

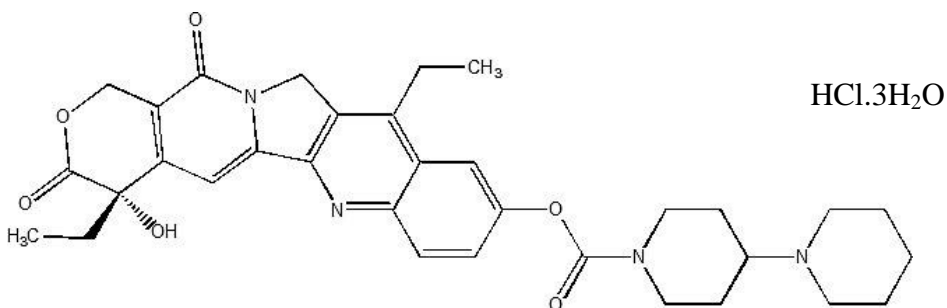
New Zealand Data Sheet

IRINOTECAN ACTAVIS

Irinotecan hydrochloride injection 20mg/mL

NAME OF MEDICINE

Non- Proprietary Name: Irinotecan hydrochloride.



Chemical name: (4S)-4,11-diethyl- 4-hydroxy-9- [(4-piperidinopiperidino) carbonyloxy]-1H- pyrano [3',4':6,7] indolizino [1,2-b]quinolone- 3,14(4H,12H)dione hydrochloride trihydrate.

Molecular Formula: C₃₃H₃₈N₄O₆.HCl.3H₂O

Molecular Weight: 677.19

CAS Registry Number: 136572-09-3.

DESCRIPTION

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.

Irinotecan Concentrated Injection is supplied as a sterile, pale yellow, clear, aqueous solution of pH 3.5. It is intended for dilution with 5% glucose injection or 0.9% sodium chloride injection prior to infusion. In addition to irinotecan hydrochloride, the ingredients are sorbitol, lactic acid, sodium hydroxide and water for injections.

PHARMACOLOGY

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 ADVERSE EFFECTS).

Pharmacokinetics

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/m² 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/m², 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/m² were determined in two clinical studies in patients with solid tumours as depicted in **Table 1**.

TABLE 1 - 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
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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). Albumin is the plasma protein to which irinotecan hydrochloride and SN-38 predominantly binds to.

Metabolism and Excretion

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/m²) to 50% (300 mg/m²).

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 Population

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 AUC₀₋₂₄ 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 DOSAGE AND ADMINISTRATION).

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 DOSAGE and 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 (FU), and leucovorin (LV) in 26 patients with solid tumours the disposition of irinotecan hydrochloride was not substantially altered when the drugs 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 FU and LV administration compared with when irinotecan hydrochloride was given alone. Formal *in vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan hydrochloride on the disposition of FU and LV have not been conducted.

CLINICAL TRIALS

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 2**).

TABLE 2 - 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 3**.

TABLE 3 - 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 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 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
C1	LV 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 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 asphyllaxis 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 flouroquinolone antibiotic prophylaxis was given. Treatment with oral flouroquinolone 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 flouroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) <0.5x10⁹/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/FU/LV therapy resulted in significant improvements in objective tumour response rate, time to tumour progression (TTP) and survival when compared with 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 4**.

TABLE 4 - Combination Therapy in First Line of Treatment of Metastatic Colorectal Cancer.

	Study 1			Study 2	
	Irinotecan + bolus FU/LV	Bolus FU/LV	Irinotecan	Irinotecan + Infusional FU/LV	Infusional 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	1.9	1.7	1.8	4.5	2.7

to Randomisation (month, range)	(0-161)	(0-203)	(0.1-185)	(0-88)	(0-104)
Prior Adjuvant 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 (%)	72	--	75	87	--
Irinotecan 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 Tumor 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 [12.6-17.2]

a Refer to Table 2

b Confirmed \geq 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 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/FU/LV combination and 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 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 FU based chemotherapeutic regimen. Starting dose of irinotecan hydrochloride in these trials were 100, 125 and 150 mg/m² with 150 mg/m²

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 5**.

