Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Irinotecan Hydrochloride 20 mg/ml Concentrate for Solution for Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 20 mg Irinotecan hydrochloride trihydrate, equivalent to 17.33 mg Irinotecan.

Each vial with 2 ml contains 40 mg Irinotecan hydrochloride trihydrate.

Each vial with 5 ml contains 100 mg Irinotecan hydrochloride trihydrate.

Each vial with 25 ml contains 500 mg Irinotecan hydrochloride trihydrate.

Excipients with known effects:
Sorbitol (E420), 45.0 mg/ml

Each 40 mg/2ml vial contains 0.069 mg/ml of sodium (0.14 mg).

Each 100mg/5 ml vial contains 0.071 mg/ml of sodium (0.35 mg)

Each 500 mg/25 ml vial contains 0.071 mg/ml of sodium (1.77 mg).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear, colourless to pale yellow solution.

pH: 3.0 – 3.8

Osmolarity: 276 mOsm/kg.

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 not having undergone previous chemotherapy for advanced cancer.
- As a single agent in patients who have not been successful with an established treatment regimen containing 5-FU.

Irinotecan in combination with Cetuximab is indicated for the treatment of patients with metastatic colorectal cancer (*KRAS wild-type*) with expression of epidermal growth factor receptor (EGFR) who have not received prior treatment for metastatic disease or after failure of a cytotoxic therapy that included Irinotecan (see section 5.1).

Irinotecan in combination with 5-FU, FA and Bevacizumab is indicated as first-line treatment for patients with colon or

rectum metastatic carcinoma.

Irinotecan in combination with a Capecitabine with or without Bevacizumab is indicated as first-line treatment for patients with metastatic colorectal carcinoma.

4.2 Posology and method of administration

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

Recommended posology

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

In monotherapy (in patients previously treated)

The recommended dose of Irinotecan is 350 mg/m^2 administered in the form of intravenous infusion over a period of 30 to 90 minutes, every three weeks (see sections 4.4 and 6.6).

In combination therapy (in patients not previously treated)

The safety and effectiveness of Irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) were evaluated as per the following schedule (see section 5.1).

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

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

For the dosage and mode of administration of concomitant Cetuximab, see the prescribing information for this medicinal product. Normally, the same dose of Irinotecan is used as that administered over the last cycles of the previous regimen containing Irinotecan. Irinotecan should not be given before an hour after the end of the infusion of Cetuximab.

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

For the dosage and mode of administration of Capecitabine used in combination, see section 5.1 and the appropriate sections of the Summary of Product Characteristics of Capecitabine.

Dose adjustments

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

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

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

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

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

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

Duration of the treatment

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

Special populations

Patients with impaired hepatic function

Monotherapy:
Bilirubin levels (up to 3 times the upper limit of normal [ULN]) in patients with a WHO performance status ≤ 2 should determine the initial dose of Irinotecan. In these 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, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin levels up to 1.5 times the 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).

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.

Lactation (see sections 4.4 and 4.6).

Bilirubin > 3 times the ULN (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 prescribing information for these medicinal products.

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, in the following cases Irinotecan should be prescribed only after consideration of the expected benefits in relation to the possible therapeutic risks:

- in patients with a risk factor, particularly those with a WHO performance status = 2.
- in the few rare cases where it is considered likely that the patients will not be aware of the recommendations for the control of adverse effects
  (immediate need for prolonged anti-diarrhoeal treatment combined with a high fluid intake at the onset of late diarrhoea). Careful supervision in hospital is recommended for these patients.

When Irinotecan is used in monotherapy, it is usually prescribed using the three week dosage schedule. However, a weekly-dosage schedule (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 $\geq$ 2 and women. If not appropriately treated, the diarrhoea can be life threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of liquid containing electrolytes, and an adequate anti-diarrhoeal therapy must be initiated immediately. Appropriate arrangements must be made to ensure that the clinician who administers Irinotecan will also prescribe the anti-diarrhoeal treatment. After discharge from the hospital, the patients should obtain the prescribed drugs so that the diarrhoea can be treated as soon as it occurs. In addition, they must inform their physician, or the institution where Irinotecan was administered, when/if diarrhoea has occurred.

The anti-diarrhoeal treatment currently recommended consists of high doses of Loperamide (4 mg at the start, followed by 2 mg every 2 hours). This treatment should be continued for 12 hours after the last liquid stool and must not be modified. In no event shall Loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, and the treatment should last at least 12 hours.

