NEW ZEALAND DATA SHEET

1 IRINOTECAN (ALCHEMY), 100mg/5mL, Concentrated Solution for Infusion

Irinotecan (Alchemy), Concentrated Solution for Infusion, 100 mg/5mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mL concentrated solution contains 100 mg irinotecan hydrochloride trihydrate.

1 mL concentrated solution contains 20 mg irinotecan hydrochloride trihydrate

Excipient with known effect: Sorbitol
This medicine contains 225 mg sorbitol in each 5mL which is equivalent to 45 mg per mL.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Concentrated Solution for Infusion.

Clear yellow solution with pH 3.0 – 4.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Irinotecan (Alchemy) is indicated as a component of first line therapy for patients with metastatic carcinoma of the colon or rectum, in combination with 5-FU/Leucovorin. Irinotecan (Alchemy) is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial therapy.

4.2 Dose and method of administration

Dose

Combination Agent Therapy

Dosage Regimens

Irinotecan (Alchemy) in combination with fluorouracil (5-FU) and Leucovorin (LV)

The recommended regimens are shown in **Table 1**.

Table 1 - Combination Agent Dosage Regimens & Dose Modifications [a]

Regimen 1 6 week cycle Treatment resumes Day 43	IRINOTECAN (Alchemy) LV 5-FU	125mg/m^2 IV over 90 mins on day 1,8,15,22 then 2 week rest 20mg/m^2 IV bolus injection day 1, 8, 15, 22 then 2 week rest 500mg/m^2 IV bolus injection day 1,8,15, 22 then 2 week rest		
		Starting dose and modified dose levels [b] **(mg/m^2)**		
		Starting Dose	Dose Level 1	Dose Level 2
	IRINOTECAN (Alchemy) LV 5-FU	125 20 500	100 20 400	75 20 300
Regimen 2 6 week cycle Treatment resumes Day 43	IRINOTECAN (Alchemy) LV 5-FU Bolus 5-FU Infusion	180 mg/m^2 IV over 90 mins on day 1,15, 29 then 1 week rest 200 mg/m^2 IV over 2 hrs on day 1, 2, 15, 16, 29, 30 then 1 week rest 400 mg/m^2 IV on day 1, 2, 15, 16, 29, 30 then 1 week rest 600 mg/m^2 IV over 22hrs on day 1, 2, 15,16, 29, 30 then 1 week rest		
		Starting dose and modified dose levels [b] **(mg/m^2)**		
		Starting Dose	Dose Level 1	Dose Level 2
	IRINOTECAN (Alchemy) LV 5-FU Bolus 5-FU Infusion [c]	180 200 400 600	150 200 320 480	120 200 240 360

a Dose reduction beyond dose level-2 by decrements of ≈20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefits.

b Refer to **Table 2**.

c Infusion follows bolus administration.

Dose Modifications

It should be carefully monitored for toxicity and assessed prior to each treatment, especially during the first cycle of therapy. Dose of Irinotecan (Alchemy) and 5-FU should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose levels described in **Table 1**, subsequent doses should be adjusted as suggested in **Table 2**, which shows the recommended dose modifications for combination schedules. All dose modifications should be based on the worst preceding toxicity. Patients should be diarrhoea free (return to pre-treatment bowel function) without requiring antidiarrheal medications for at least 24 hours before receiving the next chemotherapy administration.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less, the granulocyte count has recovered to ≥ 1.5 x 10^9/L, the platelet count has recovered to ≥ 100 x 10^9/L and treatment-related diarrhoea is fully resolved. Treatment should be delayed for 1 to 2 weeks to allow recovery from treatment-related toxicity. If the patient has not recovered after a 2 week delay, consideration should be given to discontinuing therapy. Provided intolerable toxicity does not develop, treatment with additional cycles of Irinotecan (Alchemy)/5-FU/LV may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 2 - Recommended dose modification during a cycle of therapy with the Irinotecan (Alchemy)/5-FU/LV combination and at the start of each subsequent cycle of therapy.

Toxicity NCI CTC Grade [a]	**Duration of Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy** [b]
No Toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level.	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels
Neutropenia fever	Omit dose until resolved, then decrease by 2 dose levels	
Other haematological 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.	
Diarrhoea		
1	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2	Omit dose until resolved to baseline, then decrease by 1 dose level	Maintain dose level
3	Omit dose until resolved to baseline, then decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to baseline, then decrease by 2 dose levels	Decrease by 2 dose levels
Other non-haematological toxicities [c]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then decrease by 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels

a Severity of adverse events based on NCI CTC (version 2.0) see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_archive

b Relative to the starting dose used in the previous cycle

c For mucositis/stomatitis decrease only FU, not Irinotecan (Alchemy)

Single Agent Therapy

Dosage Regimens

Irinotecan (Alchemy) should be administered as an intravenous infusion (refer to Preparation of Infusion Solutions) over 90 minutes in a recommended weekly or once every 3 week dosage schedule as shown in **Table 3**.

Table 3 - Single agent regimens of Irinotecan (Alchemy) and dose modification

Weekly Regimen [a] 6 week cycle Treatment resumes Day 43	125mg/m^2 IV over 90 mins day 1, 8,15, 22 then 2 week rest		
	Starting dose and modified dose level [c] **(mg/m^2)**		
	Starting Dose	Dose Level - 1	Dose Level - 2
	125	100	75
Once every 3 week regimen [b]	350mg/m^2 IV over 90 mins once every 3 weeks		
	Starting dose and modified dose level [c] **(mg/m^2)**		
	Starting Dose	Dose Level - 1	Dose Level - 2
	350	300	250

a Subsequent dose may be adjusted as high as 150 mg/m^2 or as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending on individual patient tolerance.

b Subsequent dose may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending on individual patient tolerance.

c Refer to **Table 5**.

A reduction in the starting dose by one level of Irinotecan (Alchemy) may be considered for patients with any of the following circumstances: over 65 years, prior pelvic/abdominal radiotherapy, performance status of 2 or moderately increased bilirubin levels (17 – 34 μmol/L).

Patients with Impaired Hepatic Function (Single Agent)

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

Table 4 - Starting Doses in Patients with Hepatic Dysfunction – Single Agent Regimens

Regimen	Serum Total Bilirubin Concentration	Serum ALT/AST Concentration	Starting Dose mg/m^2
Single Agent Weekly	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
Single Agent Weekly Once Every 3 Weeks	1.5-3.0 x IULN	--	200
	>3.0 x IULN	--	Not Recommended [a]

a A safety and pharmacokinetics of Irinotecan given once every 3 weeks have not been defined in patients with biliruin >3.0 x IULN and this schedule cannot be recommended in these patients.

Dose Modifications

Patients should be carefully monitored for toxicity and doses of Irinotecan (Alchemy) should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in **Table 3** & **Table 4**, subsequent doses of Irinotecan (Alchemy) should be adjusted as suggested in **Table 5**. 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 NCI grade 1 or less. The granulocyte count has recovered to ≥ 1.5 x 10^9/L, the platelet count has recovered to ≥ 100 x 10^9/L and treatment-related diarrhoea is fully resolved. Treatment may be delayed for 1 to 2 weeks to allow recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinue Irinotecan (Alchemy) therapy. Provided intolerable toxicity dose not develop, treatment with additional cycle of Irinotecan (Alchemy) may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 5 - Recommended Dose Modification for Single Agent Regimens.

