IRINOTECAN GP PHARM
Irinotecan hydrochloride, trihydrate

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Solution for injection
100 mg/5 ml
40 mg/2 ml
MEDICINAL PRODUCT SUBJECT TO MEDICAL PRESCRIPTION
MANUFACTURED IN ARGENTINA
FORMULA
Each ml contains:

Irinotecan hydrochloride, trihydrate	20 mg
Sorbitol	45 mg
Lactic acid	0.9 mg
Water for injection	e.q.
Sodium hydroxide or hydrochloride acid	e.q. to adjust pH

THERAPEUTIC ACTION
Antineoplastic agent of the topoisomerase I inhibitor class.

INDICATIONS
IRINOTECAN GP PHARM is indicated as a component of first-line therapy for patients with metastatic carcinoma of colon and rectum in combination with 5-fluorouracil and leucovorin.
IRINOTECAN GP PHARM is also indicated as a single agent in patients with metastatic carcinoma of colon and rectum whose disease has recurred or progressed after the baseline treatment with 5-fluorouracilo.

PHARMACOLOGICAL CHARACTERISTICS
- PHARMACOLOGICAL ACTION
Irinotecan hydrochloride is a semi-synthetic derivative of camptothecin, an alkaloid extracted from the Camptotheca acuminata plant.
Irinotecan is metabolised in most tissues by carboxyl esterase to SN-38, a more potent metabolite. The camptothecin analogs, including irinotecan and its metabolite SN-38, act inhibiting the topoisomerase I-DNA, a cellular enzyme that keeps the topographic structure of the DNA during the translation, the transcription and the mitosis.
The topoisomerase I relieves the torsion strain of the double helix DNA during the replication and the transcription breaking temporarily one of the strands of the double helix, forming a DNI- topoisomerase I complex, and binding it again. The derivatives of camptothecin fix to the DNI- topoisomerase I complex and avoid this union. Nevertheless, in order to make these compounds show the potent toxicity, a DNA synthesis is needed to re-start. At this moment, when the fork consisting of two DNA strands meet the topoisomerase irinotecan complex, it results in a double break of the strands, in this case, irreversible.

- PHARMACOKINETICS
After intravenous infusion of irinotecan, plasma concentrations in humans decline in an exponential manner, with a terminal-elimination half-life of about 6 to 12 hours. The terminal-elimination mean half-life of the active metabolite SN-38 is approximately 10 to 20 hours.
Over the recommended dose range (50 to 350 mg/m²), the AUC of irinotecan increases linearly with the dose.
Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion or IRINOTECAN GP PHARM.
Irinotecan exhibits moderate plasma protein binding (30% to 68%). SN-38 is highly bound to human plasma proteins (approximately 95%). Both are predominantly bound to albumin.
The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxyl esterase enzyme and primarily occurs in the liver. SN-38 subsequently undergoes conjugation, predominantly through the enzyme UDP-glucuronosil-tranferase 1A1 (UGT1A1) to form a glucuronide metabolite. The activity of the UGT1A1 is reduced in individuals with genetic polymorphisms which lead to a reduction of the enzyme activity, such as the polymorphism of UGT1A128. In a prospective study, where irinotecan was administered as a single agent given once every three weeks, patients who were homozygote for UGT1A128 had a greater exposition to SN-38 than the patients with the germline/wild-kind allele UGT1A1.
In cytotoxicity assays in vitro, SN-38 glucoronide had 1/50 to 1/100 the activity of SN-38. The urinary excretion of irinotecan is 11% to 20%; SN-38 is <1.0%; and SN-38 glucuronide is 3%. The bile cumulative and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).
Pharmacokinetics parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m² determined in two clinical studies in patients with solid tumors are summarized in Table 1:

Table 1. Summary of irinotecan and SN-38 pharmacokinetic parameters in patients with solid tumors (mean SD)

Dose (mg/m²)	Irinotecan					**SN38**		
	C_{max} (ng/ml)	AUC_{0-24} (ng-h/ml)	T1/2 (h)	Vd (L/m²)	CL (L/h/m²)	C_{max} (ng/ml)	AUC_{0-24} (ng-h/ml)	T1/2 (hs)
125 (N=64)	1660 ±797	10200 ±3270	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)	3392 ±874	20640 ±6027	11.7[a] ±1.0	234 ±69.6	13.8 ±4.0	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max}: Maximum plasma concentration
AUC : Area under the plasma concentration-time curve from 0 to 24 hours after the end of the 90-minute 0-24 infusion.
T½: Terminal elimination half-life
Vd: Volume of distribution of terminal elimination phase.
CL: Total systemic clearance.
* Plasma sample collected for 24 hours following the end of the 90-minute infusion.
* Plasma sample collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide more accurate data of the terminal elimination half-lives of irinotecan and SN-38.

Special population
Geriatric: In studies using the weekly schedule, the half-life of irinotecan was 6 hours in patients who were 65 years old or older and 5.5 hours in patients younger than 65 years old. Dose-normalized AUC for SN-38 in patients who were older than 65 years old was 11% higher than in patients younger than 65 years old. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule. The pharmacokinetics given once every three weeks has not been studied in the geriatric population; a lower starting dose is recommended in patients who are 70 years or older.
Pediatrics: The pharmacokinetics parameters of irinotecan and SN-38 were determined in two studies in children with solid tumors at dose-levels of 50 mg/m^2 (60 minutes-infusion, N=48) and 125 mg/m^2 (90 minutes-infusion, N=6). Irinotecan clearance was 17.3 ± 6.7 l/h/m^2 with doses of 50 mg/m^2 and 16.2 ± 4.6 l/h/m^2 with doses of 125 mg/m^2, what is comparable to the clearance in adults. The SN-38 AUC values were comparable both in adults and children. A minimal accumulation of irinotecan and SN-38 in children receiving daily dose regimen (5 consecutive days every 3 weeks or 5 consecutive days for 2 weeks every 3 weeks) was
observed.
Hepatic insufficiency: The clearance of irinotecan is decreased in patients with hepatic insufficiency. The exposition to the active metabolite SN-38 is increased in patients with hepatic insufficiency in relation to the one observed in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of impairment of the hepatic function, determined by the increase in the total bilirrubin and transaminases. However, the tolerance to irinotecan in patients with hepatic impairment (bilirrubin higher than 2 mg/dl) has not been evaluated sufficiently; therefore doses can not be recommended.
Renal insufficiency: The influence of renal insufficiency on the pharmacokinetics of irinotecan and its metabolites has not been evaluated. Irinotecan should be used with caution in this kind of patients. The use of irinotecan is not recommended for patients with dialysis.

