IRNIZET
P1524463

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Summary of Product Characteristics

IRNIZET 100

Rx **Irinotecan Hydrochloride Concentrate for Solution for Infusion 100 mg/5mL**

1. Name of the medicinal product

Irnizet 100 Irinotecan Hydrochloride Concentrate for Solution for Infusion 100 mg/5mL

2. Qualitative and quantitative composition

Not all presentations may be available locally.
Each mL contains Irinotecan Hydrochloride Trihydrate Ph. Eur 20 mg.
Each vial with 5 ml contains 100 mg Irinotecan hydrochloride trihydrate.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Concentrate for solution for infusion
Clear colorless to slightly yellow solution.

4. Clinical particulars

4.1 Therapeutic indications

Irinotecan is indicated for the treatment of patients with advanced colorectal cancer.

- In combination with 5-fluorouracil (5-FU) and folinic acid (FA) in patients without prior chemotherapy for advanced cancer.
- As a single agent in patients who have failed an established treatment regimen containing 5-FU.

4.2 Posology and method of administration

Dosage
For adults only

- In monotherapy (for previously treated patient):
  The recommended dose of Irinotecan is 350 mg/m^2 administered in the form of intravenous infusion over 30 to 90 minute period every three weeks.
- In combination therapy (for previously untreated patient):
  Safety and efficacy of Irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) have been assessed with the following schedule: Irinotecan plus 5-FU/FA in every 2 weeks schedule.The recommended dose of Irinotecan is 180 mg/m^2 administered once every 2 weeks as an intravenous infusion over 30 to 90 minute period, followed by infusion with FA and 5-FU.

Dose adjustments
Irinotecan should be administered after an appropriate recovery from all adverse events to 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).

Duration of the treatment
The treatment with Irinotecan should be continued until there is objective disease progression or unacceptable toxicity.
Special populations

Patients with impaired hepatic function
In Monotherapy: In patients with hyperbilirubinemia and a prothrombin time greater than 50%, clearance of Irinotecan is reduced (see section 5.2), and therefore the risk of haematological toxicity is increased. Thus, frequent monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin levels up to 1.5 times the upper limit of normal (ULN), the recommended dose of Irinotecan is 350 mg/m^2
- In patients with bilirubin levels between 1.5 to 3 times the ULN, the recommended dose of Irinotecan is 200 mg/m^2
- Patients with bilirubin levels above 3 times the ULN, should not be treated with Irinotecan (see sections 4.3 and 4.4).

No data are available for patients with impaired hepatic function treated with Irinotecan in combination therapy.

Patients with impaired renal function
Irinotecan is not recommended for use in patients with impaired renal function, as the product has not been studied in this patient group (see sections 4.4 and 5.2).

Elderly
No specific pharmacokinetic studies have been conducted in the elderly. However, the dose should be chosen carefully in this patient group due to their greater frequency of decreased biological functions. This population should require more intense surveillance (see section 4.4).

Administration
Irinotecan solution for infusion should be infused into a peripheral or central vein. Irinotecan should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

4.3 Contraindications

Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
History of severe hypersensitivity reactions to Irinotecan hydrochloride trihydrate or to any of the excipients listed in section 6.1.
Pregnant or breast-feeding women (see sections 4.4 and 4.6).
Bilirubin > 3 times the ULN (see section 4.4).
Severe bone marrow failure.
Patients presenting a risk factor, particularly those with a WHO performance status > 2.

4.4 Special warnings and precautions for use

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, Irinotecan should be prescribed in the following cases 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 patients are deemed unlikely to observe the recommendations for the management of adverse effects (need for immediate and prolonged anti-diarrhoeal treatment combined with a high fluid intake at the onset of delayed diarrhoea). Careful supervision in hospital is recommended for these patients.