Toxicity NCI [a] Grade	**During a cycle of therapy**	**At the Start of Subsequent Cycles of Therapy**	
	Weekly	Weekly	Once every 3 weeks
No Toxicity	Maintain dose level	Increase by 1 dose level up to a maximum dose of 150mg/m^2	Maintain dose level
Neutropenia			
1	Maintain does level	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Maintain dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Neutropenia fever	Omit dose until resolved then decrease by 2 dose levels.	Decrease by 2 dose levels	Decrease by 1 dose levels
Other haematological toxicities	Dose modifications for leukopenia, thrombocytopenia and anaemia 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.		
Diarrhoea			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Maintain dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Other non-haematological toxicities			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	Decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
3	Omit dose until resolved to ≤ grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to ≤ grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level

a Severity of adverse events based on NCI CTC (version 2.0) see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_archive

Method of administration

Irinotecan (Alchemy) should be administered as an intravenous infusion over 90 minutes (refer to Section 6.6 Special precautions for disposal and other handling). For all regimens, the dose of LV should be administered immediately after Irinotecan (Alchemy), with the administration of 5-FU to follow immediately after the administration of LV.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms (See Section 4.4 Special warnings and precautions for use).

Precautions to be taken before handling or administrating the medicine

For instructions on dilution of the medicine before administration, see Section 6.6 Special precautions for disposal and other handling.

As with other potential toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from Irinotecan (Alchemy). The use of gloves is recommended. If a solution of Irinotecan (Alchemy) contacts the skin, wash the skin immediately and thoroughly with soap and water. If Irinotecan (Alchemy) contacts the mucous membrane, flush thoroughly with water.

Preparation of Infusion Solutions

For instructions on dilution of the medicine before administration, see Section 6.6 Special precautions for disposal and other handling.

4.3 Contraindications

Irinotecan is contraindicated in patients with a known hypersensitivity to irinotecan or its excipients listed in Section 6.1 List of excipients.

Irinotecan is also contraindicated for women who intend to become pregnant, are pregnant or are lactating (see Section 4.6 Fertility, pregnancy and lactation, Section 5.3 Preclinical safety data, Genotoxicity and Carcinogenesis).

4.4 Special warnings and precautions for use

Administration

Irinotecan should be administered only under the supervision of a doctor 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 diarrhoea). Strict hospital supervision is recommended for such patients.

Extravasation

Irinotecan is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and application of ice are recommended.

Mayo Clinic Regimen

Except in a well designed clinical study, Irinotecan should not be used in combination with the *Mayo Clinic* regimen of 5-FU/ LV (administration for four to five consecutive days every four weeks [see **Table 9**]) because of reports of increased toxicity, including toxic deaths. Irinotecan should be used as recommended in Section 4.2 Dose and method of administration.

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 hydrochloride. The specific cause of these events has not been determined (see Section 4.8 Undesirable effects).

Diarrhoea

Irinotecan can induce both an early and a late form of diarrhoea that appear to be mediated by different mechanisms. Both forms of diarrhoea may be severe.

Early diarrhoea (occurring during or shortly after infusion of Irinotecan) 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 Irinotecan . 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 of Irinotecan) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life threatening. Late diarrhoea should be treated promptly with loperamide. Patients should be instructed to have loperamide readily available and begin treatment 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. One dosage regimen for loperamide used in clinical trials consisted of 4 mg at the first onset of late diarrhoea and then 2 mg every 2 hours until the patient was diarrhoea-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 diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated and should be given antibiotics if they develop ileus, fever or severe neutropenia. After the first treatment, subsequent chemotherapy should be delayed until patients are diarrhoea-free (return to pre-treatment bowel function) for at least 24 hours without the need for anti-diarrhoea medication. If NCI grade 2, 3 or 4 diarrhoea occurs, subsequent doses of Irinotecan should be reduced within the current cycle (see Section 4.2 Dose and method of administration).

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

- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Patients with vomiting associated with delayed (i.e., late) diarrhoea,
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy,
- 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 diarrhoea).

Haematology

Irinotecan commonly causes neutropenia, leukopenia and anaemia, any of which may be severe and therefore should not be used in patients with severe bone marrow failure (see Section 4.8 Undesirable effects, Haematological). Serious thrombocytopenia is uncommon.

Neutropenia

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 omitted if neutropenic fever occurs or if the absolute neutrophil count drops below 1.5 x 10^9/L. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥ 1.5 x 10^9/L. After the patient recovers, subsequent doses of Irinotecan should be reduced depending upon the level of neutropenia observed (see Section 4.2 Dose and method of administration). Routine administration of a colony stimulating factor is not necessary, but doctors may consider colony stimulating factor use in individual patients experiencing problems related to neutropenia.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic and anaphylactoid reactions have been observed.

Colitis/ ileus

Cases of colitis have been reported. In some cases, colitis was complicated by ulceration, bleeding, ileus and infection. Cases of ileus without preceding colitis have also been reported. Patients experiencing ileus should receive prompt antibiotic support.

Chronic inflammatory bowel disease and/or bowel obstruction

Patients must not be treated with irinotecan hydrochloride until resolution of the bowel obstruction.

Patients with reduced UGT1A1 Activity

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1), which mediates the conjugation of the active metabolite SN-38 (see Section 5.2 Pharmacokinetic properties), is encoded by the UGT1A1 gene. This 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 UGT1A128 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 UGT1A128 allele (also referred to as UGT1A1 7/7 genotype) compared to 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.

Use with caution in the following circumstances

Patients with poor performance status

Doctors should exercise particular caution in monitoring the effects of Irinotecan in patients with poor performance status, in elderly patients and in patients who have previously received pelvic/abdominal irradiation (see Section 4.8 Undesirable effects). Patients with poor performance status are at an increased risk of irinotecan related adverse events. 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 of 0 or 1. Patients with performance status of 3 or 4 should not receive Irinotecan.

Impaired renal function

Studies in patients with impaired renal function have not been conducted. Therefore, caution should be undertaken in patients with impaired renal function (See Section 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations). Irinotecan hydrochloride is not recommended in patients on dialysis.

Irradiation therapy

Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of Irinotecan. The concurrent administration with irradiation has not been adequately studied and is not recommended.

Hepatic insufficiency

In patients with hyperbilirubinaemia, the clearance of irinotecan hydrochloride is decreased and therefore the risk of haematotoxicity is increased. (See Section 5.2 Pharmacokinetic properties, Pharmacokinetics in Special Populations)

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 three weeks schedule has not been established. In clinical trials of the single agent weekly dosage schedule, patients with even modest elevations in total baseline serum bilirubin levels (17 to 34 µmol/L) had a significantly greater likelihood of experiencing first cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 17 µmol/L (50% versus 18%; p<0.001) (See Section 5 Pharmacological properties & Section 4.2 Dose and method of administration). Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with Irinotecan.

Cholinergic effects

Irinotecan has cholinergic effects and should be used with caution in patients with asthma or cardiovascular diseases, and in patients with mechanical intestinal or urinary obstruction.