TABLE 5 - 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/m² but was reduced to 100 mg/m² 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/m² 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/m²/wk corresponding with 150, 125 and 100 mg/m² 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 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/m² starting dose (53.4%; 103/193) than with the 100mg/m² 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/m² 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/m². 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 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 6**.

TABLE 6 - Phase III Clinical Studies with the Once Every 3 Week Dosage Schedule.

	Study 1		Study 2	
	Irinotecan hydrochloride	Best supportive care	Irinotecan hydrochloride	FU ^a
Number of Patients	189	90	127	129
Prior 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)	5.9 [3.8-7.6]	4.1 [2.2-6.9]	8.1 [6.1-10.7]	7.0 [4.4-8.7]

[95% CI]				
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 \geq 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 FU regimen was used:
- i. Leucovorin 200mg/m² IV over 2 hours; followed by FU 400mg/m² IV bolus; followed by FU 600mg/m² continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks.
 - ii. FU 250-300mg/m²/day protracted continuous IV infusion until toxicity.
 - iii. FU 2.6-3g/m²/day IV over 24 hours every week for 6 weeks with or without leucovorin 20-500mg/m²/day every week IV for 6 weeks with a 2 week rest between cycles
- b Study 1 \leq 6 months; Study 2 \leq 3 months
- c Relative dose intensity for irinotecan hydrochloride based on planned dose intensity of 116.7 mg/m²/week. Dose intensity in patients receiving FU in Study 2 varied depending upon type of regimen
- ** Cannot be determined 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 FU.

Other studies

An open-label, uncontrolled, late phase II Japanese 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/m² 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).

INDICATIONS

IRINOTECAN ACTAVIS is indicated as a component of first line therapy for patients with metastatic carcinoma of the colon or rectum. IRINOTECAN ACTAVIS is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial therapy.

CONTRAINDICATIONS

IRINOTECAN ACTAVIS is contraindicated in patients with a known hypersensitivity to the drug or its excipients. Irinotecan hydrochloride antigenicity has not been observed in clinical trials, but irinotecan hydrochloride antigenicity occurred in tests for passive cutaneous anaphylaxis in guinea pigs and rabbits, and in tests for active systemic anaphylaxis in guinea pigs. In these tests, both animal species produced antibodies against irinotecan hydrochloride, and some deaths occurred in guinea pigs sensitised to irinotecan hydrochloride.

IRINOTECAN ACTAVIS is also contraindicated for women who intend to become pregnant, are pregnant or are lactating (**see Use in Pregnancy, Use in Lactation, Effects on Fertility, Carcinogenicity and Mutagenicity**).

PRECAUTIONS

Administration

IRINOTECAN ACTAVIS 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.

Extravasation

IRINOTECAN ACTAVIS 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 ACTAVIS should not be used in combination with the *Mayo Clinic* regimen of FU/ LV (administration for four to five consecutive days every four weeks [see Table 3]) because of reports of increased toxicity, including toxic deaths. IRINOTECAN ACTAVIS should be used as recommended in DOSAGE AND 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 ADVERSE EFFECTS, cardiovascular)

Diarrhoea and its Management

IRINOTECAN ACTAVIS can induce both early and late forms 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 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 intravenous or subcutaneous atropine 0.25 to 1 mg should be considered (unless clinically contraindicated) in patients experiencing cholinergic symptoms occurring during or shortly after infusion of IRINOTECAN ACTAVIS.

Late diarrhoea (generally occurring more than 24 hours after administration of IRINOTECAN ACTAVIS) can be prolonged, may lead to dehydration, electrolyte imbalance or infection 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. A 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 two hours until the patient was diarrhoea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every four 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. Pre-medication 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-diarrhoeal medication. If NCI grade 2, 3 or 4 diarrhoea occurs, subsequent doses of IRINOTECAN ACTAVIS should be reduced within the current cycle (see DOSAGE AND ADMINISTRATION).