When Irinotecan is used in monotherapy, it is usually prescribed using the every-three-week dosage schedule. However, a weekly-dosage schedule (see section 5) 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 diarrhea 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-diarrheal therapy must be initiated immediately. Appropriate arrangements must be made to ensure that the clinician who administers Irinotecan will also prescribe the anti-diarrheal treatment. After discharge from the hospital, the patients should obtain the prescribed drugs so that the diarrhea can be treated as soon as it occurs. In addition, they must inform their physician, or the institution where Irinotecan was administered, when/if diarrhea has occurred.
The anti-diarrheal 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-diarrheal treatment, a broad spectrum prophylactic antibiotic should be administered when the diarrhea is associated with severe neutropenia (neutrophil count <500 cells/mm^3).
In addition to the antibiotic treatment, hospitalization is recommended for the control of diarrhea in the following cases:

- Diarrhea associated with fever,
- Severe diarrhea (requiring intravenous hydration),
- Vomiting associated with delayed (i.e., late) diarrhea,
- Diarrhea 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 diarrhea during previous administrations of the medicinal product.
If the patient has experienced severe diarrhea, a dose reduction is recommended in subsequent cycles (see 4.2).

Impaired hepatic function
Liver function tests must be performed at baseline and prior to each cycle of drug administration.
Frequent monitoring of complete blood counts should be conducted in patients with hyperbilirubinemia due to decreased clearance of Irinotecan (see section 5.2) and thus increased risk of haematotoxicity in this population. For patients with a bilirubin > 3 times the ULN, irinotecan should not be used (see section 4.3).

Nausea and vomiting
Irinotecan is emetogenic. Nausea and vomiting can be severe and usually occurs during or shortly after infusion of irinotecan. It is recommended that patients receive pre-medication with antiemetic agents. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed. 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 certain other signs and symptoms such as sweating, abdominal cramps, lacrimation, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8).
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.

Hematology. Irinotecan commonly causes neutropenia, leukopenia, and anemia, any of which may be severe and therefore should not be used in patients with severe bone marrow failure. Serious thrombocytopenia is uncommon. Patients who have previously received
Pelvic /abdominal irradiation are at increased risk of severe myelosuppression following the administration of Irinotecan. The concurrent administration with irradiation has not been adequately studied and is not recommended.
Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing firstcycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. There were no significant differences in the frequency of Grade 3 and 4 neutropenia by age.
Neutropenic fever (concurrent NCI Grade 4 neutropenia and ≥Grade 2 fever) occurred in fewer than 10% of patients in clinical studies; however, deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. Therapy with irinotecan should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 1000/mm^3.
Weekly monitoring of complete blood cell counts is recommended during Irinotecan treatment. Patients should be aware of the risk of neutropenia and the significance of fever. In patients who experienced severe hematological events, a dose reduction is recommended for subsequent administration (see section 4.2, Dose Adjustments). There is an increased risk of infections and hematological toxicity in patients with severe diarrhea. In patients with severe diarrhea, complete blood cell counts should be performed.

Respiratory diseases
NCI Grade 3 or 4 dyspnea has been observed. The extent to which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnea is unknown. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had pre-existing non-malignant pulmonary disease.
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 pre-existing lung disease, 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 exctravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.

Patients with reduced UGT1A1 activity
The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form the inactive glucuronide metabolite SN-38G. This glucuronidation reaction is mediated primarily by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which is encoded by the UGT1A1 gene (see section 5.2). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1*28 variant allele. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced enzyme activity and increased systemic exposure to SN-38. Higher plasma concentrations of SN-38 are observed in individuals who are homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype) versus patients who have one or two wild-type alleles.
Another specific polymorphism of UGT1A1 gene (that reduces the activity of this enzyme) is a missense mutation known as UGT1A1*6 variant.
Patients with UGT1A1*28 or *6 variants (especially if homozygous) are at increased risk of experiencing adverse events such as neutropenia and diarrhea. A reduced irinotecan starting dose should be considered for homozygous patients (see section 4.2). In addition, *28 and *6 homozygous and heterozygous patients should be closely monitored for neutropenia and diarrhea.
The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on individual patient tolerance to treatment.
In order to identify patients at increased risk of experiencing neutropenia and diarrhea, UGT1A1 genotyping can be useful. More in detail, UGT1A1*28 genotyping can be useful in Caucasians, Africans and Latinos, UGT1A1*6 in East-Asians and combined UGT1A1*28 and *6 in Chinese and Japanese, since these are the populations in which these variants are more prevalent.