POSOLOGY/DOSAGE – METHOD OF ADMINISTRATION
IRINOTECAN GP PHARM should be administered as intravenous infusion.
DOSE REGIMENS:
IRINOTECAN GP PHARM in combination with 5-fluorouracil (5-FU) and leucovorin (LV)
IRINOTECAN GP PHARM should be administered as an intravenous infusion over 90 minutes. For all regimens, the dose of LV should be administered immediately after IRINOTECAN GP PHARM, and the administration of 5-FU immediately after receiving LV. IRINOTECAN GP PHARM should be used as recommended; the recommended regimens are shown in Table 2.

Table 2. Combination dose regimen with LV/5-FU and dose modifications*

REGIMEN 1 6-week cycle with bolus 5-FU/LV (the next cycle starts on day 43)	IRINOTECAN GP PHARM LV 5-FU	125 mg/m^2 infusion IV for 90 minutes; days 1, 8, 15 22 20 mg/m^2 bolus IV; days 1, 8, 15, 22 500 mg/m^2 bolus IV; days 1, 8, 15, 22		
		Starting dose levels & modified dose (mg/ml^2)		
		Starting dose	Dose level-1	Dose level-2
	IRINOTECAN GP PHARM LV 5-FU	125 20 500	100 20 400	75 20 300
REGIMEN 2 6-week cycle with infusion 5-FU/LV (the next cycle starts on day 43)	IRINOTECAN GP PHARM LV 5-FU in bolus 5-FU infusion	180 mg/m^2 infusion IV for 90 minutes; days 1,15,29 200 mg/m^2 infusion IV for 2 hours; days 1,2,15,16,29,30 400 mg/m^2 bolus IV; days 1,2,15,16,29,30 600 mg/m^2 infusion IV for 22 hours; days 1,2,15,16,29,30		
		Starting dose levels & modified dose (mg/ml^2)		
		Starting dose	Dose level-1	Dose level-2
	IRINOTECAN GP PHARM LV 5-FU in bolus 5-FU infusion	180 200 400 600	150 200 320 480	120 200 240 360

* Dose reductions beyond dose level – 2 in decrements of ≈20% should be performed to patients who continue experiencing toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue experiencing a clinical benefit.
** Infusion follows bolus administration.

Dose for patients with bilirrubin >2 mg/dl can not be recommended since such patients were not included in the clinical trials. It is recommended that patients receive previous medication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

Dose modifications
Patients should be carefully monitored for toxicity. Doses of IRINOTECAN GP PHARM and 5-FU should be modified as necessary to accommodate individual patient tolerance. Based on the recommended dose-levels described in Table 2, subsequent doses should be adjusted as suggested in Table 3.
All dose modifications should be based on the worst preceding toxicity.
A new cycle of therapy should not begin until the toxicity has been recovered to grade 1 or less according to NCI (National Cancer Institute) classification. Treatment may be delayed 1 or 2 weeks to allow the recovery from treatment-related toxicity. If the patient has not recovered after the 2 weeks of delay, consideration should be given to discontinuing therapy with IRINOTECAN GP PHARM. Provided intolerable toxicity does not develop, treatment with additional cycles of IRINOTECAN GP PHARM /5-FU/LV may be continued indefinitely as long as patients continue experiencing a clinical benefit.
Table 3. Recommended dose modifications for 5-FU/LV combination regimen.
Patients should return to previous-treatment bowel function without requiring antidiarrhea medication for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte

count has been recovered to ≥ 1500/mm³, the platelet count has been recovered to ≥ 100000/mm³ and the treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow the recovery from treatment-related toxicities. If the patient has not recovered after 2-week delay, discontinuing therapy with IRINOTECAN GP PHARM should be considered.

Toxity grade NCI-CTC*	**During a cycle of therapy**	**At the start of new cycles (after adequate recovery)****
WITH NO TOXICITY	Keep dose level	Keep dose level
NEUTROPENIA 1 (1500 to 1999/mm³)	Keep dose level	Keep dose level
2 (1000 to 1499/mm³)	↓1 dose level	Keep dose level
3 (500 to 999/mm³)	Omit dose until resolved to≤2, then ↓ 1 dose level	1 dose level
4 (< to 500/mm³)	Omit dose until resolved to≤2, then ↓ 2 dose levels	2 dose levels
FEBRILE NEUTROPENIA	Omit dose until resolved, then ↓2 dose levels	
OTHER HEMATOLOGIC TOXICITIES	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles are also based on NCI toxicity criteria and they are the same as recommended for neutropenia	
DIARRHEA 1 (2-3 stools/day>prett***)	Delay close until resolved to baseline, then give the same dose	Keep dose level
2 (4-6 stools/day>prett)	Omit dose until resolved to baseline, then ↓ 1 dose level	Keep dose level
3 (500 to 999/mm³>prett)	Omit dose until resolved to baseline, then ↓ 1 dose level	1 dose level
4 (<500/mm³>prett)	Omit dose until resolved to baseline, then ↓ 2 dose levels	2 dose levels
OTHER NON-HEMATOLOGIC TOXICITIES ** 1	Keep dose level	Keep dose level
2	Omit dose until resolved to grade ≤ 1, then ↓1 dose level	Keep dose level
3	Omit dose until resolved to grade ≤ 2, then ↓1 dose level	↓ 1 dose level
4	Omit dose until resolved to grade ≤ 2, then ↓2 dose level	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU not IRINOTECAN GP PHARM	*For mucositis/stomatitis decrease only 5-FU not IRINOTECAN GP PHARM*

* NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0)
** Related to the starting dose used in the previous cycle.
*** Previous to the treatment
**** It does not include alopecia, anorexia and asthenia
- Single agent dosage:
IRINOTECAN GP PHARM should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules. Single-agent dosage regimen is shown in the Table 4.
The reduction in the starting dose by one dose level of IRINOTECAN GP PHARM may be considered for patients who show any of the following conditions: age ≥ 65 years old, previous pelvic/abdominal radiotherapy, performance status of 2, increased bilirrubin levels. Dosing for patients with bilirrubin > 2 mg/dl can not be recommended since there is no sufficient information to recommend a dose in this kind of patients.
It is recommended that patients receive previous medication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