In addition to the anti-diarrhoeal treatment, a broad spectrum prophylactic antibiotic should be administered when the diarrhoea is associated with severe neutropenia (neutrophil count <500 cells/mm^3).

In addition to the antibiotic treatment, hospitalization is recommended for the control of diarrhoea in the following cases:

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours after initiation of treatment with high doses of Loperamide.

Loperamide should not be administered prophylactically, even in patients who have had delayed diarrhoea during previous administrations of the medicinal product.

If the patient has experienced severe diarrhoea, a dose reduction is recommended in subsequent cycles (see 4.2).

Haematology

During Irinotecan treatment, weekly monitoring of complete blood cell counts is recommended. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38°C and neutrophil count ≤1000 cells/mm^3) should be urgently treated in hospital with broad-spectrum intravenous antibiotics.

A dose reduction for subsequent administration is recommended in patients who have experienced severe haematological events (see section 4.2).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In these patients, a complete blood cell count should be taken.

Impaired hepatic function

Liver function tests must be performed at baseline and prior to each cycle of drug administration.

Weekly monitoring of complete blood counts should be conducted in patients with bilirubin values ranging from 1.5 to 3 times the ULN due to decreased clearance of Irinotecan (see section 5.2) and thus increased risk of haematotoxicity in this population. For patients with a bilirubin > 3 times the ULN, see section 4.3.

Nausea and vomiting

Prophylactic treatment with an antiemetic before each administration of Irinotecan is recommended. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalized for treatment as soon as possible.

Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and certain other signs and symptoms such as sweating, abdominal cramps, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (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.

Respiratory diseases

During therapy with Irinotecan, conditions with pulmonary infiltrates indicating the occurrence of interstitial lung disease have been uncommon. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicinal products, radiotherapy and cell growth factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during therapy with Irinotecan.

Extravasation
While irinotecan is not a known vesicant, care should be taken to avoid exctravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is

recommended.

Cardiac Disorders

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8 Undesirable Effects).

Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including irinotecan, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Elderly

Due to a greater frequency of decreased biological functions, e.g., of the hepatic function in elderly patients, dose adjustment of Irinotecan in this population should require more caution (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).

Concomitant administration of Irinotecan with a strong inhibitor (e.g. Ketoconazole) or inducer (e.g., Rifampicin, Carbamazepine, Phenobarbital, Phenytoin, St John's wort) of Cytochrome P450 3A4 (CYP3A4) may alter the metabolism of Irinotecan and should be avoided (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. Irinotecan is an anticholinesterase, and medicines which have anticholinesterase activity may prolong the neuromuscular blocking effects of Suxamethonium and antagonise the neuromuscular blockade of non-depolarising agents.

Several studies have shown that concomitant administration of cytochrome P450 3A (CYP3A) inducers as anticonvulsant drugs (e.g., Carbamazepine, Phenobarbital or Phenytoin) leads to a reduced exposure to Irinotecan, SN-38 and SN-38 glucuronide, and to reduced pharmacodynamic effects.
The effects of such anticonvulsant drugs were reflected by a decrease in the AUC of SN-38 and SN-38G by 50% or more. In addition, the induction of CYP3A enzymes enhances both glucuronidation and biliary excretion, and these effects may play an important role in reducing exposure to Irinotecan and its metabolites.

A study has shown that the co-administration of Ketoconazole resulted in a decrease in the AUC of the principal oxidative metabolite APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to Irinotecan given alone. Caution should be exercised in patients concomitantly taking drugs known to inhibit (e.g. Ketoconazole) or induce (e.g. Carbamazepine, Phenobarbital, Phenytoin, Rifampicin) drug metabolism by CYP3A4.
Concomitant administration of Irinotecan with an inhibitor/inducer of this metabolic pathway can alter the metabolism of Irinotecan and should be avoided (see section 4.4).

In a small pharmacokinetic study (n=5), in which Irinotecan 350 mg/m^2 was co-administered with 900 mg St. John's wort (*Hypericum perforatum*), a 42% decrease in plasma concentrations of the active metabolite of Irinotecan, SN-38, was observed.

St John’s wort decreases SN-38 plasma levels. Consequently St John’s wort should not be administered with Irinotecan (see section 4.3).

