PT. Pfizer Indonesia
Local Product Document

Generic Name: Irinotecan hydrochloride trihydrate
Trade Name: CAMPTO
CDS Effective Date: September 17, 2019
Supersedes: July 19, 2018

NAME OF THE MEDICINAL PRODUCT

CAMPTO

QUALITATIVE AND QUANTITATIVE COMPOSITION

Concentrate for solution for infusion composition
Active ingredient: irinotecan hydrochloride trihydrate.

The concentrate contains 20 mg/mL irinotecan hydrochloride trihydrate (equivalent to 17.33 mg/mL irinotecan). Excipients: sorbitol, lactic acid and water for injections. The pH of the solution is adjusted to 3.5 with sodium hydroxide. Vials of CAMPTO contain 40 mg or 100 mg of irinotecan hydrochloride trihydrate.

CLINICAL PARTICULARS

Therapeutic indications
CAMPTO (irinotecan hydrochloride) 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 combination with cisplatin is indicated for treatment of patients with small-cell lung cancer.

Strictly follow the recommended dosage unless directed otherwise by the physician.

Posology and method of administration
For adults only. CAMPTO solution for infusion should be infused into a peripheral or central vein.

• **In monotherapy** (for previously treated patients):
  The recommended dosage of CAMPTO is 350 mg/m^2 administered as an intravenous infusion over a 30- to 90-minute period every three weeks.
• **In combination therapy** (for previously untreated patients):
  Safety and efficacy of CAMPTO in combination with 5-fluorouracil (5 FU) and folinic acid (FA) have been assessed with the following schedule. The recommended dosage 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.

Irinotecan in Combination with Cisplatin
The recommended starting dose is 65 mg/m^2 of irinotecan and 30 mg/m^2 of cisplatin. Cisplatin infused prior irinotecan. A lower starting dose of irinotecan may be considered for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels, or gastric cancer. Treatment should be given in repeated 6-week cycles, comprising Days 1 and 8, every 21 days.

Irinotecan should be administered as an intravenous infusion over 30 to 90 minutes.

Dosage adjustment
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 diarrhea is fully resolved.

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: hematological toxicity (Neutropenia Grade 4), febrile neutropenia (neutropenia Grade 3-4 and fever Grade 2-4), thrombocytopenia and leukopenia (Grade 4), non-hematological toxicity (Grade 3-4).

Duration of treatment
For both single-agent and combination-agent regimens, treatment with additional cycles of irinotecan may be continued indefinitely in patients who attain a tumor response or in patients whose cancer remains stable. Patients should be carefully monitored for toxicity and should be removed from therapy if unacceptable toxicity occurs that is not responsive to dose modification and routine supportive care.

Dose Modification Recommendations
The recommended dose modifications for irinotecan and cisplatin for the start of each cycle of therapy are described in Table 1, while recommended dose modifications during a cycle of therapy are described in Table 2.

Table 1. Dose Modifications at the Start of a New Cycle of the Cisplatin and Irinotecan (mg/m^2) Combination Schedule - Based on the Worst Toxicity Observed in the Prior Cycle

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, serum creatinine ≤1.7 mg/dL or ≤130 µmol/L, and treatment-related non-hematologic toxicities (excluding alopecia) are resolved to ≤Grade 1. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing irinotecan.

Toxicity NCI Grade[a]	Cisplatin[b]	Irinotecan[c]
HEMATOLOGIC		
Neutropenia/Thrombocytopenia		

