

**LEUCOVORINA SERVYCAL
LEUCOVORIN 50 mg
Lyophilized Powder for Injection**

**LEUCOVORINA SERVYCAL
CALCIUM LEUCOVORIN 15 mg
Tablets**

Made in Argentina

Sale under filed prescription

CALCIUM LEUCOVORIN, CALCIUM FOLINATE, CITROVORUM FACTOR

All medicines having calcium leucovorin or calcium folinate as active ingredient may produce the effects mentioned below.

Calcium leucovorin must only be administered by a physician specialized in the use of this type of medicine.

QUALI-QUANTITATIVE COMPOSITION:

Each vial of Leucovorina Servycal 50 mg contains:

Calcium Leucovorin (equivalent to leucovorin base)	54.25 mg
Sodium chloride	40.00 mg

Sodium hydroxide and/or hydrochloric acid q.s. to
adjust pH 8.1

Each tablet of Leucovorina Servycal 15 mg contains:

Calcium Leucovorin (equivalent to 15 mg of leucovorin base)	16.22 mg
Lactose	144.75 mg
Sodium starch glycollate	8.50 mg
Pregelatinized starch	12.10 mg
Magnesium stearate	10.00 mg

DRUG CATEGORY AND ACTION: antidote to drugs which act as folic acid antagonists; antianemic; antineoplastic modulator.

INDICATIONS:

Leucovorina Servycal – Lyophilized Powder for Injection x 50 mg:

Calcium leucovorin rescue is indicated as rescue after high dose methotrexate therapy in osteosarcoma.

Calcium leucovorin is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

Calcium leucovorin is indicated in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.

Calcium leucovorin is also indicated for use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

Calcium leucovorin infusion should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

Leucovorina Servycal - tablets x 15 mg:

Calcium leucovorin rescue is indicated as rescue after high dose methotrexate therapy in osteosarcoma.

Calcium leucovorin is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

PHARMACOLOGY

Physicochemical characteristics:

Molecular weight: 601.58

pKa: 3.1; 4.8 and 10.4

Mechanism of action: leucovorin is a reduced form of folic acid, which is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate). Because it does not require reduction by dihydrofolate reductase as folic acid does, calcium leucovorin is not affected by blockage of this enzyme by folic acid antagonists (dihydrofolate reductase inhibitors). This allows purine and thymidine synthesis, and thus DNA, RNA, and protein synthesis, to occur. Calcium leucovorin may limit methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell. Calcium leucovorin rescues bone marrow and gastrointestinal cells from methotrexate but has no apparent effect on pre-existing methotrexate nephrotoxicity.

Absorption: it is rapidly absorbed after oral administration. The bioavailability is about 97% for a 25-mg, 75 % for a 50-mg dose and 37% for a 100-mg dose.

Distribution: Crosses blood-brain barrier in moderate amounts; largely concentrated in liver.

Metabolism: Hepatic and intestinal, mainly to 5-methyltetrahydrofolate (active). After oral administration, leucovorin is substantially (greater than 90%) and rapidly (within 30 minutes) metabolized. Metabolism is less extensive (about 66% after intravenous

and 72% after intramuscular administration) and slower with parenteral administration.

Time to peak serum concentration of reduced folate:

Oral: 1.72 ± 0.8 hours

Intramuscular: 0.71 ± 0.09 hours

Peak serum concentration of reduced folate:

After a 15-mg dose:

Oral: 268 ± 18 mg/mL (approximately 1 micromolar or 1×10^{-6} M).

Intramuscular: 241 ± 17 mg/mL (approximately 1 micromolar or 1×10^{-6} M).

Half-life: half-life for total reduced folates in serum: intramuscular, intravenous or oral: 6.2 hours.

Onset of action:

Oral: 20 to 30 minutes.

Intramuscular: 10 to 20 minutes.

Intravenous: less than 5 minutes.

Action duration: for every route of administration, from 3 to 6 hours.

Elimination:

In urine: 80 to 90 %

In feces: 5 to 8 %

PRECAUTIONS

Pregnancy/Reproduction: no human or animal studies have been conducted so far.

Breastfeeding: it is unknown whether this drug is excreted in breast milk. However, no problems have been reported in humans.

Pediatric patients: in children with seizures, calcium leucovorin may increase the number of seizures, counteracting the anticonvulsant effects of barbiturates, hydantoin, anticonvulsants, and primidone.