Table 4. Single-Agent regimen and Dose modifications

Weekly Regimen*	125 mg/m^2 infusion IV for 90 minutes; days 1,8,15,22 after 2 week-rest		
	Starting dose & modified dose levels * (mg/m^2)**		
	Starting dose	Dose level-1	Dose level-2
	125	100	75
Once every 3-week regimen**	350 mg/m^2 infusion IV for 90 minutes; once every 3-week		
	Starting dose & modified dose levels*(mg/m^2)**		
	Starting dose	Dose level-1	Dose leve-2
	350	300	250

* Subsequent doses may be adjusted, increasing up to 150 mg/m^2 or reducing up to 50 mg/m^2 in 25 to 50 mg/m^2 reductions, depending on individual patient tolerance.
** Subsequent doses may be adjusted up to 200 mg/m^2 level in 50 mg/m^2 decrements depending on individual patient tolerance.
*** Provided intolerable toxicity does not develop, treatment with IRINOTECAN GP PHARM with additional cycles may be continued indefinitely as long as patients continue experiencing clinical benefit.
Dose modification

Patients should be monitored for toxicity and doses of IRINOTECAN GP PHARM should be modified as necessary to accommodate the individual patient tolerance. Based on the recommended dose-levels in Table 4, subsequent doses should be adjusted as suggested in Table 5.

Table 5. Recommended dose modifications for single-agent schedules
A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, the platelet count has recovered to ≥100000/mm^3 and the treatment-related diarrhea is fully resolved. Treatment should be delayed 1 t 2 weeks to allow the recovery from treatment-relates toxicities. If the patient has not recovered after 2-week delay, discontinuing the treatment with IRINOTECAN GP PHARM should be considered.

Toxicity grade NCI-CTC**	**During a cycle of therapy**	**At the start of new therapy cycles (after adequate recovery)***	
	Weekly	**Weekly**	**Once every 3 weeks**
NO TOXICITY	Keep dose level	↑25 mg/mup to a max. dose of 150 mg/m²	Keep dose level
NEUTROPENIA 1 (1500 to 1999/mm³)	Keep dose level	Keep dose level	Keep dose level
2 (1000 to 1499/mm³)	↓25 mg/m^2	Keep dose level	Keep dose level
3 (500 to 999/mm³)	Omit dose until resolved to grade ≤ 2, then ↓25mg/m^2	↓25 mg/m²	↓50 mg/m^2
4 (< to 500/mm³)	Omit dose until resolved to grade ≤ 2, then ↓50mg/m^2	↓50 mg/m²	↓50 mg/m^2
FEBRILE NEUTROPENIA	Omit dose until resolved to grade ≤ 2, then ↓50mg/m^2	↓50 mg/m²	↓50 mg/m^2
OTHER HEMATOLOGIC TOXICITIES	Dose modifications due to leukopenia, thrombocytopenia and anemia during a cycle of therapy and at the start of subsequent cycles are also based on NCI toxicity criteria and they are the same as recommended for neutropenia		
DIARRHEA 1 (2-3 stools/day > prett)***	Keep dose level	Keep dose level	Keep dose level
2 (4-6 stools/day > prett)	↓25 mg/m^2	Keep dose level	Keep dose level
3 (7-9 stools/day > prett)	Omit dose until resolved to grade ≤ 2, then ↓25mg/m^2	↓25 mg/m²	↓50 mg/m^2
4 (>10 stools/day > prett)	Omit dose until resolved to grade ≤ 2, then ↓50mg/m^2	↓50 mg/m²	↓50 mg/m^2
OTHER NON-HEMATOLOGIC TOXICITIES ****			
1	Keep dose level	Keep dose level	Keep dose level
2	↓25 mg/m^2	↓25 mg/m²	↓50 mg/m^2
3	Omit dose until resolved to grade ≤ 2, then ↓25mg/m^2	↓25 mg/m²	↓50 mg/m^2
4	Omit dose until resolved to grade ≤ 2, then ↓50mg/m^2	↓50 mg/m²	↓50 mg/m^2

* Related to the starting dose used in the previous course. All dose modifications should be based on the worst preceding toxicity.
** NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0)
*** Previous to the treatment
**** It does not include alopecia, anorexia, and asthenia

Preparation of the solution for infusion
As with other potentially toxic antineoplastic agents, care should be exercised in handling and preparation of the solutions for infusion with IRINOTECAN GP PHARM. The use of gloves is recommended. If the solution of IRINOTECAN GP PHARM contacts the skin, wash the skin with lot of water and soap; if it contacts the mucous membranes, flush with lot of water.
Inspect vial contents for particulate matter and repeat the inspection drug product is extracted from vial into syringe.
IRINOTECAN GP PHARM must be diluted previous to infusion in 5% dextrose for injection, USP (preferred) or 0.9% sodium chloride for injection USP to a final concentration range of approximately 0.12 to 2.8 mg/ml. In most clinical trials, irinotecan was diluted in 250 to 500 ml of 5% dextrose injection, USP.
The solution is physically and chemically stable for 24 hours at room temperature (approximately 25ºC) and in a room with fluorescent lighting. Solutions diluted in 5% dextrose injection USP, and stored at refrigerated temperature (2ºC to 8ºC), and protected from light are physically and chemically stable for 48 hours.
Refrigeration of mixtures using 0.9% sodium chloride injection, USP, is not recommended due to the low and sporadic incidence of visible particles.

Freezing IRINOTECAN GP PHARM and its mixtures should be avoided since it may result in precipitation of the drug.
Because of possible microbial contamination during dilution, it is advisable to use the mixture within 6 hours if kept at room temperature (15ºC to 30ºC) and within 24 hours if refrigerated (2ºC to 8ºC).

PRECAUTIONS

General

- Care in the injection site: IRINOTECAN GP PHARM is administered by intravenous infusion; extravasation should be avoided. The infusion site should be monitored for possible signs of inflammation. Should extravasation occur, rinsing the site with sterile water and applications of ice are recommended.
- Previous medicine with antiemetics: IRINOTECAN GP PHARM is emetogenic. It is recommended that patients receive previous antiemetic medicine. In clinical studies, most of the patients received 10 mg of dexamethasone joint with another type pf antiemetic agent, such as 5-HT3 (e.g. Ondansetron or Granisetron). Antiemetic agents should be given on the day of the treatment, starting at least 30minutes before IRINOTECAN GP PHARM administration.

