APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

CAMPTO® 40 mg/2 ml Solution for Infusion

CAMPTO® 100 mg/5 ml Solution for Infusion

CAMPTO® CSV 300 mg/15 ml Solution for Infusion

COMPOSITION:

Single-dose vials containing 40 mg, 100 mg or 300 mg irinotecan hydrochloride trihydrate.

Each 1 ml contains 20 mg irinotecan hydrochloride trihydrate.

Excipients: D-sorbitol, lactic acid, sodium hydroxide, hydrochloric acid, water for injections, nitrogen.

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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 to be time-dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were found not 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 antitumour activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinoma) 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 the antitumour activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

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/m^2 every three weeks, irinotecan showed a biphasic or three-phasic elimination profile. The mean plasma clearance was 15 l/h/m^2 and the volume of distribution at steady state (Vss) quite large: 157 l/m^2. 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 recommended dose of 350 mg/m^2, the mean irinotecan and SN-38 peak plasma concentrations were 7,7 µg/ml and 56 ng/ml, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large inter-individual 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 CPT-11 and SN-38 pharmacokinetics are independent of the administered dose, of the number of previous cycles and of the administration schedule.

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

Mass balance and metabolism studies with ^{14}C-labelled irinotecan have shown that more than 50 % of an intravenously administered dose of irinotecan is excreted as unchanged substance, with 33 % in the faeces via the bile and 22 % in urine. Two metabolic pathways, each representing at least 12 % of the dose, have been identified: oxidative metabolism at the terminal piperidine ring by cytochrome P450 3A enzymes which results in an aminopentanoic acid derivative (APC) and a primary amine derivate and hydrolysis by carboxylesterases into the 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). Unchanged irinotecan is the major entity in plasma followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected. 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 irinotecan exposure comparable to that observed at 350 mg/m² in cancer patients with normal liver parameters. Co-administration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

INDICATIONS:

CAMPTO is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:

- 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.

CONTRAINDICATIONS:

Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with CAMPTO until resolution of the ileus.

History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of CAMPTO.

Pregnancy and lactation. Women of childbearing age receiving CAMPTO should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur (see PREGNANCY AND LACTATION).

Bilirubin > 1,5 times the upper limit of the normal range.

The safety and efficacy of CAMPTO in children have not been established.

Severe bone marrow failure.

WHO performance status > 2.

Concomitant administration of azole antifungals, St. John's Wort.

WARNINGS AND SPECIAL PRECAUTIONS:

CAMPTO should be used in patients with a WHO good performance status of less than 2.

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 qualified oncologist.

It is strongly recommended that CAMPTO be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

In all instances where the use of CAMPTO is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In rare cases where it is predictable that the patient would comply poorly with the guidances for the management of side effects, a strict follow-up of the patient by the treating medical practitioner or hospitalisation is recommended.

Given the nature and frequency of adverse events, the expected benefit must be balanced in case of risk factors, especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

Delayed diarrhoea:

Apart from the diarrhoea shortly after the infusion of CAMPTO, patients should be aware of the high 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 medical practitioner 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 leukocytosis and those with performance status ≥ 2. 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 medicines so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their medical practitioner or the department administering CAMPTO that diarrhoea is occurring.

The currently recommended antidiarrhoeal treatment is 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 case should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm^3).

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

- Diarrhoea associated with fever,

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

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

In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.

Haematology:

Weekly monitoring of complete blood cell counts should be performed during CAMPTO treatment. Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 ºC and neutrophil count ≤ 1 000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.

CAMPTO administration should be delayed until the neutrophil count is ≥ 1 500 cells/mm^3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3), fever or infections associated with neutropenia, the dose of CAMPTO should be reduced.

In patients who experienced severe haematologic events, a dose reduction is recommended for subsequent administration.

There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea.

Liver Impairment:

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

Patients with impaired liver function (bilirubin > 1,0 and ≤ 1,5 times the upper limit of the normal range [ULN] and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored, including complete blood counts. CAMPTO should not be used in patients with a bilirubin > 1,5 times the ULN and the patients with bilirubin > ULN should be followed with caution. In patients with a bilirubin of < 1,5 times ULN a dose of 350 mg/m^2 is recommended once every 3 weeks (see DOSAGE AND DIRECTIONS FOR USE).

