1. NAME OF THE MEDICINAL PRODUCT

Irinotecan Hydrochloride medac 20 mg/mL, concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One millilitre of the concentrate for solution for infusion contains 20 mg irinotecan hydrochloride trihydrate, equivalent to 17.33 mg irinotecan.

Each vial of 2 mL contains 40 mg of irinotecan hydrochloride trihydrate (40 mg/2 mL).
Each vial of 5 mL contains 100 mg of irinotecan hydrochloride trihydrate (100 mg/5 mL).
Each vial of 15 mL contains 300 mg of irinotecan hydrochloride trihydrate (300 mg/15 mL).
Each vial of 25 mL contains 500 mg of irinotecan hydrochloride trihydrate (500 mg/25 mL).
Each vial of 50 mL contains 1000 mg of irinotecan hydrochloride trihydrate (1000 mg/50 mL).

Excipients with known effect
Sorbitol (E 420)
This medicine contains 45 mg sorbitol per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear yellow solution.

pH 3.0 – 3.8

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Irinotecan Hydrochloride medac is indicated for the treatment of patients with advanced colorectal cancer:

- in combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
- as a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.

Irinotecan Hydrochloride medac 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 Hydrochloride medac in combination with 5-fluorouracil, folinic acid and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

Irinotecan Hydrochloride medac 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

Posology

For adults only. After dilution the irinotecan solution for infusion should be infused into a peripheral or central vein.

Recommended dose:

In monotherapy (for previously treated patients)
The recommended dose of irinotecan is 350 mg/m² administered as an intravenous infusion over a 30- to 90-minute period every 3 weeks (see sections 4.4 and 6.6).

In combination therapy (for previously untreated patients)
Safety and efficacy of irinotecan in combination with 5-fluorouracil (5-FU) and folinic acid (FA) have been assessed with the following schedule (see section 5.1).

- Irinotecan plus 5-FU/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.

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.

Dose 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 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 – 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 – 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 leukocytopenia [grade 4]).

- non-haematological toxicity (grade 3 – 4).

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

In combination with capecitabine for patients 65 years of age or more, a reduction of the starting dose of capecitabine to 800 mg/m² twice daily is recommended according to the summary of product characteristics for capecitabine. Refer also to the recommendations for dose modifications in combination regimen given in the summary of product characteristics for capecitabine.

Treatment duration:

Treatment with irinotecan 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 [ULN]) in patients with WHO performance status ≤ 2 should determine the starting dose of irinotecan. In these patients with hyperbilirubinaemia and prothrombin time greater than 50%, the clearance of irinotecan is decreased (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 up to 1.5 times the ULN, the recommended dose of irinotecan is 350 mg/m².

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

- Patients with bilirubin beyond 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).

Paediatric population
The safety and efficacy of irinotecan in children have not yet been established. No data are available.

Method of administration

Precautions to be taken before handling or administering the medicinal product

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Breast-feeding (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).
- Live attenuated vaccines (see section 4.5).

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

4.4 Special warnings and precautions for use

The use of irinotecan 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-dose schedule. However, the weekly-dose 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 hyperleukocytosis, those with WHO 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 medicinal products 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 antidiarrhoeal treatment, a prophylactic broad-spectrum antibiotic should be given, when 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

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

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

Haematology

In clinical studies, the frequency of NCI CTC grade 3 and 4 neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1.0 mg/dl or more have also had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dl.

Weekly monitoring of complete blood cell counts is recommended during irinotecan treatment. 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/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.

Patients with reduced UGT1A1 activity

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment. This risk increases with the irinotecan dose level.
Although a precise dose reduction in starting dose has not been established, a reduced irinotecan starting dose should be considered for patients that are UGT1A1 poor metabolisers, especially patients who are administered doses >180 mg/m² or frail patients. Consideration should be given to applicable clinical guidelines for dose recommendations in this patient population. Subsequent doses may be increased based on individual patient tolerance to treatment.
UGT1A1 genotyping can be used to identify patients at increased risk of severe neutropenia and diarrhoea, however the clinical utility of pre-treatment genotyping is uncertain, since UGT1A1 polymorphism does not account for all the toxicity seen from irinotecan therapy (see section 5.2).