Respiratory

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 medicines, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy.

Before administration

Monitoring

Careful monitoring of the white blood cell count with differential, haemoglobin, and platelet count is recommended before each dose of Irinotecan. Liver function should be monitored before initiation of treatment and monthly or as clinically indicated.

Nausea and vomiting

Irinotecan hydrochloride is emetogenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT3 blocker (e.g. ondansetron or granisetron). 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 (e.g. prochlorperazine) for subsequent use as needed. Patients with vomiting associated with delayed (i.e. late) diarrhoea should be hospitalised as soon as possible for treatment.

Advice for patients

Patients should be advised of the expected toxic effects of Irinotecan, particularly of gastrointestinal complications such as nausea, vomiting, abdominal cramping, diarrhoea and infection.

Patients should be advised to consult their doctor if any of the following occur after treatment with Irinotecan:

- diarrhoea for the first time;
- inability to control diarrhoea within 24 hours;
- vomiting;
- fever or evidence of infection;
- symptoms of dehydration such as faintness, light headedness or dizziness;
- bloody or black stools;
- inability to take fluids by mouth due to nausea or vomiting.

Patients should also be alerted to the possibility of alopecia. Laxatives should be avoided (see Section 4.5 Interaction with other medicines and other forms of interaction) and patients should contact their doctor to discuss any laxative use.

Others

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

Paediatric Use

The safety and effectiveness of Irinotecan in children has not been established.

4.5 Interaction with other medicines and other forms of interaction

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 5.2 Pharmacokinetic properties). 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 medicines.

Ketoconazole. Irinotecan hydrochloride clearance is greatly reduced in patients receiving concomitant ketoconazole (anti-fungal agent), leading to increased exposure to the active metabolite SN-38. Ketoconazole should be discontinued at least one week prior to starting irinotecan therapy and should not be administered during irinotecan therapy.

Atazanavir sulfate. Coadministration of atazanavir sulfate (HIV-1 protease inhibitor), a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Doctors should take this into consideration when co-administering these medicines.

CYP3A4 Inducers

Anticonvulsants. Concomitant administration of CYP3A inducing anticonvulsant medicines (e.g. carbamazepine, phenobarbital (phenobarbitone) 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 one week prior to the first cycle of irinotecan, and should not be administered during irinotecan hydrochloride therapy.

Other interactions

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

Antineoplastic agents. The adverse effects of Irinotecan, such as myelosuppression and diarrhoea, would be expected to be exacerbated by other antineoplastic agents having similar adverse events.

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

Hyperglycaemia has also been reported in patients receiving irinotecan hydrochloride. Usually this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of irinotecan hydrochloride. It is probable that the administration of dexamethasone contributes to hyperglycaemia in some patients.

Prochlorperazine. The incidence of akathisia in clinical trials of the single agent weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine (antiemetics and anti-nauseants) was administered on the same day as irinotecan hydrochloride than when these medicines were given on separate days (1.3%, 1/80 patients). However, the 8.5% incidence of akathisia is within the range reported for use of prochlorperazine when given as a pre-medication for other chemotherapies.

Laxatives. It would be expected that the incidence or severity of diarrhoea would be worsened by laxative use during therapy with Irinotecan, but this has not been studied.

Diuretics. In view of the potential risk of dehydration secondary to vomiting and/or diarrhoea, the doctor may wish to withhold diuretics during dosing with Irinotecan and, certainly, during periods of active vomiting or diarrhoea.

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

Effects on laboratory tests

There are no known interactions between Irinotecan and laboratory tests

4.6 Fertility, pregnancy and lactation

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 one-fifteenth the value in patients administered 125 mg/m^2 weekly).

Pregnancy: Category D

There are no adequate and well controlled studies of irinotecan hydrochloride in pregnant women. Irinotecan may cause foetal harm when administered to a pregnant woman. Administration of irinotecan hydrochloride 6 mg/kg/day intravenously to rats (AUC about 0.2 times the corresponding values in patients administered 125mg/m^2) and rabbits (about one-half the recommended human weekly starting dose on a mg/m^2 basis) during the period of organogenesis is embryotoxic as characterised by increased post-implantation loss and decreased numbers of live foetuses. Irinotecan hydrochloride was teratogenic in rats at doses greater than 1.2 mg/kg/day (AUC about one-fortieth the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6.0mg/kg/day. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.

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

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 hydrochloride.

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 hydrochloride.

If the patient becomes pregnant while receiving this medicine, the patient should be informed about the potential hazard to the foetus.

Breast-feeding

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. As many medicines are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended not to breastfeed when receiving therapy with Irinotecan.

Radioactivity appeared in rat milk within five minutes of intravenous administration of radio labelled irinotecan hydrochloride and was concentrated up to 65-fold at four 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 hydrochloride, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Combination Therapy

In the two phase III clinical studies, a total of 955 patients with metastatic colorectal cancer received irinotecan hydrochloride in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan hydrochloride alone (See **Table 10**, Clinical Trials). In these studies, 370 patients received irinotecan hydrochloride in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan hydrochloride alone.

Fifty nine (6.1%) patients died within 30 days of last study treatment: 27 (7.3%) received irinotecan hydrochloride in combination with 5-FU/LV, 19 (5.3%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan hydrochloride alone. Deaths potentially related to treatment occurred in three (0.7%) patients who received irinotecan hydrochloride in combination with 5-FU/LV (two neutropenic fever/sepsis, one treatment toxicity), three (0.7%) patients who received 5-FU/LV alone (one neutropenic fever/sepsis, one CNS bleeding during thrombocytopenia, one unknown) and two (0.9%) patients who received irinotecan hydrochloride alone (two neutropenic fever). Deaths within 60 days of study treatment were reported for 18 (4.9%) patients who received irinotecan hydrochloride in combination with 5-FU/LV, 18 (5.0%) patients who received 5-FU/LV alone and 15 (6.7%) patients who received irinotecan hydrochloride alone. Discontinuations due to adverse events were reported for 26 (7.0%) patients who received irinotecan hydrochloride in combination with 5-FU/LV, 15 (4.1%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan hydrochloride alone.

Table 6 lists the grade 3 and 4 clinically relevant adverse events reported in the combination treatment arms of the two phase III studies.

Table 6 – Percent (%) of Patients Experiencing Clinically Relevant Grade 3 & 4 Adverse Events in Phase III Studies of Combination Therapies [a].

