Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Irinotecan Teva 20 mg/ml concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients: Sorbitol
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
The solution is clear, from colourless to pale yellow and free from visible particles.
pH: 3.0 – 3.8
osmolarity: 300 – 310 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Irinotecan Teva concentrate for solution for infusion 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 Teva concentrate for solution for infusion 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 (see section 5.1).

Irinotecan Teva concentrate for solution for infusion 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 Teva concentrate for solution for infusion in combination with capecitabine with or without bevacizumab is indicated for first-line treatment of patients with metastatic colorectal carcinoma.

4.2 Posology and method of administration

For adults only!

Irinotecan Teva 20 mg/ml concentrate for solution for infusion should be infused into a peripheral or central vein.

Recommended dosage:
In monotherapy (for previously treated patient):
The recommended dosage of Irinotecan hydrochloride is 350 mg/m² administered as an intravenous infusion over a 30- to 90- minute period every three weeks (see sections 6.6 and 4.4).

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

Irinotecan hydrochloride plus 5FU/FA in every 2 weeks schedule
The recommended dose of Irinotecan hydrochloride 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.

Dosage adjustments:
Irinotecan Teva concentrate for solution for infusion 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 hydrochloride, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20% should be applied for Irinotecan hydrochloride and/or 5FU when applicable:
- haematological toxicity (neutropenia grade 4, febrile neutropenia (neutropenia grade 3-4 and fever grade 2-4), thrombocytopenia and leukopenia (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 product of characteristics for dose modifications of bevacizumab when administered in combination with Irinotecan/5FU/FA.

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

Treatment Duration:

Treatment with Irinotecan Teva concentrate for solution for infusion should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Special populations

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

- In patients with bilirubin up to 1.5 times the upper limit of the normal range (ULN), the recommended dosage of Irinotecan hydrochloride is 350 mg/m²,
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of Irinotecan hydrochloride is 200 mg/m²,
- Patients with bilirubin beyond to 3 times the ULN should not be treated with Irinotecan concentrate for solution for infusion (see sections 4.3 and 4.4).

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

Patients with Impaired Renal Function:
Irinotecan Teva concentrate for solution for infusion 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)

- Hypersensitivity to irinotecan hydrochloride trihydrate or to one of the excipients of Irinotecan Teva concentrate for solution for infusion

- Pregnancy and lactation (see sections 4.6 and 4.4)

- Bilirubin> 3 times the upper limit of the normal range (see section 4.4)

- Severe bone marrow failure

- WHO performance status> 2

- Concomitant use with St. John's Wort (see section 4.5).

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 Teva 20 mg/ml concentrate for solution for infusion 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 concentrate for solution for infusion 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 hydrochloride 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 Teva concentrate for solution for infusion 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 concentrate for solution for infusion. Patients should quickly inform their physician of its occurrence and start appropriate therapy immediately.

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

As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately. This antidiarrhoeal treatment will be prescribed by the department where Irinotecan Teva concentrate for solution for infusion 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 Teva concentrate for solution for infusion when/if diarrhoea is occurring.

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

In addition to the anti-diarrhoeal treatment, a prophylactic broad-spectrum antibiotic should be given, when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm³).

In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea, in the following cases:
- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.
In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles (see section 4.2).

Haematology:
Weekly monitoring of complete blood cell counts is recommended during Irinotecan Teva concentrate for solution for infusion treatment. Patients should be aware of the risk of neutropenia and the significance of fever. Febrile neutropenia (temperature > 38°C and neutrophil count $\leq$ 1,000 cells/mm^3) 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.

Patient with impaired liver function
Liver function tests should be performed at baseline and before each cycle.

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

Nausea and vomiting
A prophylactic treatment with antiemetics is recommended before each treatment with Irinotecan hydrochloride.
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 hydrochloride.

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 hydrochloride should be cautious in this population (see section 4.2).

Patients with bowel obstruction
Patients must not be treated with Irinotecan Teva concentrate for solution for infusion 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 medicine contains sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine**.**
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially ‘sodium- free’.

Infrequent cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

Contraceptive measures must be taken during and for at least three months after cessation of therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Several studies have shown that concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to irinotecan, SN-38 and SN-38 glucuronide and reduced pharmacodynamic effects. The effects of such anticonvulsant drugs were reflected by a decrease in AUC of SN-38 and SN-38G by 50% or more. In addition to induction of cytochrome P450 3A enzymes, enhanced glucuronidation and enhanced biliary excretion may play a role in reducing exposure to irinotecan and its metabolites.

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

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

In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m^2 was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed. St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).