Elder patients: no information is available on the specific relation between age and the effects of leucovorin in this type of patients. Nevertheless, elderly patients are more likely to suffer age-related renal function impairment, and thus, dose adjustment may be required in patients receiving leucovorin as rescue from the effects of high-dose methotrexate.

Drug Interactions and/or related problems: the following drug interactions and/or related problems have been selected on the basis of their potential clinical significance. Combinations containing any of the following drugs, depending on the amount, may also interact with this medicine:

- Barbiturates, hydantoin, anticonvulsants, or primidone (large doses of calcium leucovorin may counteract the anticonvulsant effects of these drugs).
- Depression of the central nervous system (caused by medicines). Caution is necessary in patients treated with calcium leucovorin oral solution due to its high alcohol level.
- Fluorouracil (concurrent use of leucovorin may increase the therapeutic and toxic effects of fluorouracil; although the two drugs may be used together to obtain therapeutic advantages, a dose adjustment may be required).

Medical considerations/contraindications:

The medical considerations/contraindications have been selected on the basis of their potential clinical significance.

Except under special circumstances, this medicine should not be used when the following medical problems exist:

For treatment of anemia (as single agent):

- Pernicious anemia, or Vitamin B 12 deficiency (a hematologic remission may occur while neurologic manifestations continue to progress).

This medicine should be used with caution when the following medical problems exist:

- Sensitivity to leucovorin.

This medicine should be used with caution in patients being treated with leucovorin as rescue after high-dose methotrexate therapy, when the following medical problems exist:

- Aciduria (urinary pH below 7), ascites, dehydration, gastrointestinal obstruction, pleural or peritoneal effusions, renal function impairment (the risk of methotrexate toxicity is increased, since its elimination may be altered and thus may accumulate; even small doses of methotrexate may cause severe myelosuppression and mucositis; higher doses of calcium leucovorin or prolonged treatments may be indicated, together with close monitoring of methotrexate concentrations); nausea and vomiting (these may alter calcium leucovorin absorption, thus parenteral administration is recommended; inadequate secondary hydration may increase methotrexate toxicity).

Patient monitoring: The following may be important in careful patient monitoring; other tests may be required in some patients, depending on their condition.

For patients receiving high-dose methotrexate:

- Creatinine clearance determinations (recommended prior to initiation of high-dose methotrexate with leucovorin rescue therapy or if serum creatinine concentrations increase by 50% or more).
- Methotrexate concentrations in serum or plasma (recommended by some clinicians every 12 to 24 hours after high-dose methotrexate administration to determine dose and duration of leucovorin treatment needed to maintain rescue. This may aid to identify patients with delayed methotrexate clearance; toxicity seems to be related both to the length of time when methotrexate concentrations are elevated and to the peak concentrations achieved. In general, monitoring should continue until concentrations are less than 5×10^{-8} M).
- Serum creatinine concentrations (recommended prior to and every 24 hours after each methotrexate dose, until plasma or serum methotrexate concentrations are less than 5×10^{-8} M, to detect the development of renal function impairment and predict methotrexate toxicity. An increase greater than 50% over the pre-treatment concentration at 24 hours is associated with severe renal toxicity).
- pH determinations in urine (recommended prior to each dose of high-dose methotrexate therapy and about every 6 hours throughout leucovorin rescue, until plasma or serum methotrexate concentrations are less than 5×10^{-8} M, to ensure that pH remains greater than 7 so as to minimize the risk of methotrexate nephropathy due to precipitation of methotrexate or its metabolites in urine).

SIDE/ADVERSE EFFECTS

The following adverse effects have been selected on the basis of their potential clinical significance:

- Effects needing medical attention:

Rare effects: allergic reaction (skin rash, itching and wheezing).

PATIENT INFORMATION

Physicians must inform patients about the following side effects:

Before using Leucovorina Servycal 50 mg/ Leucovorina Servycal 15 mg:

Conditions affecting use, especially:

- Sensitivity to leucovorin.
- **Use in children:** may increase frequency of epileptic seizures in susceptible pediatric patients.
- Other medical problems, especially renal function impairment.

Proper Use of Leucovorina Servycal 50 mg/ Leucovorina Servycal 15 mg:

- It is important to take it as directed and not to miss doses; taking it at evenly spaced times.
- Check with physician before discontinuing treatment or if vomiting occurs shortly after this medicine is taken.
- Proper dosing.