In addition to 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 and
- diarrhoea persisting beyond 48 hours following the initiation of high dose loperamide therapy and
- where patients are deemed unlikely to observe recommendations regarding management of adverse events (need for immediate and prolonged anti-diarrhoeal treatment combined with high fluid intake at onset of delayed diarrhoea).

Haematology

IRINOTECAN ACTAVIS commonly causes neutropenia, leucopenia and anaemia, any of which may be severe and therefore should not be used in patients with severe bone marrow failure (see ADVERSE EFFECTS, Haematological). Serious thrombocytopenia is uncommon.

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with IRINOTECAN ACTAVIS. Neutropenic complications should be managed promptly with antibiotic support. Therapy with IRINOTECAN ACTAVIS should be temporarily omitted if neutropenic fever occurs or if the absolute neutrophil count drops below $1.5 \times 10^9/L$. A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1.5 \times 10^9/L$. After the patient recovers, subsequent doses of IRINOTECAN ACTAVIS should be reduced depending upon the level of neutropenia observed (see DOSAGE AND 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.

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.

Use with caution in the following circumstances

Patients at particular risk

Doctors should exercise particular caution in monitoring the effects of IRINOTECAN ACTAVIS in patients with poor performance status, in elderly patients and in patients who have previously received pelvic/abdominal irradiation (see ADVERSE EFFECTS). Patients with poor performance status are at an increased risk of irinotecan related adverse events. In patients receiving either IRINOTECAN ACTAVIS/FU/LV or 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 ACTAVIS.

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 PHARMACOLOGY, 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 ACTAVIS. 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 PHARMACOLOGY, Pharmacokinetic, Pharmacokinetics in Special Populations)

The use of IRINOTECAN ACTAVIS 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 $\mu\text{mol/L}$) had a significantly greater likelihood of experiencing first cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 17 $\mu\text{mol/L}$ (50% versus 18%; $p < 0.001$) (See PHARMACOLOGY & DOSAGE AND ADMINISTRATION sections). 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 ACTAVIS.

Cholinergic effects

IRINOTECAN ACTAVIS 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 drugs, 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 pre-medication with antiemetic agents. In clinical studies with the weekly dosage schedule, the majority of patients received 10mg 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 prior to administration of IRINOTECAN ACTAVIS. Doctors 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.

Instructions to patients

Patients should be advised of the expected toxic effects of IRINOTECAN ACTAVIS, 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 ACTAVIS:

- 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 Interactions) and patients should contact their doctor to discuss any laxative use.

Others

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

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/m² weekly) and dogs at 0.4 mg/kg (AUC about one-fifteenth the value in patients administered 125 mg/m² weekly).

Use in pregnancy (Category D)

Category D - *Drugs which have caused or are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.*

IRINOTECAN ACTAVIS 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/m²) and rabbits (about one-half the recommended human weekly starting dose on a mg/m² 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/m²) and in rabbits at

6.0mg/kg/day. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities.

There are no adequate and well controlled studies of irinotecan hydrochloride in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed about the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with IRINOTECAN ACTAVIS.

Use in lactation

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. As many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants, it is recommended that the patient discontinue breastfeeding when receiving therapy with IRINOTECAN ACTAVIS.

Paediatric Use

The safety and effectiveness of IRINOTECAN ACTAVIS in children have not been established.

Carcinogenesis and mutagenesis

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/m²) 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.

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.

Interactions with other medicines

Neuromuscular blocking agents. Interactions between irinotecan hydrochloride 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 nondepolarising drugs may be antagonised.

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

Anticonvulsants. Concomitant administration of CYP3A inducing anticonvulsant drugs (e.g. carbamazepine, phenobarbital (phenobarbitone) or phenytoin) leads to reduced

exposure to SN-38. Consideration should be given to starting or substituting nonenzyme inducing anticonvulsants at least one week prior to initiation of irinotecan therapy in patients requiring anticonvulsant treatment.

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.

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.

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 drugs.

