For the use only of a Registered Medical Practitioners (Oncologist) or a Hospital or a Laboratory

Irinotecan Hydrochloride Injection I.P.
CAMPTO®

1. GENERIC NAME

Irinotecan Hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Irinotecan hydrochloride

Each milliliter (ml) of sterile solution contains 20 mg of Irinotecan Hydrochloride Trihydrate I.P.

List of Excipients

Sorbitol, Lactic acid, Sodium hydroxide, Hydrochloric acid, Water for injections

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Solution for Injection
Strength: 40 mg/ 2 ml and 100 mg / 5 ml

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Irinotecan is indicated for single-agent or combination treatment of patients with:

- Metastatic carcinoma of the colon or rectum that has recurred or progressed following 5-fluorouracil (5-FU)-based therapy.
- Irinotecan in combination with cetuximab is indicated for the treatment of patients with epidermal growth receptor (EGFR)-expressing metastatic colorectal cancer, after failure of irinotecan-including cytotoxic therapy.

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- Previously untreated metastatic carcinoma of the colon or rectum.
- Advanced cervical squamous cell carcinoma.
- Irinotecan in combination with 5-FU, folinic acid (FA) and bevacizumab is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

4.2 Posology and Method of Administration

All doses of irinotecan should be administered as an intravenous infusion over 30 to 90 minutes.

Single-agent Dosage Schedules

Single-agent dosage schedules have been extensively studied for metastatic colorectal cancer. These regimens may be used in the treatment of patients with other indicated cancers (see section **4.1 Therapeutic Indication**).

Starting Dose

Weekly Dosage Schedule. The recommended single-agent starting dose of irinotecan is 125 mg/m^2. A lower starting dose may be considered (e.g., 100 mg/m^2) for patients with any of the following conditions: prior extensive radiotherapy, performance status of 2, increased bilirubin levels. Treatment should be given in repeated 6-week cycles, comprising weekly treatment for 4 weeks, followed by a 2-week rest.

Once-every-2-week Dosage Schedule. The usual recommended starting dose of irinotecan is 250 mg/m^2 every 2 weeks by intravenous infusion. A lower starting dose may be considered (e.g., 200 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels.

Once-every-3-week Dosage Schedule. The usual recommended starting dose of irinotecan for the once-every-3-week dosage schedule is 350 mg/m^2. A lower starting dose may be considered (e.g., 300 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels.

Special Populations
Patients with Impaired Hepatic Function

In patients with hepatic dysfunction, the following starting doses are recommended:

Table 1 Starting Doses in Patients with Hepatic Dysfunction: Single-agent Weekly Regimen

Serum Total Bilirubin Concentration	Serum ALT/AST Concentration	Starting Dose, mg/m^2
1.5-3.0 x IULN	≤5.0 x IULN	60
3.1-5.0 x IULN	≤5.0 x IULN	50
<1.5 x IULN	5.1-20.0 x IULN	60
1.5-5.0 x IULN	5.1-20.0 x IULN	40

Table 2 Starting Doses in Patients with Hepatic Dysfunction: Single-agent Once-every-3-week Regimen

Serum Total Bilirubin Concentration	Starting Dose, mg/m^2
1.5-3.0 x IULN	200
>3.0 x IULN	Not Recommended[a]

[a]The safety and pharmacokinetics of irinotecan given once-every-3-weeks have not been defined in patients with bilirubin >3.0 x institutional upper limit of normal (IULN) and this schedule cannot be recommended in these patients.

Patients with Impaired Renal Function

Studies in this population have not been conducted (see section **5.3 Pharmacokinetic Properties**, *Special Populations*). Therefore, caution should be undertaken in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis.

Combination-agent Dosage Schedules

Starting Dose

Irinotecan in Combination with 5-Fluorouracil (5-FU) and Leucovorin in Every 2 Weeks Schedule. Irinotecan in combination with 5-FU and leucovorin is recommended for use in patients with metastatic colorectal cancer. For all regimens, the dose of leucovorin should be administered immediately after irinotecan, with the administration of 5-FU to occur immediately after receipt of leucovorin. The currently recommended regimens are shown below:

Regimen 1 (6-week cycle with bolus 5-FU/LV): The recommended starting dose is 125 mg/m^2 of irinotecan, 500 mg/m^2 bolus 5-FU, and 20 mg/m^2 bolus leucovorin.

