SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of the medicinal product

Irinotecan 20 mg/ml concentrate for solution for infusion (40 mg/2mL, 100 mg/5mL, and 300 mg/15mL)

2. Qualitative and quantitative composition

Each mL contains 20 mg lrinotecan Hydrochloride Trihydrate.

3. Pharmaceutical form

Injection,

Pale yellow clear aqueous solution filled into amber vial with rubber stopper and aluminium seal.

4. Clinical particulars

4.1 Therapeutic indications

Irinotecan 20 mg/ml concentrate for solution for infusion 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 20 mg/ml concentrate for solution for infusion 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 (please see 5.1).

Irinotecan 20 mg/ml concentrate for solution for infusion 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 20 mg/ml concentrate for solution for infusion in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

4.2 Posology and method of administration

For adults only. Irinotecan Hydrochloride Injection solution for infusion should be infused into a peripheral or central vein.

Recommended dosage:

In monotherapy (for previously treated patient): The recommended dosage of Irinotecan Hydrochloride Injection is 350 mg/m2 administered as an intravenous infusion over a 30- to 90-minute period every three weeks (see section 6.6 and section 4.4).

In combination therapy (for previously untreated patient): Safety and efficacy of Irinotecan 20 mg/ml concentrate for solution for infusion in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with the following schedule (see section 5.1):

• Irinotecan Hydrochloride Injection plus 5FU/FA in every 2 weeks schedule

The recommended dose of Irinotecan Hydrochloride 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 of product characteristics.

For the posology and method of administration of capecitabine combination, please see section 5.1 and refer to the appropriate sections in the capecitabine summary of product characteristics.

Dosage adjustments:

Irinotecan Hydrochloride Injection 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 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 20 mg/ml concentrate for solution for infusion 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/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 20 mg/ml concentrate for solution for infusion 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 (UNL)) in patients with performance status $\leq$ 2, should determine the starting dose of Irinotecan Hydrochloride Injection. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (see section 5.2) 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 Injection is 350 mg/m2,

• In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan 20 mg/ml concentrate for solution for infusion is 200 mg/m2,

• Patients with bilirubin beyond to 3 times the ULN should not be treated with Irinotecan 20 mg/ml concentrate for solution for infusion (see section 4.3 and section 4.4).

No data are available in patients with hepatic impairment treated by Irinotecan 20 mg/ml concentrate for solution for infusion in combination.

Patients with impaired renal function: Irinotecan 20 mg/ml concentrate for solution for infusion is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted. (See section 4.4 and section 5.2).

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 (see section 4.4).

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 one of the excipients of Irinotecan Hydrochloride Injection.

• Lactation (see section 4.6 and section 4.4).

• Bilirubin > 3 times the upper limit of the normal range (see section 4.4).

• Severe bone marrow failure.

• WHO performance status > 2.

• Concomitant use with St John's Wort (see section 4.5).

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

4.4 Special warnings and precautions for use

The use of Irinotecan 20 mg/ml concentrate for solution for infusion 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 20 mg/ml concentrate for solution for infusion 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 antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When Irinotecan 20 mg/ml concentrate for solution for infusion is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see section 5) 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 20 mg/ml concentrate for solution for infusion 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 20 mg/ml concentrate for solution for infusion Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status $\geq$ 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 antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where Irinotecan 20 mg/ml concentrate for solution for infusion 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 20 mg/ml concentrate for solution for infusion when/if diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and 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, 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 (see section 4.2).

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 20 mg/ml concentrate for solution for infusion treatment. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38°C and neutrophil count $\leq$ 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 (see section 4.2).

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 (see section 5.2) and thus increasing the risk of hematotoxicity in this population. For patients with a bilirubin > 3 times ULN (see section 4.3).

Nausea and vomiting

A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan Hydrochloride Injection. 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 (see section 4.8).

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 20 mg/ml concentrate for solution for infusion.

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 20 mg/ml concentrate for solution for infusion should be cautious in this population (see section 4.2).

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with Irinotecan 20 mg/ml concentrate for solution for infusion until resolution of the bowel obstruction (see section 4.3).

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 (see section 4.2).

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 (see section 4.8).

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 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.

Others

Since this medicinal 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 (see section 4.5).

4.5 Interaction with Other medicinal products and other forms of Interaction

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan 20 mg/ml concentrate for solution for infusion has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

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 was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and

enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

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.

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 (see section 4.4).

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 (see section 4.3).

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

Atazanavir sulphate. Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor, has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

Interactions common to all cytotoxics:

The use of anticoagulants is common due to increased risk of thrombotic events in tumoral diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required due to their narrow therapeutic index, the high intra-individual variability of blood thrombogenicity and the possibility of interaction between oral anticoagulants and anticancer chemotherapy.