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 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 the 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 signs and symptoms such as sweating, abdominal cramping, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see section 4.8).
These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more frequently with higher irinotecan doses.
Caution should be exercised in patients with asthma. In patients who experienced an acute and severe cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of irinotecan.

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 medicinal products, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

Extravasation

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

Elderly

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

Patients with chronic inflammatory bowel disease and/or bowel obstruction

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

Renal function

Increases in serum creatinine or blood urea nitrogen have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhoea. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Irradiation therapy

Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in treating patients with extensive prior irradiation (e.g. > 25% of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan). Dosing adjustment may apply to this population (see section 4.2).

Cardiac disorders

Myocardial ischaemic events have been observed following irinotecan therapy predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8).
Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Vascular disorders

Irinotecan has been rarely associated with thromboembolic events (pulmonary embolism, venous thrombosis, and arterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Others

Concomitant administration of irinotecan with a strong inhibitor (e.g., ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, apalutamide) of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided (see section 4.5).

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.

Contraception in women of childbearing potential/men

Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.
Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan (see section 4.6).

Breast-feeding
Due to the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of irinotecan therapy (see sections 4.3 and 4.6).

Excipients

This medicine contains sorbitol (see section 2). Sorbitol is a source of fructose. Patients with hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.

Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use contraindicated (see section 4.3)
Saint John’s wort: Decrease in the active metabolite of irinotecan, SN-38, plasma levels. 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. As a result, St. John’s wort should not be administered together with irinotecan.

Live attenuated vaccines (e.g. yellow fever vaccine): Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with irinotecan and for 6 months following discontinuation of chemotherapy. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Concomitant use not recommended (see section 4.4)
Concurrent administration of irinotecan with an inducer of cytochrome P450 3A4 (CYP3A4) may alter the metabolism of irinotecan and should be avoided (see section 4.4):

Strong CYP3A4 and/or UGT1A1 inducing medicinal products: (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, or apalutamide)
Risk of reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. Several studies have shown that concomitant administration of CYP3A-inducing anticonvulsant medicinal products leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant medicinal products were reflected by a decrease in AUC of SN-38 and SN-38 glucuronide by 50% or more. In addition to induction of cytochrome P450 3A4 enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites. Additionally with phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products.

Strong CYP3A4 inhibitors: (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, protease inhibitors, clarithromycine, erythromycine, telithromycine)
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.

UGT1A1 inhibitors: (e.g. atazanavir, ketoconazole, regorafenib)
Risk to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration if the combination is unavoidable.

Other CYP3A4 inhibitors: (e.g. crizotinib, idelalisib)
Risk of increase in irinotecan toxicity, due to a decrease in irinotecan metabolism by crizotinib or idelalisib.

Caution for use
Vitamin K antagonists: Increased risk of haemorrhage and thrombotic events in tumoural diseases. If vitamin K antagonists are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Concomitant use to take into consideration
Immunodepressant agents: (e.g. ciclosporine, tacrolimus): Excessive immunosuppression with risk of lymphoproliferation.

Neuromuscular blocking agents: Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since irinotecan has anticholinesterase activity, the neuromuscular blocking effects of suxamethonium may be prolonged and the neuromuscular blockade of non-depolarising active substances may be antagonised.

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

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38. However, this does not preclude any increase of toxicities due to their pharmacological properties.

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

Antineoplastic agents (including flucytosine as a prodrug for 5-fluorouracil): Adverse effects of irinotecan, such as myelosuppression, may be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

4.6 Fertility, pregnancy and lactation

Contraception
Due to the potential for genotoxicity, advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan (see section 4.4).

Due to the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of irinotecan (see section 4.4).

