

IRINOTECAN SERVYCAL
IRINOTECAN HYDROCHLORIDE (TRIHYDRATE)
Solution for Injection 100 mg/ 5 mL
Solution for Injection 40 mg/ 2 mL

Sale under filed prescription

Made in Argentina

All medicines having irinotecan as active ingredient may produce the effects mentioned below.

Irinotecan must only be administered by an oncologist.

QUALI-QUANTITATIVE COMPOSITION:

Each mL contains:

Irinotecan hydrochloride (trihydrate)	20.00 mg
Sorbitol	45.00 mg
Lactic acid	0.90 mg
Sodium hydroxide or hydrochloric acid q.s. to adjust pH	
Water for injection q.s. to	1.00 mL

CATEGORY: cytostatic, antineoplastic.

INDICATIONS:

Irinotecan Servycal is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. This medicine is also indicated for patients whose disease has recurred or progressed following initial 5-fluorouracil therapy.

PHARMACOLOGY

Pharmacological action

Mechanism of action: Irinotecan chlorhydrate is a semi-synthetic derivative of camptothecin, an alkaloid extracted from the tree *Camptotheca acuminata*.

Camptothecins interact specifically with the enzyme topoisomerase, which relieves the torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its metabolite SN-38 bind to topoisomerase I-DNA complex and prevent religation of the single-strand breaks. Recent research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage during the DNA synthesis when replication enzymes interact with the ternary complex formed by I topoisomerase, DNA, and irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is a thousand times more potent than irinotecan as inhibitor of topoisomerase I purified from human and rodent tumor cells. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2 to 2,000 times. However, plasma area under the concentration versus time curve (AUC) for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan. The precise contribution of SN-38 to irinotecan activity is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxyl acid anion form. A pH-dependent equilibrium exists between these two forms, as an acid pH promotes the formation of lactone while a more basic pH promotes the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in different cell types of rodent origin and in human xenografts of various histological types.

Pharmacokinetics:

Protein binding: Irinotecan shows moderate plasma protein binding (30% to 68%). SN-38 is highly plasma protein bound (approximately 95%). Both mainly bind to albumin.

Half-life and plasma concentration: After I.V. administration of irinotecan in humans, irinotecan plasma concentration decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 hs. The mean terminal elimination half-life of active metabolite SN-38 is about 10 to 17 hs. The half-lives of the active forms (lactones) of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the dose range of 50 to 350 mg/m², the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Concentrations of the active metabolite SN-38 are generally reached within 1 hr after the end of a 90-minute infusion of irinotecan.

Metabolism and elimination: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzyme and it mainly occurs in the liver. SN-38 subsequently forms a glucuronide metabolite by conjugation. In cytotoxic assays using 2 cell lines in vitro, SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38. The disposition of irinotecan has not been completely elucidated in humans.

The urinary excretion of irinotecan is 11 to 20%; that of SN-38 is lower than 1.0%, and that of SN-38 glucuronide is 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hs following administration in 2 patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Summary of mean pharmacokinetics parameters (\pm standard deviation) of irinotecan and SN-38 in patients with metastatic carcinoma of colon and rectum

Dose (mg/m ²)	Irinotecan					SN-38		
	C _{max} (ng/mL)	AUC 0-24 (ng.hr/mL)	T _{1/2} (h)	V _z (L/m ²)	CL (L/h/m ²)	C _{max} (ng/mL)	AUC 0-24 (ng.hr/mL)	T _{1/2} (h)
125	1,660±	10,200±	5.8±	110±	13.3±	26.3±	229±	10.4±
N:64	797	3,270	0.7	48.5	6.01	11.9	108	3.1

C_{max}: maximum plasma concentration

AUC 0-24: area under the plasma concentration-time curve from 0 to 24 hs after the end of the 90-minute infusion

