Irinotecan

Core Safety Profile

4.3 Contraindications

- Chronic inflammatory bowel disease and/or bowel obstruction (see « Special Warnings and Special Precautions for Use »).
- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of CAMPTO.
- Lactation (see « Pregnancy and Lactation » and « Special Warnings and Special Precautions for Use » sections).
- Bilirubin > 3 times the upper limit of the normal range (see « Special warnings and Special Precautions for Use » section).
- 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 CAMPTO 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, CAMPTO 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 CAMPTO is used in monotherapy, it is usually prescribed with the every-3-week-dosage schedule. However, the weekly-dosage schedule (see « Pharmacological properties ») 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 CAMPTO 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 CAMPTO®. 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 CAMPTO 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 CAMPTO 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 « Posology and Method of Administration » section).

Haematology

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

In patients who experienced severe haematological events, a dose reduction is recommended for subsequent administration (see « Posology and Method of Administration » section).

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

Liver impairment

Liver function tests should be performed at baseline and before each cycle.
Weekly monitoring of complete blood counts should be conducted in patients with bilirubin ranging from 1.5 to 3 times ULN, due to decrease of the clearance of irinotecan (see "Pharmacokinetic properties" section) and thus increasing the risk of hematotoxicity in this population. For patients with a bilirubin > 3 times ULN (see « Contraindications » section).

Nausea and Vomiting

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

Acute cholinergic syndrome

If acute cholinergic syndrome appears (defined as early diarrhoea and various other signs and symptoms such as sweating, abdominal cramping, myosis and salivation), atropine sulphate (0.25 mg subcutaneously) should be administered unless clinically contraindicated (see « Undesirable Effects » section).

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 CAMPTO.

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.

Extravasation

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

Elderly

Due to the greater frequency of decreased biological functions, in particular hepatic function, in elderly patients, dose selection with CAMPTO should be cautious in this population (see « Posology and Method of Administration » section).

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with CAMPTO until resolution of the bowel obstruction (see « Contraindications »).

Patients with Impaired Renal Function

Studies in this population have not been conducted. (see « Posology and Method of Administration » and « Pharmacokinetic Properties »).

Cardiac Disorders

Myocardial ischaemic events have been observed following irinotecan therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see « Undesirable Effects » section).

Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)

Immunosuppressant Effects / Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including irinotecan, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving irinotecan. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Others

Since this medicinal contains sorbitol, it is unsuitable in hereditary fructose intolerance. 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 CAMPTO has anticholinesterase activity, drugs with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising drugs may be antagonised.

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

A study has shown that the co-administration of ketoconazole resulted in a decrease in

the AUC of APC of 87% and in an increase in the AUC of SN-38 of 109% in comparison to irinotecan given alone.

Caution should be exercised in patients concurrently taking drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital or phenytoin) drug metabolism by cytochrome P450 3A4. Concurrent administration of irinotecan with an inhibitor/inducer of this metabolic pathway may alter the metabolism of irinotecan and should be avoided (see section 4.4).
In a small pharmacokinetic study (n=5), in which irinotecan 350 mg/m2 was co-administered with St. John's Wort (Hypericum perforatum) 900 mg, a 42% decrease in the active metabolite of irinotecan, SN-38, plasma concentrations was observed. St. John's Wort decreases SN-38 plasma levels. As a result, St. John's Wort should not be administered with irinotecan (see section 4.3).

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

Atazanavir sulphate. Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor, has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

Interactions common to all cytotoxic:

The use of anticoagulants is common due to increased risk of thrombotic events in tumoral diseases. If vitamin K antagonist anticoagulants are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required due to their narrow therapeutic index , the high intra-individual variability of blood thrombogenicity and the possibility of interaction between oral anticoagulants and anticancer chemotherapy.

Concomitant use contraindicated
- Yellow fever vaccine: risk of fatal generalised reaction to vaccines

Concomitant use not recommended
- Live attenuated vaccines (except yellow fever): risk of systemic, possible fatal disease (eg-infections). This risk is increased in subjects who are already immunosuppressed by their underlying

Use an inactivated vaccine where this exists (poliomyelitis)

- Phenytoin: Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic drug

Concomitant use to take into consideration
- Ciclosporine, Tacrolimus: Excessive immunosuppression with risk of lymphoproliferation

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

In one study (AVF2107g), irinotecan concentrations were similar in patients receiving

bolus CAMPTO/5FU/FA (125 mg/m^2 of irinotecan, 500 mg/m^2 of 5-FU, and 20 mg/m^2 of leucovorin, given in repeated 6-week cycles, comprising weekly treatment for 4 weeks, followed by a 2-week rest) alone and in combination with bevacizumab. Plasma 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 bolus CAMPTO/5FU/FA in combination with bevacizumab compared with bolus CAMPTO/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 grades 3/4 diarrhoea and leukopenia adverse events in the arm receiving bevacizumab. More dose reductions of irinotecan were reported for patients receiving CAMPTO/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 Posology and method of administration.

4.6 Pregnancy and lactation

Pregnancy
There is no information on the use of irinotecan in pregnant women. Irinotecan was embryotoxic and teratogenic in animals (see section 5.3). Based on results from animal studies and the mechanism of action of irinotecan, this substance must not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case.

Women of child-bearing potential
Women of childbearing potential and men have to use effective contraception during and up to 3 months after treatment.

Fertility
There are no human data on the effect of irinotecan on fertility. In animals adverse effects of irinotecan on the fertility of offspring has been documented (see section 5.3).