Grade 0, 1, 2, or 3	Maintain dose level	Maintain dose level
Grade 4	↓ 1 dose level	↓ 1 dose level
Febrile neutropenia,[d] sepsis, thrombocytopenia requiring transfusion	↓ 2 dose level	↓ 2 dose level
NON-HEMATOLOGIC		
Diarrhea		
Grade 0, 1 or 2	Maintain dose level	Maintain dose level
Grade 3 or 4	Maintain dose level	↓ 1 dose level
Vomiting		
Grade 0, 1 or 2	Maintain dose level	Maintain dose level
Grade 3	↓ 1 dose level	Maintain dose level
Grade 4	↓ 1 dose level	↓ 1 dose level
Serum Creatinine		
≤1.7 mg/dL	Maintain dose level	Maintain dose level
>1.7-2.0 mg/dL	↓ 3 dose levels	Maintain dose level
>2.0 mg/dL	Discontinue cisplatin	Maintain dose level
Ototoxicity		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	↓ 2 dose level	Maintain dose level
Grade 3 or 4	Discontinue cisplatin	Maintain dose level
Neurotoxicity		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	↓ 2 dose level	Maintain dose level
Grade 3 or 4	Discontinue cisplatin	Maintain dose level
OTHER NON-HEMATOLOGIC TOXICITIES (Except Alopecia)		
Grade 0, 1 or 2	Maintain dose level	Maintain dose level
Grade 3 or 4	↓ 1 dose level	↓ 1 dose level

[a] National Cancer Institute Common Toxicity Criteria
[b] Cisplatin: dose level reductions = 5 mg/m^2 decrements
[c] Irinotecan: dose level reductions = 10 mg/m^2 decrements
[d] Febrile neutropenia is defined as in CTC version 2: temperature ≥38.5°C concomitant with an ANC <1.0 x 10^9/L.

Table 2. Dose Modifications for Day 8 of the Cisplatin and Irinotecan (mg/m^2) Combination Schedule Based on the Worst Toxicity Observed in the Prior Cycle

Toxicity NCI Grade[a]	Cisplatin[b]	Irinotecan[c]
HEMATOLOGIC		
Neutropenia/Thrombocytopenia		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	↓ 1 dose level	↓ 1 dose level
Grade 3	↓ 2 dose level	↓ 2 dose level
Grade 4	Omit dose	Omit dose
Febrile neutropenia,[d] sepsis, thrombocytopenia requiring transfusion	Omit dose	Omit dose
NON-HEMATOLOGIC		
Diarrhea		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	↓ 1 dose level
Grade 3	Maintain dose level	Omit dose
Grade 4	Omit dose	Omit dose
Vomiting		

Grade 0, 1 or 2	Maintain dose level	Maintain dose level
Grade 3	↓ 1 dose level	Maintain dose level
Grade 4	↓ 1 dose level	↓ 1 dose level
Serum Creatinine		
≤1.7 mg/dL	Maintain dose level	Maintain dose level
>1.7-2.0 mg/dL	↓ 2 dose levels	Maintain dose level
>2.0 mg/dL	Discontinue cisplatin	Maintain dose level
Ototoxicity		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	↓ 1 dose level	Maintain dose level
Grade 3 or 4	Discontinue cisplatin	Maintain dose level
Neurotoxicity		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2	↓ 1 dose level	Maintain dose level
Grade 3 or 4	Discontinue cisplatin	Maintain dose level
OTHER NON-HEMATOLOGIC TOXICITIES (Except Alopecia)		
Grade 0 or 1	Maintain dose level	Maintain dose level
Grade 2, 3 or 4	Omit dose	Omit dose

[a] National Cancer Institute Common Toxicity Criteria
[b] Cisplatin: dose level reductions = 5 mg/m^2 decrements
[c] Irinotecan: dose level reductions = 10 mg/m^2 decrements
[d] Febrile neutropenia is defined as in CTC version 2: temperature ≥ 38.5°C concomitant with an ANC <1.0 x 10^9/L.

Special populations

Elderly

No specific pharmacokinetic study has been performed in elderly. However, the dose should be chosen carefully in this population due to their greater frequency of decreased biological functions. These populations should require more intensive surveillance.

Patients with impaired hepatic function

In monotherapy: in patients with hyperbilirubinemia and prothrombin greater than 50%, the clearance of irinotecan is decreased and therefore, the risk of hematotoxicity is increased. Thus, frequent 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 CAMPTO is 350 mg/m^2.
- In patients with bilirubin ranging from 1.5 to 3 times the ULN, the recommended dosage of CAMPTO is 200 mg/m^2.
- Patients with bilirubin beyond to 3 times the ULN should not be treated with CAMPTO (see Sections **Contraindications, Warning and precautions**).