T_{1/2}: terminal elimination half-life

V_z: volume of distribution of terminal elimination phase

CL: total systemic clearance

DOSAGE AND ADMINISTRATION

Parenteral dosage form

The recommended initial dose for irinotecan injection is 125 mg/m². Irinotecan should be administered as intravenous infusion over 90 minutes. The recommended regimen (one cycle of treatment) is 125 mg/m² once a week for 4 weeks, followed by a medicine-free period of 2 weeks. Thus, additional cycles of treatment may be repeated every 6 weeks. Subsequent doses may be adjusted as high as 150 mg/m² or as low as 50 mg/m² in decrements of 25 to 50 mg/m² depending on individual patient tolerance. Provided intolerable toxicity does not develop, additional cycles of treatment may be continued indefinitely in patients responsive to therapy or whose disease remains stable. It should be considered that during the first 2 or 3 cycles of irinotecan treatment the disease may remain stable and start to respond in subsequent cycles.

Patients should be carefully monitored for toxicity. The following table describes the recommended dose modifications during a cycle of therapy and at the beginning of each subsequent cycle.

TOXICITY GRADE (VALUE)	DURING A CYCLE OF THERAPY	AT THE BEGINNING OF NEXT CYCLES OF THERAPY (AFTER ADEQUATE RECOVERY), COMPARED TO THE INITIAL DOSE IN THE PREVIOUS CYCLE
No toxicity	Maintain dose level	Increase 25 mg/m ² up to a max. Dose of 150 mg/m ²
NEUTROPENIA 1 (1500 to 1900/mm ³) 2 (1000 to 1400/mm ³) 3 (500 to 900/mm ³)	Maintain dose level Decrease 25 mg/m ² Omit dose, then Decrease 25 mg/m ² when resolved to grade ≤2.	Maintain dose level Maintain dose level Decrease 25 mg/m ² .
4 (< to 500/mm ³)	Omit dose, then Decrease 50 mg/m ² when resolved to grade ≤2.	Decrease 50 mg/m ² .
NEUTROPENIC FEVER (grade 4 neutropenia and grade 2 fever).	Omit dose, then Decrease 50 mg/m ² when resolved to grade ≤2.	Decrease 50 mg/m ² .

TOXICITY GRADE (VALUE)	DURING A CYCLE OF THERAPY	AT THE BEGINNING OF NEXT CYCLES OF THERAPY (AFTER ADEQUATE RECOVERY), COMPARED TO THE INITIAL DOSE IN THE PREVIOUS CYCLE
OTHER HEMATOLOGIC TOXICITIES	Modifications for leukopenia, thrombocytopenia and anemia during a cycle of therapy and at the beginning of subsequent cycles of therapy are also based on NCI toxicity and are the same as recommended for neutropenia.	
DIARRHEA		
1 (2-3 stools/day).	Maintain dose level	Maintain dose level
2 (4-6 stools /day).	Decrease 25 mg/ m ² .	Maintain only if toxicity grade 2.
3 (7-9 stools /day).	Omit dose, then Decrease 25 mg/m ² when resolved to grade ≤2.	Decrease 25 mg/m ² only if toxicity grade 3.
4 (≥ a 10 stools/day).	Omit dose, then Decrease 50 mg/m ² when resolved to grade ≤2.	Decrease 50 mg/m ² .
OTHER NONHEMATOLOGIC TOXICITIES		
1	Maintain dose level	Maintain dose level
2	Decrease 25 mg/ m ² .	Decrease 25 mg/ m ² .
3	Omit dose, then Decrease 25 mg/m ² when resolved to grade ≤2.	Decrease 50 mg/m ² .
4	Omit dose, then Decrease 50 mg/m ² when resolved to grade ≤2.	Decrease 50 mg/m ² .

