

## **1. NAME OF THE MEDICINAL PRODUCT**

Irinotecan 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).

Excipients: Sorbitol (E420).

For a 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 medac is indicated for the treatment of patients with advanced colorectal cancer

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

Irinotecan medac in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer after failure of irinotecan-including cytotoxic therapy.

Irinotecan 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.

## 4.2 Posology and method of administration

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

### Recommended dosage

*In monotherapy (for previously treated patients):*

The recommended dosage of irinotecan is 350 mg/m<sup>2</sup> 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/m<sup>2</sup> 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.

### 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 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.

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

### 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  $\leq 2$ , 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 dosage of irinotecan is 350 mg/m<sup>2</sup>.
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of irinotecan is 200 mg/m<sup>2</sup>.
- 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).

### **4.3 Contraindications**

- Chronic inflammatory bowel disease and/or bowel obstruction (see section 4.4).
- Severe hypersensitivity to irinotecan hydrochloride trihydrate or to any of the excipients of Irinotecan medac.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- Bilirubin > 3 times the ULN (see section 4.4).

- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant use with St. John's wort (see section 4.5).

For additional contraindications of cetuximab or bevacizumab, 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-dosage schedule. However, the weekly-dosage schedule (see section 5.1) 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  $\geq 2$  and women. If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where irinotecan 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 antidiarrhoeal treatment, a prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm<sup>3</sup>).

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 ≤ 1,000 cells/mm<sup>3</sup>) 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 uridine diphosphate glucuronosyltransferase (UGT1A1) activity

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

### 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 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 product contains sorbitol, patients with rare hereditary problems of fructose intolerance should not use this medicine.

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 3 months after cessation of therapy (see section 4.6).

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

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Since irinotecan has anticholinesterase activity, the neuromuscular blocking effects of suxamethonium may be prolonged 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, phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs were reflected by a decrease in AUC of SN-38 and SN-38 glucuronide 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 the principal oxidative metabolite APC of 87 % and in an increase in the AUC of SN-38 of 109 % in comparison to irinotecan given alone.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin) drug metabolism by CYP3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided (see section 4.4).

In a small pharmacokinetic study (n = 5), in which irinotecan 350 mg/m<sup>2</sup> 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. Therefore, St. John's wort should not be administered together with irinotecan (see section 4.3).

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

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

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

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

#### **4.6 Pregnancy and lactation**

##### Pregnancy

There is no information on the use of irinotecan in pregnant women.

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

##### Women of child-bearing potential

Women of child-bearing potential and men must use effective contraception during and up to 3 months after treatment. Women should inform the treating physician immediately should pregnancy occur (see sections 4.3 and 4.4).

##### Lactation

In lactating rats, <sup>14</sup>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**

Undesirable effects detailed in this section refer to irinotecan. There is no evidence that the safety profile of irinotecan is influenced by cetuximab or *vice versa*. In combination with cetuximab, additional reported undesirable effects were those expected with cetuximab (such as acne form rash 88 %). Therefore also refer to the product information for cetuximab.

For information on adverse reactions in combination with bevacizumab, refer to the bevacizumab summary of product characteristics.

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

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

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

#### *Delayed diarrhoea*

In 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.

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 severe diarrhoea.

#### Blood disorders

##### *Neutropenia*

Neutropenia was reversible and not cumulative; the median day to nadir was 8 days whatever the use in monotherapy or in combination therapy.

In monotherapy:

Neutropenia was observed in 78.7 % of patients and was severe (neutrophil count < 500 cells/mm<sup>3</sup>) in 22.6 % of patients. Of the evaluable cycles, 18 % had a neutrophil count < 1,000 cells/mm<sup>3</sup> including 7.6 % with a neutrophil count < 500 cells/mm<sup>3</sup>.

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 two cases.

In combination therapy:

Neutropenia was observed in 82.5 % of patients and was severe (neutrophil count < 500 cells/mm<sup>3</sup>) in 9.8 % of patients.

Of the evaluable cycles, 67.3 % had a neutrophil count < 1,000 cells/mm<sup>3</sup> including 2.7 % with a neutrophil count < 500 cells/mm<sup>3</sup>.

Total recovery was usually reached within 7 – 8 days.

Fever with severe neutropenia was reported in 3.4 % of patients and in 0.9 % of cycles.

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

### Anaemia

In monotherapy:

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

In combination therapy:

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

### Thrombocytopenia

In monotherapy:

Thrombocytopenia (< 100,000 cells/mm<sup>3</sup>) was observed in 7.4 % of patients and 1.8 % of cycles with 0.9 % with platelets ≤ 50,000 cells/mm<sup>3</sup> and 0.2 % of cycles.

Nearly all the patients showed a recovery by day 22.