Adverse Event	Study 1			Study 2	
	Irinotecan hydrochloride 5-FU/LV N=225[b]	5-FU/LV N=219[b]	Irinotecan hydrochloride N=223[b]	Irinotecan hydrochloride 5-FU/LV N=145[c]	5-FU/LV N=143[c]
TOTAL Grade ¾ Adverse Events	**53.3**	**45.7**	**45.7**	**72.4**	**39.2**
Gastrointestinal					
Diarrhoea – Late	22.7	13.2	31.0	14.4	6.3
Grade 3	15.1	5.9	18.4	10.3	4.2
Grade 4	7.6	7.3	12.6	4.1	2.1
Diarrhoea – Early	4.9	1.4	6.7	--	--
Nausea	15.6	8.2	16.1	2.1	3.5
Abdominal pain	14.6	11.5	13.0	2.1	0.7
Vomiting	9.7	4.1	12.1	3.5	2.8
Anorexia	5.8	3.7	7.2	2.1	0.7
Constipation	3.1	1.8	0.4	0.7	1.4
Mucositis	2.2	16.9	2.2	4.1	2.8
Haematological					
Neutropenia	53.8	66.7	31.0	46.2	13.4
Grade 3	29.8	23.7	19.3	36.4	12.7
Grade 4	24.0	42.5	12.1	9.8	0.7
Leukopenia	37.8	23.3	21.5	17.4	3.5
Anaemia	8.4	5.5	4.5	2.1	2.1
Neutropenic fever	7.1	14.6	5.8	3.4	0.7
Thrombocytopenia	2.6	2.7	1.7	0	0
Neutropenic infection	1.8	0	2.2	2.1	0
Body as a Whole					
Asthenia	19.5	11.9	13.9	9.0	4.2
Pain	3.1	3.6	2.2	9.7	8.4
Fever	1.7	3.6	0.4	0.7	0.7
Infection	0	1.4	0.4	7.6	3.5
Metabolic and Nutritional					
Increased bilirubin	7.1	8.2	7.2	3.5	10.6
Dermatological					
Exfoliative dermatitis	0	0.5	0	--	--
Rash	0	0.9	0.4	--	--
Hand and Foot Syndrome	--	--	--	0.7	0.7
Cutaneous Signs	--	--	--	0.7	0
Respiratory					
Dyspnoea	6.3	0.5	2.2	1.4	0
Increased Coughing	1.3	0	0.4	--	--
Pneumonia	2.7	1.0	1.3	--	--
Neurological					
Dizziness	1.3	0	1.8	--	--
Somnolence	1.8	1.8	1.3	--	--
Confusion	1.8	0	0	--	--
Cardiovascular					
Vasodilation	0.9	0	0	--	--
Hypotension	1.3	0.5	1.7	1.4	0
Thrombophlebitis	2.7	3.2	1.8	--	--

Pulmonary embolus	2.7	1.4	0.4	--	--
Myocardial infarction	1.3	0	0.4	--	--

a Severity of adverse events based on NCI CTC (version 1.0) see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_archive

b Number of patients in the as-treated population for each group

c Number of patients treated in the de Gramont regimen (B2/C2 treatment arms of **Table 9**)

The most clinically significant adverse events for patients receiving irinotecan hydrochloride-based therapy were diarrhoea nausea, vomiting, neutropenia and alopecia (complete hair loss = Grade 2). The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhoea neutropenia, neutropenic fever and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as ≥ grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with irinotecan hydrochloride/5-FU/LV than with administration of 5-FU/LV.

Single Agent Therapy

Information on adverse reactions for irinotecan hydrochloride as single agent therapy is available from 304 patients with metastatic carcinoma of the colon or rectum treated in phase II trials with the once weekly dosage schedule, 316 patients treated with the once every three weeks dosage schedule and over 1,100 patients with a variety of tumour types treated in Japan. In general, the types of toxicities observed were similar. 4.3% of patients treated with the weekly dosage schedule and 8% of patients treated with the once every three weeks dosage schedule discontinued treatment with irinotecan hydrochloride because of medical events. Seventeen of the 304 patients treated with the weekly dosage schedule died within 30 days of the administration of irinotecan hydrochloride and in five cases (1.6%), the deaths were potentially medicine related. Eleven patients treated with irinotecan hydrochloride in the once every three weeks dosage schedule died within 30 days of treatment and in three cases (1%), the deaths were potentially related to treatment with irinotecan hydrochloride. The main causes of the deaths potentially related to treatment were neutropenic infection, grade 4 diarrhoea and asthenia.

The frequency of the most common adverse events reported from the single agent second line studies is presented in **Table 7**. Additional information on adverse events follows the table, organised by body system category.

Table 7 - Adverse Events Reported From the Second Line Single Agent Therapy In 304 Patients [a]

	Weekly dosage schedule		**3 weekly dosage schedule (NCI grade 3 & 4 only)**	
Event	**% of patients**	**% NCI grade 3 & 4**	**Study 1 (%)**	**Study 2 (%)**
Gastrointestinal				
Diarrhoea (Late)	87.8	30.6	21.7	22.0
Nausea	86.2	16.8	13.8	11.0
Vomiting	66.8	12.5	13.8	14.2
Abdominal Cramping/Pain	56.9	16.4	13.8	8.7
Anorexia	54.9	5.9	5.3	5.5
Diarrhoea (Early)	50.7	7.9	12.2	1.6
Constipation	29.9	2.0	9.5	7.9
Flatulence	12.2	-	-	-
Stomatitis	11.8	0.7	-	-
Dyspepsia	10.5	-	-	-

	Weekly dosage schedule		3 weekly dosage schedule (NCI grade 3 & 4 only)	
Event	**% of patients**	**% NCI grade 3 & 4**	**Study 1 (%)**	**Study 2 (%)**
Haematological				
Leukopenia [b]	63.2	28.0	22.2	14.2
Anaemia	60.5	6.9	7.4	6.3
Neutropenia [b]	53.9	26.3	22.2	14.2
Thrombocytopenia	-	-	1.1	3.9
Body as a Whole				
Asthenia	75.7	12.2	14.8	13.4
Fever	45.4	0.7	-	-
Pain	23.7	2.3	18.5[c]	16.5[d]
Headache	16.8	0.7	-	-
Back Pain	14.5	1.6	-	-
Chills	13.8	0.3	-	-
Minor Infection	14.5	0	-	-
Oedema	10.2	1.3	-	-
Abdominal enlargement	10.2	0.3	-	-
Metabolic and Nutritional				
Weight reduction	30.3	0.7		
Dehydration	14.8	4.3		
Increased alkaline	13.2	3.9		
phosphatase	10.5	1.3		
Increased SGOT (AST)				
Dermatological				
Alopecia	60.5	Not applicable [e]	Not applicable [e]	Not applicable [e]
Sweating	16.4	0	-	-
Rash	12.8	0.7	1.6	0.8
Respiratory				
Dyspnoea	22.0	3.6		
Increased Coughing	17.4	0.3		
Rhinitis	15.5	0		

a Severity of adverse events based on NCI CTC (version 1.0) see https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_archive

b Combined results for leukopenia/neutropenia are presented for the once every 3 week dosage schedule.

c In this study, 22.2% of patients treated with best supportive care experienced NCI grade3/4 pain.

d In this study, 13.2% of patients treated with infusional FU experienced NCI Grade 3/4 pain

e Complete hair loss = NCI Grade 2.

Gastrointestinal

Nausea, vomiting and diarrhoea are common adverse events following treatment with irinotecan hydrochloride and can be severe. Among those patients treated at the 125 mg/m^2 single agent weekly dose, the median duration of any grade of late diarrhoea was three days and for grade 3 or 4 late diarrhoea was seven days. The frequency of grade 3 and 4 late diarrhoea was significantly greater in patients 65 years or older (39.8% versus 23.4%, p = 0.0025).