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/5FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of irinotecan, were analyzed in a subset of patients (approximately 30 per treatment arm). Concentrations of SN-38 were on average 33% higher in patients receiving Irinotecan/5FU/FA in combination with bevacizumab compared with Irinotecan/5FU/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 leukopenia adverse events. More dose reductions of irinotecan were reported for patients receiving Irinotecan/5FU/FA in combination with bevacizumab.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
There is no information on the use of Irinotecan hydrochloride in pregnant women.
Irinotecan hydrochloride has been shown to be embryotoxic, foetotoxic and teratogenic in rabbits and rats. Therefore, Irinotecan Teva concentrate for solution for infusion must not be used during pregnancy (see sections 4.3 and 4.4).

Women of childbearing potential and men have to use effective contraception during and up to 3 months after treatment (see sections 4.3 and 4.4).

Lactation:
In lactating rats, ^{14}C-irinotecan was detected in milk. It is not known whether irinotecan is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding must be discontinued for the duration of Irinotecan hydrochloride 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 Teva concentrate for solution for infusion, 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 acneform 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 product of characteristics.

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

Grade 3 and Grade 4 adverse drug reactions reported in patients treated with capecitabine in combination with irinotecan and bevacizumab in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy include: Common, grade 3 and grade 4 adverse drug reactions: neutropenia, thrombosis/embolism, hypertension, and cardiac ischemia/infarction. For complete information on adverse reactions of capecitabine and bevacizumab, refer to the respective capecitabine and bevacizumab summary of product characteristics.

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

The most common (>1/10), dose-limiting adverse reactions of Irinotecan concentrate are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.
Commonly severe transient acute cholinergic syndrome was observed. The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lachrimation 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:
In monotherapy severe diarrhoea was observed in 20% of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 14% have a severe diarrhoea. The median time of onset of the first liquid stool was on day 5 after the infusion of Irinotecan concentrate for solution for infusion.

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

Blood disorders

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

In monotherapy:

Neutropenia was observed in 78.7% of patients and was severe (neutrophil count < 500 cells/mm^3) in 22.6% of patients. Of the evaluable cycles, 18% had a neutrophil count below 1,000 cells/mm³ including 7.6% with a neutrophil count < 500 cells/mm³.
Total recovery was usually reached by day 22.
Fever with severe neutropenia was reported in 6.2% of patients and in 1.7% of cycles.
Infectious episodes occurred in about 10.3% of patients (2.5% of cycles) and were associated with severe neutropenia in about 5.3% of patients (1.1% of cycles), and resulted in death in 2 cases.

In combination therapy:

Neutropenia was observed in 82.5% of patients and was severe (neutrophil count < 500 cells/mm^3) in 9.8% of patients. Of the evaluable cycles, 67.3% had a neutrophil count below 1,000 cells/mm³ including 2.7% with a neutrophil count < 500 cells/mm³.
Total recovery was usually reached within 7-8 days.
Fever with severe neutropenia was reported in 3.4% of patients and in 0.9% of cycles.
Infectious episodes occurred in about 2% of patients (0.5% of cycles) and were associated with severe neutropenia in about 2.1% of patients (0.5% of cycles), and resulted in death in 1 case.

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^3) was observed in 7.4% of patients and 1.8% of cycles with 0.9% with platelets $\leq$ 50,000 cells/mm^3 and 0.2% of cycles.
Nearly all the patients showed a recovery by day 22.

In combination therapy:

Thrombocytopenia (< 100,000 cells/mm³) was observed in 32.6% of patients and 21.8% of cycles. No severe thrombocytopenia (< 50,000 cells/mm³) has been observed.
One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported in the post-marketing experience.

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

Very common:	≥ 1/10
Common:	≥ 1/100 to < 1/10
Uncommon:	≥ 1/1000 to < 1/100
Rare:	≥ 1/10,000 to < 1/1,000
Very rare	< 1/10,000; not known (cannot be estimated from the available data)

Organ system Frequency	Side effects
Gastrointestinal disorders:	
Very common	- Delayed diarrhoea
Common	- Nausea and vomiting - Episodes of dehydration (associated with diarrhoea and/or vomiting) - Constipation relative to Irinotecan hydrochloride and/or loperamide
Uncommon	- Pseudo-membranous colitis (one has been documented bacteriologically: Clostridium difficile) - Renal insufficiency, hypotension or cardio-circulatory failure as a consequence of dehydration associated with diarrhoea and/or vomiting - Intestinal obstruction, ileus, or gastrointestinal haemorrhage
Rare	- Colitis, including typhlitis, ischemic and ulcerative colitis, - Intestinal perforation - Other mild effects include anorexia, abdominal pain and mucositis - Symptomatic or asymptomatic pancreatitis
Blood and lymphatic system disorders:	
Very common	- Neutropenia (reversible and not cumulative) - Anaemia - Thrombocytopenia in case of combination therapy
Common	- Febrile neutropenia - Infectious episodes (some cases associated with severe neutropenia and resulted in death in 2 cases) - Thrombocytopenia in case of monotherapy
Very rare	- One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.
Skin and subcutaneous tissue disorders	
Very common	- Alopecia (reversible)
Uncommon	- Mild cutaneous reactions
General disorders and administration site reactions:	
Very common	- Fever in the absence of infection and without concomitant severe neutropenia
Common	- Severe transient acute cholinergic syndrome (The main symptoms were defined as early diarrhoea and various other symptoms such as abdominal pain, conjunctivitis, rhinitis, hypotension, vasodilatation, sweating, chills, malaise, dizziness, visual disturbances, myosis, lachrimation and increased salivation) - Asthenia
Uncommon	- Infusion site reactions
Investigations:	
Very common	- 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.
Common	- 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. - Transient and mild to moderate increases of serum levels of creatinine