Pregnancy
There are limited data from the use of irinotecan in pregnant women. Irinotecan has been shown to be embryotoxic and teratogenic in animals (see section 5.3). Therefore, based on results from animal studies and the mechanism of action of irinotecan, irinotecan should not be used during pregnancy unless clearly necessary.
Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

Breast-feeding
The available data are limited but suggested that irinotecan and its metabolite are excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding should be discontinued for the duration of irinotecan therapy (see section 4.3 and 4.4).

Fertility
There are no human data on the effect of irinotecan on fertility. In animals adverse effects of irinotecan on the fertility of offspring has been documented (see section 5.3). **Prior to starting to take Irinotecan medac consider advising patients on the preservation of gametes.**

4.7 Effects on ability to drive and use machines

Irinotecan has moderate influence on the 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

CLINICAL STUDIES
Adverse reaction data have been extensively collected from studies in metastatic colorectal cancer; the frequencies are presented below. The adverse reactions for other indications are expected to be similar to those for colorectal cancer.

The most common (≥ 1/10), dose-limiting adverse reactions of irinotecan are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.

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

Very commonly severe transient acute cholinergic syndrome was observed.

The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, sweating, myosis and increased salivation occurring during or within the first 24 hours after the infusion of irinotecan. These symptoms disappear after atropine administration (see section 4.4).

MONOTHERAPY
The following adverse reactions considered to be possibly or probably related to the administration of irinotecan have been reported from 765 patients at the recommended dose of 350 mg/m² in monotherapy. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Adverse reactions reported with irinotecan in monotherapy (350 mg/m² every 3 weeks schedule)		
MedDRA System Organ Class	**Frequenc Category**	**Preferred Term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Neutropenia
	Very common	Anaemia
	Common	Thrombocytopenia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Very common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Pyrexia
	Very common	Asthenia
Investigations	Common	Blood creatinine increased
	Common	Transaminases (ALT and AST) increased
	Common	Blood bilirubin increased
	Common	Blood alkaline phosphatase increased

Description of selected adverse reactions (monotherapy)
Severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of irinotecan.
Nausea and vomiting were severe in approximately 10% of patients treated with antiemetics.
Constipation has been observed in less than 10% of patients.
Neutropenia was observed in 78.7% of patients and was severe (neutrophil count < 500 cells/mm ^{3}) in 22.6% of patients. Of the evaluable cycles, 18 % had a neutrophil count below 1,000 cells/mm³ including 7.6% with a neutrophil count < 500 cells/mm³.
Total recovery was usually reached by day 22.
Febrile neutropenia was reported in 6.2% of patients and in 1.7% of cycles.
Infections occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.
Anaemia was reported in about 58.7% of patients (8% with haemoglobin < 8 g/dl and 0.9% with haemoglobin < 6.5 g/dl).
Thrombocytopenia (< 100,000 cells/mm³) was observed in 7.4 % of patients and 1.8% of cycles with 0.9% with platelets count ≤ 50,000 cells/mm^{3} and 0.2% of cycles.
Nearly all the patients showed a recovery by day 22.
Acute cholinergic syndrome
Severe transient acute cholinergic syndrome was observed in 9 % of patients treated in monotherapy.
Asthenia was severe in less than 10% of patients treated in monotherapy. The causal relationship to irinotecan has not been clearly established.
Pyrexia in the absence of infection and without concomitant severe neutropenia, occurred in 12 % of patients treated in monotherapy.
Laboratory tests
Transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2 %, 8.1 % and 1.8 % of the patients, respectively, in the absence of progressive liver metastasis.
Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3 % of the patients.

COMBINATION THERAPY
Adverse reactions detailed in this section refer to irinotecan.

There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*. In combination with cetuximab, additional reported adverse reactions were those expected with cetuximab (such as dermatitis acneiform 88%). For information on adverse reactions on irinotecan in combination with cetuximab, also refer to their respective summary of product characteristics.

Adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: *Very common, all grade adverse drug reactions*: thrombosis/embolism*; Common, all grade adverse drug reactions*: hypersensitivity, myocardial ischaemia/infarction; *Common, Grade 3 and Grade 4 adverse drug reactions*: febrile neutropenia. For complete information on adverse reactions of capecitabine, refer to the capecitabine summary product of characteristics.

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan and bevacizumab in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include*: Common, Grade 3 and Grade*

4 adverse drug reactions: neutropenia, thrombosis/embolism, hypertension, and myocardial ischemia/infarction. For complete information on adverse reactions of capecitabine and bevacizumab, refer to the respective capecitabine and bevacizumab summary of product characteristics.

Grade 3 hypertension was the principal significant risk involved with the addition of bevacizumab to bolus irinotecan/5-FU/FA. In addition, there was a small increase in the Grade 3/4 chemotherapy adverse events of diarrhoea and leukopenia with this regimen compared to patients receiving bolus irinotecan/5-FU/FA alone. For other information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary of product characteristics.

Irinotecan has been studied in combination with 5-FU and FA for metastatic colorectal cancer.

Safety data of adverse reactions from clinical studies demonstrate very commonly observed NCI Grade 3 or 4 possibly or probably related adverse events in the blood and the lymphatic system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders MedDRA System Organ Classes.

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

Adverse reactions reported with irinotecan in combination therapy (180 mg/m^2 every 2 weeks schedule)		
MedDRA System Organ Class	**Frequency Category**	**Preferred Term**
Infections and infestations	Common	Infection
Blood and lymphatic system disorders	Very common	Thrombocytopenia
	Very common	Neutropenia
	Very common	Anaemia
	Common	Febrile neutropenia
Metabolism and nutrition disorders	Very common	Decreased appetite
Nervous system disorders	Very common	Cholinergic syndrome
Gastrointestinal disorders	Very common	Diarrhoea
	Very common	Vomiting
	Very common	Nausea
	Common	Abdominal pain
	Common	Constipation
Skin and subcutaneous tissue disorders	Very common	Alopecia (reversible)
General disorders and administration site conditions	Very common	Mucosal inflammation
	Very common	Asthenia
	Common	Pyrexia
Investigations	Very common	Transaminases (ALT and AST) increased
	Very common	Blood bilirubin increased
	Very common	Blood alkaline phosphatase increased

Description of selected adverse reactions (combination therapy)
Severe diarrhoea was observed in 13.1% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9% have a severe diarrhoea.
A lower incidence of severe **nausea and vomiting** was observed (2.1% and 2.8% of patients respectively).
Constipation relative to irinotecan and/or loperamide has been observed in 3.4% of patients.

Neutropenia was observed in 82.5% of patients and was severe (neutrophil count < 500 cells/mm3) in 9.8% of patients. Of the evaluable cycles, 67.3% had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count < 500 cells/mm³. Total recovery was usually reached within 7-8 days.
Febrile neutropenia was reported in 3.4% of patients and in 0.9% of cycles.
Infections occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles), and resulted in death in 1 case.
Anaemia was reported in 97.2% of patients (2.1% with haemoglobin < 8 g/dl).
Thrombocytopenia (< 100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (< 50,000 cells/mm³) has been observed.
Acute cholinergic syndrome Severe transient acute cholinergic syndrome was observed in 1.4% of patients treated in combination therapy.
Asthenia was severe in 6.2% of patients treated in combination therapy. The causal relationship to irinotecan has not been clearly established.
Pyrexia in the absence of infection and without concomitant severe neutropenia, occurred in 6.2% of patients treated in combination therapy.
Laboratory tests Transient serum levels (Grades 1 and 2) of either SGPT, SGOT, alkaline phosphatase or bilirubin were observed in 15%, 11%, 11% and 10% of the patients, respectively, in the absence of progressive liver metastasis. Transient Grade 3 were observed in 0%, 0%, 0% and 1% of the patients, respectively. No Grade 4 was observed.
Increases of amylase and/or lipase have been very rarely reported.
Rare cases of hypokalaemia and hyponatraemia mostly related with diarrhoea and vomiting have been reported.