Regimen 2 (6-week cycle with infusional 5-FU/LV): The recommended starting dose is 180 mg/m^2 of irinotecan, 400 mg/m^2 bolus 5-FU, 600 mg/m^2 5-FU infusion, and 200 mg/m^2 leucovorin.

Lower starting doses may be considered for irinotecan (e.g., 100 mg/m^2) and 5-FU (e.g., 400 mg/m^2) for patients with any of the following conditions: age 65 years and older, prior extensive radiotherapy, performance status of 2, increased bilirubin levels. Treatment should be given in repeated 6-week cycles, comprising weekly treatment for 4 weeks,

followed by a 2-week rest.

Irinotecan in Combination with Cisplatin. Irinotecan has been studied in combination with cisplatin in cervical cancer. The recommended starting dose is 65 mg/m^2 of irinotecan and 30 mg/m^2 of cisplatin A lower starting dose of irinotecan (e.g., 50 mg/m^2) 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. Treatment should be given in repeated 6-week cycles, comprising weekly treatment for 4 weeks, followed by a 2-week rest.

Irinotecan in Combination with Cetuximab. For the posology and method of administration of concomitant cetuximab, refer to the full prescribing information for cetuximab. Normally, the same dose of irinotecan is used as administered in the last cycles of the prior irinotecan-containing regimen. Irinotecan must not be administered earlier than 1 hour after the end of the cetuximab infusion.

Irinotecan in Combination with Bevacizumab. For the posology and method of administration of bevacizumab, refer to the full prescribing information for bevacizumab. Bevacizumab is recommended in combination with irinotecan (125 mg/m^2)/bolus 5-FU (500 mg/m^2)/folinic acid (20 mg/m^2) given once weekly for 4 weeks every 6 weeks.

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 during a cycle of therapy and at the start of each subsequent cycle of therapy for single-agent dosage schedules are described in Table 3. These recommendations are based on toxicities commonly observed with the administration of irinotecan. For modifications at the start of a subsequent cycle of therapy, the dose of irinotecan should be decreased relative to the initial dose of the previous cycle.

The recommended dose modifications during a cycle of therapy and at the start of each subsequent cycle of therapy for irinotecan, 5-FU, and leucovorin are described in Table 4.

Recommendations for dose modifications of cetuximab when administered in combination with irinotecan must be followed according to the full prescribing information for cetuximab.

Refer to the full prescribing information for bevacizumab for dose modifications of

bevacizumab when administered in combination with irinotecan/5-FU/FA.

All dose modifications should be based on the worst preceding toxicity. A new cycle of therapy should not begin until the toxicity has recovered to grade 2 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing irinotecan.

Table 1 Recommended Dose Modifications for Single-agent Schedules

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, and treatment-related diarrhea is fully resolved. 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[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycle of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[a]**	
	Weekly	**Weekly**	**Once Every 2 or 3 Week**
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3)	Maintain dose level ↓ 25 mg/m^2	Maintain dose level	Maintain dose level
2 (1000 to 1499/ mm^3)	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤grade 2	Maintain dose level ↓ 25 mg/m^2	Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
3 (500 to 999/ mm^3)	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤grade 2	↓ 50 mg/m^2	
4 (<500/mm^3)			
Neutropenic fever (grade 4 neutropenia & ≥grade 2 fever)	Omit dose, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea 1 (2-3 stools/day > pretx[c])	Maintain dose level ↓ 25 mg/m^2	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx[c])	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤ grade 2	Maintain dose level ↓ 25 mg/m^2 ↓ 50 mg/m^2	Maintain dose level ↓ 50 mg/m^2↓ 50 mg/m^2
3 (7-9 stools/day > pretx[c])	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤ grade 2		
4 (≥10 stools/day > pretx[c])			

Table 1 Recommended Dose Modifications for Single-agent Schedules

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, and treatment-related diarrhea is fully resolved. 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[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycle of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[a]**	
Other non-hematologic toxicities[d]			
1	Maintain dose level ↓ 25 mg/m^2	Maintain dose level ↓ 25 mg/m^2 ↓ 25 mg/m^2	Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
2	Omit dose, then ↓ 25 mg/m^2 when resolved to ≤grade 2	↓ 50 mg/m^2	↓ 50 mg/m^2
3	Omit dose, then ↓ 50 mg/m^2 when resolved to ≤grade 2		
4			

[a] All dose modifications should be based on the worst preceding toxicity.
[b] National Cancer Institute Common Toxicity Criteria.
[c] Pre-treatment.
[d] Excludes alopecia, anorexia, asthenia.