- Missed dose: Check with physician immediately; it is possible that additional calcium leucovorin may be needed; it is important not to increase dose unless otherwise directed by physician.
- Proper storage.

Side/Adverse effects:

- Signs of potential side effects, especially allergic reaction.

GENERAL DOSING INFORMATION

A 15-mg dose produces a serum reduced folate concentration of approximately 1 micromolar (1×10^{-6} M).

As an antidote to folic acid antagonists:

- Patients receiving Leucovorina Servycal 50 mg/Leucovorina Servycal 15 mg as a “rescue” from the toxic effects of methotrexate should be under supervision of a physician experienced in high-dose methotrexate therapy.

- If absorption is impaired due to nausea and vomiting, parenteral administration of calcium leucovorin is recommended.

- Methotrexate administration must not be indicated unless creatinine clearance and serum creatinine concentrations are normal. If renal function impairment is developed during therapy, methotrexate must be interrupted until renal function becomes acceptable.

High-dose methotrexate administration should not be indicated unless calcium leucovorin is ready to be administered, since rescue is critical.

- A variety of dosage schedules of leucovorin in combination with high-dose methotrexate have been used. Since these schedules are still under investigation, the prescriber physician should consult the medical literature when choosing a specific dosage. Alkalinization of urine (with bicarbonate and/or acetazolamide) and intravenous hydration (1,000 mL /m² of body surface area every six hours prior to the methotrexate infusion and 3,000 mL/ m² of body surface area per day during the methotrexate infusion and for two days after the infusion is completed) are also important to prevent renal toxicity caused by methotrexate and/or its metabolites.

- Administration of calcium leucovorin should be as rapid as possible, and after methotrexate administration rather than simultaneously with it so as not to interfere with methotrexate's antineoplastic effects. However, calcium leucovorin has been administered simultaneously with pyrimethamine and trimethoprim in oral or intramuscular doses ranging from 400 µg (0.4 mg) to 5 mg to prevent megaloblastic anemia due to high doses of these medicines.

- In general, it is recommended that the first dose of calcium leucovorin be administered within the first 24 to 42 hours of starting a high-dose methotrexate infusion (within 1 hour in the case of an overdose), at a dose producing blood concentrations equal to or greater than methotrexate blood concentrations (calcium leucovorin at a dose of 15 mg/m² of body surface area produces peak plasma concentrations of approximately 1 micromolar or 1×10^{-6} M). The duration of calcium

leucovorin administration varies with the dosage of methotrexate and plasma concentrations achieved (including rate of elimination); in general, calcium leucovorin administration is continued until methotrexate concentrations fall to less than 5×10^{-8} M.

- A higher dose and/or longer calcium leucovorin treatment may be required in patients with aciduria, ascites, dehydration, gastrointestinal obstruction, renal function impairment, or pleural edema because elimination of methotrexate is delayed and the length of time for plasma methotrexate concentrations to decrease to nontoxic levels ($< 5 \times 10^{-8}$ M) is increased. It is recommended that the duration of calcium leucovorin administration in these patients be based on determinations of plasma methotrexate concentrations.

As an adjunct to 5-fluorouracil for the treatment of colorectal carcinoma:

Patients receiving leucovorin in combination with fluorouracil should be under the supervision of a physician experienced in chemotherapy.

ORAL DOSAGE FORMS

Leucovorina Servycal 15 mg, tablets

Usual dose for adolescents and adults:

As antidote to folic acid antagonists:

- To methotrexate: oral, 10 mg (base)/m² of body surface area every 6 hours until methotrexate blood concentrations fall to less than 5×10^{-8} M.
- To pyrimethamine or trimethoprim:
- Prevention: oral, 400 µg (0.4 mg) to 5 mg (base) with each dose of the folic acid antagonist.
- Treatment: oral, 5 to 15 mg (base) a day.

As antianemic: megaloblastic anemia, secondary to folate deficiency: oral, up to 1 mg (base) per day.

Note: Doses higher than 25 mg should be administered parenterally because oral absorption is saturable at doses above 25 mg.

Usual dose for pediatric patients: see Usual dose for adolescents and adults.

Storage: keep between 15° C and 30° C, protected from light and moisture.