OTHER ADVERSE EVENTS REPORTED IN CLINICAL STUDIES WITH THE WEEKLY REGIMEN FOR IRINOTECAN
The following additional drug-related events have been reported in clinical studies with irinotecan: pain, sepsis, anorectal disorder, GI candida infection, hypomagnesaemia, rash, skin signs, gait disturbance, confusion, headache, syncope, flushing, bradycardia, urinary tract infection, breast pain, gamma-glutamyltransferase increased, extravasation, and tumour lysis syndrome, cardiovascular disorders (angina pectoris, cardiac arrest, myocardial infarction, myocardial ischaemia, peripheral vascular disorder, vascular disorder), and thromboembolic events (arterial thrombosis, cerebral infarction, cerebrovascular accident, deep vein thrombosis, peripheral embolism, pulmonary embolism, thrombophlebitis, thrombosis, and sudden death) (see section 4.4).

POST-MARKETING SURVEILLANCE
Frequencies from post-marketing surveillance are not known (cannot be estimated from available data).

MedDRA System Organ Class	**Preferred Term**
Infections and infestations	• Pseudomembranous colitis one of which has been documented bacteriologically (*Clostridium difficile*) • Sepsis • Fungal infections* • Viral infections†

Blood and lymphatic system disorders	• Thrombocytopenia with antiplatelet antibodies
Immune system disorders	• Hypersensitivity • Anaphylactic reaction
Metabolism and nutrition disorders	• Dehydration (due to diarrhoea and vomiting) • Hypovolaemia
Nervous system disorders	• Speech disorder generally transient in nature, in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan • Paraesthesia • Muscular contractions involuntary
Cardiac disorders	• Hypertension (during or after infusion) • Cardio circulatory failure‡
Vascular disorders	• Hypotension‡

Respiratory, thoracic and mediastinal disorders	• Interstitial lung disease presenting as lung infiltration is uncommon during irinotecan therapy; early effects such as dyspnoea have been reported (see section 4.4). • Dyspnoea (see section 4.4) • Hiccups
Gastrointestinal disorders	• Intestinal obstruction • Ileus: cases of ileus without preceding colitis have also been reported • Megacolon • Gastrointestinal haemorrhage • Colitis; in some cases, colitis was complicated by ulceration, bleeding, ileus, or infection. • Typhlitis • Colitis ischaemic • Colitis ulcerative • Symptomatic or asymptomatic pancreatic enzymes increased • Intestinal perforation
Hepatobiliary disorders	• Steatohepatitis • Hepatic steatosis
Skin and subcutaneous tissue disorders	• Skin reaction

Musculoskeletal and connective tissue disorders	• Cramps
Renal and urinary disorders	• Renal impairment and acute renal failure generally in patients who become infected and/or volume depleted from severe gastrointestinal toxicities[‡] • Renal insufficiency[‡]
General disorders and administration site conditions	• Infusion site reaction
Investigations	• Amylase increased • Lipase increased • Hypokalaemia • Hyponatraemia mostly related with diarrhoea and vomiting • Transaminases increased (i.e. AST and ALT) in the absence of progressive liver metastasis have been very rarely reported.

[*]e.g. Pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, systemic candida.
[†]e.g. Herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis.
[‡] Infrequent cases of renal insufficiency, hypotension or cardio circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
There have been reports of overdose 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.

Management
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

Pharmacotherapeutic group: Antineoplastic agents, topoisomerase 1 (TOP1) inhibitors, ATC code: L01CE02

Mechanism of action

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 block the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found to be 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 display cytotoxic activities 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 also active against tumours expressing the P-glycoprotein MDR (vincristine- and doxorubicin-resistant P388 leukaemias).

