection is 200 mg/m²,
- Patients with bilirubin beyond 3 times the ULN should not be treated with Irinotecan Hydrochloride Trihydrate Injection.

No data are available in patients with hepatic impairment treated by Irinotecan Hydrochloride Trihydrate Injection in combination.

Patients with Impaired Renal Function

Irinotecan Hydrochloride Trihydrate Injection 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 undergo more intense surveillance.

Paediatric population

Irinotecan should not be used in children.

Method of administration

Precautions should be taken before handling or administering the medicinal product.
Irinotecan Hydrochloride Trihydrate Injection is cytotoxic. For information regarding dilution, and special precautions for disposal and other handling see under the section Special precautions for disposal and other handling.
Irinotecan concentrate for solution for infusion should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction.
- History of severe hypersensitivity reactions to Irinotecan hydrochloride trihydrate or to one of the excipients of Irinotecan Hydrochloride Trihydrate Injection 20 mg/ml.
- Lactation
- Bilirubin > 3 times the ULN.
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant use with St John's Wort.

For additional contraindications of Cetuximab or Bevacizumab or Capecitabine, refer to the product information for these medicinal products.

Special warnings and precautions for use

The use of Irinotecan Hydrochloride Trihydrate Injection should be confined to units specialized in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Given the nature and incidence of adverse events, Irinotecan Hydrochloride Trihydrate Injection 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 rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When Irinotecan Hydrochloride Trihydrate Injection is used in monotherapy, it is usually prescribed with the every 3 week dosage schedule. However, the weekly dosage schedule may be considered in patients who may need a closer follow up or who are at particular risk of severe neutropenia.

Delayed diarrhea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of Irinotecan Hydrochloride Trihydrate Injection and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan Hydrochloride Trihydrate Injection. 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 hyper leucocytosis, those with performance status ≥ 2 and women. If not properly treated, diarrhoea can be life threatening, especially if the patient is concomitantly neutropaenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate anti diarrhoeal therapy must be initiated immediately. This anti diarrhoeal treatment will be prescribed by the department where Irinotecan Hydrochloride Trihydrate Injection has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering Irinotecan Hydrochloride Trihydrate Injection when/if diarrhoea is occurring.
The currently recommended anti diarrhoeal treatment consists of high doses of Loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should Loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the anti diarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm³).

In addition to the antibiotic treatment, hospitalization 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 with 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 count is recommended during treatment with Irinotecan Hydrochloride Trihydrate Injection. 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 broadspectrum intravenous antibiotics.

In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration. There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In patients with severe diarrhoea, complete blood cell counts should be performed.

Liver impairment

Liver function tests should be performed at baseline and before each cycle. Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to decrease of the clearance of Irinotecan and thus increasing the risk of hematotoxicity in this population. For patients with a bilirubin > 3 times ULN.

Nausea and vomiting

A prophylactic treatment with antiemetic is recommended before each treatment with Irinotecan Hydrochloride Trihydrate Injection. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalized 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 (0.25mg 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 Trihydrate Injection.

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 Hydrochloride Trihydrate Injection should be cautious in this population.
Chronic inflammatory bowel disease and/or Patients with bowel obstruction Patients must not be treated with Irinotecan Hydrochloride Trihydrate Injection 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 tumor 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 treatment with Irinotecan . Dosing adjustment may apply to this population.

Cardiac Disorders

Myocardial ischemic 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.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients, immune 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

Since Irinotecan Hydrochloride Trihydrate Injection contains Sorbitol, it is unsuitable in hereditary fructose intolerance. Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with 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.
This medicinal product contains less than 1 mmol sodium per dose, i.e. essentially 'sodium-free'.

Interaction with other medicinal products and other forms of interaction

Interaction between Irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan Hydrochloride Trihydrate Injection 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 antagonized.

Several studies have shown that 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 were 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.

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.

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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.

In a small pharmacokinetic study (n=5), in which Irinotecan 350 mg/m2 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 was observed.
St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with Irinotecan.