Abdominal pain and cramping are associated with early onset diarrhoea (diarrhoea which occurs within 24 hours of medicine administration). In studies it has been found that atropine is useful in ameliorating these events. Colonic ulceration, sometimes with gastrointestinal bleeding, ileus and infection, has been observed in association with administration of irinotecan hydrochloride.

Haematological

Irinotecan hydrochloride commonly causes neutropenia, leukopenia (including lymphocytopenia) and anaemia. Serious thrombocytopenia is uncommon. In clinical studies with the single agent weekly dosage schedule, one death due to neutropenic sepsis without fever was judged to be potentially medicine related (0.3%, 1/304). Blood transfusions were given to 9.9% of patients. When evaluated in the trials of single agent weekly administration, the frequency of grade 3 or 4 neutropenia was significantly higher in patients who had received previous pelvic/abdominal irradiation (48.1% versus 24.1%, $p = 0.0356$). In these same studies, patients with total baseline serum bilirubin levels of 17 µmol/L or more also had a significantly greater likelihood of experiencing first cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 17 µmol/L (50% versus 17.7%, $p < 0.001$).

Cholinergic symptoms

Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhoea. If these symptoms occur, they manifest during or shortly after medicine infusion. They are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are more likely to occur at higher doses. The timing of the symptoms is most consistent with the occurrence of peak irinotecan hydrochloride serum levels during parenteral administration.

Metabolic and nutritional

The dehydration observed in 14.8% of patients in clinical studies was as a consequence of diarrhoea, nausea and vomiting.

Hepatic

In the clinical studies evaluating the single agent weekly dosage schedule, NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases. For the once every three week dosage schedule, hepatic events, such as ascites and jaundice of NCI Grade 3/4 severity occurred in 8.5% of patients in one study and 8.7% of patients in another study.

Renal

Increases in serum creatinine or blood urea nitrogen, generally attributable to complications of infection or to dehydration related to nausea, vomiting or diarrhoea have been observed. There have been cases of acute renal failure. Rare instances of renal dysfunction due to tumour lysis syndrome have also been reported.

Dermatological

Alopecia has been reported during treatment with irinotecan hydrochloride. Rashes have also been reported but did not result in discontinuation of treatment.

Respiratory

Severe pulmonary events are infrequent. Over one-half the patients with dyspnoea in the clinical studies evaluating the single agent weekly dosage schedule had lung metastases; the extent to which malignant pulmonary involvement or other pre-existing lung disease may have contributed to dyspnoea in these patients is unknown. For the once every three weeks dosage schedule, respiratory events, such as dyspnoea and cough of NCI grade 3/4 severity, occurred in 10.1% of patients in one study and 4.7% of patients in another study.

A potentially life threatening pulmonary syndrome, consisting of dyspnoea, 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 hydrochloride to these preliminary events was difficult to assess because these patients also had lung tumours and some had pre-existing non-malignant pulmonary disease. As a result of these observations, however, clinical studies in the US enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

Neurological

Insomnia and dizziness were observed in 19.4 and 14.8% respectively of patients studied in clinical trials of the single agent weekly dosage schedule but were not usually considered to be directly related to the administration of irinotecan hydrochloride. Dizziness may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Cardiovascular

Vasodilation (flushing) may occur during administration of Irinotecan. Irinotecan hydrochloride has anticholinesterase activity. As such, there are possible cardiovascular effects due to its administration. These include sudden death, blackout and bradycardia. Patients should be monitored for cholinergic effects during administration of Irinotecan, and atropine should be readily available for treatment of these effects. There were no cases of sudden death reported in the phase II clinical studies of the single agent weekly dosage schedule involving 304 patients. In these studies, two patients (0.7%) suffered syncope and one patient (0.3%) suffered bradycardia.

Thromboembolic events including angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischaemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis and vascular disorder have been observed rarely in patients receiving Irinotecan. The specific cause of these events has not been determined.

Other

Other NCI grade 3 or 4 medicine related adverse events observed in 1 to 10% of patients in clinical trials included mucositis, bilirubinaemia and hypovolaemia. In less than 1% of patients, NCI grade 3 or 4 rectal disorder, gastrointestinal monilia, hypokalaemia, hypomagnesaemia, increased GGTP, malaise, sepsis, urinary tract infection, breast pain and abnormal gait were observed.

Post-marketing surveillance

Cardiac disorders

Myocardial ischaemic events have been observed following irinotecan hydrochloride therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease or previous cytotoxic chemotherapy.

Gastrointestinal disorders

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

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

Hypovolaemia

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 diarrhoea 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 also been reported.

Investigations

Rare cases of hyponatraemia mostly related with diarrhoea and vomiting have been reported.

Increases in serum levels of transaminases (i.e. AST and ALT) in the absence of progressive liver metastasis; transient increase of amylase and occasionally transient increase of lipase have been very rarely reported.

Musculoskeletal and connective tissue disorders

Early effects such as muscular contraction or cramps and paraesthesia 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 dyspnoea have been reported (see Section 4.4 Special warnings and precautions for use). Hiccups have also been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Signs and symptoms

In humans, at single doses up to 750 mg/m^2, adverse events were similar to those reported with the recommended dosage 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 diarrhoea.

Management/treatment

There is no known antidote for overdosage of Irinotecan. Support respiratory and cardiovascular functions. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

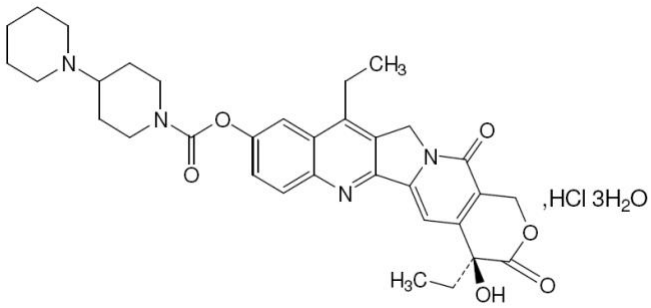
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, plant alkaloids and other natural products, topoisomerase 1 (TOP1) inhibitors, irinotecan. ATC code: L01CE02

Irinotecan hydrochloride is an anti-neoplastic agent belonging to the class of topoisomerase I inhibitors. It is a semi-synthetic derivative of camptothecin, an alkaloid extracted from plants such as *Camptotheca acuminata*. It is a pale yellow to yellow crystalline powder and is slightly soluble in water and organic solvents.

Non- Proprietary Name: Irinotecan hydrochloride.



Chemical name: [1,4'-Bipiperidine]-1'-carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester, monohydrochloride, trihydrate, (S)-

Molecular formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$

Molecular weight: 677.18

CAS Registry Number: 136572-09-3.

Irinotecan hydrochloride is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I. Topoisomerase I relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I – DNA complex and prevent religation of these single-strand breaks in the DNA. Current research suggests that cytotoxicity of irinotecan hydrochloride 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 hydrochloride or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan hydrochloride serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is approximately 1000 times more potent as irinotecan hydrochloride as an inhibitor of topoisomerase I purified from human and rodent tumour cell lines. However, the precise contribution of SN-38 to the activity of irinotecan hydrochloride is unknown.