Physicians should consider the indication of an antiemetic regimen for subsequent use as needed by the patient.

- Treatment of cholinergic symptoms: Prophylactic or therapeutic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (unless contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea occurring during or within 8 hours after the administration of IRINOTECAN GP PHARM. These symptoms are expected to occur more frequently with higher doses of irinotecan.
- Myelosuppression: IRINOTECAN GP PHARM commonly causes neutropenia, leukopenia and anemia that may be severe so it must not be administered to patients with severe bone marrow failure.
- Bowel obstruction: Patients with bowel obstruction must not be treated with IRINOTECAN GP PHARM until resolution of it.
- Lactose intolerance: IRINOTECAN GP PHARM is not recommended to patients with hereditary fructose intolerance since it contains sorbitol.

Laboratory tests

Differential leukocites count, hemoglobin determination and platelet count are recommended before starting the treatment with each dose of IRINOTECAN GP PHARM. These analyses should be repeated every time the doctor thinks it is necessary.

Interactions with laboratory tests

Interactions between IRINOTECAN GP PHARM and laboratory tests are unknown.

Interactions with other drugs

- Leucovorin and 5-fluorouracil: In 1 phase clinical studies with 26 patients with solid tumours who were administered irinotecan, following 5-FU and LV, plasma level of irinotecan was not substantially altered when it was co-administered. Though C_{max} and $AUC_{0\text{-}24}$ of SN-38, the active metabolite was reduced (14% and 8%, respectively) when irinotecan was followed by 5-FU and LV compared when administered alone; this combination was used in many trials and it is recommended. Formal *in vivo* or *in vitro* drugs interaction studies to evaluate the influence of irinotecan in the plasma level of 5-FU and LV have not been performed.
- Anticonvulsant drugs: Concomitant administration of CYP3A-inducing anticonvulsant drugs (e.g., phenytoin, phenobarbital or carbamazepine,) reduces substantially the plasma level of irinotecan and its active metabolite SN-38 in adults and children. An appropriate starting dose for patients needing anticonvulsant treatment has not been defined. In patients requiring anticonvulsant treatment, the possibility of replacing these anticonvulsant drugs by non-inducer enzyme anticonvulsants at least 2 weeks before starting the therapy with irinotecan should be analyzed.
- St. John's Wort (*Hypericum perforatum*): The plasma level of the active metabolite SN-38 gets reduced in patients who receive concomitantly St. John's Wort (CYP3A-4 inducer). St. John's Wort should be discontinued, at least 2 weeks before starting the first cycle of irinotecan and it must not be administered during the treatment with irinotecan.
- Ketoconazole: Concomitant administration of ketoconazole (CYP3A4 inhibitor), increases plasma level of irinotecan and its active metabolite SN-38. Ketoconazole should be discontinued for at least 1 week before starting the therapy with irinotecan and it must not be administered during the treatment with irinotecan.
- Neuromuscular blockers: It is not possible to rule out the interaction between irinotecan and the neuromuscular blockers since irinotecan has an anticholinesterase activity. Drugs with anticholinesterase activity may extend the neuromuscular blockers' effects of the suxamethonium and antagonize the neuromuscular blockers' effects of the non-depolarizing drugs.
- Atazanavir sulfate: the coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor, increases the plasma levels of SN-38, the active metabolite of irinotecan.
- Dexamethasone: Dexamethasone seems not to alter irinotecan pharmacokinetics.

The adverse effects of irinotecan, such as myelosuppression and diarrhea, are expected to be exacerbated by other antineoplastic agents which have similar adverse effects.

Patients who have previously received pelvic or abdominal irradiation are at increased risk of severe myelosuppression following the administration of irinotecan. The concurrent administration of irinotecan with irradiation has not been studied adequately and it is no recommended.

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

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

The incidence of akathisia in clinical trials was greater (8.5% in 4/47 patients) when prochlorperazine was administered on the same day as irinotecan than when these drugs were given on separate days (1.3%, 1/80 patients). However, the 8.5% of incidence of akathisia is within the range reported when prochlorperazine is administered as a previous medication for other chemotherapies.

It is expected that the laxative use during therapy with irinotecan, shall worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by irinotecan, the physician may wish to withhold diuretics during treatment with irinotecan and, certainly, during periods of vomiting and active diarrhea.

Patients on clinical trials who received irinotecan 5-FU/LV or 5-FU/LV with general state 2, had a higher rate of hospitalization, febrile neutropenia, thromboembolism, discontinuation of treatment in the first-cycle therapy and early deaths than patients with general state 0 or 1.

Carcinogenesis, mutagenesis & impairment on fertility

Long-term carcinogenicity studies with irinotecan were not conducted. However, rats were administered intravenous doses of 2 mg/kg and 25 mg/kg irinotecan once a week for 13 weeks with a subsequent observation for 91 weeks (the 25 mg/kg dose produced an irinotecan C_{max} and $AUC_{0\text{-}24}$ that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly). There was a significant linear trend to the dose for the combined incidence of endometrial stromal polyps and endometrial stromal sarcomas.

Neither irinotecan nor SN-38 was mutagenic in the Ames test. Irinotecan was clastogenic both *in*

vitro(choromosome aberrations in Chinese-hamster ovary cells) and *in vivo* (micronucleous test in mice). No significant adverse effects on fertility or general reproductive performance were observed after intravenous administration of irinotecan to rats and rabbits. However, atrophy of male reproductive organs was observed after multiple daily doses of irinotecan, both in rodents and dogs.

Pregnancy
Category D.
IRINOTECN GP PHARM may cause fetal harm when administered to a pregnant woman. Radioactivity crossed the placenta of rats following irinotecan-C14 intravenously administration.
Administration of irinotecan intravenously to rats and rabbits during the period of organogenesis was embryotoxic characterized by increased post-implementation loss and decreased number of live fetuses.
Irinotecan was teratogenic in rats and rabbits. Teratogenic effects included a variety of external, visceral and skeletal abnormalities. Irinotecan administered to rat dams after organogenesis and during weaning caused decreased learning ability and decreased body weights of the female offspring.
There are no adequate and well controlled studies with irinotecan in pregnant women. If IRINOTECAN GP PHARM is used during pregnancy, or if the patient becomes pregnant while receiving IRINOTECAN GP PHARM, the patient should be apprised of the potential hazard to the fetus. Women of potential childbearing should be advised to avoid becoming pregnant while receiving treatment with IRINOTECAN GP PHARM.
Excretion of maternal milk and possible breast-fed baby effects.
After intravenous administration of irinotecan radio-marked to rats, radioactivity has been observed in their milk within 5 minutes following administration and after 4 hours a relative concentration up to 65 times higher than the plasmatic one was obtained. Since many drugs are excreted in the human milk and because of the potential serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during irinotecan treatment.