In combination therapy:

Thrombocytopenia (< 100,000 cells/mm<sup>3</sup>) was observed in 32.6 % of patients and 21.8 % of cycles. No severe thrombocytopenia (< 50,000 cells/mm<sup>3</sup>) has been observed.

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

Side effects have been summarised in the table below with MedDRA frequencies. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common: ≥ 1/10

Common: ≥ 1/100 to < 1/10

Uncommon: ≥ 1/1,000 to < 1/100

Rare: ≥ 1/10,000 to < 1/1,000

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

Organ system	
Frequency	Side effects
Gastrointestinal disorders	
Very common	<ul style="list-style-type: none"><li>● Severe delayed diarrhoea</li><li>● Severe nausea and vomiting in case of monotherapy</li></ul>
Common	<ul style="list-style-type: none"><li>● Severe nausea and vomiting in case of combination therapy</li><li>● Episodes of dehydration (associated with diarrhoea and/or vomiting)</li><li>● Constipation relative to irinotecan and/or loperamide</li></ul>
Uncommon	<ul style="list-style-type: none"><li>● Pseudo-membranous colitis (one has been documented bacteriologically: <i>Clostridium difficile</i>)</li><li>● Renal insufficiency, hypotension or cardio-circulatory failure as a consequence of dehydration associated with diarrhoea and/or vomiting</li><li>● Intestinal obstruction, ileus, gastrointestinal haemorrhage</li></ul>

<b>Organ system</b>	
<b>Frequency</b>	<b>Side effects</b>
Rare	<ul style="list-style-type: none"> <li>● Colitis, including typhlitis, ischemic and ulcerative colitis</li> <li>● Intestinal perforation</li> <li>● Other mild effects include anorexia, abdominal pain and mucositis.</li> <li>● Symptomatic or asymptomatic pancreatitis</li> </ul>
<b>Blood and lymphatic system disorders</b>	
Very common	<ul style="list-style-type: none"> <li>● Neutropenia (reversible and not cumulative)</li> <li>● Anaemia</li> <li>● Thrombocytopenia in case of combination therapy</li> <li>● Infectious episodes in case of monotherapy</li> </ul>
Common	<ul style="list-style-type: none"> <li>● Febrile neutropenia</li> <li>● Infectious episodes in case of combination therapy</li> <li>● Infectious episodes associated with severe neutropenia resulting in death in three cases</li> <li>● Thrombocytopenia in case of monotherapy</li> </ul>
Very rare	<ul style="list-style-type: none"> <li>● One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.</li> </ul>
<b>Skin and subcutaneous tissue disorders</b>	
Very common	<ul style="list-style-type: none"> <li>● Alopecia (reversible)</li> </ul>
Uncommon	<ul style="list-style-type: none"> <li>● Mild cutaneous reactions</li> </ul>
<b>General disorders and administration site conditions</b>	
Very common	<ul style="list-style-type: none"> <li>● Fever in the absence of infection and without concomitant severe neutropenia in case of monotherapy</li> </ul>
Common	<ul style="list-style-type: none"> <li>● Fever in the absence of infection and without concomitant severe neutropenia in case of combination therapy</li> <li>● Severe transient acute cholinergic syndrome (The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lacrimation and increased salivation.)</li> <li>● Asthenia</li> </ul>
Uncommon	<ul style="list-style-type: none"> <li>● Infusion site reactions</li> </ul>
<b>Investigations</b>	
Very common	<ul style="list-style-type: none"> <li>● In combination therapy, transient serum levels (grade 1 and 2) of serum transaminases, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis.</li> </ul>
Common	<ul style="list-style-type: none"> <li>● In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in the absence of progressive liver metastasis.</li> <li>● In combination therapy, transient grade 3 serum levels of bilirubin</li> <li>● Transient and mild to moderate increases of serum levels of creatinine</li> </ul>
Rare	<ul style="list-style-type: none"> <li>● Hypokalemia and hyponatremia</li> </ul>
Very rare	<ul style="list-style-type: none"> <li>● Increases of amylase and/or lipase</li> </ul>
<b>Respiratory, thoracic and mediastinal disorders</b>	
Uncommon	<ul style="list-style-type: none"> <li>● Interstitial pulmonary disease presenting as pulmonary infiltrates</li> <li>● Early effects such as dyspnoea</li> </ul>
<b>Immune system disorders</b>	
Uncommon	<ul style="list-style-type: none"> <li>● Mild allergic reactions</li> </ul>

Organ system	
Frequency	Side effects
Rare	● Anaphylactic/anaphylactoid reactions
Infections and infestations	
Uncommon	● Renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.
Cardiac disorders	
Rare	● Hypertension during or following the infusion
Musculoskeletal and connective tissue disorders	
Rare	● Early effects such as muscular contraction or cramps and paraesthesia
Nervous system disorders	
Very rare	● Transient speech disorders
Metabolism and nutrition disorders	
Very rare	● Tumour lysis syndrome

## 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

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX19

#### Experimental data

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which 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).