Renal impairment:

No specific pharmacokinetic studies have been performed in patients with renal impairment.

Nausea and vomiting:

Prophylactic treatment with an anti-emetic 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 an acute cholinergic syndrome appears (defined as early diarrhoea and a group of symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contraindicated. These symptoms may disappear after atropine administration. Caution should be exercised in patients with asthma. In patients who experienced an acute cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of CAMPTO.

Immunosuppressant effects/increased susceptibility to infections:

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

Elderly:

Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with CAMPTO should be cautious in this population.

Effects on ability to drive and use machines:

Patients should be warned about the potential for dizziness or visual disturbances, and advised not to drive or operate machinery if these symptoms occur.

Others:

Contraceptive measures must be taken during and for at least three months after cessation of therapy (see PREGNANCY AND LACTATION).

Since CAMPTO contains sorbitol, it is unsuitable for use in patients with hereditary fructose intolerance.

INTERACTIONS:

Pharmacokinetic parameters of CAMPTO combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy.

Neuromuscular blocking agents: Interaction between CAMPTO and neuromuscular blocking agents cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising agents may be antagonised. Excess acetylcholine may impair the muscle relaxant action of the non-depolarising agents and may impair the return of normal muscle tone at the end of anaesthesia.

Antineoplastic agents: The adverse effects of CAMPTO, such as myelosuppression and diarrhoea, is expected to be exacerbated by other antineoplastic agents having a similar adverse-effect profile.

Dexamethasone: Lymphocytopenia has been reported in patients receiving CAMPTO, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. Hyperglycaemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTO. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives: Laxative use during therapy with CAMPTO is expected to worsen the incidence or severity of diarrhoea.

Diuretics: Dehydration secondary to vomiting and/or diarrhoea may be induced by CAMPTO. The medical practitioner may wish to withhold diuretics during dosing with CAMPTO and during periods of active vomiting or diarrhoea.

Anticonvulsants: Concomitant administration of CYP3A enzyme-inducing anticonvulsant medicines (e.g. carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to the active metabolite SN-38. Consideration should be given to starting or substituting non-enzyme inducing anticonvulsants at least one week prior to initiation of CAMPTO therapy in patients requiring anticonvulsant treatment.

Azole antifungals: CAMPTO clearance is greatly reduced in patients receiving concomitant azole antifungals, leading to increased exposure to the active metabolite, SN-38. Azole antifungals should be discontinued at least 1 week prior to starting CAMPTO therapy and should not be administered during CAMPTO therapy (see CONTRAINDICATIONS).

St. John's Wort (Hypericum perforatum): Exposure to the active metabolite of CAMPTO is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be discontinued at least 1 week prior to the first cycle of CAMPTO, and should not be administered during CAMPTO therapy (see CONTRAINDICATIONS).

Atazanavir sulphate: Coadministration of atazanavir sulphate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of CAMPTO.
Atazanavir should not be used with CAMPTO.

Bevacizumab: In one study, CAMPTO plasma concentrations were similar in patients receiving CAMPTO/5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of CAMPTO, were analysed in a subset of patients. Concentrations of SN-38 were on average 33 % higher in patients receiving CAMPTO/5-FU/FA in combination with bevacizumab compared with CAMPTO/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

leukopenia adverse events. More dose reductions of CAMPTO were reported for patients receiving CAMPTO/5-FU/FA in combination with bevacizumab.

Loperamide should not be given prophylactically.

PREGNANCY AND LACTATION:

Pregnancy

CAMPTO is contraindicated during pregnancy and lactation as it may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of CAMPTO in pregnant women. If CAMPTO is used during pregnancy, or if the patient becomes pregnant, while receiving CAMPTO, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTO (see CONTRAINDICATIONS).

Lactation

Patients receiving CAMPTO should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

Recommended Dosage:

In monotherapy (for previously treated patient):

The recommended dosage of CAMPTO is 350 mg/m² administered as an intravenous infusion over a 30- to 90-minute period every three weeks.