Rare	-	Hypokalemia and hyponatremia
Very rare	-	Increases of amylase and/or lipase
Respiratory, thoracic and mediastinal disorders:		
Uncommon	-	Interstitial pulmonary disease presenting as pulmonary infiltrates
	-	Early effects such as dyspnoea
Immune system disorders:		
Uncommon	-	Mild allergy reactions
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 paresthesia
Nervous system disorders:		
Very rare	-	Transient speech disorders

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: Antineoplastic agent; Cytostatic topoisomerase I inhibitor
ATC code: L01XX19

Experimental data
Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found time-dependent and was specific to the S phase.

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

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

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

Clinical data

In monotherapy (for the second-line treatment of metastatic colorectal carcinoma):
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 the medicinal product was evaluated in 765 patients with documented progression on 5-FU at study entry.

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

NA : Non Applicable ** : Statistically significant difference*

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

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

In combination therapy (for the first-line treatment of metastatic colorectal carcinoma):

In combination 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 hydrochloride concentrate for solution for infusion at 180 mg/m^2 once every 2 weeks is followed by infusion with folinic acid (200 mg/m^2 over a 2-hour intravenous infusion) and 5-fluorouracil (400 mg/m^2 as an intravenous bolus, followed by 600 mg/m^2 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 hydrochloride concentrate for solution for infusion at 80 mg/m^2 is followed by infusion with folinic acid (500 mg/m^2 over a 2-hour intravenous infusion) and then by 5-fluorouracil (2300 mg/m^2 over a 24-hour intravenous infusion) over 6 weeks.

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

	Combined regimens (n=198)		**Weekly schedule (n=50)**		**Every 2 weeks schedule (n=148)**	
	Irinotecan +5FU/FA	**5FU/FA**	**Irinotecan +5FU/FA**	**5FU/FA**	**Irinotecan +5FU/FA**	**5FU/FA**
Response rate (%)	40.8 *	23.1 *	51.2 *	28.6 *	37.5 *	21.6 *
p value	p<0.001		p=0.045		p=0.005	
Median time to progression (months)	6.7	4.4	7.2	6.5	6.5	3.7
p value	p<0.001		NS		p=0.001	
Median duration of response (months)	9.3	8.8	8.9	6.7	9.3	9.5
p value	NS		p=0.043		NS	
Median duration of response and stabilisation (months)	8.6	6.2	8.3	6.7	8.5	5.6
p value	p<0.001		NS		p=0.003	
Median time to treatment failure (months)	5.3	3.8	5.4	5.0	5.1	3.0
p value	p=0.0014		NS		p<0.001	
Median survival (months)	16.8	14.0	19.2	14.1	15.6	13.0
p value	p=0.028		NS		p=0.041	

5FU: 5-fluorouracil
FA: folinic acid
NS: Non Significant
**: As per protocol population analysis*

In the weekly schedule, the incidence of severe diarrhoea was 44.4% in patients treated by Irinotecan hydrochloride concentrate for solution for infusion in combination with 5FU/FA and 25.6% in patients treated by 5FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500 cells/mm^3) was 5.8% in patients treated by Irinotecan concentrate for solution for infusion in combination with 5FU/FA and in 2.4% in patients treated by 5FU/FA alone.

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

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

<u>In combination with cetuximab:</u>
EMR 62 202-013: This randomised study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of cetuximab and irinotecan plus infusional 5-fluorouracil /folinic acid (5-FU/FA) (599 patients) to the same chemotherapy alone (599 patients). The proportion of patients with KRAS wild-type tumours from the patient population evaluable for KRAS status comprised 64%.