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 antinauseants) was administered on the same day as irinotecan hydrochloride than when these drugs 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 ACTAVIS, 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 ACTAVIS and, certainly, during periods of active vomiting or diarrhoea.

Effects on laboratory tests

There are no known interactions between IRINOTECAN ACTAVIS and laboratory tests

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.

ADVERSE 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 FU/LV, FU/LV alone, or irinotecan hydrochloride alone (See Table 3, Clinical Trials). In these studies, 370 patients received irinotecan hydrochloride in combination with FU/LV, 362 patients received 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 FU/LV, 19 (5.3%) received 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 FU/LV (two neutropenic fever/sepsis, one treatment toxicity), three (0.7%) patients who received 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 FU/LV, 18 (5.0%) patients who received 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 FU/LV, 15 (4.1%) patients who received FU/LV alone, and 26 (11.7%) patients who received irinotecan hydrochloride alone.

Table 7 lists the grade 3 and 4 clinically relevant adverse events reported in the combination treatment arms of the two phase III studies.

TABLE 7 – 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 FU/LV N=225 ^b	FU/LV N=219 ^b	Irinotecan hydrochloride N=223 ^b	Irinotecan hydrochloride FU/LV N=145 ^c	FU/LV N=143 ^c
TOTAL Grade 3/4 Adverse Events	53.3	45.7	45.7	72.4	39.2
<i>Gastrointestinal</i>					
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
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
<i>Haematological</i>					
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
Leucopenia	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
<i>Body as a Whole</i>					
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
<i>Metabolic and Nutritional</i>					
Increased bilirubin	7.1	8.2	7.2	3.5	10.6
<i>Dermatological</i>					
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
<i>Respiratory</i>					

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					
<i>Dizziness</i>	1.3	0	1.8	--	--
<i>Somnolence</i>	1.8	1.8	1.3	--	--
<i>Confusion</i>	1.8	0	0	--	--
Cardiovascular					
<i>Vasodilation</i>	0.9	0	0	--	--
<i>Hypotension</i>	1.3	0.5	1.7	1.4	0
<i>Thrombophlebitis</i>	2.7	3.2	1.8	--	--
<i>Pulmonary embolus</i>	2.7	1.4	0.4	--	--
<i>Myocardial infarction</i>	1.3	0	0.4	--	--

- a Severity of adverse events based on NCI CTC (version 1.0) see <http://ctep.info.nih.gov/CTC3/default.htm>
- 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 3**)

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 FU/LV therapy were diarrhoea neutropenia, neutropenic fever and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as \geq grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with irinotecan hydrochloride/FU/LV than with administration of 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 drug 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 8**. Additional information on adverse events follows the table, organised by body system category.

TABLE 8 - Adverse Events Reported From the Second Line Single Agent Therapy In 304 Patients^a.

Event	Weekly dosage schedule		3 weekly dosage schedule (NCI grade 3 & 4 only)	
	% of patients	% NCI grade 3 & 4	Study 1 (%)	Study 2 (%)
<i>Gastrointestinal</i>				
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	-	-	-
<i>Haematological</i>				
Leucopenia ^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
<i>Body as a Whole</i>				
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	-	-
<i>Metabolic and Nutritional</i>				
Weight reduction	30.3	0.7		
Dehydration	14.8	4.3		
Increased alkaline phosphatase	13.2	3.9		
Increased SGOT (AST)	10.5	1.3		
<i>Dermatological</i>				
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
<i>Respiratory</i>				
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 <http://ctep.info.nih.gov/CTC3/default.htm>
- b Combined results for leucopenia/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 grade 3/4 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/m² 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 drug 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, leucopenia (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 drug 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 drug 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 nonmalignant 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 ACTAVIS. 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 ACTAVIS, 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 ACTAVIS. The specific cause of these events has not been determined.

Other

Other NCI grade 3 or 4 drug 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 and abnormal gait were observed.

Postmarketing surveillance

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.

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.

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.

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 PRECAUTIONS). Hiccups have also been reported.

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.