Concomitant use contraindicated

- Yellow fever vaccine: risk of fatal generalised reaction to vaccines

Concomitant use not recommended

- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease (eg- infections). This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis)

- Phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug or risk of toxicity enhancement due to increased hepatic metabolism by phenytoin

Concomitant use to take into consideration

- Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation

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

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.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/ Contraception in males and females

Women of childbearing potential and men have to use effective contraception during and up to 1 month and 3 months after treatment respectively.

Pregnancy

There is no data from the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals. Therefore, based on results from animal studies and the mechanism of action of irinotecan, Irinotecan 20 mg/ml concentrate for solution for infusion should not be used during pregnancy unless clearly necessary.

Breast-feeding

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, breast-feeding should be discontinued for the duration of Irinotecan 20 mg/ml concentrate for solution for infusion therapy (see section 4.3)

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 (see section 5.3).

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 20 mg/ml concentrate for solution for infusion, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The adverse reactions for other indications are expected to be similar to those for colorectal cancer.

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 whatever the use 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/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 in Monotherapy (350 mg/m^2 every 3 weeks schedule)		
MedDRA System Organ Class	**Frequency Category**	**Preferred Term**
Infections and infestations	Common	Infection

Blood and lymphatic system disorders	Very common	Neutropenia
	Very common	Anaemia
	Common	Thrombocytopenia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Very common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Pyrexia
	Very common	Asthenia
Investigations	Common	Blood creatinine increased
	Common	Transaminases (SGPT and SGOT) increased
	Common	Bilirubin increased
	Common	Blood alkaline phosphatase increased

Description of selected adverse reactions (monotherapy)

Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have 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 has been 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/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.

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/mm^3) 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.

Acute cholinergic syndrome

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.

<u>COMBINATION THERAPY</u>

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 summary 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 /5-FU/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 5-FU 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/m^2.

Adverse Reactions Reported with irinotecan in Combination Therapy (180 mg/m^2 every 2 weeks schedule)		
MedDRA System Organ Class	**Frequency Category**	**Preferred Term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Thrombocytopenia

	Very common	Neutropenia
	Very common	Anaemia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Asthenia
	Common	Pyrexia
Investigations	Very common	Transaminases (SGPT and SGOT) increased
	Very common	Bilirubin increased
	Very common	Blood alkaline phosphatase increased

Description of selected adverse reactions (combination therapy)

Severe diarrhoea was observed in 13.1 % of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9 % have a 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/or 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/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.

Anaemia was reported in 97.2% of patients (2.1% with haemoglobin < 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.

Acute cholinergic syndrome

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 serum levels (grades 1 and 2) of either 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 were observed in 0%, 0%, 0% and 1% of the patients, respectively. No grade 4 was observed.

Increases of amylase and/or lipase have been very rarely reported.

Rare cases of hypokalemia and hyponatremia mostly related with diarrhea and vomiting have been reported.

4.9 Overdose

There have been reports of over dosage 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 20 mg/ml concentrate for solution for infusion. 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

Cytostatic topoisomerase I inhibitor. ATC Code: L01XX19

Experimental data:

Irinotecan is a semi-synthetic derivative of Irinotecanthecin. 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 tumors expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemia's).

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

5.2 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/m^2 every three weeks, irinotecan showed a biphasic or thriphasic elimination profile. The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss): 157 L/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. 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.

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 (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.

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

Mass balance and metabolism studies with 14 C-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 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 SN-38. 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 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

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 Injection 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

1. Sorbitol 400
2. Lactic Acid
3. Sodium Hydroxide
4. Hydrochloric Acid

6.2 Shelf life

Unopened vials:

2 years.

Reconstituted solution:

Irinotecan 20 mg/ml concentrate for solution for infusion is physically and chemically stable with infusion solutions (0.9% (w/v) sodium chloride solution and 5% (w/v) glucose solution) for up to 28 days when stored in LDPE or PVC containers at 5°C or at 30°C and protected from light. When exposed to light, physico-chemical stability has been demonstrated for up to 3 days.

It is recommended, however, that in order to reduce microbiological hazard, the infusion solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior

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

6.3 Special precautions for storage

Store below 30°C.

6.4 Nature and contents of container

20mm Amber tubular USP type-1 glass vial, 20mm Grey Bromo Butyl Omniflex plus coated Rubber stopper [RFS], 20mm Aluminium Flip off Light Blue Colour Seal (Suitable for Terminal Sterilization.

Each pack contains 1 single-use vial.

6.5 Special precautions for disposal and other handling

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

If Irinotecan 20 mg/ml concentrate for solution for infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan Hydrochloride Injection 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 20 mg/ml concentrate for solution for infusion must be prepared aseptically (see « Shelflife »).

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 20 mg/ml concentrate for solution for infusion 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:

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

7. Manufacturer and Marketing Authorization Holder:

Shilpa Medicare Limited

Jadcherla – 509301, India.

8. Market authorization number

06327/06974/NMR/2018

9. Date of authorization

Jul 25, 2021

10. Date of Revision of the text

12/2017