These recommendations are based on toxicities commonly observed with irinotecan administration. Irinotecan therapy should be discontinued when grade 3 or 4 diarrhea occurs or when other intolerable toxicities are observed. Dose modifications for hematologic toxicities other than neutropenia (i.e. leukopenia, anemia, or thrombocytopenia) during a cycle of therapy and at the beginning of subsequent cycles of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities such as nausea, vomiting, etc, during a cycle of therapy are the same as recommended for diarrhea. At the beginning of a subsequent cycle of therapy, dose should be decreased by 25 mg/m², compared to the initial dose of the previous cycle, for other nonhematologic grade 2 toxicities, or by 50 mg/m² for other nonhematologic toxicities grade 3 or 4. All dose modifications should be based on the worst preceding toxicity. A new cycle of therapy should not be commenced until the granulocyte count has recovered to ≥ 1500/mm³, the platelet count has recovered to ≥ 100,000/mm³, and treatment-related diarrhea has been fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered after 2 weeks, discontinuation of therapy should be considered. It is recommended that patients receive premedication with antiemetic agents.

General dosage information:

-Irinotecan is administered by intravenous infusion. Care should be taken to avoid extravasation, and infusion site should be monitored for signs of inflammation. If extravasation occurs, flush site with sterile water and application of ice is recommended.

-Irinotecan is emetogenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies, the majority of patients received 10 mg of dexamethasone in conjunction with other type of antiemetic agents such as a 5-HT₃ (ondansetron or granisetron). Antiemetic agents should be administered on the day of treatment, starting at least 30 minutes before irinotecan infusion.

-Treatment of cholinergic syndrome with early diarrhea: administration of 0.25 to 1 mg of intravenous atropine should be considered (unless clinically contraindicated) in patients with diaphoresis, abdominal cramps, or early diarrhea.

-Physicians should be particularly careful in the monitoring of side effects of irinotecan in patients older than 65 years of age and in those who have previously received pelvic/abdominal irradiation.

-The use of irinotecan in patients with significant hepatic impairment has not been established. However, in these patients doses should be lower and gradually increased on the basis of tolerance and hepatic enzymes values. In clinical trials, irinotecan was not administered to patients with serum bilirubin > 2.0 mg/dL, or transaminases > three times the upper limit of normal without liver metastasis.

Recommended dose modifications

A new cycle of therapy should not be commenced until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, the platelet count has recovered to $\geq 100,000/\text{mm}^3$, and treatment-related diarrhea has been fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered after 2 weeks, discontinuation of therapy should be considered.

Form of Administration:

Preparation of Infusion Solution:

Examine vial content for particulate matter and repeat examination when product is withdrawn from vial into syringe. Irinotecan solution should be diluted before infusion. Irinotecan should be diluted in 5% dextrose injection (preferred) or 0.9% sodium chloride injection, to a final concentration of approximately 0.12 to 1.1 mg/mL. In most clinical trials irinotecan was administered to 500 mL of 5% dextrose injection.

The solution is physically and chemically stable for 24 hours at room temperature (approximately 25° C) and in fluorescent lighting. Solutions diluted in 5% dextrose injection and kept under refrigeration (approximately from 2° C to 8° C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of mixtures using 0.9% sodium chloride injection is not recommended due to the low and sporadic incidence of visible particles. **Freezing irinotecan and irinotecan mixtures may result in drug precipitation and should be avoided.**

Due to possible microbiological contamination during dilution, it is advisable to use the mixture prepared with 5% dextrose injection within 24 hours if refrigerated (between 2° C and 8° C). In the case of mixtures prepared with 5% dextrose injection or sodium chloride injection, solutions should be used within 6 hours if kept at room temperature (15° C to 30° C).

Other drugs should not be added to the solution. Prior to administration, parenteral drug products should be visually inspected for particulate matter and discoloration whenever solution and container so permit.

Safety Considerations for Handling:

There is limited but increasing evidence about the risk to which personnel involved in the preparation and administration of parenteral antineoplastic are exposed due to the mutagenic, teratogenic, and/or carcinogenic potential of these agents; however, actual risk is unknown.

Suggested precautions include the following:

- * Use of a biological safety cabinet during reconstitution and dilution of parenteral drugs, as well as use of masks and disposable protective gloves.
- * Use of proper techniques to prevent contamination of the medicine, workplace, and operator when the drug is moved from one container to another (including appropriate training of personnel on said techniques).
- * Precaution and adequate disposition of needles, syringes, vials, ampoules, and no longer used medicines.
- * If irinotecan solution comes into contact with skin, wash it immediately and thoroughly with water and soap. And if irinotecan solution comes into contact with mucous membranes, wash them thoroughly with water.