Co administration of 5 fluorouracil/ folinic acid in the combination regimen does not change the pharmacokinetics of Irinotecan.
Co administration 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 tumoural diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency in the monitoring of INR (International Normalized 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 (e.g. infections). This risk is increased in subjects who are already immune suppressed 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.
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.

Fertility, pregnancy and lactation

Women of childbearing 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 information on 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, Irinotecan should not be used during pregnancy unless clearly necessary.

Lactation

In lactating rats, 14C-Irinotecan was detected in milk. It is not known whether Irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breastfeeding 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.

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 Irinotecan Hydrochloride Trihydrate Injection, and advised not to drive or operate machinery if these symptoms occur.

Undesirable effects

Adverse reaction data have been extensively collected from studies in metastatic colorectal cancer; the frequencies are presented below.

The most common (≥ 1/10), dose limiting adverse reactions of Irinotecan are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.

Neutropenia is a dose limiting toxic effect. Neutropenia was reversible and not cumulative; The median day to nadir was 8 days whether in monotherapy or in combination therapy.
Very commonly severe transient acute cholinergic syndrome was observed. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, sweating, myosis and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration.

Monotherapy

The following adverse reactions considered to be possibly or probably related to the administration of Irinotecan have been reported from 765 patients at the recommended dose of 350 mg/m² 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), not known (cannot be estimated from the available data).

Infections and infestations	
Common:	Infection
Not known:	Pseudomembranous colitis, sepsis
Blood and lymphatic system disorders	
Very common:	Neutropenia, anaemia
Common:	Thrombocytopenia, febrile neutropenia
Not known:	Peripheral thrombocytopenia with antiplatelet antibodies.
Immune system disorders	
Not known:	Hypersensitivity reaction, anaphylactic reaction
Metabolism and nutrition disorders	
Very common:	Decreased appetite
Not known:	Dehydration (due to diarrhoea and vomiting), hypovolaemia, hypomagnesaemia, tumour lysis syndrome, hypokalaemia, hyponatraemia
Psychiatric disorders	
Not known:	Confusion
Nervous system disorders	
Very common:	Cholinergic syndrome
Not known:	Transient speech disorders, paraesthesia, headache, syncope
Cardiac disorders	
Not known:	Hypertension (during or after infusion), cardio circulatory failure*, cardiovascular disorders (angina pectoris, cardiac arrest, myocardial infarction, myocardial ischaemia, bradycardia.
Vascular disorders	
Not known:	Hypotension, flushing, thromboembolic events (arterial thrombosis, cerebral infarction, cerebrovascular accident, deep thrombophlebitis, embolus of the lower extremity, pulmonary embolus, thrombophlebitis, thrombosis, and sudden death), peripheral vascular disorder
Respiratory, thoracic and mediastinal disorders	
Not known:	Interstitial pulmonary disease presenting as pulmonary infiltrates, dyspnoea, hiccups
Gastrointestinal disorders	
Very common:	Diarrhoea, vomiting, nausea, abdominal pain
Common:	Constipation
Not known:	Intestinal obstruction, ileus, megacolon,gastrointestinal haemorrhage, colitis, including typhlitis, ischemic and ulcerative colitis, gastrointestinal bleeding, symptomatic or asymptomatic elevation in pancreatic enzymes, intestinal perforation, , GI monilia,
Hepatobiliary disorders	
Common:	Increased blood creatinine, increased transaminases (SGPT and SGOT) increased bilirubin, increased blood alkaline phosphatase.
Not known:	Increases in serum levels of transaminases (i.e., AST and ALT), increased GGTP
Skin and subcutaneous tissue disorders	
Very common:	Alopecia (reversible)
Not known:	Skin reactions, rash
Musculoskeletal connective tissue disorders	
Not known:	Muscular contraction or cramps
Renal and urinary disorders	
Not known:	Renal impairment and acute renal failure, renal insufficiency, urinary tract infection
Reproductive system and breast disorders	
Not known:	Breast pain
General disorders and administration site conditions	
Very common:	Mucosal inflammation, pyrexia, asthenia
Not known:	Infusion site reactions, pain, abnormal gait, extravasation

* 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

Description of selected adverse reactions (monotherapy)

Severe diarrhoea was observed in 20 % of patients who followed the recommendations for the management of diarrhoea. Of the evaluable cycles, 14 % had severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan.