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

Patients with impaired renal functions

CAMPTO is not recommended for use in patients with impaired renal functions, as studies in this population have not been conducted.

Preparation and handling

As with other antineoplastic agents, CAMPTO must be prepared and handled with caution. The usage of glasses, mask and gloves is required. If CAMPTO solution or infusion solution come into contact with the mucous membranes, wash immediately with water.

Preparation for intravenous infusion administration
As with any other injectable drugs, the CAMPTO solution must be prepared aseptically. 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 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 is then thoroughly mixed by manual rotation.

Administration
CAMPTO solution for infusion 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.

Disposal
All material used for dilution and administration should be disposed of according to hospital standard procedure applicable to cytotoxic agents.

Contraindications
CAMPTO is contraindicated in patients with:
• A chronic inflammatory bowel disease and/or a bowel obstruction (see Section **Warning and precautions**).
• A history of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of CAMPTO (see Section **Warning and precautions**).
• In pregnant or breast feeding women.
• In patient with bilirubin >3 times the ULN (see Section **Warning and precautions**).
• In patient with a severe bone marrow failure.
• In patients presenting a risk factor, particularly those with a WHO performance status >2.

Warning and precautions
Administration. Irinotecan should be administered only under the supervision of a physician, who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Irinotecan will only be prescribed in the following cases after the expected benefits have been weighted against the possible therapeutic risks:
• in patients presenting a risk factor, particularly those with a WHO performance status = 2.
• in the few rare instances where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged antidiarrheal treatment combined with high fluid intake at onset of delayed diarrhea). Strict hospital supervision is recommended for such patients.

Cholinergic symptoms. Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing (vasodilation), bradycardia, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea (i.e., diarrhea generally occurring during or within 8 hours of administration of irinotecan). These symptoms may be observed during or shortly after infusion of irinotecan, are thought to be related to the anticholinesterase activity of the irinotecan parent compound, and are expected to occur more

frequently with higher irinotecan doses. Therapeutic or prophylactic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing cholinergic symptoms.

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 extravasations occur, flushing the site and application of ice is recommended.

Hepatic. In clinical studies, National Cancer Institute (NCI) Common Toxicity Criteria Grade 3 or 4 liver enzyme abnormalities have been observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases and are not clearly related to irinotecan.

Hematology. Irinotecan commonly causes neutropenia, leukopenia, and anemia, any of which may be severe and therefore, should not be used in patients with severe bone marrow failure. Serious thrombocytopenia is uncommon. In clinical studies, the frequency of NCI Grade 3 and 4 neutropenia has been significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation. Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing first-cycle Grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL. There were no significant differences in the frequency of Grade 3 and 4 neutropenia by age or gender (see Section **Posology and method of administration**).

Neutropenic fever (concurrent NCI Grade 4 neutropenia and ≥Grade 2 fever) occurred in fewer than 10% of patients in clinical studies; however, deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. Therapy with irinotecan should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 1000/mm^3. The dose of irinotecan should be reduced if clinically significant neutropenia occurs (see Section **Posology and method of administration**).

Patients with reduced UGT1A1 activity. The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form the inactive glucuronide metabolite SN-38G. This glucuronidation reaction is mediated primarily by uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which is encoded by the UGT1A1 gene (see Section **Pharmacokinetic properties**). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. One specific variation of the UGT1A1 gene includes a polymorphism in the promoter region known as the UGT1A1 28 variant allele. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar and Gilbert's syndrome) are associated with reduced enzyme activity and increased systemic exposure to SN-38. Higher plasma concentrations of SN-38 are observed in individuals who are homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/6 genotype) versus patients who have one or two wild-type alleles.

Data from a meta-analysis of nine studies involving a total of 821 patients indicate that individuals with Crigler-Najjar syndrome (types 1 and 2) or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of hematological toxicity (Grades 3 and 4) following administration of irinotecan at moderate or high doses (>150 mg/m^2). A

relationship between UGT1A1 genotype and the occurrence of irinotecan-induced diarrhea was not established.

