Certificate Number: PP10112214

SUMMARY OF PRODUCT CHARACTERISTICS

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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:

Includes sorbitol, (E420) 45.0 mg/ml

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

A clear colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Irinotecan 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 (see section 5.1).

Irinotecan in combination with 5-FU, FA and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

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

Recommended dosage

Dosages of irinotecan mentioned in this summary of product characteristics refer to mg of irinotecan hydrochloride trihydrate.

In monotherapy (for previously treated patients)

SUMMARY OF PRODUCT CHARACTERISTICS

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The recommended dose of irinotecan is 350 mg/m^2 administered as an intravenous infusion over a 30 to 90 minute period every three weeks (see sections 4.4 and 6.6).

In combination therapy (for previously untreated patients)

The safety and efficacy of irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) have been assessed in the following schedule (see section 5.1)

- Irinotecan plus 5-FU/FA every 2 weeks schedule

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

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

At the start of a subsequent infusion treatment, the dose of irinotecan, and 5-FU 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 and/or 5-FU when applicable:

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

Recommendations for dose modifications of cetuximab when administered in combination with irinotecan must be followed according to the product information for this medicinal product.

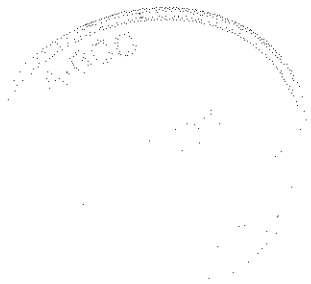
Refer to the bevacizumab summary of product characteristics for dose modifications of bevacizumab when administered in combination with irinotecan/5-FU/FA.

In combination with capecitabine for patients 65 years of age or more, a reduction of the starting dose of capecitabine to 800 mg/m^2 twice daily is recommended according to the summary of product characteristics for capecitabine. Refer also to the recommendations for dose modifications in combination regimen given in the summary of product characteristics for capecitabine.

Treatment duration

Treatment with irinotecan should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations



SUMMARY OF PRODUCT CHARACTERISTICS

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Patients with impaired hepatic function

Monotherapy:

Blood bilirubin levels (up to 3 times the upper limit of the normal range [ULN]), in patients with WHO performance status ≤ 2, should determine the initial dose of irinotecan. In these patients with hyperbilirubinaemia and prothrombin time greater than 50%, the clearance of irinotecan is reduced (see section 5.2), and therefore the risk of haematotoxicity 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 carried out 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.

Pregnancy and lactation (see sections 4.4 and 4.6).

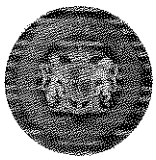
Bilirubin > 3 times the ULN (see section 4.4).

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 product information for these medicinal products.



SUMMARY OF PRODUCT CHARACTERISTICS

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4.4 Special warnings and precautions for use

The use of irinotecan 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 will only be prescribed in the following cases after the expected benefits have been weighed 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 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 ≥ 2 and women. If not appropriately treated, the diarrhoea can be life threatening, especially if the patient is concomitantly neutropenic.

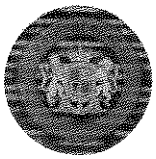
As soon as the first liquid stool occurs, the patient should start drinking large volumes of liquid containing electrolytes, and an adequate antidiarrhoeal therapy must be initiated immediately. Specific arrangements must be made to ensure that the clinic which administers irinotecan will also prescribe the antidiarrhoeal 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 clinic where irinotecan was administered, when/if diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment consists of high doses of loperamide (4 mg initially, followed by 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, and the treatment should last at least 12 hours.

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

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

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high dose loperamide therapy.



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Loperamide should not be given prophylactically, even to patients who have experienced delayed diarrhoea during previous drug administrations.

If the patient has had severe diarrhoea, a reduction in the dose is recommended for subsequent cycles (see section 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 ≤ 1,000 cells/mm^3) should be urgently treated in hospital with broad-spectrum intravenous antibiotics.