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

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

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.

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

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

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

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease (eg-infections). This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Use an inactivated vaccine where this exists (poliomyelitis)

- Phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug.

Concomitant use to take into consideration
- Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is no data from the use of Irinotecan in pregnant women.Studies in animals have shown reproductive toxicity (see section 5.3). Irinotecan should not be used during pregnancy, unless the clinical condition of the woman requires treatment with Irinotecan. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case.

Fertility:

Women of fertile age receiving Irinotecan should inform the treating physician immediately should pregnancy occur (see section 4.4). Contraceptive measures must be taken by women of fertile age and also by male patients during and up to 1 month and 3 months after treatment, respectively. In animals adverse effects of irinotecan on the fertility of offspring has been documented (see section 5.3).

Breastfeeding

It is unknown whether Irinotecan is excreted in human milk. ^{14}C-Irinotecan has been detected in the milk of lactating rats. Irinotecan is contraindicated during breast-feeding (see section 4.3).

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

4.8 Undesirable effects

Undesirable effects 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 undesirable effects were those expected with Cetuximab (such as acne form rash 88 %). Therefore also refer to the prescribing information for Cetuximab.

For information on adverse reactions to this medicinal product in combination with Bevacizumab, refer to the Summary of Product Characteristics for Bevacizumab.

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 to Capecitabine, refer to the Summary of Product Characteristics for Capecitabine.

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with Capecitabine in combination with Irinotecan and Bevacizumab in addition to those observed with Capecitabine monotherapy or observed 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 to Capecitabine and Bevacizumab, refer to the respective Summary of Product Characteristics for Capecitabine or Bevacizumab.

The following adverse reactions, considered to be possibly or probably related to the administration of Irinotecan, have been reported in 765 patients at the recommended dose of 350 mg/m^2 in monotherapy, and in 145 patients treated with Irinotecan in combination therapy with 5-FU/FA every two weeks at the recommended dose of 180 mg/m^2.

Side effects have been summarised in the table below with MedDRA frequencies. Undesirable effects are presented in order of decreasing seriousness within each frequency class.

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
Very rare: < 1/10,000; not known (cannot be calculated from the available data).

Body System	Frequency	Adverse Reaction
Infections and infestations	Uncommon	Renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who had had sepsis.
	Unknown	Fungal infections* Viral infections†
Blood and lymphatic system disorders	Very common	Neutropenia (reversible and not cumulative). Anaemia Thrombocytopenia (in case of combination therapy). Infectious episodes (with monotherapy).
	Common	Febrile neutropenia Infectious episodes (with combination therapy). Infectious episodes associated with severe neutropenia resulting in death in 3 cases. Thrombocytopenia (with monotherapy).
	Very rare	One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.
	Unknown	Leukopenia
Immune System Disorders	Uncommon	Moderate allergy reactions.
	Rare	Anaphylactic/ Anaphylactoid reactions.
Metabolism and Nutrition Disorders	Very rare	Tumour lysis syndrome.
Nervous System Disorders	Very rare	Transient speech disorder.
Cardiac disorders	Rare	Hypertension during or following the infusion.
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Interstitial pulmonary disease presenting as pulmonary infiltrates. Early effects such as dyspnoea.
Gastrointestinal disorders	Very common	Severe delayed diarrhoea. Severe nausea and vomiting (with monotherapy).
	Common	Severe nausea and vomiting (with combination therapy). Episodes of dehydration (associated with diarrhoea and/or vomiting). Constipation related to Irinotecan and/or Loperamide.

Body System	Frequency	Adverse Reaction
Gastrointestinal disorders	Uncommon	Pseudomembranous colitis (one case has been documented bacteriologically: Clostridium difficile).

		Renal insufficiency, hypotension or cardio-circulatory failure as a consequence of dehydration associated with diarrhoea and/or vomiting. Intestinal obstruction, paralytic ileus, or gastrointestinal haemorrhage.
	Rare	Colitis, including typhlitis, ischaemic and ulcerative colitis. Intestinal perforation. Other mild effects include anorexia, abdominal pain and mucositis. Symptomatic or asymptomatic pancreatitis.
Skin and Subcutaneous Tissue Disorders	Very common	Alopecia (reversible)
	Uncommon	Moderate skin reaction
	Unknown	Rash
Musculoskeletal and Connective Tissue Disorders	Rare	Early effects such as muscular contraction or cramps and paraesthesia
General Disorders and Administration Site Reactions	Very common	Fever in the absence of infection and without concomitant severe neutropenia (with monotherapy).
	Common	Severe transient acute cholinergic syndrome (the main symptoms were early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, miosis, lacrimation and increased salivation). Asthenia. Fever in the absence of infection and without concomitant severe neutropenia with combination therapy.
	Uncommon	Infusion site reactions.