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

	Overall Population		KRAS wild-type population	
Variable/statistic	**Cetuximab plus FOLFIRI (N = 599)**	**FOLFIRI (N = 599)**	**Cetuximab plus FOLFIRI (N = 172)**	**FOLFIRI (N = 176)**
ORR				
% (95%CI)	46.9 (42.9, 51.0)	38.7 (34.8, 42.8)	59.3 (51.6, 66.7)	43.2 (35.8, 50.9)
p-value	0.0038		0.0025	
PFS				
Hazard ratio (95%CI)	0.85 (0.726, 0.998)		0.68 (0.501, 0.934)	
p-value	0.0479		0.0167	

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

In combination with bevacizumab:
A phase III randomised, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with Irinotecan/5FU/FA as first-line treatment for metastatic carcinoma of the colon or rectum (Study AVF2107g). The addition of bevacizumab to the combination of Irinotecan/5FU/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 summarized in the table below.

	AVF2107g	
	Arm 1 IRINOTECAN/5FU/FA + Placebo	**Arm 2 IRINOTECAN/5FU/FA + Avastin [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		0.54
p-value		<0.0001
Overall response rate		
Rate (%)	34.8	44.8
95% CI	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 with capecitabine:
Data from a randomised, controlled phase III study (CAIRO) support the use of capecitabine at a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. 820 patients were randomized to receive either sequential treatment (n=410) or combination treatment (n=410). Sequential treatment consisted of first-line treatment with capecitabine (1250 mg/m² twice daily for 14 days), second-line irinotecan (350 mg/m² on day 1), and third-line combination of capecitabine (1000 mg/m² twice daily for 14 days) with oxaliplatin (130 mg/m² on day 1). Combination treatment consisted of first-line treatment of capecitabine (1000 mg/m² twice daily for 14 days) combined with irinotecan (250 mg /m² on day 1) (XELIRI) and second-line capecitabine (1000 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 multi-centre, 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. 115 patients were randomised to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: capecitabine (800 mg/m² twice daily for two 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 (1000 mg/m² twice daily for two 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 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).

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

5.2 Pharmacokinetic properties

In a phase I study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m² every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/m² and the volume of distribution at steady state (Vss): 157 L/m². The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2.5 hours, and the terminal phase half-life was 14.2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13.8 hours. At the end of the infusion, at the recommended dose of 350 mg/m², the mean peak plasma concentrations of irinotecan and SN-38 were 7.7 µg/ml and 56 ng/ml, respectively, and the mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large interindividual variability in pharmacokinetic parameters is generally observed for SN-38.

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

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

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

Two metabolic pathways account each for at least 12% of the dose:
- Hydrolysis by carboxylesterase into active metabolite SN-38, SN-38 is mainly eliminated by glucuronidation, and further by biliary and renal excretion (less than 0.5% of the irinotecan dose) The SN-38 glucuronite is subsequently probably hydrolysed in the intestine.
- Cytochrome P450 3A enzymes-dependent oxidations resulting in opening of the outer piperidine ring with formation of APC (aminopentanoic acid derivate) and NPC (primary amine derivate) (see section 4.5).

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

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

5.3 Preclinical safety data

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol
lactic acid
sodium hydroxide and hydrochloric acid
water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The shelf-life of unopened vials is 2 years

The Irinotecan Teva concentrate for solution for infusion should be diluted immediately after opening.

Chemical and physical stability has been demonstratedafter dilution in 0.9% sodium chloride or 5% dextrose solution for 24 hours at room temperature or in case of dilution with 5% Dextrose solution for 48 hours between 2°-8°C as well.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

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 Teva 40 mg/2ml Concentrate:
One 2 ml or 5 ml amber glass vial, with a coated bromobutyl rubber stopper and an aluminium seal covered with a red polypropylene cover.

Irinotecan Teva 100 mg/5ml Concentrate:
One 5 ml or 8 ml amber glass vial, with a coated bromobutyl rubber stopper and an aluminium seal covered with a blue polypropylene cover.

Irinotecan Teva 300 mg/15ml Concentrate:
One 20R amber glass vial, with a coated bromobutyl rubber stopper and an aluminium seal covered with a yellow polypropylene cover.

Irinotecan Teva 500 mg/25ml Concentrate:
One 25R or 37 ml amber glass vial, with a coated bromobutyl rubber stopper and an aluminium seal covered with a yellow polypropylene cover.

Pack sizes: 1 or 5 vials per carton
Vials may be sheated in protective sleeves.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

As with other antineoplastic agents, Irinotecan Teva concentrate for solution for infusion must be prepared and handled with caution. The use of glasses, mask and gloves is required. Pregnant women should not manipulate cytotoxics.

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

Preparation for the intravenous infusion administration:

As with any other injectable drugs, THE IRINOTECAN TEVA CONCENTRATE MUST BE DILUTED ASEPTICALLY (see section 6.3).

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

Aseptically withdraw the required amount of Irinotecan Teva Concentrate 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 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.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/44/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th March 2008

10 DATE OF REVISION OF THE TEXT

September 2011