A dose reduction for subsequent administration is recommended for 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 patients with severe diarrhoea, a complete blood cell count should be taken.

Patients with reduced uridine diphosphate glucuronosyltransferase (UGT1A1) activity

SN-38 is detoxified by UGT1A1 to SN-38 glucuronide. Individuals with a congenital deficiency of UGT1A1 (Crigler-Najjar syndrome type 1 and type 2 or individuals who are homozygous for the UGT1A1*28 allele [Gilbert's syndrome]) are at increased risk of toxicity from irinotecan. A reduced initial dose should be considered for these patients.

Impaired hepatic function

Liver function tests should be taken at baseline and before each drug administration cycle.

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

Nausea and vomiting

Prophylactic treatment with an antiemetic is recommended before each administration of irinotecan. Nausea and vomiting occur frequently. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

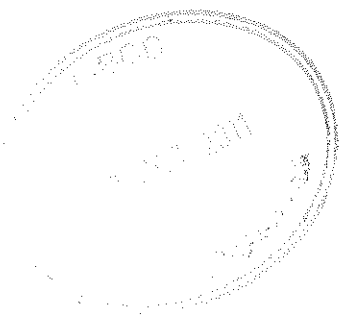
Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and certain other symptoms such as sweating, abdominal cramps, lacrimation, miosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8).

Caution should be exercised in the treatment of patients with asthma. If the patient experiences an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent administration of irinotecan.

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.



SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Elderly

Due to the greater frequency of decreased biological functions, for example hepatic function, in elderly patients, dose selection with irinotecan treatment should be used with caution in this population (see section 4.2).

Patients with 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 carried out 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 where the patients have been dehydrated in association with diarrhoea and/or vomiting, or had sepsis.

Women of childbearing potential and men must use effective contraceptive measures 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.

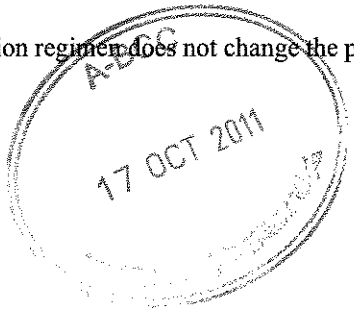
Several studies have shown that concomitant administration of cytochrome P450 3A (CYP3A) inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs were reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of CYP3A 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 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 concurrently taking drugs known to inhibit (e.g. ketoconazole) or induce (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin) drug metabolism by CYP3A4. 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. 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.



SUMMARY OF PRODUCT CHARACTERISTICS

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

In one study, irinotecan concentrations were similar in patients receiving irinotecan/5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analysed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN-38 were on average 33 % higher in patients receiving irinotecan/5-FU/FA in combination with bevacizumab compared with irinotecan/5-FU/FA alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leukocytopenia adverse events. More dose reductions of irinotecan were reported for patients receiving irinotecan/5-FU/FA in combination with bevacizumab.

Patients who develop severe diarrhoea, leukocytopenia or neutropenia with the bevacizumab and irinotecan combination should have irinotecan dose modifications as specified in section 4.2.

4.6 Pregnancy and lactation

Pregnancy

There is no information on the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, irinotecan should not be used during pregnancy (see sections 4.3 and 4.4).

Women of child-bearing potential:

Women of childbearing age receiving irinotecan should inform the treating physician immediately should pregnancy occur (see sections 4.3 and 4.4). Contraceptive measures must be taken by women of childbearing potential and also by male patients during and for at least three months after treatment.

Lactation

In lactating rats, ^{14}C-irinotecan has been detected in milk. It is not known whether irinotecan is excreted in human milk. Breast-feeding must be discontinued for the duration of irinotecan treatment due to the potential of adverse effects in nursing infants (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 product information for cetuximab.

For information on adverse reactions in combination with bevacizumab, refer to the bevacizumab 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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

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.