Nausea and vomiting were severe in approximately 10 % of patients treated with antiemetics.

Constipation was observed in less than 10% of patients.

Neutropenia was observed in 78.7 % of patients and was severe (neutrophil count < 500 cells/mm3) in 22.6 % of patients. Of the evaluable cycles, 18 % had a neutrophil count below 1,000 cells/mm3 including 7.6 % with a neutrophil count < 500 cells/mm3. Total recovery was usually reached by day 22.

Fever with severe neutropenia was reported in 6.2 % of patients and in 1.7 % of cycles.
Infectious episodes occurred in about 10.3 % of patients (2.5 % of cycles) and were associated with severe neutropenia in about 5.3 % of patients (1.1 % of cycles), and resulted in death in 2 cases.
Anaemia was reported in about 58.7 % of patients (8 % with haemoglobin < 8 g/dl and 0.9 % with haemoglobin < 6.5 g/dl).

Thrombocytopenia (< 100,000 cells/mm3) was observed in 7.4 % of patients and 1.8 % of cycles with 0.9 % with platelets count ≤ 50,000 cells/mm3 and 0.2 % of cycles. Nearly all the patients showed a recovery by day 22.

Severe transient acute cholinergic syndrome was observed in 9 % of patients treated in monotherapy.

Asthenia was severe in less than 10 % of patients treated in monotherapy. The causal relationship to Irinotecan has not been clearly established. Fever in the absence of infection and without concomitant severe neutropenia, occurred in 12 % of patients treated in monotherapy.

Laboratory tests

Transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2 %, 8.1 % and 1.8 % of the patients, respectively, in the absence of progressive liver metastasis.

Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3 % of the patients.

Combination Therapy

Adverse reactions detailed in this section refer to Irinotecan. There is no evidence that the safety profile of Irinotecan is influenced by Cetuximab or vice versa. In combination with Cetuximab, additional reported adverse reactions were those expected with Cetuximab (such as acneform rash 88%). For information on adverse reactions on Irinotecan in combination with Cetuximab, also refer to their respective summaries of product characteristics.

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 reaction, cardiac ischemia/infarction; Common, grade 3 and grade 4 adverse drug reactions: febrile neutropenia. For complete information on adverse reactions of Capecitabine, refer to the Capecitabine summary product of characteristics.

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with Capecitabine in combination with Irinotecan and Bevacizumab in addition to those seen with Capecitabine monotherapy or seen at a higher frequency grouping compared to Capecitabine monotherapy include: Common, grade 3 and grade 4 adverse drug reactions: neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction. For complete information on adverse reactions of Capecitabine and Bevacizumab, refer to the respective Capecitabine and Bevacizumab summary of product characteristics.
Grade 3-hypertension was the principal significant risk involved with the addition of Bevacizumab to bolus Irinotecan/5FU/FA.

In addition, there was a small increase in the grade 3/4 chemotherapy adverse events of diarrhoea and leukopenia with this regimen compared to patients receiving bolus Irinotecan/5-FU/FA alone. For other information on adverse reactions in combination with Bevacizumab, refer to the Bevacizumab summary of product characteristics.

Irinotecan has been studied in combination with 5FU and FA for metastatic colorectal cancer. Safety data of adverse reactions from clinical studies demonstrate very commonly observed NCI Grade 3 or 4 possibly or probably related adverse events in the blood and the lymphatic system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders MedDRA System Organ Classes.
The following adverse reactions considered to be possibly or probably related to the administration of Irinotecan have been reported from 145 patients treated by Irinotecan in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

Adverse Reactions Reported with Irinotecan in Combination Therapy (180 mg/m2 every 2 weeks schedule)