Patients who are homozygous (UGT1A1*6/*6 of UGT1A1*28/*28) or heterozygous (UGT1A1*6/*28) in allele UGT1A1*6, UGT1A1*28 of UGT may be at increased risk for serious adverse reactions (especially neutropenia) caused by reduced glucuronidation of SN-38. Added caution should be exercised when administering in such patients. Patients known to be homozygous for UGT1A1*28 should be administered the normally indicated irinotecan starting dose. However, these patients should be monitored for hematologic toxicities. A reduced irinotecan starting dose should be considered for patients who have experienced prior hematologic toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on individual patient tolerance to treatment.

Hypersensitivity reactions. Hypersensitivity reactions, including severe anaphylactic/ anaphylactoid reactions, have been reported.

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.

Late diarrhea. Late diarrhea (generally occurring more than 8 hours after administration of irinotecan) can be prolonged, may lead to dehydration, electrolyte imbalance, or sepsis and may be life-threatening.

In the clinical studies testing the every 3-week-dosage schedule, the median time to the onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 11 days following administration of irinotecan. For patients starting treatment at the 125 mg/m^2 weekly dose, the median duration of any grade of late diarrhea was 3 days. Among those patients treated at the 125 mg/m^2 weekly dose who experienced Grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. Results from a prospective study of the weekly dosage schedule did not demonstrate any difference in the rate of late onset diarrhea in patients ≥65 years of age than patients <65 years of age. However, patients ≥65 years of age should be closely monitored due to a greater risk of early diarrhea observed in this population. Colonic ulceration, sometimes with bleeding, has been observed in association with irinotecan-induced diarrhea.

Late diarrhea should be treated promptly with loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

The recommended dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours. Premedication with loperamide is not recommended. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they

become dehydrated and should be given antibiotic support if they develop ileus, fever, or severe neutropenia. In addition to the antibiotic treatment, hospitalization is recommended for management of the diarrhea, in the following cases:
-Diarrhea associated with fever,
-Severe diarrhea (requiring intravenous hydration),
-Patients with vomiting associated with delayed (i.e., late) diarrhea,
-Diarrhea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

After the first treatment, subsequent weekly chemotherapy treatments should be delayed in patients until return of pre-treatment bowel function for at least 24 hours without need for anti-diarrhea medication. If NCI Grade 2, 3, or 4 diarrhea occurs, subsequent doses of irinotecan should be reduced within the current cycle (see Section **Posology and method of administration**).

***Chronic inflammatory bowel disease and/or bowel obstruction*.** Patients must not be treated with CAMPTO until resolution of the bowel obstruction.

***Nausea and vomiting*.** Irinotecan is emetogenic. Nausea and vomiting can be severe and usually occurs during or shortly after infusion of irinotecan. It is recommended that patients receive premedication with antiemetic agents. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of irinotecan. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed. Patients with vomiting associated with delayed diarrhea should be hospitalised as soon as possible for treatment.

Neurologic. Dizziness has been observed and may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

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

Respiratory. NCI Grade 3 or 4 dyspnea has been observed. The extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea is unknown. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest X-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease.

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 pre-existing lung disease, 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.

***Others*.** Since this product contains sorbitol, it is unsuitable in hereditary fructose intolerance.

Overdose. Single doses of up to 750 mg/m^2 irinotecan have been given to patients with various cancers. The adverse events in these patients were similar to those reported with the recommended dosages and regimens. 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 diarrhea. 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.

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 (see Section **Warning and precautions**).

Geriatric. Specific dosing recommendations may apply to this population depending upon the regimen used (see Section **Posology and method of administration**).

Hepatic insufficiency. In patients with hyperbilirubinemia, the clearance of irinotecan is decreased (see Section **Pharmacokinetic properties**) and therefore, the risk of hematotoxicity is increased. The use of irinotecan in patients with a serum total bilirubin concentration of >3.0 x institutional upper limit of normal (IULN) given as a single-agent on the once-every-3-weeks schedule has not been established (see Section **Posology and method of administration**). Liver function should be monitored before initiation of treatment and monthly, or as clinically indicated.