Lactation
It is unknown if irinetocan is excreted in human breast milk. In lactating rats, 14C-labelled irinotecan was excreted in milk. Consequently, because of the potential for adverse reactions in nursing infants, breast-feeding is contraindicated during treatment with Irinotecan (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 CAMPTO, 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 of cetuximab. For information on adverse reactions on irinotecan in combination with cetuximab , only refer to the summary of product characteristics.

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

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

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

Gastrointestinal disorders

Delayed diarrhoea
Diarrhoea (occurring more than 24 hours after administration) is a dose-limiting toxicity of CAMPTO.
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 CAMPTO.
In combination therapy :
Severe diarrhoea was observed in 13.1 % of patients who follow recommendations for the management of diarrhoea. Of the evaluable cycles, 3.9 % have a severe diarrhoea.

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

Nausea and vomiting
In monotherapy :
Nausea and vomiting were severe in approximately 10 % of patients treated with antiemetics.
In combination therapy :
A lower incidence of severe nausea and vomiting was observed (2.1 % and 2.8 % of

patients respectively).

Dehydration
Episodes of dehydration commonly associated with diarrhoea and/or vomiting have been reported.
Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting.

Other gastrointestinal disorders
Constipation relative to CAMPTO and/or loperamide has been observed, shared between :
- in monotherapy : in less than 10 % of patients
- in combination therapy : 3.4 % of patients.

Infrequent cases of intestinal obstruction, ileus, or gastrointestinal haemorrhage and rare cases of colitis, including typhlitis, ischemic and ulcerative colitis, were reported. Rare cases of intestinal perforation were reported. Other mild effects include anorexia, abdominal pain and mucositis.
Rare cases of symptomatic or asymptomatic pancreatitis have been associated with irinotecan therapy.

BLOOD DISORDERS

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

In monotherapy :
Neutropenia was observed in 78.7 % of patients and was severe (neutrophil count < 500 cells/mm3) in 22.6 % of patients. Of the evaluable cycles, 18 % had a neutrophil count below 1,000 cells/mm^3 including 7.6 % with a neutrophil count < 500 cells/mm^3.
Total recovery was usually reached by day 22.
Fever with severe neutropenia was reported in 6.2 % of patients and in 1.7 % of cycles.
Infectious episodes occurred in about 10.3 % of patients (2.5 % of cycles) and were associated with severe neutropenia in about 5.3 % of patients (1.1 % of cycles), and resulted in death in 2 cases.
Anaemia was reported in about 58.7 % of patients (8 % with haemoglobin < 8 g/dl and 0.9 % with haemoglobin < 6.5 g/dl).
Thrombocytopenia (< 100,000 cells/mm^3) was observed in 7.4 % of patients and 1.8 % of cycles with 0.9 % with platelets count $\leq$ 50,000 cells/mm3 and 0.2 % of cycles.
Nearly all the patients showed a recovery by day 22.

In combination therapy :
Neutropenia was observed in 82.5 % of patients and was severe (neutrophil count < 500 cells/mm3) in 9.8 % of patients.
Of the evaluable cycles, 67.3 % had a neutrophil count below 1,000 cells/mm³ including 2.7 % with a neutrophil count < 500 cells/mm³.
Total recovery was usually reached within 7-8 days.
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 was reported in 97.2 % of patients (2.1 % with haemoglobin < 8 g/dl).
Thrombocytopenia (< 100,000 cells/mm³) was observed in 32.6 % of patients and 21.8 % of cycles. No severe thrombocytopenia (< 50,000 cells/mm³) has been observed.

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

INFECTION AND INFESTATION
Infrequent cases of renal insufficiency, hypotension or cardio-circulatory failure have been observed in patients who experienced sepsis.

GENERAL DISORDERS AND INFUSION SITE REACTIONS

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

Asthenia was severe in less than 10 % of patients treated in monotherapy and in 6.2 % of patients treated in combination therapy. The causal relationship to CAMPTO has not been clearly established. Fever in the absence of infection and without concomitant severe neutropenia, occurred in 12 % of patients treated in monotherapy and in 6.2 % of patients treated in combination therapy.
Mild infusion site reactions have been reported although uncommonly.

CARDIAC DISORDER
Rare cases of hypertension during or following the infusion have been reported.

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

SKIN AND SUBCUTANEOUS TISSUE DISORDERS
Alopecia was very common and reversible. Mild cutaneous reactions have been reported although uncommonly.

IMMUNE SYSTEM DISORDERS
Uncommon mild allergy reactions and rare cases of anaphylactic/anaphylactoid reactions have been reported.

Musculoskeletal disorders
Early effects such as muscular contraction or cramps and paresthesia have been reported.

Laboratory tests
In monotherapy, transient and mild to moderate increases in serum levels of either transaminases, alkaline phosphatase or bilirubin were observed in 9.2 %, 8.1 % and 1.8 % of the patients, respectively, in the absence of progressive liver metastasis.
Transient and mild to moderate increases of serum levels of creatinine have been observed in 7.3 % of the patients.
In combination therapy transient serum levels (grades 1 and 2) of either SGPT, SGOT, alkaline phosphatase or bilirubin were observed in 15 %, 11 %, 11 % and 10 % of the patients, respectively, in the absence of progressive liver metastasis. Transient grade 3 were observed in 0 %, 0%, 0 % and 1 % of the patients, respectively. No grade 4 was observed.
Increases of amylase and/or lipase have been very rarely reported.
Rare cases of hypokalemia and hyponatremia mostly related with diarrhea and vomiting have been reported.

NERVOUS SYSTEM DISORDERS
There have been very rare postmarketing reports of transient speech disorders associated with CAMPTO infusions.

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 CAMPTO. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.