Hypersensitivity reactions
Hypersensitivity reactions, including severe anaphylactic/ anaphylactoid reactions, have been reported.

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 selection of Irinotecan in this population should require more caution (see section 4.2).

Chronic inflammatory bowel disease and/or bowel obstruction
Patients must not be treated with Irinotecan until the bowel obstruction is resolved (see section 4.3).

Patients with impaired renal function
Studies have not been conducted in this patient group (see sections 4.2 and 5.2).

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 (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

CYP3A4 and/or UGT1A1 inhibitors
Irinotecan and active metabolite SN-38 are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphateglucuronosyl transferase 1A1 (UGT1A1) (see section 5.2). Co-administration of irinotecan with inhibitors of CYP3A4 and/ or UGT1A1 may result in increased systemic exposure to irinotecan and the active metabolite SN-38. Physicians should take this into consideration when administering irinotecan with these drugs.

Ketoconazole: Irinotecan clearance is greatly reduced in patients receiving concomitant ketoconazole, leading to increased exposure to SN-38. Ketoconazole should be discontinued at least 1 week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

Atazanavir sulfate: 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.

CYP3A4 inducers
Anticonvulsants: Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to the active metabolite SN-38.
Consideration should be given to starting or substituting non-enzyme-inducing anticonvulsants at least one week prior to initiation of irinotecan therapy in patients requiring anticonvulsant treatment.
St. John's Wort (Hypericum perforatum): Exposure to the active metabolite SN-38 is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be discontinued at least 1 week prior to the first cycle of irinotecan, and should not be administered during irinotecan therapy.

Other interactions
Neuromuscular blocking agents: Interactions between irinotecan hydrochloride and neuromuscular blocking agents cannot be ruled out since irinotecan has anticholinesterase activity. Drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonized.
Antineoplastic agents: The adverse effects of irinotecan, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.
Dexamethasone: Lymphocytopenia has been reported in patients receiving irinotecan, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. However, serious opportunistic infections have not been observed and no complications have specifically been attributed to lymphocytopenia.
Hyperglycemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.
Laxatives: Laxative use during therapy with irinotecan is expected to worsen the incidence or severity of diarrhea.
Diuretics: Dehydration secondary to vomiting and/or diarrhea may be induced by irinotecan. The physician may wish to withhold diuretics during dosing with irinotecan and during periods of active vomiting or diarrhea.
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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies of irinotecan in pregnant women. Irinotecan is teratogenic in rats and rabbits (see section 5.3). Irinotecan may cause fetal harm when administered to a pregnant woman.
Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.
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.

Lactation
The available data are limited to one patient only. Irinotecan and its active metabolite SN-38 were measured in the milk of one lactating patient. The effect on newborn/infants is unknown. Because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with irinotecan.
In rats, radioactivity appeared in the milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

4.7 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, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The 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/m^2 in monotherapy and from 145 patients treated by irinotecan treated in combination with 5-FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m^2.

Gastrointestinal disorders

- Delayed diarrhea

Diarrhea (occurring more than 24 hours after administration) is a dose-limiting toxicity of irinotecan. In monotherapy severe diarrhea was observed in 20% of patients who follow recommendations for the management of diarrhea. Of the evaluable cycles, 14% have a severe diarrhea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.
In combination therapy severe diarrhea was observed in 13.1% who follow recommendations for the management of diarrhea. Of the evaluable cycles, 3.9% have a severe diarrhea. Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically (*Clostridium difficile*).

- Nausea and vomiting

In monotherapy, nausea and vomiting were severe in approximately 10% of patients treated with antiemetics. In combination therapy a lower incidence of nausea and vomiting was observed (2.1% and 2.8% of patients, respectively).

- Dehydration

Episodes of dehydration commonly associated with diarrhea and/or vomiting have been reported.
Infrequent cases or renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting.

