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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Irinotecan 20 mg/ml Concentrate for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution contains 20 mg/ml irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/ml irinotecan). Each vial of 2 ml contains 40 mg; each vial of 5 ml contains 100 mg; each vial of 15 ml contains 300 mg and each vial of 25 ml contains 500 mg of irinotecan hydrochloride trihydrate.

Also contains sorbitol. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for Solution for Infusion.
Light yellow coloured 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 and folinic acid in patients without prior chemotherapy for advanced disease,
- as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2 Posology and method of administration

For adults only. After dilution, Irinotecan concentrate for solution for infusion should be infused into a peripheral or central vein.

Recommended dosage

In monotherapy (for previously treated patient)

The recommended dosage of Irinotecan is 350 mg/m² 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 patient)

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

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

The recommended dose of Irinotecan is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.

Dosage adjustments

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

At the start of a subsequent infusion of therapy, the dose of Irinotecan, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15% to 20% should be applied for Irinotecan and/or 5FU when applicable:

- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3 to 4 and fever grade 2 to 4), thrombocytopenia and leukopenia (grade 4)),

- non haematological toxicity (grade 3 to 4).

Treatment Duration

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

Special populations

Patients with Impaired Hepatic Function: In monotherapy: Blood bilirubin levels (up to 3 times the upper limit of the normal range (UNL)) in patients with performance status ≤2, should determine the starting dose of Irinotecan. In these patients with hyperbilirubinemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (see section 5.2) and therefore the risk of hematotoxicity is increased. Thus, weekly monitoring of complete blood counts should be conducted in this patient population.

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of Irinotecan is 350 mg/m²,

- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan is 200 mg/m²,

- Patients with bilirubin beyond to 3 times the ULN should not be treated with Irinotecan (see sections 4.3 and 4.4).

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

Patients with Impaired Renal Function: Irinotecan is not recommended for use in patients with impaired renal function, as studies in this population have not been conducted. (See sections 4.4 and 5.2).

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

4.3 Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of Irinotecan.
- Pregnancy and lactation (see sections and 4.4 and 4.6).
- Bilirubin >3 times the upper limit of the normal range (see section 4.4).
- Severe bone marrow failure.
- WHO performance status >2
- Concomitant use with St John's Wort (see section 4.5)

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 weighted against the possible therapeutic risks:

- in patients presenting a risk factor, particularly those with a WHO performance status = 2.
- in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea). Strict hospital supervision is recommended for such patients.

When Irinotecan is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see section 5) may be considered in patients who may need a closer follow-up or who are at particular risk of severe neutropenia.

Delayed diarrhoea

Patients should be made aware of the risk of delayed diarrhoea occurring more than 24 hours after the administration of Irinotecan and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline hyperleucocytosis, those with performance status ≥2 and women. If not properly treated, diarrhoea can be life threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where Irinotecan has been administered. After discharge from the hospital, the patients should obtain the prescribed drugs so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their physician or the department administering Irinotecan when/if diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment consists of high doses of loperamide (4 mg for the first intake and then 2 mg every 2 hours). This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the anti-diarrhoeal treatment, a prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count <0,5 x 10^9/l, i.e. <500 cells/mm³).

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

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

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).

Haematology

Weekly monitoring of complete blood cell counts is recommended during Irinotecan treatment. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature >38 °C and neutrophil count ≤1.0 x 10^9/l, i.e. ≤1,000 cells/mm³) should be urgently treated in the hospital with broad-spectrum intravenous antibiotics.

In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration (see section 4.2).

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea. In patients with severe diarrhoea, complete blood cell counts should be performed.

Liver impairment

Liver function tests should be performed at baseline and before each cycle.

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

Nausea and vomiting

A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan. Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and various other symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8). Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of Irinotecan.

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.

Elderly

Due to the greater frequency of decreased biological functions, in particular hepatic function, in elderly patients, dose selection with Irinotecan should be cautious in this population (see section 4.2).

Patients with bowel obstruction

Patients must not be treated with Irinotecan until resolution of the bowel obstruction (see section 4.3).

Patients with Impaired Renal Function

Studies in this population have not been conducted. (see sections 4.2 and 5.2).

Others

Since this medicinal contains sorbitol, it is unsuitable in hereditary fructose intolerance. Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis. Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Concomitant administration of irinotecan with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's Wort) of CYP3A4 may alter the metabolism of irinotecan and should be avoided (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since Irinotecan has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

Several studies have shown that concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects.

The effects of such anticonvulsant drugs was reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

A study has shown that the co-administration of ketoconazole resulted in a decrease in the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided (see section 4.4).

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

St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).

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

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4.6 Pregnancy and lactation

Pregnancy

There is no information on the use of Irinotecan in pregnant women. Contraceptive measures must be taken during and for at least three months after cessation of therapy.