Pediatric use

Irinotecan effectiveness in pediatric patients has not been established. The results of two open studies were evaluated. One of the studies in phase 2 was performed in 170 children with refractary solid tumors who 2 received infusion of 50 mg/m² irinotecan for 5 consecutive days every 3 weeks. Fifty four patients out of them (31.8%) developed neutropenia of grade 3-4. Neutropenia got complicated with fever in 15 (8.8%) patients.
Diarrhea in grade 3-4 was observed in 35 (20.6%) patients. This profile of adverse effects was comparable to the one informed in the adult population. Twenty one children with rhabdomyosarcoma not treated previously 3 participated in the second study in phase 2; they received 20 mg/m^{2}irinotecan as infusion for 5 consecutive days the weeks 0, 1, 3 and 4, after this, they received a treatment of polychemiotherapy. Irinotecan as multiple agent was suspended due to the high rate of the disease progression (28.6%) and early deaths (14%). The profile of adverse effects of this study was different to the one observed in adults, the most significant events of grade 3 or 4 were: dehydration in 6 patients (28.6%) associated with acute hypokaliemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%), it was also reported infection in grade 3-4 in patients (23.8%).
Geriatric use
Patients greater than 65 years old should be monitored closely because of the greatest risk of this population to develop late diarrhea. The initial dose of IRINOTECAN GP PHARM in patients older than 70 years old for the regimen of 2 one dose every 3 weeks should be 300 mg/m^2.
Use in hepatic dysfunction
The use of IRINOTECAN GP PHARM in patients with significant hepatic dysfunction has not been evaluated. In clinical trials for either dosing schedule, irinotecan was not administered to patients with serum bilirrubin levels > 2.0 mg/dl, or with transaminase levels > 3 times the normal upper limit (with no liver metastasis), or > 5 times the upper normal limit (with hepatic metastasis). In clinical studies of the weekly dosage schedules, patients with moderate elevated baseline levels of the total bilirrubin (1.0 to 2.0 mg/dl) show a significantly greater likehood of experiencing grade 3 or 4 neutropenia in the first cycle than those with bilirrubin levels less than 1.0 mg/dl.
Patients with abnormal glucuronidation of bilirrubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with IRINOTECAN GP PHARM.
Use in renal failure
Irinotecan should be used with caution in this kind of patients. It is not recommended the use of irinotecan in patients with dialysis.
Effects on ability to drive and use machines
The effect of irinotecan on the ability to drive and use machines has not been evaluated. Nevertheless, patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of IRINOTECAN GP PHARM, and they should not drive or operate machines if these symptoms occur.
CONTRAINDICATIONS
IRINOTECAN GP PHARM is contraindicated in patients with a known hypersensitivity to the drug or any excipient of the formula.
WARNINGS
General
IRINOTECAN GP PHARM should not be used in combination with the “Mayo Clinic” regimen of 5-FU/LV (administration for 4-5 consecutive days every 4 weeks) because of reports of increased toxicity, and also toxic death. IRINOTECAN GP PHARM should be used as recommended (see POSOLOGY AND ADMINISTRATION).
Diarrhea
IRINOTECAN GP PHARM may induce both early and late forms of diarrhea that appear to be mediated by different mechanisms.
Early diarrhea (occurring during or shortly after administration of IRINOTECAN GP PHARM), is cholinergic in nature. It is usually transient and infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation,miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis that can cause abdominal cramping.
Early diarrhea and other cholinergic symptoms may be prevented or reduced by the administration of atropine.
Late diarrhea (generally occurring after 24 hours after administration of IRINOTECAN GP PHARM) can be life threatening since it may be prolonged and it may lead to dehydration, electrolyte imbalance or sepsis. Late diarrhea should be treated promptly with loperamide.
Patients with diarrhea should be carefully monitored, they should be given fluids and electrolyte replacement if they become dehydrated; they should receive antibiotic support if they develop ileus, fever or severe neutropenia. After the first treatment, the subsequent weekly administration of IRINOTECAN GP PHARM should be delayed in patients until returning of pre-treatment bowel function for at least 24 hours without needing antidiarrhea medication.
If grade 2, 3 or 4 late diarrhea occurs, subsequent doses of IRINOTECAN GP PHARM should be decreased within the current cycle of treatment.
Neutropenia
Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan.
Neutropenic complications should be treated promptly with antibiotic therapy. The cycle of therapy with IRINOTECAN GP PHARM should be suspended temporarily if febrile neutropenia occurs or if the absolute

neutrophil count is < 1000/mm^2. Once the patient has an absolute neutrophil count ≥ 1000/mm^2, IRINOTECAN GP PHARM doses should be reduced depending on the level of neutropenia observed.
Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

Patients with reduced UGT1A1 enzyme activity

Individuals who are homozygote for the UGT1A1*28 allele are at high risk for neutropenia following initiation of IRINOTECAN GP PHARM treatment. A reduction of the initial dose of IRINOTECAN GP PHARM in patients homozygote for the UGT1A1*28 allele should be considered. Patients heterozygote (intermediate activity of UGT1A1) are also at risk of developing neutropenia, but less than those homozygote, however, the clinical studies have been so variable and those patients have demonstrated the tolerance to the normal initial doses.

Hypersensitivity

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

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus and infection have been observed. Patients experiencing ileus should receive prompt antibiotic and support treatment.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan regimen, the cause has not been determined.

Renal impairment

Rare cases of renal impairment and acute renal failure have been observed in patients who had experienced severe dehydration associated with diarrhea and/or vomiting.