- Other gastrointestinal events

Constipation relative to Irinotecan and/or loperamide has been observed; in monotherapy, in less than 10% of patients and in combination therapy in 3.4% of patients. Infrequent cases of intestinal obstruction, ileus, or gastrointestinal hemorrhage and rare cases of colitis were reported. Rare cases of intestinal perforation were reported. Other mild effects include anorexia, abdominal pain and mucositis.

Blood disorders

- Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.
- In monotherapy, neutropenia was observed in 78.7% of patients and was severe (neutrophil count <500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count <1,000 cells/mm^3 including 7.6% with a neutrophil count <500 cells/mm^3. 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. Anemia was reported in about 58.7% of patients (8% with hemoglobin <8 g/dL and 0.9% with hemoglobin <6.5 g/dL). Thrombocytopenia (<100,000 cells/mm^3) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelet count <50,000 cells/mm^3 and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.
- In combination therapy, neutropenia was observed in 82.5% of patients and was severe (neutrophil count <500 cells/mm^3) in 9.8% of patients. Of the evaluable cycles, 67.3% had a neutrophil count <1,000 cells/mm^3 including 2.7% with a neutrophil count <500 cells/mm^3. Total recovery was usually reached within 7-8 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. Anemia was reported in about 97.2% of patients (2.1% with hemoglobin <8 g/dL). Thrombocytopenia (<100,000 cells/mm^3) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50,000 cells/mm^3) has been observed. Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis. One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported in the post-marketing experience.

General disorders and infusion site reactions

- *Acute cholinergic syndrome:* Severe transient acute cholinergic syndrome was observed in 9% of patients treated in monotherapy and in 1.4% of patients treated in combination therapy. The main symptoms were defined as early diarrhea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after atropine administration (see section 4.4). Asthenia was severe in less than 10% of patients treated in monotherapy and 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 12% of patients treated in monotherapy and in 6.2% of

patients treated in combination therapy. Mild infusion site reactions have been reported although uncommonly.

Respiratory disorders: Interstitial pneumonia and pneumonitis presenting as pulmonary infiltrates have rarely been observed. Early effects such as dyspnea have been reported.

Skin and subcutaneous tissue disorders: Alopecia was very common and reversible. Mild cutaneous reactions have been reported although uncommonly.

Immune system disorders: Mild allergic reactions although uncommon and rare anaphylactoid reactions have been reported.
Musculoskeletal disorders: Early effects such as muscular contraction or cramps and paresthesia have been reported.

Laboratory tests: In monotherapy, 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 in serum levels of creatinine have been observed in 7.3% of the patients.
In combination therapy transient serum levels (Grades 1 and 2) of either ALT, AST, 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 was observed in 0%, 0%, 0% and 1% of the patients, respectively. No Grade 4 was observed.
Transient increase of amylase and occasionally transient increase of lipase have been very rarely reported. Rare cases of hypokalemia mostly related with diarrhea and vomiting have been reported.

Post-marketing surveillance
Cardiac disorders:
Myocardial ischemic events have been observed following irinotecan therapy predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease or previous cytotoxic chemotherapy.

Gastrointestinal disorders:
Infrequent cases of intestinal obstruction, ileus, megacolon, or gastrointestinal hemorrhage, and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis were reported. In some cases, colitis was complicated by ulceration, bleeding, ileus, or infection. Cases of ileus without preceding colitis have also been reported. Rare cases of intestinal perforation were reported.
Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypovolemia:
There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities.
Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhea and/or vomiting, or sepsis.

Infections and infestations:
Bacterial, fungal and viral infections have been reported.

Immune system disorders
Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported (see section 4.4).

Musculoskeletal and connective tissue disorders
Early effects such as muscular contraction or cramps and paresthesia have been reported.

Nervous system disorders
Speech disorders, generally transient in nature, have been reported in patients treated with irinotecan; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Respiratory, thoracic and mediastinal disorders
Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnea have been reported (see section 4.4). Hiccups have also been reported.