Table 4 Recommended Dose Modifications for Irinotecan/5-Fluorouracil/Leucovorin Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. 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, and treatment-related diarrhea is fully resolved. 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[b] (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3) 2 (1000 to 1499/mm^3) 3 (500 to 999/mm^3) 4 (<500/mm^3) Neutropenic fever (grade 4 neutropenia & ≥grade 2 fever)	Maintain dose level[c] ↓ 1 dose level[d] Omit dose, then ↓ 1 dose level when resolved to ≤grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤grade 2[d] Omit dose, then ↓ 2 dose levels when resolved	Maintain dose level[c] Maintain dose level ↓ 1 dose level[d] ↓ 2 dose levels ↓ 2 dose levels
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. 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, and treatment-related diarrhea is fully resolved. 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[b] (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy**
1 (2-3 stools/day > pretx[e]) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Delay dose until resolved to baseline (bsl), then give same dose Omit dose, then ↓ 1 dose level when resolved to bsl Omit dose, then ↓ 1 dose level when resolved to bsl Omit dose, then ↓ 2 dose levels when resolved to bsl	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels
Other non-hematologic Toxicities[f] 1 2 3 4	 Maintain dose level Omit dose, then ↓ 1 dose level when resolved to ≤grade 1 Omit dose, then ↓ 1 dose level when resolved to ≤grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤grade 2 For mucositis/stomatitis decrease only 5-FU, not irinotecan[g]	 Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels For mucositis/stomatitis decrease only 5-FU, not irinotecan.[g]
[a] Dose modification refers to irinotecan and 5-FU; LV dose remains fixed at 20 mg/m^2 (not adjusted). [b] National Cancer Institute Common Toxicity Criteria. [c] Refers to initial dose used in previous cycle. [d] Irinotecan: dose level reductions = 25 mg/m^2 decrements; 5-Fluorouracil: dose level reductions = 100 mg/m^2 decrements. [e] Pre-treatment. [f] Excludes alopecia, anorexia, asthenia [g] For mucositis/stomatitis decrease only 5-FU, not irinotecan.		

4.3 Contraindications

Irinotecan is contraindicated in patients with a known hypersensitivity to the drug or its excipients (see section **4.4 Special Warnings and Precautions for Use**, *Hypersensitivity Reactions*).

4.4 Special Warnings and Precautions for Use

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 extravasation 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 sections **4.4 Special Warnings and Precautions for Use - Special Populations**, *Hepatic Insufficiency* and **4.2 Posology and Method of Administration, Single-agent and Combination-Agent Dosage Schedules**).

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 **4.2 Posology and Method of Administration**, ***Dose Modification Recommendations***).

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. 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 7/7 genotype) versus patients who have one or two wild-type alleles.

Another specific polymorphism of UGT1A1 gene (that reduces the activity of this enzyme) is a missense mutation known as UGT1A1*6 variant.

Patients with UGT1A1*28 or *6 variants (especially if homozygous) are at increased risk of experiencing adverse events such as neutropenia and diarrhoea. A reduced irinotecan starting dose should be considered for homozygous patients. In addition, *28 and *6 homozygous and heterozygous patients should be closely monitored for neutropenia and diarrhoea.

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.

In order to identify patients at increased risk of experiencing neutropenia and diarrhoea, UGT1A1 genotyping can be useful. More in detail, UGT1A1*28 genotyping can be useful in Caucasians, Africans and Latinos, UGT1A1*6 in East-Asians and combined UGT1A1*28 and *6 in Chinese and Japanese, since these are the populations in which these variants are more prevalent.

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.

Cardiovascular: Thromboembolic events have been observed rarely in patients receiving irinotecan. The specific cause of these events has not been determined.

Early diarrhoea (occurring during or shortly after infusion of CAMPTO) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, bradycardia and intestinal hyperperistalsis that can cause abdominal cramping. Administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless clinically contraindicated) in patients experiencing cholinergic symptoms occurring during or shortly after infusion of CAMPTO. Patients ≥65 years of age should be closely monitored due to a greater risk of early diarrhoea observed in this population. Late diarrhoea (generally occurring more than 24 hours after administration).

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 **4.2 Posology and Method of Administration**, ***Dose Modification Recommendations***).