Irinotecan has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan must not be used during pregnancy (see sections 4.3 and 4.4).

Women of childbearing potential

Women of childbearing age receiving Irinotecan should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur (see sections 4.3 and 4.4).

Lactation

In lactating rats, ^{14}C-irinotecan was detected in milk. It is not known whether irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding must be discontinued for the duration of Irinotecan therapy (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

The following adverse reactions considered to be possibly or probably related to the administration of irinotecan have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy, and from 145 patients treated by irinotecan in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m².

The most serious and/or most frequently occurring adverse events of irinotecan, both in monotherapy and in combination therapy, were gastrointestinal (diarrhoea, nausea, vomiting constipation), haematological (neutropenia, anaemia, thrombocytopenia), fever, asthenia, Acute Cholinergic Syndrome, infections and alopecia.

The frequencies in the following table are defined using the following convention: 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).

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Further details are given after this table.

MedDRA System Organ Classes	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)
Gastrointestinal Disorders					
Monotherapy	Diarrhoea[1] Abdominal pain Severe nausea Severe vomiting	Mucositis Constipation[2]	Pseudo-membranous colitis Intestinal obstruction Ileus Gastrointestinal haemorrhage	Colitis[3] Intestinal perforation	
Combination Therapy	Diarrhoea[1] Abdominal pain Mucositis	Severe nausea Severe vomiting Constipation[2]	Pseudo-membranous colitis Intestinal obstruction Ileus Gastrointestinal haemorrhage	Colitis[3] Intestinal perforation	
Blood and Lymphatic System Disorders					
Monotherapy	Neutropenia Anaemia	Neutropenia with fever Thrombocytopenia			
Combination Therapy	Neutropenia Anaemia Thrombocytopenia	Neutropenia with fever			Autoimmune Thrombocytopenia
General Disorders and Administration Site Conditions					
Monotherapy	Fever[4]	Acute Cholinergic Syndrome Severe asthenia	Infusion Site Reactions		
Combination Therapy		Acute Cholinergic Syndrome Severe asthenia Fever[4]			
Infections and Infestations					
Monotherapy	Infectious Episodes[5]				
Combination Therapy		Infectious Episodes[5]			
Metabolism and Nutrition Disorders					
Monotherapy	Dehydration[6]	Anorexia			
Combination Therapy	Dehydration[6] Anorexia				
Vascular Disorders					
Monotherapy			Hypotension[7] Cardio-circulatory failure[7]	Hypertension	
Combination Therapy					
Renal and urinary disorders					
Monotherapy			Renal insufficiency[7]		
Combination Therapy					
Respiratory, Thoracic and Mediastinal Disorders					
Monotherapy	Dyspnoea		Interstitial		

Combination Therapy		Dyspnoea	pulmonary disease		

Skin and Subcutaneous Tissue Disorders					
Monotherapy	Alopecia		Cutaneous reactions		
Combination Therapy					
Immune System Disorders					
Monotherapy			Allergic reactions	Anaphylactic reactions	
Combination Therapy					
Investigations					
Monotherapy		Serum transaminases increase Serum alkaline phosphatase increase Serum bilirubin increase Serum creatinine increase		Hypokalemia Hyponatremia	Amylase and/or lipase increase
Combination Therapy	Serum SGOT increase (Grades 1 and 2) Serum SGPT increase (Grades 1 and 2) Serum alkaline phosphatase increase (Grades 1 and 2) Serum bilirubin increase (Grades 1 and 2)	Serum bilirubin increase (Grade 3)			
Nervous System Disorders					
Monotherapy					Transient speech disorders
Combination Therapy					

[1] Can be severe, delayed and associated with fever.
[2] Associated with irinotecan and/or loperamide
[3] Including typhlitis, and ischemic or ulcerative colitis.
[4] Fever, in the absence of infection and severe neutropenia.
[5] With or without severe neutropenia.
[6] Commonly associated with diarrhoea and/or vomiting.
[7] Due to dehydration associated with diarrhoea and/or vomiting, or sepsis.

Gastrointestinal disorders

Delayed diarrhoea

Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity of Irinotecan.

In monotherapy

Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have a 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 patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have a severe diarrhoea.

Uncommon cases of pseudo-membranous colitis have been reported, one of which has been documented bacteriologically *(Clostridium difficile)*.

Blood disorders

Neutropenia is a dose-limiting toxic effect. Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy

Neutropenia was observed in 78.7% of patients and was severe (neutrophil count <0.5 x 10^9/l, i.e. <500 cells/mm³) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1.0 x 10^9/l (<1,000 cells/mm³) including 7.6% with a neutrophil count <0.5 x 10^9/l (<500 cells/mm³).

Total recovery was usually reached by day 22.

Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles.

Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.

Anaemia was reported in about 58.7% of patients (8% with haemoglobin <80 g/l and 0.9% with haemoglobin <65 g/l).

Thrombocytopenia (<100 x 10^9/l, i.e. <100,000 cells/mm³) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets count ≤50 x 10^9/l (≤50,000 cells/mm³) and 0.2% of cycles.

Nearly all the patients showed a recovery by day 22.

In combination therapy

Neutropenia was observed in 82.5% of patients and was severe (neutrophil count <0.5 x 10^9/l, i.e. <500 cells/mm³) in 9.8% of patients.

Of the evaluable cycles, 67.3% had a neutrophil count below 1.0 x 10^9/l (<1,000 cells/mm³) including 2.7% with a neutrophil count below 0.5 x 10^9/l, i.e. <500 cells/mm³.

Total recovery was usually reached within 7 to 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 one case.

Anaemia was reported in 97.2% of patients (2.1% with haemoglobin <80 g/l).

Thrombocytopenia (<100 x 10^9/l, i.e. <100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (<50 x 10^9/l, i.e. <50,000 cells/mm³) has been observed.

One case of peripheral autoimmune thrombocytopenia has been reported in the post-marketing experience.

General disorders and infusion site reactions

Acute cholinergic syndrome

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

Asthenia was severe in less then 10% of patients in monotherapy and in 6.2 % of patients in combination therapy. Fever without infection and without severe neutropenia was present in 12% of patients in monotherapy and in 6.3% in patients in combination therapy.

Respiratory disorders

Interstitial pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects such as dyspnoea have been reported (see section 4.4).

Skin and subcutaneous tissue disorders

Alopecia was very common and reversible.

Musculoskeletal disorders

Early effects such as muscular contraction or cramps have been reported.

Nervous system disorders

Paresthesia has been reported.

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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 care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were not found to be significantly recognised by the P-glycoprotein MDR, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumor activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinomas) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemia's).

Beside the antitumor activity of Irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetyl cholinesterase.

Clinical data

In monotherapy

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

	Phases III					
	Irinotecan versus supportive care			Irinotecan versus 5FU		
	Irinotecan n=183	Supportive care n=90	P values	Irinotecan n=127	5FU n=129	p values
Progression Free Survival at 6 months (%)	NA	NA		33.5*	26.7	p=0.03
Survival at 12 months (%)	36.2*	13.8	P=0.0001	44.8*	32.4	p=0.0351
Median survival (months)	9.2*	6.5	p=0.0001	10.8*	8.5	p=0.0351

NA : Not Applicable
* : Statistically significant difference

In phase II studies, performed on 455 patients in the every 3-week dosage schedule, the progression free survival at 6 months was 30% and the median survival was 9 months. The median time to progression was 18 weeks.

Additionally, non-comparative phase II studies were performed in 304 patients treated with a weekly schedule regimen, at a dose of 125 mg/m² administered as an intravenous infusion over 90 minutes for 4 consecutive weeks followed by 2 weeks rest. In these studies, the median time to progression was 17 weeks and median survival was 10 months. A similar safety profile has been observed in the weekly-dosage schedule in 193 patients at the starting dose of 125 mg/m², compared to the every 3-week-dosage schedule. The median time of onset of the first liquid stool was on day 11.

In combination therapy

A phase III study was performed in 385 previously untreated metastatic colorectal cancer patients treated with either every 2 weeks schedule (see section 4.2) or weekly schedule regimens. In the every 2 weeks schedule, on day 1, the administration of Irinotecan at 180 mg/m² once every 2 weeks is followed by infusion with folinic acid (200 mg/m² over a 2-hour intravenous infusion) and 5-fluorouracil (400 mg/m² as an intravenous bolus, followed by 600 mg/m² over a 22-hour intravenous infusion). On day 2, folinic acid and 5-fluorouracil are administered at the same doses and schedules. In the weekly schedule, the administration of Irinotecan at 80 mg/m² is followed by infusion with folinic acid (500 mg/m² over a 2-hour intravenous infusion) and then by 5-fluorouracil (2300 mg/m² over a 24-hour intravenous infusion) over 6 weeks.

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

	Combined regimens (n=198)		Weekly schedule (n=50)		Every 2 weeks schedule (n=148)	
	Irinotecan +5FU/FA	5FU/FA	Irinotecan +5FU/FA	5FU/FA	Irinotecan +5FU/FA	5FU/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 & 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	

5FU : 5-fluorouracil, FA : folinic acid
NS : Not Significant
*: As per protocol population analysis

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in patients treated by Irinotecan in combination with 5FU/FA and 25.6% in patients treated by 5FU/FA alone. The incidence of severe neutropenia (neutrophil count <0.5 x 10^9/l, i.e. <500 cells/mm³) was 5.8% in patients treated by Irinotecan in combination with 5FU/FA and in 2.4% in patients treated by 5FU/FA alone.