Investigations
Rare cases of hyponatremia mostly related with diarrhea and vomiting have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been very rarely reported.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group: Cytostatic topoisomerase I inhibitor
ATC Code: L01CE02

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

Clinical data
In monotherapy
Clinical Phase II/III studies were performed in more than 980 patients in the every-3-week dosage schedule with metastatic colorectal cancer who failed a previous 5-FU regimen. The efficacy of Irinotecan was evaluated in 765 patients with documented progression on 5-FU at study entry.

Table 1 – Efficacy of Irinotecan monotherapy in patients with documented progression on 5-FU at study entry.

	Phase III					
	Irinotecan versus best supportive care			Irinotecan versus 5-FU		
	Irinotecan	Supportive care	p values	Irinotecan	5-FU	p values
	n = 189	n = 90		n = 127	n = 129	
Progression Free Survival at 6 months (%)	NA	NA		33.5*	26.7	p=0.03
Survival at 12 months (%)	36.2*	13.8	p=0.0001	44.8*	32.4	p=0.0351
Median Survival (months)	9.2*	6.5	p=0.0001	10.8*	8.5	p=0.0351

NA: Not Applicable
*: Statistically significant difference.
In Phase II studies, performed on 455 patients in every 3 week dosage schedule, the progression free survival at 6 months was 30% and the median survival was 9 months. The median time to progression was 18 weeks. In addition, non-comparative Phase II studies were performed in 304 patients treated with a weekly schedule regimen, at a dose of 125 mg/m^2 administered as an intravenous infusion over 90 minutes for 4 consecutive weeks followed by 2 weeks rest. In these studies, the median time to progression was 17 weeks and median to survival was 10 months. A similar safety profile has been observed in the weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m^2, compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination therapy
A Phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of irinotecan at 180 mg/m^2 once every 2 weeks is followed by infusion with FA (200 mg/m^2 over a 2-hour intravenous infusion) and 5-FU (400 mg/m^2) as an intravenous bolus, followed by 600 mg/m^2 over a 22-hour intravenous infusion). On day 2, FA and 5-FU are administered at the same doses and schedules. In the weekly schedule, the administration of irinotecan at 80 mg/m^2 is followed by infusion with FA (500 mg/m^2 over a 2-hour intravenous infusion) and then by 5-FU (2300 mg/m^2 over a 24-hour intravenous infusion) over 6 weeks.

In the combination therapy trial with the 2 regimens described above, the efficacy of irinotecan was evaluated in 198 patients.

Table 2 – Efficacy of irinotecan in combination therapy

	Combined regimens (n=198)		Weekly schedule (n=50)		2 weekly schedule (n=148)	
	Irinotecan+5-FU/FA	5-FU/FA	Irinotecan +5-FU/FA	5-FU/FA	Irinotecan +5-FU/FA	5-FU/FA
Response rate (%) p value	40.8 *	23.1*	51.2 *	28.6 *	37.5 *	21.6 *
	p < 0.001		p = 0.045		p = 0.005	
Median time to progression (months) p value	6.7	4.4	7.2	6.5	6.5	3.7
	p < 0.001		NS		p = 0.001	
Median duration of response (months) p value	9.3	8.8	8.9	6.7	9.3	9.5
	NS		P =0.043		NS	
Median duration of response and stabilisation (months) p value	8.6	6.2	8.3	6.7	8.5	5.6
	p < 0.001		NS		p = 0.003	
Median time to treatment failure (months) p value	5.3	3.8	5.4	5.0	5.1	3.0
	p = 0.0014		NS		p < 0.001	
Median survival (months) p value	16.8	14.0	19.2	14.1	15.6	13.0
	p = 0.028		NS		p = 0.041	

5-FU: 5-fluorouracil
FA: folinic acid,
NS: non significant,
*: as per protocol analysis.

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in the patients treated with Irinotecan in combination with 5-FU/FA, and 25.6% in the patients treated with 5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm^3) was 5.8% in the patients treated with Irinotecan in combination with 5-FU/FA and 2.4% in the patients treated with 5-FU/FA alone. In addition, median time to definitive performance status deterioration was significantly longer in irinotecan combination group than in 5-FU/FA alone group (p=0.046). Quality of life was assessed in this Phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the irinotecan groups. The evolution of the Global Health Status/Quality of life was slightly better in irinotecan combination group, although not significant, showing that efficacy of irinotecan in combination could be reached without affecting the quality of life.