Both irinotecan hydrochloride 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 a low pH (acidic conditions) promotes the formation of the active lactone, whilst a more basic pH forces the equilibrium to shift to form the inactive hydroxy acid anion form.

Administration of irinotecan has resulted in anti-tumour activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

Irinotecan hydrochloride is a non-competitive inhibitor of acetyl cholinesterase and a cholinergic syndrome is associated with its administration (see Section 4.8 Undesirable effects).

Clinical Efficacy and Safety

Irinotecan hydrochloride has been studied in clinical trials in combination with FU and LV as a first line agent in metastatic colorectal cancer and as single agent used after failure of initial therapy. Weekly and once every 3 weeks dosage schedules were studied using irinotecan hydrochloride as the single

agent. Weekly and once every 2 week schedules were studied with irinotecan hydrochloride used in combination treatment. Patients with WHO performance status of 3 or 4 have been studied in clinical trials (**Table 8**).

Table 8 - WHO Scale of Performance Status

0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed and chair more than 50% of waking hours
4	Completely disable; cannot carry out any self-care; totally confined to bed or chair

Combination therapy for first-line treatment of metastatic colorectal cancer

Two randomised, open-label, controlled, multinational, phase III clinical trials support the use of irinotecan hydrochloride at first line of treatment of patients with metastatic carcinoma of the colon or rectum. The dosing regimens of these studies are given in **Table 9**.

Table 9 - Dosage Regimen of The Studies Evaluating the First Line of Treatment of Metastatic Colorectal Cancer.

Arm	Agent	Study 1 Dosing Regimen	Study 2 Dosing Regimen
A	Irinotecan hydrochloride	125mg/m^2 irinotecan hydrochloride IV infusion over 90 mins. Treatment was administered once weekly for four weeks with treatment resuming on Day 43.	N/A
B1	Irinotecan hydrochloride LV 5-FU	125mg/m^2 irinotecan hydrochloride IV infusion over 90 mins followed immediately by 20mg/m^2 LV administered as an IV bolus injection and then 500mg/m^2 FU as an IV bolus injection. Treatment was administered once weekly for four weeks with treatment resuming on Day 43 (Saltz regimen)[a]	80 mg/m^2 IV infusion over 90 mins of irinotecan hydrochloride plus a 500 mg/m^2 LV IV infusion over 2 hours followed immediately by an 2300 mg/m^2 FU IV infusion over 24 hours. Treatment was administered once weekly for six weeks with treatment resuming on Day 50 (AIO regimen)[a]
B2	Irinotecan hydrochloride LV 5-FU	N/A	180 mg/m^2 IV infusion over 90 mins of irinotecan hydrochloride on day 1, plus one hour later a 200 mg/m^2 LV IV infusion over two hours followed immediately by a 400 mg/m^2 FU IV bolus injection and a 600 mg/m^2 FU IV infusion over 22 hours on day 1 and 2. Treatment was administered every two weeks (de Gramont regimen) [a]

Arm	Agent	Study 1 Dosing Regimen	Study 2 Dosing Regimen
C1	LV 5-FU	20 mg/m^2 LV administered as an IV bolus injection followed immediately by 425 mg/m^2 FU as an IV bolus injection. Treatment was given for 5 consecutive days with the treatment repeating on Day 29 (Mayo Clinic regimen)[a].	500 mg/m^2 LV IV infusion over two hours followed immediately by a 2600 mg/m^2 FU IV infusion over 24 hours. Administration was weekly for six weeks with treatment resuming on day 50 (AIO regimen)[a]
C2	LV 5-FU	N/A	200 mg/m^2 LV IV infusion over two hours followed immediately by a 400 mg/m^2 FU IV bolus injection and a 600 mg/m^2 FU IV infusion over 22 hours on day 1 and 2. Treatment was administered every two weeks (de Gramont regimen) [a]

a Based on the Saltz, Mayo Clinic, de Garmont and Association of Medical Oncology of the German Cancer Society (AIO) doing regimens.

In both studies, concomitant medications such as antiemetics, atropine and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In study 2, if late diarrhoea persisted for greater than 24 hours despite loperamide, a 7 day course of fluoroquinolone antibiotic prophylaxis was given. Treatment with oral fluoroquinolone was initiated in patients whose diarrhoea persisted for greater than 24 hours despite loperamide or if they developed fever in addition to diarrhoea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) < 0.5 x 10^9/L, even in the absence of fever or diarrhoea. Patients also received treatment with intravenous antibiotics if they had persistent diarrhoea or fever or if ileus developed.

In both studies the combination of irinotecan hydrochloride/5-FU/LV therapy resulted in significant improvements in objective tumour response rate, time to tumour progression (TTP) and survival when compared with 5-FU/LV alone. These differences in survival were observed despite the use of post-study second-line therapy, including irinotecan-containing regimens in patients in the control arm. Patient characteristics and major efficacy results are shown in **Table 10**.

Table 10 - Combination Therapy in First Line of Treatment of Metastatic Colorectal Cancer. Study Results

	Study 1			Study 2	
	Irinotecan + bolus 5-FU/LV	**Bolus 5-FU/LV**	**Irinotecan**	**Irinotecan + Infusional 5-FU/LV**	**Infusional 5-FU/LV**
Number of Patients	231	226	226	198	187
Demographics & Treatment Administration					
Female/Male(%)	34/65	45/54	35/64	33/67	47/53
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance Status (%)[a]					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Median Primary Tumour (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median Time from Diagnosis to Randomisation (month, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior Adjuvant 5-FU Therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median Duration of Study Treatment (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)					
Irinotecan	72	--	75	87	--
FU	71	86	--	86	93
Efficacy Results					
Confirmed Objective Tumour Response Rate [b] (%) [95% CI]	39 [33-46]	21 [16-27]	18 [13-24]	35 [28-42]	22 [16-29]
Median Time to Tumour Progression (months) [95% CI]	7.0 [5.4-8.0]	4.3 [3.7-4.6]	4.2 [3.9-5.0]	6.7 [5.7-8.0]	4.4 [3.2-5.5]
Median Survival (months) [95% CI]	14.8 [12.3-17.1]	12.6 [11.1-14.6]	12.0 [11.3-13.5]	17.4 [15.2-20.2]	14.1 [12.6-17.4]

a Refer to **Table 8**

b Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

Improvement was noted when response rates and time to tumour progression were examined across all demographic and disease-related subgroups (as categorised by age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline laboratory abnormalities), with irinotecan hydrochloride-based combination therapy relative to 5-FU/LV.

The European Organisation of Research & Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used in both studies. While there was no statistical evidence that there were significant difference between irinotecan hydrochloride/5-FU/LV combination and 5-FU/LV alone with regard to QOL improvement, descriptive evidence suggested a general trend favouring QOL improvement or less-worsening in favour of the irinotecan hydrochloride combination regimen.

Single Agent Treatment in Recurrent or Progressive Metastatic Colorectal Cancer after 5-FU Based Treatment.