ADVERSE REACTIONS

First-line combination therapy

A total of 955 patients with metastatic colorectal cancer participated in 2 clinical trials; they were administered: irinotecan in combination with 5-FU/LV (370 patients), 5-FU/LV alone (362 patients) and irinotecan alone (223 patients).
In the Study 1: 49 (7.3%) patients died within 30 days after treatment: 21 (9.3%) had received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone and 13 (5.8%) received irinotecan alone.
Deaths potentially related to treatment occurred in 2 (0.9%) patients who had received irinotecan in combination with 5-FU/LV, 3 (1.4%) patients received 5-FU/LV alone and 2 (0.9%) patients who received irinotecan alone.
Deaths within 60 days after treatment were observed: 15 (6.7%) had received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone and 15 (6.7%) patients who received irinotecan alone.
Discontinuation of the treatment due to adverse effects was reported in 17 (7.6%) patients who had received irinotecan in combination with 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.
In the Study 2: 10 patients (3.5%) patients died within 30 days post-treatment: 6 (4.1%) had received irinotecan in combination with 5-FU/LV and 4 (2.8%) patients received 5-FU/LV alone. There was a potentially treatmentrelated death which occurred in a patient (0.7%) who had received irinotecan in combination with 5-FU/LV.
Deaths within 60 days post-treatment have been observed: 3 (2.1%) patients who received irinotecan in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV. Discontinuation of the treatment due to adverse effects was reported in 9 (6.2%) patients who had received irinotecan in combination with 5-FU/LV and 1(0.7%) patient who received 5-FU/LV alone.
The most clinically significant adverse effects in patients receiving irinotecan were: diarrhea, nausea, vomiting, neutropenia and alopecia. The most clinically significant adverse effects in patients receiving 5-FU/LV were: diarrhea, neutropenia, febrile neutropenia and mucositis.
Tables 6 and 7 describe the clinically relevant adverse effects reported in studies 1 and 2.

Table 6: Study 1: Percent (%) of patients experiencing relevant adverse effects in combination therapies*

Study 1						
ADVERSE EFFECTS	**Irinotecan + Bolus 5-FU/LV weekly for 4 weeks, 2 resting weeks N=225**		**Bolus 5-FU/LV daily for 5 days every 4 weeks N=219**		**Irinotecan weekly for 4 weeks, 2 resting weeks N=223**	
	Grade 1-4	**Grade 3 & 4**	**Grade 1-4**	**Grade 3 & 4**	**Grade 1-4**	**Grade 3 & 4**
Total adverse effects	100	53.3	100	45.7	99.6	45.7
Gastrointestinal						
Late diarrhea	84.9	22.7	69.4	13.2	83.0	31.0
Grade 3 diarrhea	-	15.1	-	5.9	-	18.4
Grade 4 diarrhea	-	7.6	-	7.3	-	12.6
early diarrhea	45.8	4.9	31.5	1.4	43.0	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
Hematologic						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
Grade 3 neutropenia	-	29.8	-	23.7	-	19.3
Grade 4 neutropenia	-	24.0	-	42.5	-	12.1
Leucopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Febrile neutropenia	-	7.1	-	14.6	-	5.8
Thrombocytopenia	96.9	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	-	1.8	-	0	-	2.2
Body as a whole						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4

Metabolic						
↑Bilirrubin	87.6	7.1	92.2	8.2	83.9	7.2
Dermatologic						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia**	43.1	-	26.5	-	46.1	-
Respiratory						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
Neurologic						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
Cardiovascular						
Vasodilatation	9.3	0.9	5.0	0	9.0	0
Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolitic effects***	9.3	-	11.4	-	5.4	-

* Severity of the adverse effect based on NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0).
** Complete hair loss = Grade 2 NCI.
*** It includes: angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, thromboflebitis, extremity embolism, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolism, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Table 7. Study 2: Percent (%) of patients experiencing relevant adverse effects in combination therapies*

ADVERSE EFFECTS	**Irinotecan + 5-FU/LV infusion. Days 1 & 2 every 2 weeks N=145**		**5-FU/LV infusion. Days 1 & 2 every 2 weeks N=143**	
	Grade 1-4	**Grade 3&4**	**Grade 1-4**	**Grade 3&4**
Total adverse effects	100	72.4	100	39.2
Gastrointestinal				
Late diarrhea	72.4	14.4	44.8	6.3
Grade 3 diarrhea	-	10.3	-	4.2
Grade 4 diarrhea	-	4.1	-	2.1
Cholinergic syndrome**	28.3	1.4	0.7	0
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	28.7	2.8
Hematologic				
Neutropenia	82.5	46.2	47.9	13.4
Grade 3 neutropenia	-	36.4	-	12.7
Grade 4 neutropenia	-	9.8	-	0.7
Leucopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.9	2.1
Febrile neutropenia	-	3.4	-	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	-	2.1	-	0
Body as a whole				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
Metabolic				
↑Bilirrubin	19.1	3.5	33.5	10.6
Dermatologic				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia***	56.6	-	16.8	-
Respiratory				
Dyspnea	9.7	1.4	4.9	0
Cardiovascular				
Hypotension	3.4	1.4	0.7	0
Thromboembolitic effects****	11.7	-	5.6	-

* Severity of the adverse effect based on NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0).
** It includes: rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after infusion).

*** Complete hair loss = grade 2 NCI
**** It includes: angina pectoris, arterial thrombosis, cerebral infarct, cerebro-vascular accident, thrombophlebitis, extremity embolism, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolism, sudden death, thrombophlebitis, thrombosis, vascular disorder.
Second-line single-agent therapy
1- Weekly dosage schedule
In three clinical studies, 304 patients with metastactic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with irinotecan. Seventeen of the patients died within 30 days of the administration of irinotecan; in 5 cases (1.6%) the deaths were potentially drug-related. These five patients developed a group of medical events that included known effects of irinotecan. One of the patients died of neutropenic sepsis without fever.
Febrile neutropenia occurred in nine (3.0%) of other patients; these patients recovered with supportive care.
One hundred nineteen (39.1%) patients were hospitalized 156 times due to adverse effects, 81 (26.6%) patients were hospitalized because of events related to the administration of irinotecan. The main reasons for drugrelated hospitalizations were: diarrhea with or without nausea and/or vomiting (18.4%), neutropenia/leucopenia with or without diarrhea and/or fever (8.2%), and nausea and/or vomiting (4.9%).
Adjustments on the dose of irinotecan were made during the cycle of treatment and subsequent cycles based on individual patient tolerance. The first dose of at least one cycle of irinotecan was reduced for 67% of patients who 2 began the studies at the 125 mg/m starting dose. Dose reductions within the cycle were required for the 32% of 2 the cycles initiated with 125 mg/m dose-levels. The most common reasons for dose reduction were: late diarrhea, neutropenia and leukopenia. Thirteen (4.3%) patients discontinued treatment with irinotecan because of adverse effects.
The adverse effects in the following Table 8 are based on the experience of 304 patients enrolled in the three clinical studies.