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, and from 145 patients treated by 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. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common: ≥ 1/10

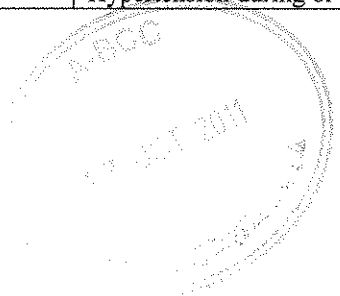
Common: ≥ 1/100 to < 1/10

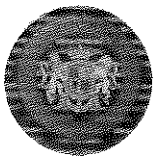
Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10,000 to < 1/1,000

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

Body System	Frequency	Adverse Reaction
Infections and Infestations	Uncommon	In patients who experienced sepsis, renal insufficiency, hypotension or cardio-circulatory failure have been observed
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
Immune System Disorders	Uncommon	Mild allergy reactions
	Rare	Anaphylactic/ Anaphylactoid reactions
Metabolism and Nutrition Disorders	Very rare	Tumour lysis syndrome
Nervous System Disorders	Very rare	Transient speech disorder
Cardiac	Rare	Hypertension during or following the infusion





SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Body System	Frequency	Adverse Reaction
Disorders		
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 in case of combination therapy Episodes of dehydration (associated with diarrhoea and/or vomiting). Constipation related to irinotecan and/or loperamide.
	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, 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	Mild cutaneous reaction
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
Investigations	Very common	In 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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Body System	Frequency	Adverse Reaction
		bilirubin were observed in the absence of progressive liver metastasis. Transient and mild to moderate increases of serum levels of creatinine. In combination therapy, transient grade 3 serum levels of bilirubin.
	Rare	Hypokalemia Hyponatremia
	Very rare	Increases of amylase and/or lipase

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, vasodilation, 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 atropine administration (see section 4.4).

Delayed diarrhoea

In monotherapy: Severe diarrhoea was observed in 20% of the patients who followed the 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.

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 day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy: Neutropenia was observed in 78.7% of patients and was severe (neutrophil count < 500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count < 1,000 cells/mm^3 including 7.6% with a neutrophil count < 500 cells/mm^3. Total recovery was usually reached by day 22. Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles. Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.

In combination therapy: Neutropenia was observed in 82.5% of patients and was severe (neutrophil count < 500 cells/mm^3) in 9.8 % of patients. Of the evaluable cycles, 67.3 % had a neutrophil count <1,000 cells/mm^3 including 2.7% with a neutrophil count < 500 cells/mm^3. Total recovery was usually reached within 7-8 days. Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles.

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

SUMMARY OF PRODUCT CHARACTERISTICS

Printed for Certificate of Pharmaceutical Product

Anaemia

In 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).

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

Thrombocytopenia

In 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/mm³ and 0.2% of cycles. Nearly all the patients showed a recovery by day 22.

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

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

4.9 Overdose

There have been reports of overdosage, at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhoea. There is no known antidote for irinotecan. 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

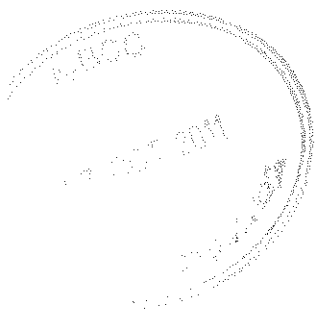
Experimental data

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which has been 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 block the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic effect has been found to be time-dependent and specific to the S-phase.

In vitro, irinotecan and SN-38 are not significantly recognised by the P-glycoprotein (MDR), and irinotecan displays cytotoxic activity against doxorubicin- and vinblastine-resistant cell lines.

Furthermore, irinotecan has a broad antitumour 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 the P-glycoprotein (MDR) (vincristine- and doxorubicin-resistant P388 leukaemias).

In addition to the antitumour effect of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.