DOSAGE AND ADMINISTRATION

It is recommended that patients receive premedication with antimetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms (See PRECAUTIONS).

Combination Agent Therapy

Dosage Regimens

IRINOTECAN ACTAVIS injection in combination with fluorouracil (FU) and Leucovorin (LV):

IRINOTECAN ACTAVIS should be administered as an intravenous infusion over 90 minutes (refer to Preparation of Infusion solution). For all regimens, the dose of LV should be administered immediately after IRINOTECAN ACTAVIS, with the administration of FU to follow immediately after the administration of LV. The recommended regimens are shown in **Table 9**.

TABLE 9 - Combination Agent Dosage Regimens & Dose Modifications^a

Regimen 1 6 week cycle Treatment resume Day 43	IRINOTECAN	125mg/m ² IV over 90 mins on day 1,8,15,22		
	ACTAVIS	then 2 wk rest		
	LV	20mg/m ² IV bolus injection day 1, 8, 15, 22		
	FU	then 2 wk rest		
		500mg/m ² IV bolus injection day 1,8,15, 22		
		then 2 wk rest		
		Starting dose and modified dose levels^b		
		Starting Dose (mg/m ²)	Dose Level -1 (mg/m ²)	Dose Level-2 (mg/m ²)
	IRINOTECAN	125	100	75
	ACTAVIS	20	20	20
	LV	500	400	300
	FU			
Regimen 2 6 week cycle Treatment resumes Day 43	IRINOTECAN	180 mg/m ² IV over 90 mins on day 1,15, 29		
	ACTAVIS	then 1 wk rest		
	LV	200 mg/m ² IV over 2 hrs on day 1, 2, 15, 16,		
	FU Bolus	29, 30 then 1 wk rest		
	FU Infusion ^c	400 mg/m ² IV on day 1, 2, 15, 16, 29, 30 then		
		1 wk rest		

		600 mg/m ² IV over 22hrs on day 1, 2, 15,16, 29, 30 then 1 wk rest		
		Starting dose and modified dose levels^b		
		Starting Dose (mg/m ²)	Dose Level -1 (mg/m ²)	Dose Level-2 (mg/m ²)
	IRINOTECAN	180	150	120
	ACTAVIS	200	200	200
	LV	400	320	240
	FU Bolus	600	480	360
	FU Infusion ^c			

- 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 10**.
- 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 ACTAVIS and FU should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose levels described in **Table 9**, subsequent doses should be adjusted as suggested in **Table 10**, 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 anti diarrhoeal 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 $\geq 1.5 \times 10^9/L$, the platelet count has recovered to $\geq 100 \times 10^9/L$ 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 ACTAVIS/FU/LV may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 10 - Recommended dose modification during a cycle of therapy with the IRINOTECAN ACTAVIS/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 \leq	Decrease by 1 dose level

4	grade 2, then decrease by 1 dose level. Omit dose until resolved to \leq 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 haemeotological toxicities	Dose modifications for leucopenia 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 1 dose level Omit dose until resolved to baseline, then decrease by 2 dose levels	Decrease by 2 dose levels
Other nonhaematological toxicities ^c		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to \leq grade 1, then decrease by 1 dose level	Maintain dose level
3	Omit dose until resolved to \leq grade 2, then decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to \leq 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 <http://ctep.info.nih.gov/CTC3/default.htm>

b Relative to the starting dose used in the previous cycle

c For mucositis/stomatitis decrease only FU, not IRINOTECAN ACTAVIS

Single Agent Therapy

Dosage Regimens

IRINOTECAN ACTAVIS should be administered as an IV infusion (refer to Preparation of Infusional solution) over 90 minutes in a recommended weekly or once every 3 week dosage schedule as shown in **Table 11**.