Leucovorina Servycal 50 mg, lyophilized powder for injection

Usual dose for adolescents and adults:

As antidote to folic acid antagonists:

- To methotrexate (inadvertent overdose): intramuscular or intravenous, 10 mg

(base)/ m² of body surface area every 6 hours until methotrexate blood concentrations fall to less than 5×10^{-8} M.

If 24 hours after methotrexate administration, the serum creatinine is increased by 50% over baseline values, or serum methotrexate is greater than 5×10^{-6} M, the dose of leucovorin should be 100 mg (base)/ m² of body surface area every three hours, administered intravenously until methotrexate concentrations are reduced to appropriate levels.

Only solutions prepared with sterile water for injection (without benzyl alcohol) should be used for doses higher than 10 mg/ m² of body surface area.

- To pyrimethamine or trimethoprim:

- Prevention: Intramuscular, 400 µg (0.4 mg) to 5 mg base with each dose of the folic acid antagonist.

- Treatment: Intramuscular, 5 to 15 mg (base) per day.

As antianemic: megaloblastic anemia, secondary to folate deficiency: intramuscular up to 1 mg (base) per day.

As treatment adjunct for metastatic colorectal carcinoma:

Intravenous: 200 mg/m² of body surface area infused over a minimum of three minutes, followed by fluorouracil 370 mg/m² of body surface area intravenously; or intravenous, 20 mg/m² of body surface area, followed by fluorouracil 425 mg/m² of body surface area intravenously.

Either regimen is administered daily for five days, and the course may be repeated at 3-to-4-week intervals for two courses and then at 4-to-5-week intervals, depending on toxicity and or tolerance to previous courses.

Even higher leucovorin doses (500 to 600 mg/m² per day) have been used for fluorouracil biomodulation.

Note: Only solutions prepared with sterile water for injection (without benzyl alcohol) should be used for doses higher than 10 mg/m² of body surface area.

Usual dose for pediatric patients: as antidote to folic acid antagonists or as antianemic, see Usual dose for adolescents and adults. As adjunct for colorectal carcinoma, dose has not been established.

Storage: prior to reconstitution, keep between 15° C and 30° C, protected from light.

Preparation of dosage forms: Leucovorina Servycal 50 mg, sterile lyophilized powder, is reconstituted for parenteral use by adding 5 mL of bacteriostatic water for injection (preserved with benzyl alcohol) to the 50 mg vial, thus obtaining a concentration of 10 mg/mL.

If doses higher than 10 mg/m² of body surface area are to be used, only sterile water for injection should be used for reconstitution and the resulting solution used immediately.

Precautions: for use in neonates, diluents containing benzyl alcohol to reconstitute sterile lyophilized powder is not recommended because cases of fatal toxic syndrome consisting of metabolic acidosis, CNS depression, respiratory problems, renal failure, hypotension, and possibly seizures and intracranial hemorrhages have been associated with them.

Stability: reconstituted solutions prepared with bacteriostatic water for injection (preserved with benzyl alcohol) should be used within 7 days. Intravenous solutions containing calcium leucovorin in 5% dextrose solution, in 0.9% sodium chloride solution, lactated Ringer's solution, or Ringer's solution, maintain about 90% of their potency when used within 24 hours.

PATIENT INFORMATION

Leucovorin is used as an antidote to the unwanted effects of methotrexate (a cancer medicine) that is given in high doses. It is used also to prevent or treat certain kinds of anemia. Leucovorin acts the same way in the body as folic acid, which may be low in these patients.

Leucovorin is also used along with fluorouracil (a cancer medicine) to treat cancer of the colon (bowel).

Leucovorin is available only under prescription and must be given only under your doctor's supervision.

Before using Leucovorina Servycal 50 mg (lyophilized powder for injection) / Leucovorina Servycal 15 mg (tablets):

Before making the decision of starting leucovorin treatment, both the risks and the benefits of taking it must be considered. You and your doctor together will make this decision.

The following should be considered concerning leucovorin administration:

Allergy: consult your doctor if you have ever had any allergic reaction to leucovorin, and also if you are allergic to any other substance, such as foods, sulfites or other preservatives, or dyes.

Pregnancy: no human or animal studies have been conducted so far.

Breastfeeding: it is unknown whether leucovorin is excreted in breast milk. However, problems in neonates have not been reported.