Irradiation therapy. Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of irinotecan. Physicians should use caution in treating patients with extensive prior irradiation. Specific dosing recommendations may apply to this population depending upon the regimen used.

Performance status. Patients with poor performance status are at increased risk of irinotecan-related adverse events. Specific dosing recommendations for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 may apply depending upon the regimen used. Patients with performance status of 3 or 4 should not receive irinotecan. In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in clinical trials comparing these agents, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

Gastric cancer. Patients with gastric cancer appear to experience greater myelosuppression and other toxicities when given irinotecan. A lower starting dose should be considered in these patients.

Pregnancy and lactation

Pregnancy: There are no adequate and well-controlled studies of irinotecan in pregnant women. Irinotecan is teratogenic in rats and rabbits (see Section **Preclinical safety data**). Irinotecan may cause fetal harm when administered to a pregnant woman.

Women of childbearing potential should not be started on irinotecan until pregnancy is excluded. Pregnancy should be avoided if either partner is receiving irinotecan.

Due to the potential for genotoxicity advise female patients of reproductive potential to use highly effective contraception during treatment and for 6 months after the last dose of irinotecan.

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

Lactation: The available data are limited to one patient only. Irinotecan and its active metabolite SN-38 were measured in the milk of one lactating patient. The effect on newborn/infants is unknown. Because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with irinotecan.

In rats, radioactivity appeared in the milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations

Interactions
CYP3A4 and/or UGT1A1 inhibitors

Irinotecan and active metabolite SN-38 are metabolized via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) (see Section **Pharmacokinetic properties**). Co-administration of irinotecan with inhibitors of CYP3A4 and/or UGT1A1 may result in increased systemic exposure to irinotecan and the active metabolite SN-38. Physicians should take this into consideration when administering irinotecan with these drugs.

Ketoconazole: Irinotecan clearance is greatly reduced in patients receiving concomitant ketoconazole, leading to increased exposure to SN-38. Ketoconazole should be discontinued at least 1 week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

*Atazanavir sulfat*e: Co-administration 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.

CYP3A4 inducers

Anticonvulsants: Concomitant administration of CYP3A-inducing anticonvulsant drugs (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 irinotecan therapy in patients requiring anticonvulsant treatment.

St. John's Wort (Hypericum perforatum): Exposure to the active metabolite SN-38 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 irinotecan, and should not be administered during irinotecan therapy.

Other interactions

Neuromuscular blocking agents: Interaction between irinotecan hydrochloride 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 antagonized.

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

Dexamethasone: Lymphocytopenia has been reported in patients receiving irinotecan, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. However, serious opportunistic infections have not been observed and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

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

Diuretics: Dehydration secondary to vomiting and/or diarrhea may be induced by irinotecan. The physician may wish to withhold diuretics during dosing with irinotecan and during periods of active vomiting or diarrhea.

Bevacizumab: Results from a dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN-38.

Undesirable effects

Clinical studies

Adverse event data has been extensively collected and analyzed for the clinical studies program in metastatic colorectal cancer that recurred or progressed following 5-FU-based therapy (second-line) and are presented below (patient population described below). The adverse events for other indications are expected to be similar to those for second-line colorectal cancer.

Clinical studies of the 100- to 125-mg/m^2 single-agent weekly dosage schedule

The weekly dosage schedule of irinotecan was evaluated in three clinical studies of 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy. Five (1.6%) deaths were potentially drug-related. These five patients experienced a constellation of medical events (myelosuppression, neutropenic sepsis without fever, small bowel obstruction, fluid accumulation, stomatitis, nausea, vomiting, diarrhea, and dehydration) that are known effects of irinotecan. Neutropenic fever, defined as NCI Grade 4 neutropenia and Grade 2 or greater fever, occurred in nine other patients; these patients recovered with supportive care.

Eighty-one (26.6%) patients were hospitalized for events judged to be related to administration of irinotecan. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting; neutropenia/leukopenia, with or without diarrhea and/or fever; and nausea and/or vomiting.

