UNILAB

Irinotecan Hydrochloride Ventera®

20 mg/mL Solution for IV Infusion
Antineoplastic Agent

Composition:
Each 5 ml contains: Irinotecan hydrochloride ..... 20 mg

Product Description:
Irinotecan hydrochloride (Ventera) is a semisynthetic derivative of camptothecin, which is supplied as a sterile, pale yellow, clear aqueous solution administered through intravenous injection.

Pharmacodynamic properties:
Irinotecan hydrochloride belongs to the class of antineoplastic agents ATC Code: L01XX19
Mechanism of action:
Irinotecan is a derivative of camptothecin. It is an antineoplastic agent which acts as a specific inhibitor of type I DNA topoisomerase. It is metabolized by carboxylesterase in mouse liver, plasma, and tumor. Only plasma SN-38, which was found to be more active than irinotecan on cellular type I topoisomerase, was detected in patients treated with irinotecan. Irinotecan and SN-38 exhibit cytotoxicity against cultured mammalian cells and induce DNA single-strand breaks (DNA replication fork arrest) are responsible for the cytotoxicity. This cytotoxicity is not specific to the phase of the cell cycle.
In vitro, irinotecan and SN-38 are not significantly recognized by P-glycoprotein (MDR), and irinotecan has a cytotoxic activity against cell lines resistant to doxorubicin and vincristine.
In addition, irinotecan has a broad antitumor activity in xenograft human tumors (human colon carcinoma, human gastric carcinoma, NCI-H460 human adenocarcinoma, CXF, and CX1 colon adenocarcinoma) and against human xenografts (Colon cancer adenocarcinoma, MX1 mammary adenocarcinoma, and human small cell lung carcinoma). Irinotecan hydrochloride is active against human xenografts (Colon cancer) which are resistant to 5-fluorouracil and vincristine.
In addition to the antitumor effect of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.
Clinical data:
Clinical efficacy for the advanced colorectal cancer treatment with irinotecan:
Two randomized controlled trials (Study 303 and Study 306) in patients treated with a bolus or a 5-FU treatment, were enrolled in clinical phase III studies, with the every 2 weeks dosage schedule. The efficacy of irinotecan was evaluated in 765 patients treated with bolus 5-FU treatment, at the moment of the study. Results are shown below:

	Phase III			
	Study 303 (Bolus versus bolus)		Study 306 (Bolus versus bolus)	
	Irinotecan	5-FU	Irinotecan	5-FU
	2 weeks	2 weeks	2 weeks	2 weeks
Progression Free Survival at 6 months (%)	45.2	18.1	33.5	20.7
Survival at 12 months (%)	36.2	13.8	p=0.0001	44.8
Median Survival time (weeks)	14.8	12.0	p=0.0127	14.1
	p=0.0012			12.0

Risk factor analysis:
Risk factor analysis conducted in 455 patients with the every 2 weeks dosing schedule of three weeks, the disease free survival at 6 months was 50% and the median survival was 15 months, in patients with a PS of 0 and a serum albumin level ≥ 3 g/dl.
Additionally, non-comparative phase II studies were conducted in 304 patients by weekly administration of a dose of 125 mg/m² as an intravenous infusion for 90 minutes, for four consecutive weeks, followed by a two weeks rest period. The median survival time was 12 months and the median time to progression was 7 weeks and the median overall time to progression was 6 weeks. Grade 4 neutropenia was observed in 9% of the patients with an initial dose of 125 mg/m² compared to the 2 weeks dosing schedule. The median time to onset of neutropenia was 3 weeks and the median duration was 1 week, with no cases of febrile neutropenia.
A phase III study was also conducted in 385 patients with metastatic colorectal cancer who had not received prior chemotherapy for treatment every 3 weeks or every week. In the every 3 weeks schedule, on the first day, the administration of irinotecan at 180 mg/m² was given 2 weeks was followed by 5-FU/LV administered as a bolus injection and a 22 hours continuous infusion, repeated every 3 weeks. In the every week schedule, on the first day, Folinic Acid (Calcium, 250 mg), 2 hours after the beginning of the 5-FU/LV administration, the bolus dose of irinotecan 90 mg/m² was given, the administration of irinotecan at 90 mg/m² was repeated for 4 consecutive weeks followed by a rest period of 2 weeks. The results of the comparison between the two arms of the study are shown in the combination treatment than with the 2 regimens separately:

	Combined regimens (n=198)		Weekly schedule (n=93)		Every 3 weeks schedule (n=105)	
	Irinotecan	5-FU/LV	Irinotecan	5-FU/LV	Irinotecan	5-FU/LV
Response rate	26.8% (95% CI: 20.8 - 33.5)	10.6% (95% CI: 6.4 - 16.4)	18.3% (95% CI: 10.8 - 28.1)	6.5% (95% CI: 2.1 - 14.5)	34.3% (95% CI: 25.4 - 44.1)	14.3% (95% CI: 8.4 - 22.2)
	2 weeks	2 weeks	2 weeks	2 weeks	3 weeks	3 weeks
Median time to progression (months)	6.7	4.4	7.2	5.3	6.3	4.2
	p=0.0001		NS		p=0.0001	
Median duration of response (months)	6.9	4.6	7.1	4.6	6.9	4.6
	p=0.0001		NS		p=0.0001	
Median duration of response and stabilization (months)	6.5	4.2	6.7	4.6	6.1	3.6
	p=0.0001		NS		p=0.0001	
Median time to treatment failure (months)	5.5	3.9	5.6	3.7	5.5	3.9
	p=0.0001		NS		p=0.0001	
Median survival (months)	14.8	12.0	14.8	13.1	14.8	11.0
	p=0.0127		NS		p=0.0127	

Inc. Irinotecan
5-FU: 5-fluorouracil,
FL: folinic acid,
NS: not significant.
Clinical efficacy in adjuvant treatment:
Two randomized controlled trials in patients of severe disease was 45.4% in the patients treated with irinotecan in combination with 5-FU/FL and 25.0% in the patients treated with 5-FU/FL alone. The incidence of severe neutropenia (neutrophil count < 500/ mm³) was 3.8% in the patients treated with irinotecan in combination with 5-FU/FL and 0.5% in the patients treated with 5-FU/FL alone.
Additionally, the median time to progression of severe diarrhea was significantly longer in the group that received irinotecan in combination with 5-FU/FA than in the group receiving 5-FU/FA alone (p = 0.0346).
Study 305 was a randomized, open, multicenter study (GERCOR) GI-CAD questionnaire. Time to definitive deterioration occurred significantly later in the irinotecan group. The overall survival was longer in the irinotecan group than in the control group, but the difference was not significant. Irinotecan was well tolerated in combination therapy with Calcium.
Study 308 was a randomized study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of irinotecan/5-FU/FA versus 5-FU/FA treatment. Irinotecan/5-FU/FA and 5-FU/FA treatment for the treatment of metastatic colorectal cancer. Calcium 299 patients. The proportion of patients with WHO and Lipsi tumors within the patient population evaluable for WHO status was 94%.
The efficacy data presented in the study are shown below:

Variable/statistic	Overall population Calculated plus 5-FU/FA (N=385)		WHO-ARS type population Calculated plus 5-FU/FA (N=299)	
	5-FU/FA	Irinotecan	5-FU/FA	Irinotecan
	(N=189)		(N=176)	
% (95% CI)	40.9 (43.5 31.0)	38.7 (34.8 42.8)	35.3 (31.6 38.7)	43.2 (38.8, 50)
p value	0.0008		0.0002	
Hazard Ratio (95% CI)	0.65 (0.50, 0.84)		0.68 (0.541, 0.854)	
p value	0.0008		0.0008	

CI = confidence interval, FU/FA = irinotecan plus infusion 5-FU/LV/FA, GWR = objective response rate (patients with complete response or partial response), PFS = progression-free survival time in combination with Calcium/ and after failure of irinotecan-including cytotoxic therapy.
Study 309 was a randomized, open, multicenter study (GERCOR) GI-CAD questionnaire. Time to definitive deterioration of QLQ-C30 EORTC QLQ-C30 questionnaire was significantly longer in the irinotecan group than in the control group. The overall survival was longer in the irinotecan group than in the control group, but the difference was not significant. Irinotecan was well tolerated in combination therapy with Calcium.
Study 310 (GERCOR) randomized study compared patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of irinotecan/5-FU/FA versus 5-FU/FA treatment. Irinotecan/5-FU/FA and 5-FU/FA treatment for the treatment of metastatic colorectal cancer. Calcium 299 patients. The proportion of patients with WHO and Lipsi tumors within the patient population evaluable for WHO status was 94%.
The efficacy data presented in the study are shown below:

	Irinotecan/5-FU/FA	5-FU/FA
Number of patients	210	222
Response rate (CR+PR)	31.9%	21.6%
Median time to progression	6.7 months	4.4 months
Median duration of response	6.9 months	4.6 months
Median duration of response and stabilization	6.5 months	4.2 months
Median time to treatment failure	5.5 months	3.9 months
Median survival	14.8 months	12.0 months
Survival at 1 year	42.4%	31.0%
Survival at 2 years	16.8%	11.7%