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

Nausea & 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 (i.e., late) diarrhea should be hospitalized 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 non-malignant 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.

Special Populations

Pediatric. The effectiveness of irinotecan in pediatric patients has not been established (see section **5.3 Pharmacokinetic Properties**, *Pharmacokinetics in Special Populations, Pediatric*). Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults.

In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m^2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3, and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalaemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition, grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

Geriatric. Specific dosing recommendations may apply to this population depending upon the regimen used (see section **4.2 Posology and Method of Administration**).

Hepatic Insufficiency. In patients with hyperbilirubinemia, the clearance of irinotecan is decreased (see section **5.3 Pharmacokinetic Properties**, *Pharmacokinetics in Special Populations*) 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 **4.2 Posology and Method of Administration**, ***Special Populations***). 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 (see section **4.2 Posology and Method of Administration**).

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 (see section **4.2 Posology and Method of Administration**). 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 hospitalisation, 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.

4.5 Drugs Interactions

CYP3A4 and/or UGT1A1 Inhibitors
Irinotecan and its active metabolite SN-38 are metabolised via the human cytochrome P450 3A4 isoenzyme (CYP3A4) and uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) (see section **5.3 Pharmacokinetic Properties**-, *Metabolism*). Coadministration 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 the active metabolite SN-38. Ketoconazole should be discontinued at least 1 week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

Atazanavir Sulfate: 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.

CYP3A4 Inducers

Anticonvulsants: Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital or phenytoin) leads to reduced exposure to 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 and neuromuscular

blocking agents cannot be ruled out. Since irinotecan 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.

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

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 SN38

Patients who develop severe diarrhea, leukopenia, or neutropenia with the bevacizumab and irinotecan in combination should have irinotecan dose modifications as specified in section **4.2 Posology and Method of Administration**.

4.6 Use in Special Populations

Effects on fertility

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan hydrochloride in doses of up to 6 mg/kg/day to rats. Atrophy of male reproductive organs was observed after multiple daily irinotecan hydrochloride doses both in rodents at 20 mg/kg (AUC approximately the same value as in patients administered 125 mg/m^2 weekly) and dogs at 0.4 mg/kg (AUC about 1/15th the value in patients administered 125 mg/m^2 weekly).

Pregnancy

Irinotecan is teratogenic in rats and rabbits (see section **6.1 Animal Toxicology or Pharmacology**). Irinotecan may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of irinotecan in pregnant women.

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 and 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. Irinotecan hydrochloride has been shown to impair learning ability and cause a delay in postnatal development in rats.

4.7 Effects on Ability to Drive and Use Machines

The effect of irinotecan on the ability to drive or use machinery has not been evaluated. However, patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of irinotecan, and advised not to drive or operate machinery if these symptoms occur (see section **4.4 Special Warnings and Precautions for Use**).

4.8 Undesirable Effects

Clinical Studies

Adverse reaction 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 reactions for other indications are expected to be similar to those for second-line colorectal cancer.

Adverse reactions 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 adverse reactions were those expected with cetuximab (such as acneiform rash). Therefore, also refer to the full prescribing information for cetuximab.

Grade 3 hypertension was the principal significant risk involved with the addition of bevacizumab to bolus irinotecan/5-FU/FA. In addition, there was a small increase in the Grade 3/4 chemotherapy adverse events of diarrhea and leukopenia with this regimen compared to patients receiving bolus irinotecan/5-FU/FA alone. For other information on adverse reactions in combination with bevacizumab, refer to the bevacizumab full prescribing information.

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 5.

Table 5 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 and 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 6 to 8.

Table 6 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 7 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 8 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: ***Reproductive system and breast disorders:***	urinary tract infection, 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 5, thromboembolic events).

Gastrointestinal disorders
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 **4.4 Special Warnings and Precautions for Use**).

Musculoskeletal 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 pulmonary disease presenting as pulmonary infiltrates is uncommon during irinotecan therapy. Early effects, such as dyspnea have been reported (see section **4.4 Special Warnings and Precautions for Use**). Hiccups have also been reported.

Renal and cardiovascular disorders
Infrequent cases of renal insufficiency including acute renal failure, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis (see section **4.4 Special Warnings and Precautions for Use**).

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.

4.9 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. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications. There is no known antidote for overdosage of irinotecan.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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.

5.2 Pharmacodynamic Properties

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.