CONTRAINDICATIONS:

Irinotecan is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS:

Diarrhea: Irinotecan may induce both forms of diarrhea, early or late, which seem to be mediated by different mechanisms. Early diarrhea (occurring during or within 24 hours following irinotecan administration) is cholinergic in nature. It may be severe but it is generally transient. It may be accompanied mainly by sweating in hands and feet, lacrimation, increased salivation and abdominal cramps. It may be ameliorated or eliminated by administration of atropine.

Late diarrhea (occurring 24 hours after irinotecan administration) can be life-threatening because it may be prolonged and lead to dehydration and electrolyte imbalance. It should be treated immediately with high doses of loperamide (2 mg every 2 hs until a minimum diarrhea-free period of 12 hs). Patients with severe diarrhea should be monitored and given fluid and electrolyte replacement in the case of dehydration. NCI grade 3 diarrhea is defined as an increase of 7 to 9 daily stools or incontinences, or severe cramps; and NCI grade 4 diarrhea is defined as an increase of ≥ 10 daily stools or bloody feces or need for parenteral support. If grade 3 or 4 diarrhea occurs, irinotecan administration should be delayed until patient recovers and subsequent doses should be decreased.

Myelosuppression: Deaths due to sepsis following severe myelosuppression have been reported in patients treated with irinotecan. If neutropenic fever occurs or if the absolute neutrophil count drops below $500/\text{mm}^3$, therapy should be temporarily discontinued. Dose should be decreased if there is a clinically significant decrease in WBC count ($<2000/\text{mm}^3$), neutrophil count ($<1.000/\text{mm}^3$), hemoglobin ($<8 \text{ gr/dL}$), or platelet count ($<100.000/\text{mm}^3$). Routine administration of a colony-stimulating factor (CSF) may not be necessary, but physicians may consider using a CSF in individual patients experiencing significant neutropenia.

Pregnancy: Irinotecan may cause fetal harm when administered to pregnant women.

The radioactivity related to ^{14}C -irinotecan crosses placenta in rats after I.V. administration of 10 mg/kg (which in separate studies produced an irinotecan maximum concentration and AUC about 3 and 0.5 times the corresponding values in patients administered 125 mg/m²). Intravenous administration of 6 mg/kg/day of irinotecan to rats (which in separate studies produced an irinotecan maximum concentration and AUC about 2 and 0.2 times the corresponding values in patients administered 125 mg/m²) and in rabbits (about half the recommended human dose on a mg/m² base) during the period of organogenesis, is embryotoxic as characterized by an increased post-implantation loss and a decreased number of life fetuses. Irinotecan was teratogenic in rats at doses higher than 1.2 mg/kg/day (which in separate studies produced an irinotecan maximum concentration and AUC about 2/3 and 1/40 of the corresponding values in patients given 125 mg/m²) and in rabbits at 6.0 mg/kg/day (about half the recommended human weekly dose on a mg/m² base). Teratogenic effects included a variety of visceral and skeletal abnormalities. Irinotecan administered to rats for a period following organogenesis and during weaning at doses of 6 mg/kg/day caused decreased learning ability and body weight of female offspring. There were no adequate well-controlled irinotecan studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant during treatment, the patient should be advised about the potential hazard to the fetus.

PRECAUTIONS:

Patient Monitoring: Before each dose of irinotecan, it is recommended to monitor carefully the WBC count with differential, hemoglobin, and platelet count.

Drug interactions and/or related problems:

Possible pharmacokinetics interactions of irinotecan with other drugs used concomitantly have not been investigated.

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

Patients who have received pelvic or abdominal irradiation are at increased risk of severe myelosuppression after irinotecan administration. The concurrent administration of irinotecan with irradiation has not been adequately studied and it is not recommended.