In combination therapy (for previously untreated patient):

Safety and efficacy of CAMPTO in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

- **CAMPTO plus 5FU/FA in weekly schedule:**

  The recommended dose of CAMPTO is 80 mg/m² administered as a weekly intravenous infusion over a 30- to 90-minute period, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week rest.

The full dosage regimen is as follows:

CAMPTO 80 mg/m^2 as a 30- to 90-minute infusion on Day 1 and then weekly for 6 weeks.

Folinic acid 500 mg/m^2 i.v. as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m^2 i.v. as a 24-hour infusion, on Day 1 and then weekly for 6 weeks. The treatment is to be repeated every 7 weeks.

- **CAMPTO plus 5FU/FA in every 2 weeks schedule:**

  The recommended dose of CAMPTO is 180 mg/m^2 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.

  The full dosage regimen is as follows:

  CAMPTO 180 mg/m^2 i.v. as a 30- to 90-minute infusion on Day 1 only.

  Folinic acid 200 mg/m^2 i.v. as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 i.v. bolus, followed by 5-fluorouracil 600 mg/m^2 i.v. as a 22-hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days.

  Repeat the cycle every two weeks.

Dosage Adjustments:

Delayed Dosing:

CAMPTO should not be administered until the neutrophil count remains above 1 500 cells/mm^3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of CAMPTO should be delayed until there has been a full recovery of these effects, especially diarrhoea.

CAMPTO 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. This must be strictly adhered to.

At the start of a subsequent infusion of therapy, the dose of CAMPTO, 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 CAMPTO 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).

Treatment Duration:

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

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of CAMPTO solution 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. CAMPTO infusion solution should be infused into a peripheral or central vein.

CAMPTO should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

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

Do not admix with other medications.

Recommendations for safe handling:

Medicine handling precautions for cytostatic medicines should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.
- CAMPTO is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing CAMPTO solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.

- If CAMPTO solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If CAMPTO solution or infusion solution should come into contact with the eyes or mucous membranes, wash immediately and thoroughly with water.
- The cytotoxic preparation must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to reconstitute the medicine.

SIDE EFFECTS:

The intensity of the major toxicities encountered with CAMPTO (e.g. leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent substance 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.

The other side effects were categorised utilising the incidence rate as follows:

Very Common: ≥ 1/10 (≥ 10 %)

Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %)

Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %)

Adverse events that occurred during clinical trials are tabulated below:

System Organ Class	Frequency	Adverse Events
Blood and lymphatic system disorders	Very common	leukopenia, *neutropenia, anaemia
	Common	thrombocytopenia
Gastrointestinal disorders	Very common	late diarrhoea, nausea, vomiting, early diarrhoea, abdominal cramping/pain, anorexia, stomatitis
	Common	constipation, mucositis
	Uncommon	rectal disorder, GI monilia
Metabolism and nutrition disorders	Very common	decreased weight, dehydration
	Common	hypovolaemia
	Uncommon	hypokalaemia, hypomagnesaemia
Skin and subcutaneous tissue disorders	Very common	alopecia
	Uncommon	rash, cutaneous signs such as dry skin, pruritus, skin discolouration
	Frequency unknown	sweating
Vascular disorders	Very common	venous and arterial thromboembolic events which includes – angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep vein thrombophlebitis, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder
	Rare	flushing
	Frequency unknown	vasodilation
Infections and infestations	Common	infection
	Uncommon	sepsis
Hepatobiliary disorders	Common	hyperbilirubinaemia

System Organ Class	Frequency	Adverse Events
Respiratory, thoracic and mediastinal disorders	Common	dyspnoea
	Rare	rhinitis
Nervous system disorders	Uncommon	abnormal gait, confusion, headache
	Rare	dizziness
Cardiac disorders	Uncommon	hypotension, syncope,
	Rare	bradycardia
Renal and urinary disorders	Uncommon	urinary tract infection
Reproductive system and breast disorders	Uncommon	breast pain
Eye disorders	Rare	increased lacrimation, miosis
	Frequency unknown	conjunctivitis
		visual disturbance
Endocrine disorders	Rare	diaphoresis, increased salivation
General disorders and administrative site conditions	Very common	asthenia, fever
	Common	pain
	Uncommon	chills, malaise
	Rare	extravasation, tumour-lysis syndrome
Investigations	Common	increased serum creatinine
	Uncommon	increased serum alkaline phosphatase, increased GGTP (gamma-glutamyl transpeptidase)
	Rare	increase in amylase, increase in lipase