Body System	**Frequency**	**Adverse Reaction**
investigations	Very common	During combination therapy, transient serum levels (grade 1 and 2) of either ALT, AST, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis.
	Common	In monotherapy, transient and mild to moderate increases in serum levels of either ALT, AST, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis. Transient, mild to moderate increases in serum levels of creatinine. During combination therapy,

		transient grade 3 serum levels of bilirubin.
	Rare	Hypokalemia Hyponatremia
	Very rare	Increases of amylase and/or lipase

*e.g., Pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, systemic candida.
†e.g., Herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis.

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.

Commonly severe transient acute cholinergic syndrome was observed. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, miosis, lacrimation and increased salivation occurring during or within the first 24 hours after the infusion of Irinotecan. These symptoms disappear after administration of atropine (see section 4.4).

Delayed diarrhoea

In monotherapy: Severe diarrhoea was observed in 20% of the patients who followed the recommendations for controlling diarrhoea. Severe diarrhoea was observed in 14% of the evaluable cycles. The median of the time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan.

In combination therapy: Severe diarrhoea was observed in 13.1% of the patients who followed recommendations for the management of diarrhoea. Of the evaluable treatment cycles, 3.9% have severe diarrhoea.

Blood Disorders

Neutropenia

Neutropenia was reversible and not cumulative; the median time to nadir was 8 days, both for the use of monotherapy or 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 treatment 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 treatment cycles. Infectious episodes occurred in about 10.3% of patients (2.5% of treatment cycles), and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and 2 cases resulted in death.

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 treatment cycles, 67.3 % had a neutrophil count <1,000 cells/mm^3 including 2.7% with a neutrophil count < 500 cells/mm^3. In general, total recovery was usually reached within 7-8 days.

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

Anaemia

With monotherapy:
Anaemia was reported in about 58.7% of patients (8% with haemoglobin < 8 g/dl and 0.9% with haemoglobin < 6.5

g/dl).
With combination therapy:
Anaemia was reported in 97.2% of patients (2.1% with haemoglobin < 8 g/dl).

Thrombocytopenia

With monotherapy:
Thrombocytopenia (< 100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% of patients with platelets count ≤ 50,000 cells/mm^3 and in 0.2% of cycles. Nearly all the patients reached a recovery by day 22.

With combination therapy:
Thrombocytopenia (< 100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No cases with severe thrombocytopenia (< 50,000 cells/mm³) have been observed.

One case of peripheral thrombocytopenia with formation of antiplatelet antibodies has been reported in the post-marketing experience.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace , IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: other antineoplastic agents

ATC Code: L01XX19

Experimental data

Irinotecan is a semisynthetic derivative of Camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of type I DNA topoisomerase. It is metabolized by carboxylesterases in most tissues, thus yielding SN-38, which was found to be more active than Irinotecan on purified type I topoisomerase and more cytotoxic than Irinotecan against several human and murine tumour lines. Inhibition of type I DNA topoisomerase by Irinotecan or SN-38 induces lesions in the single-stranded DNA, and these lesions block DNA replication fork and are responsible for the cytotoxicity. This cytotoxic effect was found to be time dependent and S-phase specific.

In vitro, Irinotecan and SN-38 are not significantly recognized by P-glycoprotein (MDR), and Irinotecan has a cytotoxic activity against cell lines resistant to Doxorubicin and Vinblastine.

In addition, 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 active against tumours expressing P-glycoprotein (MDR) (P388 leukaemia resistant to Doxorubicin and Vincristine).

In addition to the antitumor effect of Irinotecan, the most relevant pharmacological effect of Irinotecan is the inhibition of acetylcholinesterase.

Clinical data

In monotherapy for the second-line treatment of metastatic colorectal carcinoma

More than 980 patients with metastatic colorectal cancer, who had not been successful with a previous 5-FU treatment, were enrolled in clinical phase II/III studies, with the every-3-week dosage schedule. The efficacy of Irinotecan was evaluated in 765 patients with disease progression during the 5-FU treatment, at the moment of the entry to the study.