Table 8. Adverse effects occurring in more than 10% of 304 patients with metastatic carcinoma of the colon or rectum, previously treated*

ADVERSE EFFECTS	**% of patients N=304**	
	Grade 1-4	**Grade 3&4**
Gastrointestinal		
Late diarrhea **	**88**	**31**
7-9 stools/day (grade 3)	**-**	**(16)**
≥ 10 stools/day (grade 4)	**-**	**(14)**
Nausea	**86**	**17**
Vomiting	**67**	**12**
Anorexia	**55**	**6**
Early diarrhea***	**51**	**8**
Constipation	**30**	**2**
Flatulence	**12**	**0**
Stomatitis	**12**	**1**
Dyspepsia	**10**	**0**
Hematologic		
Leukopenia	**63**	**28**
Anemia	**60**	**7**
Neutropenia	**54**	**26**
3 Grade 3 neutropenia (<1000/mm³)	**-**	**(15)**
3 Grade 4 neutropenia (<500/mm³)	**-**	**(12)**
Body as a whole		
Asthenia	**76**	**12**
Abdominal cramp/Pain	**57**	**16**
Fever	**45**	**1**
Pain	**24**	**2**
Headache	**17**	**1**
Backache	**14**	**2**
Chills	**14**	**0**
Minor infection****	**14**	**0**
Edema	**10**	**1**
Abdominal enlargement	**10**	**0**
Metabolic		
↓ Body weight	**30**	**1**
Dehydration	**15**	**4**
↑ Alcaline phosphatase	**13**	**4**
↑ SGTO	**10**	**1**
Dermatologic		
Alopecia	**60**	**NA*****
Sweating	**16**	**0**
Rash	**13**	**1**
Respiratory		
Dyspnea	**22**	**4**
Cough	**17**	**0**
Rinitis	**16**	**0**
Neurological		
Insomnia	**19**	**0**
Dizziness	**15**	**0**
Cardiovascular		
Vasodilatation	**11**	**0**

* Severity of adverse effect based on NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0).
** It occurs 24 hours after the administration of irinotecan.
*** They occur during or within the first hours of the administration of irinotecan.
**** Primarily upper respiratory infections.
***** Not applicable, complete hair loss = NCI grade 2.

2- Once-every-3-week dosage schedule

A total of 535 patients with metastatic colon-rectal cancer whose disease has recurred or progressed following 5-FU based-therapy participated in two phase-3 studies: 316 patients received irinotecan, 129 patients received 5-FU, and 90 patients received better supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316) the deaths were potentially related to the drug and they were attributed to neutropenic infection, grade-4 diarrhea and asthenia. One (0.8%, 1/129) of the patient treated with 5-FU died within 30 days of treatment and this death was attributed to grade-4 diarrhea.

Hospitalizations due to serious adverse effects (related or not to the study) occurred at least once in 60% (188/316) of the patients who received irinotecan, in 63% (57/90) of the patients who received better supportive care and in the 39% (50/129) of the patients who received 5-FU. Eight percent of the patients treated with irinotecan and 7% of the patients treated with 5-FU discontinue the treatment due to adverse effects.

The most significant adverse effects in the 316 patients treated with irinotecan were: diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%) and neutropenia (30%).

Table 9 describes the grade-3-and-4 adverse effects reported by patients enrolled in the clinical studies.

Table 9. Percent of patients experiencing grade 3 & 4 adverse effects in comparative studies with irinotecan dose regimen of once every 3 weeks.*

ADVERSE EFFECTS	Study 1		Study 2	
	Irinotecan N=189	Better Support Therapy N=90	Irinotecan N=127	5-FU N=129
Total grade 3/ 4 adverse effects	79	67	69	54
Gastrointestinal				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
Hematologic				
Leucopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
Infection				
Without grade 3/4 neutropenia	8	3	1	4
With grade 3/4 neutropenia	1	0	2	0
IFever				
Without grade 3/4 neutropenia	2	1	2	0
With grade 3/4 neutropenia	2	0	4	2
Body as a whole				
Pain	19	22	17	13
Asthenia	15	19	13	12
Metabolic				
Hepatic**	9	7	9	6
Dermatologic				
Hand & foot syndrome (rash)	0	0	0	5
Cutaneous signs	2	0	1	3
Respiratory				
(Dyspnea and cough)	10	8	5	7
Neurologic				
Somnolence	12	13	9	4
Cardiovascular				
(Dysrhyhtmia, ischemia, mechanical cardiac insufficiency)	9	3	4	2
Others				
(Accidental injury, hepatomegalia, syncope, vertigo and weight loss)	32	28	12	14