* Neutropenia was reversible and not cumulative; the median day to nadir was 8 days and total recovery was usually reached by day 22 in monotherapy and within 7 - 8 days in combination therapy. Infectious episodes resulted in death in 2 cases.

Post-marketing surveillance

Cardiac disorders:

Myocardial ischaemic events have been observed following CAMPTO therapy.

Gastrointestinal disorders:

Cases of intestinal obstruction, ileus, megacolon, or gastrointestinal haemorrhage, and rare cases of colitis, including typhlitis, ischaemic and ulcerative colitis have been reported. In some cases, colitis was complicated by ulceration, bleeding, ileus or infection. Cases of ileus without preceding colitis have also been reported. Cases of intestinal perforation have been reported.

Cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been reported.

Hypovolaemia:

There have been cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities.

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.

Immune system disorders:

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported.

Musculoskeletal and connective tissue disorders:

Muscular contraction or cramps and paraesthesia have been reported.

Nervous system disorders:

Speech disorders, generally transient in nature, have been reported; in some cases the event was attributed to the cholinergic syndrome observed during or shortly after infusion of CAMPTO.

Respiratory, thoracic and mediastinal disorders:

Interstitial pulmonary disease presenting as pulmonary infiltrates may occur during CAMPTO therapy.

Early effects such as dyspnoea have been reported.

Hiccups have also been reported.

Investigations:

Cases of hyponatraemia mostly related with diarrhoea and vomiting have been reported. Increases in serum transaminases (AST, ALT) in the absence of progressive liver metastasis have been reported.

Haematology:

One case of peripheral thrombocytopenia with antiplatelet antibodies has been reported.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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 diarrhoea. There is no known antidote for CAMPTO. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

IDENTIFICATION:

A clear, slightly yellow solution.

PRESENTATION:

CAMPTO 40 mg/2 ml: Carton containing one single-dose glass or polypropylene plastic, amber coloured vial, closed with a halobutyl/chlorobutyl rubber stopper and sealed with an aluminium cap with a plastic flip-off top.

CAMPTO 100 mg/5 ml: Carton containing one single-dose glass or polypropylene plastic, amber coloured vial, closed with a halobutyl/chlorobutyl rubber stopper and sealed with an aluminium cap with a plastic flip-off top.

CAMPTO CSV 300 mg/15 ml: Carton containing one single-dose polypropylene plastic, amber coloured vial, closed with a halobutyl rubber stopper and sealed with an aluminium cap with a plastic flip-off top.

STORAGE INSTRUCTIONS:

Single-dose vials of CAMPTO solution for infusion should be stored at or below 25 °C and protected from light.

The product must be kept in the carton until required for use.

CAMPTO 40 mg/2 ml and Campto 100 mg/5 ml: After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours at a temperature at or below 25 ºC for 4 days under refrigeration (between 2 and 8 ºC). Discard any unused portion thereafter.

CAMPTO CSV 300 mg/15 ml: After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours under refrigeration (between 2 and 8 ºC). Discard any unused portion.

Do not freeze. Keep out of reach of children.

REGISTRATION NUMBERS:

CAMPTO 40 mg/2 ml:	31/26/0182
CAMPTO 100 mg/5 ml:	31/26/0183
CAMPTO CSV 300 mg/15 ml:	43/26/1067

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

SOUTH AFRICA

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

09 June 2016

BOTSWANA: S2

Campto 40 mg/2 ml - Reg. No: BOT0901513

Campto 100 mg/5 ml - Reg. No: BOT0901512

NAMIBIA: S2

Campto 40 mg/2 ml - Reg. No: 04/26/1634

Campto 100 mg/5 ml - Reg. No: 04/26/1215