TABLE 11 - Single agent regimens of IRINOTECAN ACTAVIS and dose modification

Weekly Regimen^a 6 week cycle Treatment resume 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		
	Starting Dose (mg/m ²)	Dose Level - 1(mg/m ²)	Dose Level- 2(mg/m 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		
	Starting Dose (mg/m ²)	Dose Level - 1(mg/m ²)	Dose Level- 2(mg/m ²)
	350	300	250

a Subsequent dose may be adjusted as high as 150 mg/m² or as low as 50 mg/m² in 25 to 50 mg/m² decrements depending on individual patients tolerance.

b Subsequent dose may be adjusted as low as 200 mg/m² in 50 mg/m² decrements depending on individual patients tolerance.

c Refer to **Table 13**.

A reduction in the starting dose by one level of IRINOTECAN ACTAVIS 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 12 - 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 ACTAVIS given once every 3 weeks have not been defined in patients with biliruin >3.0 x IULN and this schedule can not be recommended in these patients.

Dose Modifications

Patients should be carefully monitored for toxicity and doses of IRINOTECAN ACTAVIS should be modified as necessary to accommodate individual patients tolerance to treatment. Based on recommended dose-levels described in **Table 11 & Table 12**, subsequent doses of IRINOTECAN ACTAVIS should be adjusted as suggested in **Table 13**. 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 $\geq 1.5 \times 10^9/L$, the platelet count has recovered to $\geq 100 \times 10^9/L$ 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 ACTAVIS therapy. Provided intolerable toxicity dose not develop, treatment with additional cycle of IRINOTECAN ACTAVIS may be continued indefinitely as long as patients continue to experience clinical benefit.

TABLE 13 - 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 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 \leq grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to \leq 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 leucopenia, 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 \leq grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to \leq grade 2, then decrease by 2 dose levels	Decrease by 2 dose levels	Decrease by 1 dose level
Other nonhaematological 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 \leq grade 2, then decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
4	Omit dose until resolved to \leq 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 <http://ctep.info.nih.gov/CTC3/default.htm>

Preparation and Administration Precautions

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

Preparation of Infusional Solutions

Irinotecan Concentrated Injection is intended for single use only and any unused portion should be discarded.

Irinotecan Concentrated Injection must be diluted prior to infusion in 5% glucose injection or 0.9% sodium chloride injection to a final concentration range of 0.12 to 2.8 mg/mL. Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The diluted solution as proposed for usage as an IV infusion is stable in the proposed diluents (5% glucose, 0.9% NaCl), under normal room conditions ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\%$), in glass or polyvinyl chloride (PVC) bags, and at the lowest and highest dilution concentrations (0.12 mg/ml and 2.4 mg/mL, respectively) for a period of up to 24 hours.

It is recommended however, that in order to reduce microbiological hazard, the infusion be commenced as soon as practicable after preparation. If not used immediately, in-use storage times and conditions prior to use should not be longer than 24 hours at 2°C to 8°C or 6 hours at room temperature (25°C).

Do not freeze Irinotecan Concentrated Injection or admixtures of Irinotecan Concentrated Injection as this may result in precipitation of the drug.

OVERDOSAGE

Symptoms

In humans, at single doses up to 750 mg/m², 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.

Treatment

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

The National Poisons Centre, telephone number 0800 POISON (0800 764 766), should be contacted for advice on the management of an overdosage.

PRESENTATION AND STORAGE CONDITIONS

Irinotecan Concentrated Injection is a clear, colourless to pale yellow solution, containing 20 mg/mL irinotecan as irinotecan hydrochloride.

Irinotecan Concentrated Injection is available in single-use, brown glass vials with a bromobutyl rubber stopper, sealed with an aluminium crimp. The vials are individually packed in a carton in the following sizes:

- 40 mg/2 mL Single-Use Vial
- 100 mg/5 mL Single-Use Vial

Storage

Store below 30°C. Do not freeze. Protect from light. It is recommended that the vial should remain in the carton until time of use.

NAME AND ADDRESS OF THE SPONSOR

Australian Sponsor:

Actavis Australia Pty Ltd
Level 10, 25 Grenfell Street
Adelaide
SA 5006

New Zealand Sponsor:

CSL Biotherapies (NZ) Ltd
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CLASSIFICATION OF MEDICINE

Prescription medicine.

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