Adjustments in the dose of irinotecan were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with irinotecan because of adverse events.

Clinical studies of the 300- to 350-mg/m^2 once-every-3-week single-agent dosage schedule
A total of 316 patients with metastatic colorectal cancer whose disease had progressed following prior 5-FU therapy received irinotecan in two studies involving once-every-3-week administration. Three (1%) deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, Grade 4 diarrhea, and asthenia, respectively. Hospitalizations due to serious adverse events, whether or not related to irinotecan administration, occurred at least once in 60% of patients who received irinotecan and, 8% of patients treated with irinotecan discontinued treatment due to adverse events.

Listing of adverse events
The drug-related adverse events (NCI Grades 1-4) as judged by the investigator that were reported in greater than 10% of the 304 patients enrolled in the three studies of the weekly dosage schedule are listed by body system in descending order of frequency in Table 3.

Table 3. NCI Grade 1 to 4 Drug-related Adverse Events Observed in over 10% of Patients in Clinical Studies

Gastrointestinal disorders:	Late diarrhea, nausea, vomiting, early diarrhea, abdominal cramping/pain, anorexia, stomatitis
Blood and lymphatic system disorders:	Leukopenia, anemia, neutropenia
General disorders and administration site conditions:	Asthenia, fever
Metabolism & nutrition disorders:	Decreased weight, dehydration
Skin and subcutaneous tissue disorders:	Alopecia
Vascular disorders:	Thromboembolic events*

*Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

NCI Grade 3 or 4 adverse events reported in the clinical studies of the weekly and once-every-3-week-dosage schedules (N=620) are listed in Tables 4 to 6.

Table 4. NCI Grade 3 or 4 Drug-related Adverse Events Observed in over 10% of Patients in Clinical Studies

Gastrointestinal disorders:	Late diarrhea, nausea, abdominal cramping/pain
Blood and lymphatic system disorders:	Leukopenia, neutropenia
Skin and subcutaneous tissue disorders:	Alopecia

Table 5. NCI Grade 3 or 4 Drug-related Adverse Events Observed in 1% to 10% of Patients in Clinical Studies

Infections and infestations:	Infection
Gastrointestinal disorders:	Vomiting, early diarrhea, constipation, anorexia, mucositis
Blood and lymphatic system disorders:	Anemia, thrombocytopenia
General disorders and administration site conditions:	Asthenia, fever, pain
Metabolism and nutrition disorders:	Dehydration, hypovolemia
Hepatobiliary disorders:	Bilirubinemia
Respiratory, thoracic and mediastinal disorders:	Dyspnea
Investigations:	Increased creatinine

Table 6. NCI Grade 3 or 4 Drug-related Adverse Events Observed in Fewer than 1% of Patients in Clinical Studies

Infections and infestations:	Sepsis
Gastrointestinal disorders:	Rectal disorder, GI monilia
General disorders and administration site conditions:	Chills, malaise
Metabolism and nutrition disorders:	Decreased weight, hypokalemia, hypomagnesemia
Skin and subcutaneous tissue disorders:	Rash, cutaneous signs
Nervous system disorders:	Abnormal gait, confusion, headache
Cardiac disorders:	Hypotension, syncope, cardiovascular disorders
Renal and urinary disorders:	Urinary tract infection
Reproductive system and breast disorders:	Breast pain
Investigations:	Increased alkaline phosphatase, increased GGTP

The following additional drug-related events have been reported in clinical studies with irinotecan, but do not meet the criteria as defined above as either >10% drug-related NCI

Grades 1-4 or as a NCI Grade 3 or 4 drug-related event: rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, bradycardia, dizziness, extravasation, tumor lysis syndrome, and colonic ulceration.

Post-marketing surveillance

Cardiac disorders

Myocardial ischemic events have been observed following irinotecan therapy predominantly in patients with underlying cardiac disease, other known risk factors for cardiac disease or previous cytotoxic chemotherapy (see also Table 3, thromboembolic events).

Gastrointestinal disorder

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

Rare cases of symptomatic pancreatitis or asymptomatic elevated pancreatic enzymes have been observed.