5.2 Pharmacokinetic properties
Absorption and distribution
After intravenous infusion of irinotecan hydrochloride in humans with various cancers, irinotecan hydrochloride plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. In a study where irinotecan hydrochloride was administered at doses of 100-750 mg/m^2 by 30 minute intravenous infusion every three weeks, the plasma terminal elimination half-life was 14.2 +/- 7.7 hours for irinotecan hydrochloride and 13.8 +/- 1.4 hours for SN-38.
Over the dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan.
Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism and excretion
Irinotecan (CPT-11) is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan (CPT-11) can also undergo CYP3A4-mediated oxidative metabolism to several pharmacologically inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism (see section 4.4). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in special populations
Geriatric. The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC0-24 for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant.
Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.
Race: The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency (see section 4.2, Special Populations). Irinotecan clearance is diminished in patients with hepatic dysfunction while relative exposure to the active metabolite SN-38 is increased. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in serum total bilirubin and transaminase concentrations.

Renal Insufficiency. The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated (see section 4.2, Special Populations).

5.3 Preclinical safety data
Toxicology
The acute intravenous toxicity of irinotecan in animals is shown below in Table 3. Lethality was observed after single intravenous irinotecan doses of approximately 111 mg/kg in mice and 73 mg/kg in rats (approximately 2.6 and 3.4 times the recommended human dose of 125 mg/m^2, respectively).
Death was preceded by cyanosis, tremors, respiratory distress, and convulsions. Subacute toxicity studies show that irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes).

Table 3 – Acute toxicity of irinotecan (IV) in animals

Species	LD_{50} (mg/kg)
Mouse	132-134
Rat	84-85
Dog	40-80

Carcinogenicity/Mutagenicity
Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.
Neither irinotecan nor SN-38 was mutagenic in the *in vitro* Ames assay. However, in the *in vitro* Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration–dependent manner. Additionally, in the *in vivo* mouse micronucleus assay, a single intraperitoneal dose of irinotecan over the dosage range of 2.5 to 200 mg/kg caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells.

Reproduction
No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and I/15th, respectively, the corresponding values in patients administered 125 mg/m^2).
Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3rd and I/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6 mg/kg/day (about one-half the recommended weekly human dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

6. Pharmaceutical particulars

6.1 List of excipients
Sorbitol
Lactic acid
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
The shelf life of unopened vials is 36 months.

Stability after dilution:
Chemical and physical in-use stability has been demonstrated in glucose 50 mg/mL (5%) and in sodium chloride 9 mg/mL (0.9%) for up to 28 days when stored protected from light in LDPE container at 5°C or at 30°C. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days at 5°C and 30°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage time 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.

6.4 Special precautions for storage
Store below 30°C. Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
Glass vial tubular type-I, with grey bromobutyl rubber stopper and sealed with aluminum seal having polypropylene disc.
Each pack contains one vial.

6.6 Special precautions for disposal and other handling
The solution must be diluted before use. For single use only. Any remaining solution in the vial should be discarded.
As with other antineoplastic agents, Irinotecan infusions must be prepared and handled with caution. The use of goggles, mask and gloves is required.
Pregnant women should not handle cytotoxics.
If Irinotecan concentrate or infusion solutions should come into contact with the skin, it must be washed off immediately and thoroughly with soap and water. If Irinotecan concentrate or infusion solutions should come into contact with the mucous membranes, it must be washed off immediately with water.

Preparation of the intravenous infusion
As with any other infusion, Irinotecan infusion must be prepared aseptically.
If any precipitate is observed in the vials or in the infusion solution, the product must be discarded according to local standard procedures for discarding 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% dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

Disposal: All materials used for dilution and administration should be disposed of according to local procedures applicable to the discarding of cytotoxic agents.

7. Product Owner
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