* Severity of adverse effect based on NCI: National Cancer Institute, CTC: Common Toxicity Criteria (version 1.0).
** Hepatic events such as ascites and jaundice.
Summary of adverse effects Gastrointestinal: The common adverse effects following treatment were diarrhea, nausea and vomiting; they could have been severe. Nausea and vomiting were early observed during or short after infusion of irinotecan.
In clinical studies with 3-week-dosage schedule, the mean time of the onset of late diarrhea was 5 days after irinotecan infusion intravenously; in clinical studies with week-dosage schedule, the mean time of the offset of late diarrhea was 11 days.
The mean duration of any grade of late diarrhea was 3 days in patients who started the treatment with a week dosage of 125 mg/m². Among these patients, the ones who experienced late diarrhea of grade 3 and 4 had a mean duration of the complete episode of 7 days.
The frequency of grade-3-and-4 late diarrhea was sometimes higher in patients who started the weekly treatment with a dose of 125 mg/m² than in patients who were administered an initial dose of 100 g/m² (34% vs. 24%).
The frequency of grade-3-and-4 late diarrhea was significantly higher in patients > 65 years old than in patients < 65 years old (40% vs.23%).
In a weekly dosage schedule study, the frequency of grade-3-and-4 late diarrhea was significantly higher in male patients than in female (43% vs. 23%), however, there was no difference regarding gender in the frequency of grade-3 and-4 late diarrhea in two other studies with weekly schedule.
Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with the administration of irinotecan.
Hematology: Irinotecan commonly causes neutropenia, leukopenia (including lymphocytopenia) and anemia.
Serious thrombocytopenia is uncommon. In the clinical studies, the frequency of grade-3-and-4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% vs 24%).
In the same study, patients with baseline levels of total serum bilirrubin of 1.0 mg/dl or more had a significantly greater likelihood of experiencing grade-3-and-4 grade neutropenia in the first cycle of the therapy than the patients with bilirrubin levels under 1.0 mg/dl (50% vs. 18%).
There were no significant differences in the frequency of grade-3-or-4 neutropenia because of age or gender. In a clinical study with weekly dosage schedule, febrile neutropenia occurred in 3% of the patients, 6% of the patients received colony stimulating factors for the treatment of neutropenia. NCI grade-3-and-4 anemia was noted in 7% of the patients. Blood transfusions were performed to 10% of the patients.
Body as a whole: Asthenia, fever and abdominal pain were the most common events of this type.
Hepatic: In the clinical studies with weekly dosage schedule, NCI grade 3 or 4 hepatic enzymes abnormalities were observed in less than 10% of the patients. These events usually occur in patients with known hepatic metastases.
Dermatologic: Alopecia has been reported during the treatment with irinotecan. Rash has also been reported but the treatment was not discontinued for that reason.
Respiratory: Severe pulmonary events were infrequent. NCI grade 3 and 4 dyspnea was observed in 4% of the patients in studies with weekly dosage schedule. More than half of the patients with dyspnea had lung metastases. The extent of the pulmonary involment or another pre-existing pulmonary disease and its correlation with dyspnea is unknown.
Interstitial pulmonary disease presented as pulmonary infiltrates, is uncommon during the treatment with irinotecan. The interstitial pulmonary disease may be fatal. Risk factors possibly associated with the development of interstitial pulmonary disease include pre-existing lung disease, use of pulmonary toxic drugs, radiation therapy and colony stimulating factors. Patients with risk factors should be monitored carefully to detect respiratory symptoms before and after the therapy with irinotecan.
Neurologic: Insomnia and dizziness can occur, but they seem not to be directly related to irinotecan administration. Dizziness may be a symptomatic evidence of orthostatic hypotension in patients with dehydration.
Cardiovascular: Vasodilation has occurred during the administration of irinotecan. Bradycardia has also been observed, but it has not needed intervention. These effects have been attributed to cholinergic syndrome sometimes observed during or shortly after infusion of irinotecan. Thromboembolic events have been observed in patients receiving irinotecan, but the specific cause of these events has not been determined.
Cholinergic Symptoms: Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, rubefaction and intestinal hyperperistalsis that can cause intestinal colics and early diarrhea. These symptoms may occur during or short after irinotecan infusion, and they seem to be related to the anticholinesterase activity of the mother compound of irinotecan and they are expected to occur more frequently with higher irinotecan doses.
Post-marketing experience: The following events have been reported in the clinical practice: infrequent cases of ulcerative or ischemic colitis, some of them got complicated with ulceration, bleeding, ileus, obstruction and infection, including typhlitis. Rarely, intestinal perforation, symptomatic pancreatitis or pancreatic-enzyme asymptomatic increase.
Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions. Hyponatremia related with diarrhea and vomiting. Moderate temporary increase of the serum levels of transaminasas (AST and ALT) without hepatic progressive metastasis, temporary increase of amylase, and occasionally of lipase. Rare cases of renal failure with acute renal impairment, hypotension or circulatory failure have been observed in patients who had experienced episodes of dehydration associated with diarrhea and/or vomiting or sepsis. Early muscular contractions, cramps and paresthesia.
OVERDOSE
In USA phase-1 studies single doses of up to 345 mg/m² of irinotecan were administered to patients with different kinds of cancers. Single doses of up to 750 mg/m² of irinotecan have been given in other studies outside USA. The adverse effects in these patients were similar to those reported with the recommended doses and regimens.
There have been reports of overdose at doses more than twice the recommended therapeutic dose, which may be fatal. The most significant adverse effects which have been reported are severe neutropenia and severe diarrhea. There is not known antidote for irinotecan overdose. Maximum supportive care should be taken into account to avoid dehydration due to diarrhea, and treat any infectious complication.
INFORMATION FOR THE PATIENT
Both, patients and those people looking after them should be informed about the toxic effects expected during the treatment with IRINOTECAN GP PHARM, particularly of its gastrointestinal complication, such as nausea, vomiting, abdominal cramping, diarrhea and infection.
Each patient should be instructed to have loperamide and to begin the treatment for late diarrhea (generally occurring 24 hours after the administration of irinotecan) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected by the patient.
The dosage regimen for loperamide used in clinical trials was the following (Note: This dosage regimen exceeds the usual dosage recommended for loperamide): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient does not present any more diarrhea for at least 12 hours. Loperamide is not recommended for periods longer than 48 consecutive hours due to the risks of paralytic ileus. During the night, the patient may take 4 mg of

loperamide every 4 hours. Premedication with lopermide is not recommended.
The use of drugs with laxative properties should be avoided due to the potential to exacerbate diarrhea. Patients should contact their physician before using any laxative.
The patients should contact their physician if any of the following occurs: diarrhea for the first time during treatment, black or bloody stools, inability to take fluids by mouth due to nausea or vomiting, inability to get diarrhea under control within 24 hours, fever or evidence of infection, symptoms of dehydration such as faint, lightheadedness or dizziness after the administration of IRINOTECAN GP PHARM.
Patients should be advised about the possibility of alopecia.
Patients should be warned about the potential for dizziness or visual disturbances within 24 hours following the administration of IRINOTECAN GP PHARM, and because of this they should not drive or operate machines if any of these symptoms occurs.
HOW SUPPLIED
IRINOTECAN GP PHARM 100 mg/5 mg x 1 glass vial.
IRINOTECAN GP PHARM 40 mg/2 mg x 1 glass vial.
STORAGE CONDITIONS
Store below 30ºC. Do not freeze.
KEEP AWAY FROM CHILDREN.
Medicine Authorized by the Ministry of Health of Argentina.
Certificate Nº: 50.948
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