Pharmacodynamic effects

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

Clinical efficacy and safety

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 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 (2,300 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 + 5-FU/FA	5-FU/FA	Irinotecan + 5-FU/FA	5-FU/FA	Irinotecan + 5-FU/FA	5-FU/FA
Response rate (%)	40.8*	23.1*	51.2*	28.6*	37.5*	21.6*
p-value	< 0.001		0.045		0.005	
Median time to progression (months)	6.7	4.4	7.2	6.5	6.5	3.7
p-value	< 0.001		NS		0.001	
Median response duration (months)	9.3	8.8	8.9	6.7	9.3	9.5
p-value	NS		0.043		NS	
Median duration of response and stabilisation (months)	8.6	6.2	8.3	6.7	8.5	5.6
p-value	< 0.001		NS		0.003	
Median time to treatment failure (months)	5.3	3.8	5.4	5.0	5.1	3.0
p-value	0.0014		NS		< 0.001	
Median survival (months)	16.8	14.0	19.2	14.1	15.6	13.0
p-value	0.028		NS		0.041	
* as per protocol population analysis; 5-FU = 5-fluorouracil; FA = folinic acid; NS = not significant						

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in patients treated by irinotecan in combination with 5-FU/FA and 25.6% in patients treated by 5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm³) was 5.8% in patients treated by irinotecan in combination with 5-FU/FA and 2.4% in patients treated by 5-FU/FA alone.

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

Quality of life was assessed in this phase III study using the EORTC QLQ-C30 questionnaire. Time to definitive deterioration constantly occurred later in the irinotecan groups. The evolution of the Global Health Status/quality of life was slightly better in irinotecan combination group although not significant, showing that efficacy of irinotecan in combination could be reached without affecting the quality of life.

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.

	AVF2107g	
	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 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-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%.

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

Variable/statistic	Overall population		KRAS wild-type population	
	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 therapy with capecitabine

Data from a randomised, controlled phase III study (CAIRO) support the use of capecitabine at a starting dose of 1,000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. Eight hundred twenty (820) patients were randomised to receive either sequential treatment (n = 410) or combination treatment (n = 410). Sequential treatment consisted of first-line treatment with capecitabine (1,250 mg/m² twice daily for 14 days), second-line irinotecan (350 mg/m² on day 1), and third-line combination of capecitabine (1,000 mg/m² twice daily for 14 days) with oxaliplatin (130 mg/m² on day 1). Combination treatment consisted of first-line treatment of capecitabine (1,000 mg/m² twice daily for 14 days) combined with irinotecan (250 mg/m² on day 1) (XELIRI) and second-line capecitabine (1,000 mg/m² twice daily for 14 days) plus oxaliplatin (130 mg/m² 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).

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/m² for 2 weeks every 3 weeks in combination with irinotecan and bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. One hundred fifteen (115) patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: capecitabine (800 mg/m² twice daily for 2 weeks followed by a 7-day rest period), irinotecan (200 mg/m² 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 (1,000 mg/m² twice daily for 2 weeks followed by a 7-day rest period), oxaliplatin (130 mg/m² 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).

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

Clinical phase II/III studies were performed in the every-3-week-dose schedule in more than 980 patients 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.

Phase III trials	Irinotecan versus supportive care	Irinotecan versus 5-FU

	Irinotecan n = 183	Supportive care n = 90	p-value	Irinotecan n = 127	5-FU n = 129	p-value
Progression-free survival at 6 months (%)	NA	NA		33.5*	26.7	0.03
Survival at 12 months (%)	36.2*	13.8	0.0001	44.8*	32.4	0.0351
Median survival (months)	9.2*	6.5	0.0001	10.8*	8.5	0.0351
*statistically significant difference; NA = not applicable						

In phase II studies, performed on 455 patients in the every-3-week-dose 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-dose schedule in 193 patients at the starting dose of 125 mg/m², compared to the every-3-week-dose schedule. The median time of onset of the first liquid stool was on day 11.

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.
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).

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

In the phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 – 750 mg/m² every 3 weeks, the volume of distribution at steady state (Vss) was 157 L/m².

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

Biotransformation

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 glucuronide 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.

Elimination

In a phase I study in 60 patients with a dose regimen of a 30-minute intravenous infusion of 100 – 750 mg/m² every 3 weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/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.