Clinical Studies

<u>In combination therapy for the first-line treatment of metastatic colorectal carcinoma</u>

Irinotecan in combination with bevacizumab:

A phase III randomized, double-blind, active-controlled clinical trial evaluated bevacizumab in combination with irinotecan/5-FU/FA as first-line treatment for metastatic carcinoma of the colon or rectum (Study AVF2107g). The addition of bevacizumab to the combination of irinotecan/5-FU/FA resulted in a statistically significant increase in overall survival. The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of

primary tumor, number of organs involved, and duration of metastatic disease. Refer also to the bevacizumab full prescribing information. The efficacy results of Study AVF2107g are summarized in the table below.

Table 9 Efficacy Results from Study AVF2107g

	AVF2107g	
	Arm 1 irinotecan/5-FU/FA+Placebo	**Arm 2 irinotecan/5-FU/FA +bevacizumab[a]**
Number of Patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% CI	14.29 – 16.99	18.46 – 24.18
Hazard ratio[b]	=	0.660
p-value	=	0.00004
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	=	0.54
p-value	=	≤ 0.0001
Overall response rate		
Rate (%)	34.8	44.8
95% CI	30.2 – 39.6	39.9 – 49.8
p-value	=	0.0036
Duration of response		
Median time (months)	7.1	10.4
25–75 percentile (months)	4.7 – 11.8	6.7 – 15.0

[a]5 mg/kg every 2 weeks.
[b]Relative to control arm.
CI=confidence interval; 5-FU=5-fluorouracil; FA=folinic acid.

In combination therapy for the second-line treatment of metastatic colorectal carcinoma

Irinotecan in combination with cetuximab after failure of irinotecan-including cytotoxic therapy:

The efficacy of the combination of cetuximab with irinotecan was investigated in two clinical studies. A total of 356 patients with EGFR-expressing metastatic colorectal cancer who had recently failed irinotecan-including cytotoxic therapy and who had a minimum Karnofsky performance status of 60, but the majority of whom had a Karnofsky performance status of ≥80 received the combination treatment.

EMR 62 202-007: This randomized study compared the combination of cetuximab and irinotecan (218 patients) with cetuximab monotherapy (111 patients).

IMCL CP02-9923: This single arm open-label study investigated the combination therapy in 138 patients.

The efficacy data from these studies are summarized in Table 10 below:

Table 10 Efficacy Results from Studies EMR 62 202-007 and IMCL CP02-9923

Study	**N**	**ORR**		**DCR**		**PFS (months)**		**OS (months)**	
		n (%)	95% CI	n (%)	95% CI	Median	95% CI	Median	95% CI
Cetuximab + irinotecan									
EMR 62 202-007	218	50 (22.9)	17.5, 29.1	121 (55.5)	48.6, 62.2	4.1	2.8, 4.3	8.6	7.6, 9.6
IMCL CP02-9923	138	21 (15.2)	9.7, 22.3	84 (60.9)	52.2, 69.1	2.9	2.6, 4.1	8.4	7.2, 10.3
Cetuximab									
EMR 62 202-007	111	12 (10.8)	5.7, 18.1	36 (32.4)	23.9, 42.0	1.5	1.4, 2.0	6.9	5.6, 9.1
CI=confidence interval; DCR=disease control rate (patients with complete response, partial response, or stable disease for at least 6 weeks); ORR=objective response rate (patients with complete response or partial response); OS=overall survival time; PFS=progression-free survival									

The efficacy of the combination of cetuximab with irinotecan was superior to that of cetuximab monotherapy, in terms of objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). In the randomized trial, no effects on overall survival were demonstrated (hazard ratio 0.91, p = 0.48).

5.3 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

The complete disposition of irinotecan hydrochloride has not been fully elucidated in humans. Irinotecan hydrochloride is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and uridine diphosphate-glucuronyl transferase 1A1 (UGT1A1) mediating glucuronidation of SN-38 to form the inactive metabolite SN-38 glucuronide (SN-38G). The metabolic conversion of irinotecan hydrochloride occurs primarily in the liver.

Irinotecan hydrochloride is oxidised by cytochrome P450 isozyme 3A4 (CYP3A4) to yield two relatively inactive metabolites, APC (7 ethyl l0 [4-N-(5 aminopentanoic acid)-1 piperidino]carbonyloxycamptothecin) and the minor metabolite, NPC (7 ethyl-10 (4 amino-1 piperidino)carbonyloxycamptothecin

Excretion

The urinary excretion of irinotecan hydrochloride was 11% to 20% of the administered dose; SN-38 <1% and SN-38G 3%. The cumulative biliary and urinary excretion of irinotecan hydrochloride and its metabolites (SN-38 and SN-38G) over a period of 48 hours following administration of irinotecan hydrochloride in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Special Populations

Geriatric (≥65 years)
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.