Pharmacokinetic properties:
Absorption:
Pharmacokinetics of irinotecan and its active metabolite SN-38 were studied in 19 patients treated in combination with 5-FU/FL and 25.0% in the patients treated with 5-FU/FA alone. The incidence of severe neutropenia (neutrophil count < 500/ mm³) was 3.8% in the patients treated with irinotecan in combination with 5-FU/FL and 0.5% in the patients treated with 5-FU/FL alone.
Additionally, the median time to progression of severe diarrhea was significantly longer in the group that received irinotecan in combination with 5-FU/FA than in the group receiving 5-FU/FA alone (p = 0.0346).
Study 305 was a randomized, open, multicenter (GERCOR) GI-CAD questionnaire. Time to definitive deterioration occurred significantly later in the irinotecan group. The overall survival was longer in the irinotecan group than in the control group, but the difference was not significant. Irinotecan was well tolerated in combination therapy with Calcium.
Study 308 was a randomized study in patients with metastatic colorectal cancer who had not received prior treatment for metastatic disease compared the combination of irinotecan/5-FU/FA versus 5-FU/FA treatment. Irinotecan/5-FU/FA and 5-FU/FA treatment for the treatment of metastatic colorectal cancer. Calcium 299 patients. The proportion of patients with WHO and Lipsi tumors within the patient population evaluable for WHO status was 94%.
The efficacy data presented in the study are shown below:

Variable/statistic	Overall population Calculated plus 5-FU/FA (N=385)		WHO-ARS type population Calculated plus 5-FU/FA (N=299)	
	5-FU/FA	Irinotecan	5-FU/FA	Irinotecan
	(N=189)		(N=176)	
% (95% CI)	40.9 (43.5 31.0)	38.7 (34.8 42.8)	35.3 (31.6 38.7)	43.2 (38.8, 50)
p value	0.0008		0.0002	
Hazard Ratio (95% CI)	0.65 (0.50, 0.84)		0.68 (0.541, 0.854)	
p value	0.0008		0.0008	

CI = confidence interval, FU/FA = irinotecan plus infusion 5-FU/LV/FA, GWR = objective response rate (patients with complete response or partial response), PFS = progression-free survival time in combination with Calcium/ and after failure of irinotecan-including cytotoxic therapy.
The efficacy of the combination of Calcium/ and irinotecan was higher than that of Calcium/ and 5-FU/FA. The median time to progression was 6.7 months versus 4.4 months, the response rate was 31.9% versus 21.6%, and the median survival was 14.8 versus 12.0 months. The toxicity was higher in the Calcium/ and irinotecan group (Grade3 rates 9% v. p = 0.08).
Study 309 (EORTC 40983) randomized study compared the combination of Calcium/ and irinotecan 210 patients with Calcium/ monotherapy (111 patients).
NCI_CTCI 4003. The results are shown below:

	Calcium/	Calcium/ + Irinotecan
Number of patients	111	210
Response rate (CR+PR)	0%	4.8%
Stable disease	34.2%	40.5%
Progression free survival		
Median time to progression	4.4	6.7
Survival		
Median survival	9.2	14.8
Survival at 1 year		
Survival at 2 years	34.9	42.4
Survival at 3 years	16.2	16.8
Quality of life		
Deterioration of QLQ-C30	50.2 – 50.2	50.9 – 45.8
Deterioration of QLQ-C30	0.7 – 1.0	0.7 – 1.0
Deterioration of QLQ-C30	0.7 – 1.0	0.7 – 1.0

Clinically proven benefits, Irinotecan in combination therapy with Calcium/
In combination therapy with Calcium/
Study 305 (GERCOR) randomized study CIAREG support the use of Calcium/ as a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the treatment of metastatic colorectal cancer patients with metastatic colorectal cancer. 625 Patients were randomized to receive either sequential treatment (n = 313) or combination treatment (n = 312). Sequential treatment consisted of first-line treatment with Capecitabine (1250 mg/m²/day) and second-line treatment with Irinotecan (350 mg/m²) and Calcium/ (200 mg/m²) administered every 3 weeks. Combination treatment consisted of daily 5-FU bolus and Calcium/ (500 mg/m²) administered every 2 weeks, followed by 5-FU bolus and Calcium/ (500 mg/m²) administered every 2 weeks, followed by 5-FU bolus and Calcium/ (500 mg/m²)