Irinotecan clearance is decreased by about 40% in patients with bilirubinaemia between 1.5 and 3 times the ULN. 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.

Linearity/non-linearity

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 and SN-38 exposure increase proportionally with irinotecan administered dose; their pharmacokinetics are independent of the number of previous cycles and of the administration schedule.

Pharmacokinetic/pharmacodynamic relationships

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.

Patients with reduced UGT1A1 activity:

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. The most well-characterised UGT1A1 genetic variants are UGT1A1*28 and UGT1A1*6. These variants and other congenital deficiencies in UGT1A1 expression (such as Gilbert's syndrome and Crigler-Najjar) are associated with reduced activity of this enzyme.
Patients that are UGT1A1 poor metabolisers (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk of severe adverse reactions such as neutropenia and diarrhoea following administration of irinotecan, as a consequence of SN-38 accumulation. According to data from several meta-analyses, the risk is higher for patients receiving irinotecan doses >180 mg/m² (see section 4.4).
In order to identify patients at increased risk of experiencing severe neutropenia and diarrhoea, UGT1A1 genotyping can be used. Homozygous UGT1A1*28 occurs with a frequency of 8-20% in the European, African, Near Eastern and Latino population. The *6 variant is nearly absent in these populations. In the East Asian population the frequency of *28/*28 is about 1-4%, 3-8% for *6/*28 and 2-6% for *6/*6. In the Central and South Asian population the frequency of *28/*28 is around 17%, 4% for *6/*28 and 0.2% for *6/*6.

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.

Reproduction
Irinotecan was teratogenic in rats and rabbits at doses below the human therapeutic dose. In rats, pups born to treated animals with external abnormalities showed a decrease in fertility. This was not seen in morphologically normal pups. In pregnant rats there was a decrease in placental weight and in the offspring a decrease in foetal viability and increase in behavioural abnormalities.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol (E 420)
Lactic acid
Sodium hydroxide (to adjust to pH 3.5)
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

3 years.

Diluted medicinal product (solution for infusion)

After dilution in 0.9% sodium chloride solution or 5% glucose solution, chemical and physical in-use stability has been demonstrated for up to 6 hours at room temperature (approximately 25 °C) and ambient lighting or 48 hours if stored at refrigerated temperatures (approximately 2 °C – 8 °C).

From a microbiological point of view, the solution for infusion should be used immediately. 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 6 hours at room temperature or 24 hours if stored at 2 °C – 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Irinotecan Hydrochloride medac 40 mg:
2-mL brown glass vial, with a halobutyl rubber closure coated with a layer of an inert fluoropolymer on the inner side. Pack of one vial.

Irinotecan Hydrochloride medac 100 mg:

5-mL brown glass vial, with a halobutyl rubber closure coated with a layer of an inert fluoropolymer on the inner side. Pack of one vial.

Irinotecan Hydrochloride medac 300 mg:
15-mL brown glass vial, with a halobutyl rubber closure coated with a layer of an inert fluoropolymer on the inner side. Pack of one vial.

Irinotecan Hydrochloride medac 500 mg:
25-mL brown glass vial, with a halobutyl rubber closure coated with a layer of an inert fluoropolymer on the inner side. Pack of one vial.

Irinotecan Hydrochloride medac 1000 mg:
50-mL brown glass vial, with a halobutyl rubber closure coated with a layer of an inert fluoropolymer on the inner side. Pack of one vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

Preparation of the intravenous solution

As with any other injectable medicinal products, the Irinotecan Hydrochloride medac solution for infusion must be prepared aseptically (see section 6.3).

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

Aseptically withdraw the required amount of Irinotecan Hydrochloride medac concentrate for solution for infusion from the vial with a calibrated syringe and inject into a 250 mL infusion bag or bottle containing either 0.9% sodium chloride solution or 5% glucose solution. The solution for infusion should then be thoroughly mixed by manual rotation.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For single use only.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

PL 11587/0047

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10/2022