Lymphocytopenia has been reported in patients receiving irinotecan and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have increased the likelihood of this effect. However, serious opportunistic infections have been observed and no complications have been attributed specifically to lymphocytopenia.

Hyperglycemia has been reported in patients receiving irinotecan. Usually, it has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to irinotecan administration. It is probable that the administration of dexamethasone 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 administered on different days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the reported range when prochlorperazine is administered as premedication for other chemotherapies. It would be expected that the use of laxatives during therapy with irinotecan would worsen the incidence or severity of diarrhea, but this has not been studied. In view of the potential risks of dehydration secondary to irinotecan-induced vomiting and diarrhea, the physician may prefer to withhold diuretics during irinotecan dosing and, certainly, during the periods of active vomiting and diarrhea.

Drug/Laboratory test interactions: There are no known interactions between irinotecan and laboratory tests.

Carcinogenesis / mutagenesis: Long-term carcinogenesis studies with irinotecan have not been conducted. However, rats were intravenously administered doses of 2 mg/kg or 25 mg/kg of irinotecan once a week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan maximum concentration and AUC about 7.0 and 1.3 times the respective values in patients administered 125 mg/kg) and then observed for 91 weeks. Neither irinotecan nor SN-38 was mutagenic in the Ames assay. Irinotecan was clastogenic both in vitro (chromosome aberrations in ovarian cells of Chinese hamsters) and in vivo (micronucleus tests in mice).

Pregnancy-Reproduction:

-Fertility: in rats and rabbits, no significant adverse effect was observed on fertility or general reproductive performance after the intravenous administration of irinotecan at doses of up to 6 mg/kg/day. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses in rodents at 20 mg/kg (which in separate studies produced an irinotecan maximum concentration and AUC about 5 and 1 times, respectively, the corresponding values of patients administered 125 mg/m²) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan maximum concentration and AUC about one-half and 1/15, respectively, of the corresponding values of patients administered 125 mg/m²).

-Pregnancy: Pregnancy category D (see Warnings).

Breastfeeding: radioactivity appeared in rat milk within 5 minutes of I.V. administration of radiolabeled irinotecan and was concentrated up to 65 times at 4 hours after administration relative to plasma concentration. Because many drugs are excreted in human milk and the potential for serious adverse reactions in breastfeeding children, it is recommended that breastfeeding be interrupted during therapy with irinotecan.

Pediatric patients: The safety and effectiveness of irinotecan in pediatric patients have not been established.

Geriatric patients: the half life of irinotecan was 6 hours in 65-year-old patients or older and 5.5 hours in patients under this age. Dose-normalized AUC 0-24 for SN-38 in patients at least 65 years of age was 11% higher than in patients under this age. No dosage or administration changes are recommended in geriatric patients.

ADVERSE REACTIONS:

In three clinical studies, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed after 5-fluorouracil-based therapy were treated with irinotecan. Seventeen of these patients died within thirty days of

irinotecan administration; in 5 cases (1.6%, 5/304) deaths were potentially related to the drug. These 5 patients experienced a constellation of medical events that included known effects of irinotecan. One of these patients died of neutropenic sepsis without fever. Neutropenic fever, defined as grade 4 neutropenia and grade 2 or higher fever, occurred in 9 (3.0%) of these patients, who recovered with supportive care. One hundred nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times due to adverse effects; 81 (26.6%) were hospitalized due to events judged to be related to the administration of irinotecan. The main reasons for drug-related hospitalization were diarrhea with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia with or without diarrhea and/or fever (8.2%); and nausea and vomiting (4.9%). Adjustments in the dose of irinotecan were made during treatment and for subsequent cycles based on individual patient tolerance. The first dose of at least one cycle of irinotecan was decreased for 67% of patients who began the studies with starting doses of 125 mg/m². For 32% of cycles commenced at the 125 mg/m² dose level, dose reductions within cycle were required. Dose reductions were most frequently due to late diarrhea, neutropenia and leukopenia; 13 (4.3%) of patients interrupted treatment with irinotecan because of these adverse effects.