	Phase III					
	Irinotecan versus best supportive care (BSC)			Irinotecan versus 5-FU		
	Irinotecan	BSC	p values	Irinotecan	5-FU	p values
	n = 183	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

In phase II studies conducted in 455 patients with the every-3-week dosing schedule of three weeks, the disease-free survival at 6 months was 30% and the median survival time was 9 months. The median time to progression was 18 weeks.

Additionally, non-comparative phase II studies were conducted on 304 patients by weekly administration of a dose of 125 mg/m^2 as an intravenous infusion over a period of 90 minutes during 4 consecutive weeks, followed by a rest period of 2 weeks. In these studies, the median time to the onset of progression was 17 weeks and the median survival time was 10 months. A similar safety profile was observed on the weekly dosing schedule in 193 patients with an initial dose of 125 mg/m^2, compared to the 3-week dosing schedule. The mean time to onset of liquid stools was day 11.

In combination therapy *for the first-line treatment of metastatic colorectal carcinoma*

In combination therapy with Folinic Acid and 5-Fluorouracil

-

-

A phase III study was conducted on 385 patients with metastatic colorectal cancer receiving first line treatment, either by administering the treatment every 2 weeks (see section 4.2) or every week. In the every-2-week schedule, on the first day, the administration of Irinotecan at 180 mg/m^2 once every 2 weeks was followed by infusion of FA (200 mg/m^2 as a 2-hour intravenous infusion) and of 5-FU (400 mg/m^2 as an intravenous bolus, followed by 600 mg/m^2 as a 22-hour intravenous infusion). On day 2, FA and 5-FU were administered using the same doses and schedules. In the weekly schedule, the administration of Irinotecan at 80 mg/m^2 was followed by infusion of FA (500 mg/m^2 as a 2-hour intravenous infusion) and then of 5-FU (2,300 mg/m^2 as a 24-hour intravenous infusion) over 6 weeks.

In the combination treatment trial with the 2 regimens described above, the efficacy of Irinotecan was evaluated in 198 patients:

	Combined	Weekly schedule	Every-2-week

	regimens (n=198)		(n=50)		schedule (n=148)	
	Irin. +5-FU/FA	5-FU/FA	Irin. +5-FU/FA	5-FU/FA	Irin. +5-FU/FA	5-FU/FA
Response rate (%)	40,8 *	23,1 *	51,2 *	28,6 *	37,5 *	21,6 *
p value	p < 0,001		p = 0,045		p = 0,005	
Median time to progression (months)	6,7	4,4	7,2	6,5	6,5	3,7
p value	p < 0,001		NS		p = 0,001	
Median duration of response (months)	9,3	8,8	8,9	6,7	9,3	9,5
p value	NS		p = 0,043		NS	
Median duration of response and stabilisation (months)	8,6	6,2	8,3	6,7	8,5	5,6
p value	p < 0,001		NS		p = 0,003	
Median time to treatment failure (months)	5,3	3,8	5,4	5,0	5,1	3,0
p value	p = 0,0014		NS		p < 0,001	
Median survival (months)	16,8	14,0	19,2	14,1	15,6	13,0
p value	p = 0,028		NS		p = 0,041	

Irin.: Irinotecan
5-FU: 5-fluorouracil,
FA: folinic acid,
NS: nonsignificant,
*: as per protocol population 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.

Additionally, the median time to definitive performance status deterioration was significantly longer in the group that received Irinotecan in combination with 5-FU/FA than in the group receiving 5-FU/FA alone (p = 0.046).

Quality of life was assessed in this phase III study by using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration occurred constantly later in the Irinotecan groups. The global health status/quality of life was slightly better in the Irinotecan combination group although not significantly, showing that efficacy of Irinotecan in combination treatment could be reached without affecting the quality of life.

In combination therapy with Cetuximab

EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of Cetuximab and Irinotecan plus infusion of 5-Fluorouracil/Folinic acid (5-FU/FA) (599 patients) to the same chemotherapy without Cetuximab (599 patients). The proportion of patients with *KRAS wild- type* tumours within the patient population evaluable for KRAS status was 64%.