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

### 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.

Phase III trials	Irinotecan versus best supportive care (BSC)			Irinotecan versus 5-fluorouracil (5-FU)		
	Irinotecan	BSC	p value	Irinotecan	5-FU	p value
Number of patients	183	90		127	129	
PFS 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
PFS = progression-free survival; NA = not applicable						

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/m<sup>2</sup> 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/m<sup>2</sup>, 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/m<sup>2</sup> once every 2 weeks is followed by infusion with folinic acid (200 mg/m<sup>2</sup> over a 2-hour intravenous infusion) and 5-fluorouracil (400 mg/m<sup>2</sup> as an intravenous bolus, followed by 600 mg/m<sup>2</sup> 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/m<sup>2</sup> is followed by infusion with folinic acid (500 mg/m<sup>2</sup> over a 2-hour intravenous infusion) and then by 5-fluorouracil (2,300 mg/m<sup>2</sup> over a 24-hour intravenous infusion) over 6 weeks.

In the combination therapy trial with the two 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)
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	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 stabi- lisation [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; 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 with 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/mm<sup>3</sup>) was 5.8 % in patients treated with 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 with cetuximab*

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,  $p = 0.48$ ).

#### *In combination 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.

	Arm 1 Irinotecan/5-FU/FA/placebo	Arm 2 Irinotecan/5-FU/FA/bevacizumab <sup>a</sup>
Number of patients	411	402
Overall survival		
<i>Median time [months]</i>	15.6	20.3
<i>95% Confidence interval</i>	14.29 – 16.99	18.46 – 24.18
<i>Hazard ratio<sup>b</sup></i>		0.660
<i>p value</i>		0.00004

	Arm 1 Irinotecan/5-FU/FA/placebo	Arm 2 Irinotecan/5-FU/FA/bevacizumab <sup>a</sup>
Progression-free survival		
<i>Median time [months]</i>	6.2	10.6
<i>Hazard ratio<sup>b</sup></i>		0.54
<i>p value</i>		< 0.0001
Overall response rate		
<i>Rate [%]</i>	34.8	44.8
<i>95% Confidence interval</i>	30.2 – 39.6	39.9 – 49.8
<i>p value</i>		0.0036
Duration of response		
<i>Median time [months]</i>	7.1	10.4
<i>25 – 75 Percentile [months]</i>	4.7 – 11.8	6.7 – 15.0

<sup>a</sup> 5 mg/kg every 2 weeks; <sup>b</sup> Relative to control arm.

#### Pharmacokinetic/Pharmacodynamic data

The intensity of the major toxicities encountered with irinotecan (e.g., neutropenia 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 infusion of 100 – 750 mg/m<sup>2</sup> every 3 weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 l/h/m<sup>2</sup> and the volume of distribution at steady state (V<sub>ss</sub>) was 157 l/m<sup>2</sup>. The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2.5 hours, and the terminal phase half-life was 14.2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the end of the infusion, at the recommended dose of 350 mg/m<sup>2</sup>, 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 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.

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

Mass balance and metabolism studies with <sup>14</sup>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.

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/m<sup>2</sup> irinotecan dose leads to plasma drug exposure comparable to that observed at 350 mg/m<sup>2</sup> in cancer patients with normal liver parameters.

### 5.3 Preclinical safety data

Irinotecan and SN-38 have been shown to be mutagenic *in vitro* in the chromosomal aberration test on CHO-cells as well as in the *in vivo* micronucleus test in mice. However, they have been shown to be devoid of any mutagenic potential in the Ames test.

In rats treated once a week during 13 weeks at the maximum dose of 150 mg/m<sup>2</sup> (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 (E420)  
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**

2 years.

#### Diluted medicinal product (solution for infusion)

After dilution in 0.9 % sodium chloride solution or 5 % dextrose 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 of the diluted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

Irinotecan 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 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 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.

Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

If Irinotecan 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 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 drugs, the Irinotecan 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 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 % dextrose solution. The solution for infusion should then be thoroughly mixed by manual rotation.

### Disposal

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

For single use only.

## **7. MARKETING AUTHORISATION HOLDER**

medac  
Gesellschaft für klinische Spezialpräparate mbH  
Fehlandtstr. 3  
20354 Hamburg  
Germany

## **8. MARKETING AUTHORISATION NUMBER(S)**

PL 11587/0047

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

02/04/2009

## **10. DATE OF REVISION OF THE TEXT**

13/03/2010