The adverse effects included in the following table are based on the experience of the 304 patients enrolled in the three clinical studies:

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

Events	% of Patients NCI Classification	
	NCI Grades 1 – 4	NCI Grades 3 - 4
GASTROINTESTINAL		
Late diarrhea*	87.8	30.6
7-9 stools/day (grade 3)	-----	(16.4)
≥ 10 stools/day (grade 4)	-----	(14.1)
Nausea	86.2	16.8
Vomiting	66.8	12.5
Anorexia	54.9	5.9
Early diarrhea**	50.7	7.9
Constipation	29.9	2.0
Flatulence	12.2	0.0
Stomatitis	11.8	0.7
Dyspepsia	10.5	0.0
HEMATOLOGIC		
Leukopenia	63.2	28.0
Anemia	60.5	6.9
Neutropenia	53.9	26.3
500 a < 1000/mm ³ (grade 3)	-----	(14.8)
< 500/mm ³ (grade 4)	-----	(11.5)
BODY/GENERAL		
Asthenia	75.7	12.2
Abdominal cramps/pain	56.9	16.4
Fever	45.4	0.7
Pain	23.7	2.3
Headache	16.8	0.7
Back pain	14.5	1.6
Chills	13.8	0.3
Minor infection***	14.5	0.0
Edema	10.2	1.3

Abdominal enlargement	10.2	0.3
METABOLIC AND NUTRITIONAL		
Decreased body weight	30.3	0.7
Dehydration	14.8	4.3
Increased alkaline phosphatase	13.2	3.9
Increased SGOT	10.5	1.3
DERMATOLOGIC		
Alopecia	60.5	NA****
Sweating	16.4	0.0
Rash	12.8	0.7
RESPIRATORY		
Dyspnea	22.0	3.6
Increased coughing	17.4	0.3
Rhinitis.	15.5	0.0
NEUROLOGIC		
Insomnia	19.4	0.0
Dizziness	14.8	0.0
CARDIOVASCULAR		
Vasodilation	11.2	0.0

* occurring more than 24 hours after administration of irinotecan

** occurring \leq 24 hours after administration of irinotecan

*** primarily upper respiratory infections

**** Not applicable, complete hair loss: NCI grade 2

Gastrointestinal: Diarrhea, nausea and vomiting were common adverse effects after treatment with irinotecan and they could be severe. These effects occurred early (during or within 24 hours of irinotecan administration) or late (more than 24 hours following irinotecan administration). The mean time to the onset of late diarrhea was 11 days after irinotecan administration. For patients commencing treatment at a dose of 125 mg/m², the mean duration of any type of diarrhea was 3 days. Among those patients treated with doses of 125 mg/m² who experienced grade 3 or 4 diarrhea, the mean duration of the diarrhea episode was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients who commenced treatment at 125 mg/m² than in patients administered given an initial dose of 100 mg/m² (34% vs 24%).

The frequency of grade 4 diarrhea was significantly greater in patients older than 65 years of age than in patients under this age (39.8% vs 23.4%). In study 2, the frequency of grade 3 and 4 late diarrhea was significantly greater in male patients than in female patients (43.1% vs 15.6%). However, there was no gender difference in the frequency of grade 3 or 4 late diarrhea in the other two studies.

Hematologic: irinotecan commonly caused neutropenia, leukopenia (including lymphocytopenia) and anemia. Thrombocytopenia was uncommon. Neutropenic fever (grade 4 neutropenia and grade 2 or higher fever) occurred in 3.0% of patients; 5.6% of patients received colony-stimulating factors for the treatment of neutropenia. NCI grade 3 or 4 anemia was observed in 6.9% of patients. Blood transfusions were given to 9.9 % of patients. The frequency of grade 3 and 4 neutropenia was significantly greater in patients who received previous pelvic/abdominal irradiation than in those who did not (48.1% vs 24.1%). There were no significant differences in frequency of grade 3 and 4 neutropenia by age or gender.