The efficacy data generated in this study are summarised in the table below:

	Overall population		KRAS wild-type population	
Variable/statistic	Cetuximab plus FOLFIRI (N=599)	FOLFIRI (N=599)	Cetuximab plus FOLFIRI (N=172)	FOLFIRI (N=176)
ORR				

% (95% CI)	46.9 (42.9, 51.0)	38.7 (34.8, 42.8)	59.3 (51.6, 66.7)	43.2 (35.8, 50.9)
p value	0.0038		0.0025	
PFS				
Hazard Ratio (95% CI)	0.85 (0.726, 0.998)		0.68 (0.501, 0.934)	
P value	0.0479		0.0167	

CI = confidence interval, FOLFIRI = Irinotecan plus infusion of 5-FU/FA, ORR = objective response rate (patients with complete response or partial response), PFS = progression-free survival time

In combination with Cetuximab after failure of Irinotecan-including cytotoxic therapy

The efficacy of the combination of Cetuximab with Irinotecan was investigated in two clinical studies. A total of 356 patients with EGFR-expressing metastatic colorectal cancer in whom a cytotoxic therapy including Irinotecan had recently failed, having a minimum Karnofsky performance status of 60%, the majority of whom having a Karnofsky performance status of ≥ 80 % received the combination treatment.

EMR 62 202-007: This randomised study compared the combination of Cetuximab and Irinotecan (218 patients) with Cetuximab monotherapy (111 patients).

IMCL CP02-9923: This single arm open-label study investigated the combination therapy in 138 patients.

The efficacy data from these studies are summarised in the table below.

Study	n	ORR		DCR		PFS (months)		OS (months)	
		n [%]	95 % CI	n [%]	95 % CI	Median	95 % CI	Median	95 % CI
Cetuximab + Irinotecan									
EMR 62 202-007	218	50 (22,9)	17,5; 29,1	121 (55,5)	48,6; 62,2	4,1	2,8; 4,3	8,6	7,6; 9,6
IMCL CP02-9923	138	21 (15,2)	9,7; 22,3	84 (60,9)	52,2; 69,1	2,9	2,6; 4,1	8,4	7,2; 10,3
Cetuximab									
EMR 62 202-007	111	12 (10,8)	5,7; 18,1	36 (32,4)	23,9; 42,0	1,5	1,4; 2,0	6,9	5,6; 9,1
CI = confidence interval; DCR = disease control rate (patients with complete response, partial response or stable disease for at least 6 weeks); ORR = objective response rate (patients with complete response or partial response); OS = overall survival time; PFS = progression-free survival									

The efficacy of the combination of Cetuximab with Irinotecan was higher than that of Cetuximab monotherapy, in terms of objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). In the randomised trial, no effects on overall survival were demonstrated (hazard ratio 0.91, p = 0.48).

In combination therapy with Bevacizumab

A phase III randomised, double-blind, active-controlled clinical trial evaluated Bevacizumab in combination with Irinotecan/5-FU/FA as first-line treatment for colon or rectum metastatic carcinoma (study AVF2107g). The addition of Bevacizumab to the combination of Irinotecan/5-FU/FA resulted in a statistically significant increase in overall survival. The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved and duration of metastatic disease. Refer also to the Bevacizumab summary of product characteristics. The efficacy results of study AVF2107g are summarised in the table below.

	Arm 1	Arm 2

	Irinotecan/5-FU/FA/placebo	Irinotecan/5-FU/FA/Bevacizumab [a]
Number of patients	411	402
Overall survival		
Median time [months]	15,6	20,3
95 % Confidence interval	14,29 – 16,99	18,46 – 24,18
Hazard ratio [b]		0,660
p value		0,00004
Progression-free survival		
Median time [months]	6,2	10,6
Hazard ratio [b]		0,54
p value		<0,0001
Overall response rate		
Rate [%]	34,8	44,8
95 % Confidence interval	30,2 – 39,6	39,9 – 49,8
p value		0,0036
Duration of response		
Mean time [months]	7,1	10,4
25 – 75 Percentile [months]	4,7 – 11,8	6,7 – 15,0
[a] 5 mg/kg every 2 weeks; [b] Relative to control arm.		