Children: in children with epileptic seizures, leucovorin may increase the number of seizures.

Elderly patients: many medicines have not been tested in elderly people. Therefore, it may not be known whether they work exactly the same way they do in younger adults or if they cause different side effects or problems. There is no specific information comparing the use of leucovorin in the elderly with its use in other age groups.

Other medical problems: the presence of other medical problems may affect the use of leucovorin. If you are receiving leucovorin as an antidote to methotrexate,

make sure you tell your doctor if you have any other medical problems, especially:

- **Kidney disease:** levels of methotrexate may be increased because of its slower elimination from the body, so the dose of leucovorin may not be enough to block the unwanted effects of methotrexate
- **Nausea and vomiting:** not enough leucovorin may be absorbed to block the unwanted effects of methotrexate.

Other medicines: Although certain medicines must not be used together, in other cases two different medicines may be used at the same time even if they interact. In these cases, your doctor may want to change the dose, or take other necessary precautions. Tell your doctor if you are taking any other medicine, whether prescribed or not.

Tell your doctor before starting to take any new medicine, whether prescribed or not, or if you start suffering from any other medical problem while using this medicine.

Proper Use of Leucovorina Servycal 50 mg (lyophilized powder for injection)/ Leucovorina Servycal 15 mg (tablets):

It is very important that you take leucovorin exactly as directed, especially when it is used to counteract the unwanted effects of cancer medicines. Do not miss any dose. It is also better to take the doses at evenly spaced times, at day and night. For example, if you have to take 4 doses a day, they should be spaced about 6 hours from each other. If this interferes with your sleep or other daily activity, or if you need help to plan better the schedule to take your medicine, consult your doctor.

Do not stop taking Leucovorina Servycal 50 mg/ Leucovorina Servycal 15 mg without first consulting your doctor. It is very important that you receive the exact right amount of medicine.

Dose: The dose of leucovorin will be different for different patients. Follow the directions given by your doctor or the patient package insert. The following information includes only the average doses of leucovorin. If your dose is different, do not change it unless your doctor tells you to do so.

The number of tablets or injections that you receive depends on the strength of the medicine. The number of doses you take each day, the time allowed between doses, and the treatment duration also depend on the medical problem for which you are receiving leucovorin.

- As an antidote to methotrexate:

Oral or injection dosage forms:

Adults, adolescents and children: the dose is based on body weight and must be indicated by your doctor.

- As an antidote to other medicines:

Oral or injection dosage forms:

Adults, adolescents and children: the dose may vary from 0.4 to 15 mg a day, and must be indicated by your doctor.

- For certain types of anemia:

Oral or injection dosage forms:

Adults, adolescents and children: up to 1 mg a day.

- For colon cancer:

Injection dosage form:

Adults and adolescents: the dose is based on body weight and must be indicated by your doctor.

Children: the dose must be determined by the doctor.

Missed dose: if you miss a dose of leucovorin or if you vomit shortly after taking the dose, tell your doctor immediately, who may indicate you to take an extra dose of calcium leucovorin to make up for the one you missed. Do not take extra calcium leucovorin on your own, since it is very important that you receive just the indicated dose at the right time.

How to store this medicine:

- Keep out of the reach of children.
- Keep away from heat, moisture and direct light.

Side effects of de Leucovorina Servycal 50 mg (lyophilized powder for injection) / Leucovorina Servycal 15 mg (tablets).

As well as having therapeutic effects with proven efficacy, this medicine may also cause adverse effects.

Generally, calcium leucovorin does not cause any side effect. However, if any of the following adverse effects occur shortly after taking this medicine, consult your doctor immediately: skin rash, hives or itching, and wheezing.

Some patients may experience other side effects not included in this list. If you notice any other adverse effect, consult your doctor.

Leucovorina Servycal 50 mg, Lyophilized Powder for Injection, store between 15° C and 30° C, protected from light.

Leucovorina Servycal 15 mg, Tablets, store between 15° C and 30° C, protected from light.

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

PRESENTATION

Leucovorina Servycal 50 mg, lyophilized powder x 1 vial for sale to the public.

KEEP OUT OF REACH OF CHILDREN

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

MEDICINAL SPECIALTY AUTHORIZED BY THE ARGENTINE MINISTRY OF HEALTH (A.N.M.A.T.)- CERTIFICATE No. 50040:

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