Infections and infestations	
Common:	Infection
Blood and lymphatic system disorders	
Very common:	Thrombocytopenia, neutropenia, anaemia
Common:	febrile neutropenia
Metabolism and nutrition disorders	
Very common:	Decreased appetite
Nervous system disorders	
Very common:	Cholinergic syndrome
Gastrointestinal disorders	
Very common:	Diarrhoea, vomiting, nausea
Common:	Abdominal pain, constipation
Hepatobiliary disorders	
Very common:	Increased transaminases (SGPT and SGOT) increased bilirubin, increased blood alkaline phosphatase.
Skin and subcutaneous tissue disorders	
Very common:	Alopecia (reversible)
General disorders and administration site conditions	
Very common:	Mucosal inflammation, asthenia
Common:	Pyrexia

Description of selected adverse reactions (combination therapy)

Severe diarrhoea was observed in 13.1 % of patients who followed recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9 % had severe diarrhoea. A lower incidence of severe nausea and vomiting was observed (2.1 % and 2.8 % of patients respectively). Constipation relative to Irinotecan and Loperamide has been observed in 3.4 % of patients.

Neutropenia was observed in 82.5 % of patients and was severe (neutrophil count < 500 cells/mm3) in 9.8 % of patients. Of the evaluable cycles, 67.3 % had a neutrophil count below 1,000 cells/mm3 including 2.7 % with a neutrophil count < 500 cells/mm3. Total recovery was usually reached within 78 days.

Fever with severe neutropenia was reported in 3.4 % of patients and in 0.9 % of cycles.
Infectious episodes occurred in about 2 % of patients (0.5 % of cycles) and were associated with severe neutropenia in about 2.1 % of patients (0.5 % of cycles), and resulted in death in 1 case.

Anaemia was reported in 97.2 % of patients (2.1 % with haemoglobin < 8 g/dl). Thrombocytopenia (< 100,000 cells/mm3) was observed in 32.6 % of patients and 21.8 % of cycles. No severe thrombocytopenia (< 50,000 cells/mm3) has been observed.

Severe transient acute cholinergic syndrome was observed in 1.4 % of patients treated in combination therapy.

Asthenia was severe in 6.2 % of patients treated in combination therapy. The causal relationship to Irinotecan has not been clearly established.
Fever in the absence of infection and without concomitant severe neutropenia, occurred in 6.2 % of patients treated in combination therapy.

Laboratory tests

Transient increases in serum levels (Grades 1 and 2) of SGPT, SGOT, alkaline phosphatase or bilirubin were observed in 15 %, 11 %, 11 % and 10 % of the patients, respectively, in the absence of progressive liver metastasis. Transient Grade 3 increases were observed in 0 %, 0%, 0 % and 1 % of the patients, respectively. No Grade 4 elevation was observed.

Increases of amylase and/or lipase have been very rarely reported. Rare cases of hypokalaemia and hyponatraemia mostly related with diarrhoea and vomiting have been reported.

Overdose

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 Hydrochloride Trihydrate Injection. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

Ingredients

Lactic acid
Sorbitol
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in sections – Posology and method of administration and Special precautions for disposal and other handling.

Shelf life

The shelf-life of unopened vials is 2 years.

Irinotecan 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 25°C and protected from light. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days.

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

Storage Conditions

Do not store above 30 °C. Store in the original package in order to protect from light. Do not freeze.

For storage conditions of the diluted medicinal product, see under the section - Shelf life.

Dosage forms and packaging available

Irican 40 is available in 2 ml USP Type I amber tubular glass vial closed with chlorobutyl rubber stopper and aluminum flip off orange seal. Each carton contains 1 amber glass vial.

Irican 100 is available in 5 ml USP Type I amber tubular glass vial closed with chlorobutyl rubber stopper and aluminum flip off orange seal. Each carton contains 1 amber glass vial.

Special precautions for disposal and other handling

As with other Antineoplastic agents, Irinotecan Injection must be prepared and handled with caution. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
If Irinotecan solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.

Preparation for the intravenous infusion administration

As with any other injectable drugs, the Irinotecan solution must be prepared aseptically. If any precipitate is observed in the vials or after 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.

Disposal

For single use only. All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.

Name and address of manufacturer

Intas Pharmaceuticals Ltd.
Plot No. - 457, 458,
Village-Matoda, Bavla Road,
Dist-Ahmedabad, India

Date of revision of PI

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