SUMMARY OF PRODUCT CHARACTERISTICS

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Clinical data

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

More than 980 patients with metastatic colorectal cancer, who had failed a previous 5-FU treatment, were enrolled in clinical phase II/III studies, in the every 3 week dosage schedule. The efficacy of irinotecan was evaluated in 765 patients with disease progression during 5-FU treatment at study entry.

	Phase III					
	Irinotecan versus best supportive care (BSC)			Irinotecan versus 5-FU		
	Irinotecan	Supportive care	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, carried out on 455 patients with the 3 weekly dosage schedule, 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.

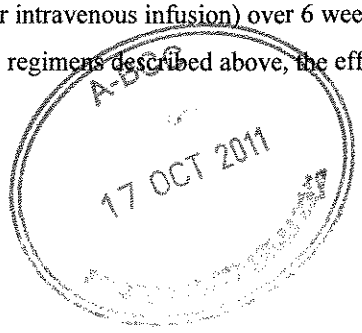
In addition, non-comparative phase II studies were carried out on 304 patients by administering weekly a dose of 125 mg/m^2 as an intravenous infusion over a 90 minute period for 4 consecutive weeks followed by a 2-week rest period. In these studies, the median time to the start of progression was 17 weeks and median survival time was 10 months. A similar safety profile has been observed in the weekly dosage schedule in 193 patients at the starting dose of 125 mg/m^2, compared to the 3 weekly dosage schedule. The median time of onset of the liquid stool was on 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 carried out 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 2 weekly 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 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 with FA (500 mg/m^2 as a 2-hour intravenous infusion) and then by 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:



SUMMARY OF PRODUCT CHARACTERISTICS

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	Combined regimens (n=198)		Weekly schedule (n=50)		Every 2 weeks 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 *
	$p < 0.001$		$p = 0.045$		$p = 0.005$	
Median time to progression (months)	6.7	4.4	7.2	6.5	6.5	3.7
	$p < 0.001$		NS		$p = 0.001$	
Median duration of response (months)	9.3	8.8	8.9	6.7	9.3	9.5
	NS		$p = 0.043$		NS	
Median duration of response and stabilisation (months)	8.6	6.2	8.3	6.7	8.5	5.6
	$p < 0.001$		NS		$p = 0.003$	
Median time to treatment failure (months)	5.3	3.8	5.4	5.0	5.1	3.0
	$p = 0.0014$		NS		$p < 0.001$	
Median survival (months)	16.8	14.0	19.2	14.1	15.6	13.0
	$p = 0.028$		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 5-FU/FA alone group ($p = 0.046$).

Quality of life was assessed in this phase III study by using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred 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 infusional 5-fluorouracil/folinic acid (5-FU/FA) (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 64%.

SUMMARY OF PRODUCT CHARACTERISTICS

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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 infusional 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 who had recently failed irinotecan-including cytotoxic therapy and who had a minimum Karnofsky performance status of 60%, but the majority of whom had 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.

SUMMARY OF PRODUCT CHARACTERISTICS

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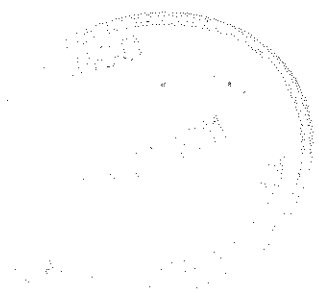
The efficacy data from these studies are summarised in the table below.

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 superior to 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 metastatic carcinoma of the colon or rectum (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.



SUMMARY OF PRODUCT CHARACTERISTICS

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	Arm 1 Irinotecan/5-FU/FA/placebo	Arm 2 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		
Median 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 irinotecan (350 mg/m^2 on day 1), and third-line 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 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 intent-to-treat population 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).

SUMMARY OF PRODUCT CHARACTERISTICS

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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 patients were randomised to treatment 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 as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks); a total of 118 patients were randomised to treatment 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 as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg 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 encountered with irinotecan (e.g., neutropenia and diarrhoea) is related to the exposure (AUC) to the parent drug and the metabolite SN-38. In monotherapy, a significant correlation was noted between the intensity of haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity, and the AUC values of both irinotecan and the SN-38 metabolite.