Weekly Dosage Schedule

Three multicentre, open-label, phase II studies, all utilising repeated cycles of once weekly treatment with irinotecan hydrochloride for four consecutive weeks, followed by a two week rest period were conducted in a total of 304 patients in the United States. These studies were designed to evaluate tumour response rate and toxicity with irinotecan hydrochloride in patients with metastatic colorectal cancer that recurred or progressed following a prior 5-FU based chemotherapeutic regimen. Starting dose of irinotecan hydrochloride in these trials were 100, 125 and 150 mg/m^2 with 150 mg/m^2 proving to be poorly tolerated due to unacceptably high rates of grade 4 late diarrhoea and febrile neutropenia. The results of the studies are shown in **Table 11**.

Table 11 - Phase II Clinical Studies with the Once Weekly Dosage Schedule

	Study			
	A	B	C [a]	C [a]
Number of Patients	48	90	64	102
Dose (mg/m^2/wk x 4)	125[b]	125	125	100
Prior FU therapy (%)				
For metastatic disease	81.3	65.5	73.4	67.7
≥ 6 months after adjuvant	14.6	6.7	26.6	27.5
>6 months after adjuvant	2.1	15.6	0.0	2.0
Classification unknown	2.1	12.2	0.0	2.9
Duration of treatment (median, months)	5.4	3.5	3.9	3.3
Median relative dose intensity (%)[c]	74	67	73	81
Objective response rate (%)[d] [95% CI]	20.8 [9.3-32.3]	13.3 [6.3-20.4]	14.1 [5.5-22.6]	8.8 [3.3-14.3]
Time to response (median, months)	2.6	1.5	2.8	2.8
Response duration (Median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3

a The initial dose in Study C was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity at the starting dose was perceived to be greater than seen in previous studies. Results are analysed separately for the two starting doses.

b Nine patients received 150 mg/m^2 as a starting dose; 2 (22.2%) responded to irinotecan hydrochloride

c Relative dose intensity for irinotecan hydrochloride based on planned dose intensity of 100, 83.3 and 66.7mg/m^2/wk corresponding with 150, 125 and 100 mg/m^2 starting doses respectively.

d There were 2 complete responses and 38 partial responses.

Of the 304 patients treated in the phase II studies, response rates to irinotecan hydrochloride were similar in males and females and among patients younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum, and in patients with single and multiple metastatic sites. Response rate was 18.5% in patients with a WHO performance status of 0 and 8.2% in patients with a performance status of 1 or 2.

Response rates with irinotecan hydrochloride were unaffected by whether or not patients had responded to prior 5-FU based treatment given for metastatic disease. Patients who had received previous irradiation to the pelvis also responded to irinotecan hydrochloride at approximately the same rate as those who had not previously received irradiation.

By and large, across the pivotal studies, stable disease was documented in 148 (48.7%) of the 304 patients in the intent to treat population and in 145 (55.6%) of the 261 patients in the evaluable

population. In line with the results in Study C, a somewhat greater percentage of patients who were treated with the 125 mg/m^2 starting dose (53.4%; 103/193) than with the 100mg/m^2 starting dose (39.2%; 40/102) had stable disease during therapy.

Once Every 3 Weeks Dosage Schedule

Two phase III, multicentre, randomised studies were conducted with a three weekly dosage regimen in patients with metastatic colorectal cancer whose disease had recurred or progressed following FU therapy (n=535). Second-line irinotecan hydrochloride was compared with the best supportive care in one study and with infusional FU-based therapy in the second study. The primary endpoint in both studies was survival. Parameters, of the clinical benefit and quality of life were also assessed. The starting dose was 350mg/m^2 infused IV over 90 mins to a maximum total dose of 700 mg. For patients 70 years or older and for patients with WHO performance status of 2 the starting dose was reduced to 300mg/m^2. Antiemetics, atropine and loperamide were provided as supportive care and late diarrhoea persisting for greater than 24 hours despite loperamide was treated with a 7 day course of a fluoroquinolone antibiotic.

A significant survival advantage for irinotecan hydrochloride over the best supportive care or infusional 5-FU based therapy was demonstrated. When adjusted for the baseline patients characteristic (e.g., performance status), survival among patients treated with irinotecan hydrochloride remained significantly longer than in the control populations (p=0.001 for Study 1 and p=0.017 for study 2). Clinical benefit in Study 1, as measured by pain-free survival and survival without weight loss were significantly longer for patients treated with irinotecan hydrochloride than for the patients in the best supportive care group (p=0.01 and p=0.05 respectively). The results are summarised in **Table 12**.

Table 12 - Phase III Clinical Studies with the Once Every 3 Week Dosage Schedule.

	Study 1		Study 2	
	Irinotecan hydrochloride	**Best supportive care**	**Irinotecan hydrochloride**	**5-FU [a]**
Number of patients	189	90	127	129
Prior 5-FU therapy (%)				
For metastatic disease	70	63	58	68
≤ 3/6 months after adjuvant [b]	27	36	38	23
> 3/6 months after adjuvant [b]	3	0	5	9
Duration of treatment (mean, months) [95% CI]	4.6 [4.2 – 5.0]	--	4.4 [3.8 – 5.0]	3.7 [3.3 – 4.1]
Median relative dose intensity (%) [c]	94	--	95	81-99
Survival (median, months) [95% CI]	9.2 [8.4 – 10.7]	6.5 [5.0 – 7.6]	10.8 [9.5 – 12.8]	8.5 [7.7 – 10.5]
1-year survival (%) [95% CI]	36.2 [29.3 – 43.1]	13.8 [6.7 – 20.9]	44.8 [36.2 – 53.4]	32.4 [24.3 – 40.5]
Progression-free survival (median, months) [95% CI]	--	--	4.2 [3.8 – 4.8]	2.9 [2.6 – 3.7]
Symptom-free survival (median, months) [95% CI]	5.9 [3.8 - 7.6]	4.1 [2.2 - 6.9]	8.1 [6.1 - 10.7]	7.0 [4.4 - 8.7]
Pain-free survival (median, months) [95% CI]	6.9 [5.8 – 8.4]	2.0 [1.8 – 5.1]	10.3 [7.8 -**]	8.5 [6.2 – 10.2]
Median survival without performance status deterioration (%) [95% CI]	5.7 [4.3 – 6.6]	3.3 [1.9 – 3.7]	6.4 [5.2 – 7.6]	5.1 [4.2 – 6.2]
Time to weight loss ≥5% (median, months) [95% CI]	6.4 [5.5 – 7.6]	4.2 [3.4 – 5.1]	8.9 [6.7 – 12.3]	7.4 [4.7 – 11.6]

a One of the following 5-FU regimens was used:
1. Leucovorin 200 mg/m^2 iv over 2 hours; followed by 5-FU 400 mg/m^2 iv bolus; followed by 5-FU 600 mg/m^2 continuous iv infusion over 22 hours on days 1 and 2 every 2 weeks.
2. 5-FU 250-300 mg/m^2/day protracted continuous iv infusion until toxicity.
3. 5-FU 2.6-3 g/m^2/day iv over 24 hours every week for 6 weeks with or without leucovorin 20-500 mg/m^2/day every week iv for 6 weeks with a 2 week rest between cycles

b Study 1 ≤6 months; Study 2 ≤3 months

c Relative dose intensity for irinotecan hydrochloride based on planned dose intensity of 116.7 mg/m^2/week. Dose intensity in patients receiving 5-FU in Study 2 varied depending upon type of regimen

** Cannot be estimated due to small sample size

In the 2 phase III studies, quality of life was assessed using the European Organisation on Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). In Study 1, the global quality of life scores were significantly higher for patients treated with irinotecan hydrochloride than for those who received best support care (p=0.0013). In Study 2, the global quality of life scores were similar for patients who received either irinotecan hydrochloride or infusional 5-FU.