Hypovolemia

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

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

Infections and infestations

Bacterial, fungal and viral infections have been reported.

Immune system disorders

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been reported (see Section **Warning and precautions**).

Musculoskeletal disorders and connective tissue disorders

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

Nervous system disorders

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

Respiratory thoracic and mediastinal disorders

Interstitial pneumonia and pneumonitis presenting as pulmonary infiltrates have rarely been observed. Early effects, such as dyspnea, have been reported (see Section **Warning and precautions**).

Investigations
Rare cases of hyponatremia mostly related with diarrhea and vomiting have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been very rarely reported.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Therapeutic class
Irinotecan hydrochloride is an antineoplastic agent of the topoisomerase I inhibitor class, clinically investigated as CPT-11. Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants, such as *Camptotheca acuminata*, or is chemically synthesized.

Mechanism of action
Irinotecan and its active metabolite SN-38 bind to the topoisomerase I – DNA complex and prevent re-ligation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. *In vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan. The precise contribution of SN-38 to the activity of irinotecan is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Pharmacokinetic properties
Absorption and distribution
After intravenous infusion in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism & excretion
Irinotecan (CPT-11) is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan (CPT-11) can also undergo CYP3A4-mediated oxidative metabolism to several pharmacologically inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as the UGT1A1*28 polymorphism (see Section **Warning and precautions)**. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in special populations
Geriatric: The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC_{0-24} for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant.

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Race. The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency: (see Section **Posology and method of administration**). Irinotecan clearance is diminished in patients with hepatic dysfunction while relative exposure to the active metabolite SN-38 is increased. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in serum total bilirubin and transaminase concentrations.

Renal Insufficiency: (see Section **Posology and method of administration**). The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

Preclinical safety data
Toxicology
The acute intravenous toxicity of irinotecan in animals is shown below. Lethality was observed after single intravenous irinotecan doses of approximately 111 mg/kg in mice and 73 mg/kg in rats (approximately 2.6 and 3.4 times the recommended human dose of 125 mg/m^2, respectively). Death was preceded by cyanosis, tremors, respiratory distress, and convulsions.

Subacute toxicity studies show that irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes).

Species	LD_{50} (mg/kg)
Mouse	132-134
Rat	84-85
Dog	40-80

Carcinogenicity/Mutagenicity
Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.

Neither irinotecan nor SN-38 was mutagenic in the *in vitro* Ames assay. However, in the *in vitro* Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration-dependent manner. Additionally, in the *in vivo* mouse micronucleus assay, a single intraperitoneal dose of irinotecan over the dosage range of 2.5 to 200 mg/kg caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells.

Reproduction
No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m^2).

Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6 mg/kg/day (about one-half the recommended weekly human dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

PHARMACEUTICAL PARTICULARS

Special Precautions for Storage
Store below 30°C. Store protected from light. Keep medicine out the reach of children.

Diluted Admixtures. The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection and stored at refrigerated temperature and protected from light are physically and chemically stable for 48 hours.

Refrigeration of admixtures using 0.9% Sodium Chloride Injection is not recommended due to a low and sporadic incidence of visible particulates. Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated or within 6 hours if kept at room temperature. Freezing irinotecan vials or admixtures of irinotecan may result in precipitation of the drug and should be avoided.

Incompatibilities
Other drugs should not be added to the infusion solution.

Special precautions for disposal and other handling
Preparation
Irinotecan must be diluted prior to infusion in 5% Dextrose Injection, (preferred) or 0.9% Sodium Chloride Injection to a final concentration range of 0.12 to 2.8 mg/mL.

Handling
As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from irinotecan. The use of gloves is recommended. If irinotecan contacts the skin, wash the skin immediately and thoroughly with soap and water. If irinotecan contacts the mucous membranes, flush thoroughly with water.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

Presentation
CAMPTO 40 mg: 2 mL amber-coloured polypropylene vial. Box of 1 vial. Reg. No. DKI0955901349A1
CAMPTO 100 mg: 5 mL amber-coloured polypropylene vial. Box of 1 vial. Reg. No. DKI0955901349A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

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