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

Quality of life was assessed in this phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the Irinotecan

groups. The evolution of the Global Health Status/Quality of life was slightly better in Irinotecan combination group although not significant; showing that efficacy of Irinotecan in combination could be reached without affecting the quality of life.

Pharmacokinetic/Pharmacodynamic data

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

5.2 Pharmacokinetic properties

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous Yinfusion of 100 mg/m² to 750 mg/m² every three weeks, irinotecan showed a biphasic or triphasic 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 of previous cycles and of the administration schedule.

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

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

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

- Hydrolysis by carboxylesterase into active metabolite SN-38, SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose) The SN-38 glucuronite is subsequently probably hydrolysed in the intestine.

- Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

Unchanged irinotecan is the major entity in plasma, followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity.

Irinotecan clearance is decreased by about 40% in patients with bilirubinemia between 1.5 and 3 times the upper normal limit. In these patients a 200 mg/m² irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters.

5.3 Preclinical safety data

Irinotecan and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice.

However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m² (which is less than half the human recommended dose), no treatment related tumours were reported 91 weeks after the end of treatment.

Single and repeated-dose toxicity studies with Irinotecan have been carried out in mice, rats and dogs. The main toxic effects were seen in the haematopoietic and lymphatic systems. In dogs, delayed diarrhoea associated with atrophy and focal necrosis of the intestinal mucosa was reported. Alopecia was also observed in the dog.

The severity of these effects was dose-related and reversible.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- sorbitol
- lactic acid
- water for injections and
- sodium hydroxide (for pH-adjustment)

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 2 years.

Chemical and physical in-use stability has been demonstrated for 24 hours below 25°C and for 48 hours at 2°C to 8°C.

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

6.4 Special precautions for storage

Store below 25 °C. Keep vial in the outer carton in order to protect from light. Do not freeze.

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

6.5 Nature and contents of container

Irinotecan 40 mg/2 ml and 100 mg/5 ml Concentrate for Solution for Infusion: 6 ml amber type – I tubular glass vials stoppered with 20 mm grey elastomeric closures sealed with 20 mm aluminium flip off overseals.

Irinotecan 300 mg/15 ml Concentrate for Solution for Infusion: 20 ml amber type – I tubular glass vials stoppered with 20 mm grey elastomeric closures sealed with 20 mm aluminium flip off overseals.

Irinotecan 500 mg/25 ml Concentrate for Solution for Infusion: 30 ml amber type – I tubular glass vials stoppered with 20 mm grey elastomeric closures sealed with 20 mm aluminium flip off overseals.

Irinotecan 20 mg/ml Concentrate for Solution for Infusion is available as 40 mg/2 ml, 100 mg/5 ml, 300 mg/15 ml and 500 mg/25 ml presentations, single-vial pack size.

6.6 Special precautions for disposal and other handling

Handling

For single use only. As with other antineoplastic agents, caution should be exercised when handling Irinotecan. The use of glasses, mask and gloves is required. Dilution should be carried out under aseptic conditions by trained personnel in a designated area. Precautions should be taken to avoid contact with the skin and mucous membranes.

If Irinotecan solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If Irinotecan solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.

Preparation for the intravenous infusion administration

As with any other injectable drugs, IRINOTECAN SOLUTION MUST BE PREPARED ASEPTICALLY (see section 6.3).

Instructions for dilution

Irinotecan concentrate for solution for infusion is intended for intravenous infusion only after diluting prior to administration in the recommended diluents, either 0.9% sodium chloride solution for infusion or 5% glucose solution for infusion. Aseptically withdraw the required amount of Irinotecan concentrate for solution from the vial with a calibrated syringe and inject into a 250 ml infusion bag or bottle. The infusion should be thoroughly mixed by manual rotation.

If any precipitate is observed in the vials or after reconstitution, the product should be discarded according to standard procedures for cytotoxic agents.

Protection instructions for preparation of Irinotecan solution for infusion.

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Opened containers, like injection vials and infusion bottles and used cannulae, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
3. Follow the instructions below in case of spillage:
   - protective clothing should be worn
   - broken glass should be collected and placed in the container for HAZARDOUS WASTE
   - contaminated surfaces should be flushed properly with copious amounts of cold water
   - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
4. In the event of Irinotecan contact with the skin, the area should be rinsed with running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
5. In case of contact of Irinotecan with eyes, wash them thoroughly with plenty of water. Contact an ophthalmologist immediately.

Disposal

All materials used for the preparation, administration or otherwise coming into contact with irinotecan should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

7. MARKETING AUTHORISATION HOLDER

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United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

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