Other studies

A Japanese open-label, uncontrolled, late phase II study in patients with non small-cell lung cancer enrolled a total of 153 patients. In this study, pneumonitis occurred in 6.2% (9/146) of the patients. One

patient died of interstitial pneumonitis. irinotecan hydrochloride was given at a dose of 100 mg/m^2 IV once a week. Dosage adjustments were made according to toxicity and the duration of treatment was until disease progression or unacceptable toxicity occurred (with each patient to receive at least three doses).

5.2 Pharmacokinetic properties

Absorption and Distribution

After intravenous infusion of irinotecan hydrochloride in human cancer patients, irinotecan hydrochloride plasma concentrations decline in a multi-exponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours.

In a study where irinotecan hydrochloride was administered at doses of 100 to 750 mg/m^2 by 30 minute intravenous infusion every three weeks, the plasma terminal elimination half-life was 14.2 ± 7.7 hours for irinotecan hydrochloride and 13.8 ± 1.4 hours for SN-38.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan hydrochloride 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 achieved within 1 hour following the end of a 90-minute infusion of irinotecan hydrochloride. Pharmacokinetic parameters for irinotecan hydrochloride and SN-38 following a 90-minute infusion of irinotecan hydrochloride at dose levels of 125 and 340 mg/m^2 were determined in two clinical studies in patients with solid tumours as depicted in **Table 13**.

Table 13 - Summary of Mean (+/- Standard Deviation) Irinotecan Hydrochloride and SN-38 Pharmacokinetic Parameters in Patients With Solid Tumours.

Dose (mg/m^2)	Irinotecan hydrochloride					SN-38		
	C_{max} ng/mL	AUC_{0-24} (ng.hr/mL)	$t_{1/2}$ (hr)	V_{area} (L/m^2)	CL (L/hr/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/mL)	$t_{1/2}$ (hr)
125 (n=64)	1,600 ± 797	10,200 ± 3,270	5.8[a] ± 0.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	10.4[a] ± 3.1
340 (n=6)	3,392 ± 874	20,604 ± 6,027	11.7[b] ± 1.0	234 ± 69.6	13.9 ± 4.00	56.0 ± 28.2	474 ± 245	21.0[b] ± 4.3

C_{max} Maximum plasma concentration
AUC_{0-24} Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{1/2}$ Terminal elimination half-life
V_{area} Volume of distribution of terminal elimination phase
CL Total systemic clearance
a Plasma specimens collected for 24 hours following the end of the 90-minute infusion
b Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan hydrochloride and SN-38

Irinotecan hydrochloride exhibits moderate plasma protein binding (30% to 68% bound) *in vitro* whilst SN-38 exhibits a higher plasma protein binding (approximately 95% bound). The plasma protein to which irinotecan hydrochloride and SN-38 predominantly bind is albumin.

Biotransformation and Elimination

The complete disposition of irinotecan hydrochloride has not been fully elucidated in humans. The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes. The metabolic conversion primarily occurs in the liver. SN-38 subsequently undergoes conjugation by UDP-glucuronyl transferase 1A1 to form a glucuronide metabolite (SN-38 glucuronide). The urinary excretion of irinotecan hydrochloride was 11 to 20% of the administered dose; SN-38 < 1%; and SN-38 glucuronide 3%. The cumulative biliary and urinary excretion of irinotecan hydrochloride and its metabolites (SN-38 and SN-38 glucuronide) 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).

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

Pharmacokinetics in Special Populations

Geriatrics

In studies using the weekly schedule, the terminal half-life of Irinotecan hydrochloride was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized $AUC_{0\text{-}24}$ for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. There are no kinetic data on the use of the once-every-three-week dosage schedule in elderly patients. A lower starting dose is recommended in patients 65 years or older based on clinical toxicity experience with this schedule (see Section 4.2 Dose and method of administration).

Gender

The pharmacokinetics of irinotecan does not appear to be influenced by gender.

Hepatic Insufficiency

Irinotecan hydrochloride 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 elevation in serum total bilirubin and transaminase concentrations. (see Section 4.2 Dose and method of administration)

Renal Insufficiency

The influence of renal insufficiency on the pharmacokinetics of irinotecan hydrochloride has not been evaluated.

Pharmacokinetics in combination therapy

In a phase I clinical study involving irinotecan hydrochloride, fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumours the disposition of irinotecan hydrochloride was not substantially altered when the medicines were co-administered. However, C_{max} and $AUC_{(0\text{ to }24)}$ of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when administration of irinotecan

hydrochloride was followed by 5-FU and LV administration compared with when irinotecan hydrochloride was given alone. Formal *in vivo* or *in vitro* medicine interaction studies to evaluate the influence of irinotecan hydrochloride on the disposition of 5-FU and LV have not been conducted.

5.3 Preclinical safety data

Genotoxicity

Irinotecan hydrochloride was clastogenic both *in vitro* (Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). Neither irinotecan hydrochloride or SN-38 was mutagenic in the *in vitro* Ames assay.

Carcinogenesis

Long-term carcinogenicity studies with irinotecan hydrochloride have not been conducted. Rats were, however, administered intravenous doses of irinotecan hydrochloride 2 mg/kg or 25 mg/kg once per week for 13 weeks (AUC about 1.3 times the values of 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol, lactic acid, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in Section 6.6 Special precautions for disposal and other handling.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Irinotecan concentrated solution for infusion is supplied as 100 mg/5 mL single dose Type 1 amber tubular glass vials with a Teflon coated rubber stopper with an aluminium sealed flip off cap.

Pack size:
1 x 5 mL vial

Irinotecan (Alchemy) is for single use in one patient only.

6.6 Special precautions for disposal and other handling

Irinotecan (Alchemy) is intended for single use only and any unused portion should be discarded.

Irinotecan (Alchemy) must be diluted prior to infusion in 5% glucose solution or 0.9% sodium chloride solution to a final concentration of 2.8 mg/mL. Other medicines should not be added to the infusion solution. Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

Irinotecan (Alchemy) has been shown to be chemically and physically stable when diluted with infusion solutions (0.9% sodium chloride solution and 5% glucose solution) for up to 28 days when stored in polyvinyl chloride (PVC) containers or up to 14 days when stored in low-density polyethylene (LDPE) containers at 5°C or at 30°C/ambient humidity and protected from light. When exposed to light, chemical and physical stability is indicated for up to 3 days when stored in PVC containers or 2 days when sored in LDPE containers.

It is recommended however, that in order to reduce microbiological hazard, the infusion be commenced as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours or 8 hours at room temperature (30°C).

Do not freeze Irinotecan (Alchemy) or admixtures of Irinotecan (Alchemy) as this may result in precipitation of the medicine.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 October 2025

10 DATE OF REVISION OF THE TEXT

23 October 2025