In combination therapy with Capecitabine

Data from a randomised, controlled phase III study (CAIRO) support the use of Capecitabine at a starting dose of 1000 mg/m^2 for 2 weeks every 3 weeks in combination with Irinotecan for the first-line treatment of patients with metastatic colorectal cancer. 820 Patients were randomized to receive either sequential treatment (n = 410) or combination treatment (n = 410). Sequential treatment consisted of first-line treatment with Capecitabine (1250 mg/m^2 twice daily for 14 days), second-line with Irinotecan (350 mg/m^2 on day 1), and third-line with a combination of Capecitabine (1000 mg/m^2 twice daily for 14 days) with Oxaliplatin (130 mg/m^2 on day 1). Combination treatment consisted of first-line treatment of Capecitabine (1000 mg/m^2 twice daily for 14 days) combined with Irinotecan (250 mg /m^2 on day 1) (XELIRI) and second-line treatment with Capecitabine (1000 mg/m^2 twice daily for 14 days) plus Oxaliplatin (130 mg/m^2 on day 1). All treatment cycles were administered at intervals of 3 weeks. In first-line treatment, the median progression-free survival in the population planned for treatment was 5.8 months (95% CI, 5.1-6.2 months) for Capecitabine monotherapy and 7.8 months (95% CI, 7.0-8.3 months) for XELIRI (p = 0.0002).

Data from an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) support the use of Capecitabine at a starting dose of 800 mg/m^2 for 2 weeks every 3 weeks in combination with Irinotecan and Bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. 115 randomised patients were treated with Capecitabine combined with Irinotecan (XELIRI) and Bevacizumab: Capecitabine (800 mg/m^2 twice daily for two weeks, followed by a 7-day rest period), Irinotecan (200 mg/m^2 administered as a 30 minute infusion on day 1 every 3 weeks), and Bevacizumab (7.5 mg/kg administered as a 30 to 90 minute infusion on day 1 every 3 weeks); a total of 118 randomised patients were treated with Capecitabine combined with Oxaliplatin plus Bevacizumab: Capecitabine (1000 mg/m^2 twice daily for two weeks followed by a 7-day rest period), Oxaliplatin (130 mg/m^2 administered as a 2 hour infusion on day 1 every 3 weeks), and Bevacizumab (7.5 mg/kg administered as a 30 to 90 minute infusion on day 1 every 3 weeks). Progression-free survival at 6 months in the intent to treat population was 80% (XELIRI plus Bevacizumab) versus 74 % (XELOX plus Bevacizumab). Overall response rate (complete response plus partial response) was 45 % (XELOX plus Bevacizumab) versus 47 % (XELIRI plus Bevacizumab).

Pharmacokinetic/Pharmacodynamic data

The intensity of the major toxic effects arising with Irinotecan (e.g., diarrhoea and neutropenia) is related to the exposure (AUC, area under the curve) to the original drug and to the metabolite SN-38. In monotherapy, a significant correlation was observed between the intensity of hematologic toxicity (decrease of leukocytes and neutrophils at nadir) or the intensity of diarrhoea and the AUC values, both of Irinotecan and of the metabolite SN-38.

Patients with Reduced UGT1A1 Activity:

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). 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. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced activity of this enzyme. Data from a meta analysis indicate that individuals with Crigler-Najjar syndrome (types 1 and 2) or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of haematological toxicity (grades 3 and 4) following administration of irinotecan at moderate or high doses (>150 mg/m^2). A relationship between UGT1A1 genotype and the occurrence of irinotecan induced diarrhea was not established.

Patients known to be homozygous for UGT1A1*28 should be administered the normally indicated irinotecan starting dose. However, these patients should be monitored for haematologic toxicities. A reduced irinotecan starting dose should be considered for patients who have experienced prior haematologic toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on a patient's tolerance of the treatment. (see sections 4.2 and 4.4)

There is at present insufficient data to conclude on clinical utility of UGT1A1 genotyping

5.2 Pharmacokinetic properties

In a phase I study in 60 patients on a dosage regimen with an intravenous infusion of 30 minutes with 100 to 750 mg/m^2, once every three weeks, Irinotecan showed biphasic or triphasic elimination. Mean plasma clearance was 15 l/h/m^2 and volume of distribution at steady state (Vdss) had a value of 157 l/m^2. The mean plasma half-life of the first phase of the three phase model was 12 minutes, that of the second phase was 2.5 hours, and the terminal phase half-life was 14.2 hours. The SN-38 showed biphasic elimination with a mean elimination half-life in the terminal phase of 13.8 hours. At the end of the infusion, with the recommended dose of 350 mg/m^2, the mean peak plasma concentrations of Irinotecan and SN-38 were 7.7 µg/ml and 56 ng/ml, respectively, and the mean of area under the curve (AUC) values were 34 µg.h/ml and 451 ng h/ml, respectively. A large interindividual variability of pharmacokinetic parameters is generally observed for SN-38.