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/m² every three weeks, irinotecan showed a biphasic or thriphasic elimination profile. The mean plasma clearance was 15 l/h/m² and the volume of distribution at steady state (Vss): 157 l/m². The mean plasma half-life of the first phase of the 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/m², the mean peak plasma concentrations of irinotecan and SN-38 were 7.7 µg/ml and 56 ng/ml, respectively, and the mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.

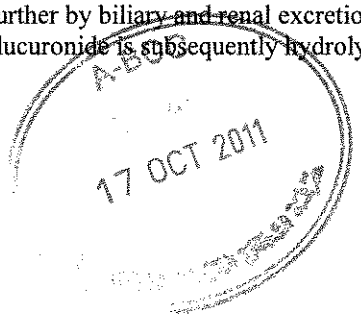
A population pharmacokinetic analysis of irinotecan has been performed in 148 patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three compartment model were similar to those observed in phase 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 or previous cycles and of the administration schedule.

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

Mass balance and metabolic studies conducted with 14-C labelled drug have shown that more than 50 % of an irinotecan dose administered intravenously eliminates as unchanged drug, 33 % eliminates via faeces mainly via the bile and 22 % via urine.

Two metabolic pathways account each for at least 12 % of the dose:

- Hydrolysis mediated by carboxylesterase to active SN-38 metabolite. SN-38 eliminates mainly by glucuronidation and excretes further by biliary and renal excretion (less than 0.5 % of the irinotecan dose). It is likely that SN-38-glucuronide is subsequently hydrolysed in the intestine.



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

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

Irinotecan clearance is decreased by about 40 % in patients with bilirubinaemia between 1.5 and 3 times above the upper normal limit. In these patients an irinotecan dose of 200 mg/m^2 leads to plasma drug exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal hepatic 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 (less than half the human recommended dose), no treatment-related tumours were reported within 91 weeks of the end of treatment.

Single- and repeated-dose toxicity studies 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 dogs. The severity of these effects was dose-related and 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.

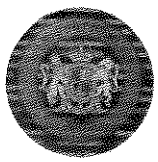
6.3 Shelf life

Unopened: 3 years.

Once opened vials should be used immediately as they contain no antibacterial preservatives.

Stability following dilution:

Chemical and physical in-use stability has been demonstrated in glucose 50 mg/ml (5%) and 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 times and conditions prior to use are



SUMMARY OF PRODUCT CHARACTERISTICS

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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 vials in the outer carton. Do not freeze.

Vials of irinotecan hydrochloride concentrate for solution for infusion should be protected from light.

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

6.5 Nature and contents of container

- 40 mg/2 ml: One 5 ml Onco-Tain® Type 1 brown glass vial, with a fluorobutyl rubber closure coated with teflon on the inner side.
- 100 mg/5 ml: One 5 ml Onco-Tain® Type 1 brown glass vial, with a fluorobutyl rubber closure coated with teflon on the inner side.
- 500 mg/25 ml: One 30 ml 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, propriety of Hospira.

6.6 Special precautions for disposal

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

As with other antineoplastic agents, irinotecan infusions must be prepared and handled with caution. The use of goggles, mask and gloves is required. Pregnant women should not handle cytotoxics.

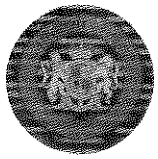
If irinotecan concentrate or infusion solutions should come into contact with the skin, it must be washed off immediately and thoroughly with soap and water. If irinotecan concentrate or infusion solutions should come into contact with the mucous membranes, it must be washed off immediately with water.

Preparation of the intravenous infusion: As with any other infusion, irinotecan infusion must be prepared 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.



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7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04515/0227

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/3/2009

10 DATE OF REVISION OF THE TEXT

20/10/2009