Pediatric (see section **4.4 Special Warnings and Precautions for Use** – **Special Populations** – *Pediatric*).

The pharmacokinetics of irinotecan and its major metabolites in the pediatric population was investigated in clinical trials conducted in the US and Europe. Overall, results and general conclusions regarding irinotecan pharmacokinetics were comparable in the US and European studies. Any differences in the findings between these studies are probably attributable to differences in the doses investigated (20 to 200 mg/m^2 and 200 to 720 mg/m^2 in the US and European studies, respectively) and the marked inter-patient variability in values determined for the pharmacokinetic parameters of irinotecan and SN-38.

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 Impairment

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 (see section **4.2 Posology and Method of Administration**, ***Special Populations***).

Renal Impairment

The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated (see section **4.2 Posology and Method of Administration, *Patients with Impaired Renal Function***).

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

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).

Table 11 Acute toxicity of irinotecan (IV) in animals

Species	LD50 (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 not 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 6mg/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 14C-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.

7. DESCRIPTION

Irinotecan sterile solution is a pale yellow, clear, aqueous solution requiring dilution for intravenous administration.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Other drugs should not be added to the infusion solution.

8.2 Shelf-life

24 Months

The Campto infusion should be used immediately after reconstitution as it contains no antibacterial preservative. If reconstitution and dilution are performed under strict aseptic conditions (e.g., on laminar Air Flow Bench) Campto infusion solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if stored at 2°C-8°C.

8.3 Packaging Information

Campto 40 mg in 2 ml: one 2 ml amber-coloured medical grade polypropylene vial (Cytosafe Vial) closed with a halobutyl rubber stopper and sealed with an aluminium crimp with a plastic flip-off top.

Campto 100 mg in 5 ml: one 5 ml amber-coloured medical grade polypropylene vial (Cytosafe vial) closed with a halobutyl rubber stopper and sealed with an aluminium crimp with a plastic flip-off top.

8.4 Storage and Handling Instructions

Store below 25°C. Store protected from light.
Keep out of 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

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 hence Avoid Freezing.

Instructions for Disposal and Other Handling of the Product

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 antineoplastic agents, Campto must be prepared and handled with caution. The use of glasses, mask and gloves is required.

If Campto solution or infusion solution should come in contact with skin, wash immediately and thoroughly with soap and water.

If Campto solution or infusion should come in contact with mucous membranes, wash immediately with water.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Inspect vials contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe. Discard the solution if content is not clear or if particulate matter or discolouration is observed.

9. PATIENT COUNSELING INFORMATION

- Patients and caregivers should be informed of gastrointestinal complications, such as nausea, vomiting, abdominal cramping, and diarrhea. Patients should have loperamide readily available to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of Irinotecan). Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One 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. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Patients should contact their physician if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours.
- Patients should be warned about the potential for dizziness or visual disturbances which

may occur within 24 hours following the administration of Irinotecan.

- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever or infection.
- Embryo-Fetal Toxicity (see section **4.3 Use in Special Populations**)
  - Advise pregnant women and females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy.
  - Advise females of reproductive potential to use effective contraception during treatment with Irinotecan and for 6 months after the final dose.
  - Advise male patients with female partners of reproductive potential to use condoms during treatment and for 3 months after the final dose of Irinotecan.
- Lactation
  - Advise women not to breastfeed during treatment with Irinotecan (see section **4.3 Use in Special Populations**)
- Patients should be alerted to the possibility of alopecia.
- Contains sorbitol.

10. DETAILS OF MANUFACTURER

M/s Bridgewest Perth Pharma Pty. Ltd., 15 Brodie Hall Drive, Bentley, Western Australia 6102, Australia

Imported and Marketed in India by

Pfizer Products India Private Limited,
The Capital- B Wing, 1802, 18th Floor Plot No. C-70,
G Block, Bandra Kurla Complex, Bandra (East),
Mumbai 400 051, India

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

FF-328-6803 dated 01-Feb-2024* (*The license is renewed every 3 years as per regulations).

12. DATE OF REVISION

October 2024