Body: Asthenia, fever and abdominal pain were the most common events of this type.

Hepatic: Grade 3 or 4 liver enzyme abnormalities were observed in less than 10% of patients. These effects typically occur in patients with known liver metastasis.

Dermatologic: Alopecia was reported during the treatment with irinotecan. Rashes have also been reported but treatment was not interrupted.

Respiratory: severe pulmonary effects were infrequent. Grade 3 or 4 dyspnea was reported in 3.6% of patients. More than half of patients with dyspnea had lung metastasis. The extent to which pulmonary involvement or any other preexisting lung disease may have contributed to dyspnea is unknown.

Neurologic: Insomnia and dizziness were observed but they were not considered to be related to irinotecan administration. Dizziness may have sometimes represented symptomatic evidence of orthostatic hypotension in dehydrated patients.

Cardiovascular: Vasodilation has been observed during the administration of irinotecan but intervention has not been required.

Patient information: Patients should be informed of the toxic effects of irinotecan during treatment, particularly of its gastrointestinal complications such as nausea, vomiting, and diarrhea. Every patient should be instructed to have loperamide available and start treatment for late diarrhea (occurring 24 hours after irinotecan administration) at the first episode of loose stools or the onset of bowel movements more frequent than normally expected for the patient. The dose regimen for loperamide in clinical trials consisted of the following (Note: this dose regimen exceeds the recommended usual dose for loperamide): 4 mg at the onset of late diarrhea and then 2 mg every two hours until diarrhea stops for at least 12 hours. During the night, the patient can take 4 mg of loperamide every 4 hours. The patient should also be advised that it is essential the patient tells his/her doctor if diarrhea occurs. Premedication with loperamide is not recommended.

The use of laxative should be avoided due to the potential for exacerbation of diarrhea. Patients should consult their doctors to discuss the use of any laxative.

Patients should inform their doctors if any of the following events occur after the administration of irinotecan: vomiting, fever or evidence of infection, dehydration symptoms such as faintness or dizziness.

Patients should be warned of the possibility of alopecia.

Overdosage: in a phase 1 trial, a single dose of up to 345 mg/m² of irinotecan injection was administered to a patient with a tumor refractory to several previous therapies. Single doses of 750 mg/m² of irinotecan have been administered in other non-American trials. The adverse effects in these patients were similar to those reported with recommended doses and regimens. There is not a known antidote for overdosage of irinotecan. Maximum supportive care should be instituted to avoid dehydration due to diarrhea and to treat any infectious complication.

Lethality was observed after the administration of a single dose of intravenous irinotecan of approximately 111 mg/kg to mice and 73 mg/kg to rats (approximately 2.6 and 3.4 times the recommended human dose of 125 mg/m², respectively); death was preceded by cyanosis, shakiness, respiratory distress and seizures.

If an overdose occurs, go to the nearest Hospital or contact Toxicology Centers:
Hospital de Niños Dr. Ricardo Gutiérrez: Ph: + 54 (11) 4962-6666 / 2247
Hospital Dr. Juan P. Garrahan: Ph: + 54 (11) 4941-6191 / 6012
Hospital Dr. Juan A. Fernández: Ph: + 54 (11) 4801-5555
Hospital A. Posadas: Ph: + 54 (11) 4654-6648 / 4658-7777

PRESENTATION:

IRINOTECAN SERVYCAL 100 mg x 1 vial.
IRINOTECAN SERVYCAL 40 mg x 1 vial.

**STORE BETWEEN 15° C AND 30° C, PROTECTED FROM LIGHT.
DO NOT FREEZE.**

KEEP OUT OF THE REACH OF CHILDREN

Medicinal Specialty Authorized by the Argentine Ministry of Health (A.N.M.A.T.).

Certificate No. 50199

Technical Director: Pamela Carla Marcuzzi – Pharmacist- Biochemist

**This medicine shall be used under medical prescription and surveillance and
it shall not be repeated without a new prescription.**

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