A population pharmacokinetic analysis of Irinotecan has been conducted in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. The pharmacokinetic parameters estimated with a three compartment model were similar to those observed in phase I studies. All studies have shown that the exposure to Irinotecan (CPT-11) or SN-38 increases proportionally with the CPT-11 dose administered; their pharmacokinetic behaviours are independent of the number or previous cycles and of the administration schedule.

Binding of plasma proteins to Irinotecan and SN-38 *in vitro* was approximately 65% and 95%, respectively.

Mass balances and metabolic studies conducted with the drug labelled with C-14 revealed that more than 50% of the dose of Irinotecan administered intravenously is excreted as unchanged drug, 33% is eliminated by the stool, especially in the bile, and 22 % through the urine.

Two metabolic pathways are responsible for at least 12% of the dose:

- Hydrolysis mediated by carboxylesterases yielding the active metabolite SN-38, which is eliminated primarily by glucuronidation and still excreted by the renal and biliary routes (less than 0.5% of the dose of Irinotecan). It is likely that the SN-38-glucuronide is subsequently hydrolyzed in the intestines.

- Oxidation promoted by the CYP3A enzymes, resulting in the opening of the outer ring of piperidine with formation of the aminopentanoic acid derivative (PCA) and of the primary amine derivative (NPC) (see section 4.5).

In the plasma, the main entity is unchanged Irinotecan, followed by APC, SN-38-glucuronide and SN-38. Only the SN-38 has a significant cytotoxic effect.

Irinotecan clearance decreases by about 40% in patients with bilirubinemia between 1.5 and 3 times above the upper normal limit. In these patients, a dose of 200 mg/m^2 Irinotecan leads to a plasma exposure to the drug comparable to that observed with 350 mg/m^2 in cancer patients with normal liver parameters.

5.3 Preclinical safety data

Irinotecan and SN-38 proved to be mutagenic in the in vitro chromosomal aberration assay in CHO cells as well as in the *in vivo* micronucleus test in mice. However, they were shown not to have any mutagenic potential in the Ames test.

In rats treated once a week for 13 weeks to a maximum dose of 150 mg/m^2 (less than half the recommended human dose), there were no treatment-related tumours reported within a period of 91 weeks after therapy.

Toxicity studies were conducted with single dose and repeated doses in mice, rats and dogs. The main toxic effects were observed in the lymphatic and hematopoietic systems. In dogs, it was reported to have occurred delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa. It was also observed alopecia in dogs. The severity of these effects was dose-related, and they were reversible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E420)
Lactic acid (E270)
Sodium hydroxide and/or 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 3 years.

The vials of Irinotecan for injections should be used immediately once they are opened, since they contain no antimicrobial preservatives.

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 72 hours at 2-8 °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

Keep the vials in the outer carton. Do not freeze

The vials Irinotecan Hydrochloride concentrate for solution for infusion shall be kept protected from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

• 2 ml in Onco-Tain® Type 1 brown glass vial, with a fluorobutyl rubber closure coated with Teflon on the inner side.

• 5 ml in Onco-Tain® Type 1 brown glass vial, with a fluorobutyl rubber closure coated with Teflon on the inner side.

• 25 ml in Onco-Tain® Type 1 brown glass vial, with a fluorobutyl rubber closure coated with Teflon on the inner side.

Each pack contains 1 vial. Not all pack sizes may be marketed.

Onco-Tain® is the vial external protection system, a property of Hospira.

6.6 Special precautions for disposal and other handling

The solution must be diluted before use. For single use only. Any remaining solution should be discarded.

The appearance of the product after dilution is a clear, colourless to pale yellow solution free from visible matter.

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 using aseptic technique (see section 6.3).

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 concentrate from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle containing either 9 mg/ml (0.9%) sodium chloride solution or 50 mg/ml (5%) glucose solution only. 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 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0437/051/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th April 2004

Date of last renewal: 10th June 2013

10 DATE OF REVISION OF THE TEXT

June 2018