SANDOZ

Levoleucovorin Injection

R_x only

Sterile

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use levoleucovorin injection safely and effectively. See full prescribing information for levoleucovorin injection.

LEVOLEUCOVORIN injection, solution for intravenous use

Initial U.S. Approval: 2008 (levoleucovorin)

RECENT MAJOR CHANGES

Indications and Usage (1)	04/2011
Dosage and Administration, Reconstitution and Infusion Instructions (2.6)	04/2011

INDICATIONS AND USAGE

Levoleucovorin injection is a folate indicated for:

- Rescue after high-dose methotrexate therapy in osteosarcoma.
- Diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Limitations of Use
Levoleucovorin injection is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress. (1.1)

DOSAGE AND ADMINISTRATION

Do not administer intrathecally. (2.1)

Levoleucovorin injection is dosed at **one-half** the usual dose of racemic *d,l*-leucovorin (2.1)

Levoleucovorin injection Rescue After High-Dose Methotrexate Therapy

Levoleucovorin injection rescue recommendations are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Levoleucovorin injection rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. Determine serum creatinine and methotrexate levels at least once daily. Continue levoleucovorin injection administration, hydration, and urinary alkalinization (pH of 7.0 or greater) until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The levoleucovorin injection dose may need to be adjusted. (2.3)

DOSAGE FORMS AND STRENGTHS

Levoleucovorin Injection: 17.5 mL of a sterile solution containing levoleucovorin pentahydrate equivalent to 175 mg levoleucovorin and 0.83% sodium chloride. (3, 11, 16)

Levoleucovorin Injection: 25 mL of a sterile solution containing levoleucovorin calcium pentahydrate equivalent to 250 mg levoleucovorin and 0.83% sodium chloride. (3, 11, 16)

CONTRAINDICATIONS

Levoleucovorin is contraindicated for patients who have had previous allergic reactions attributed to folic acid or folinic acid. (4)

WARNINGS AND PRECAUTIONS

Due to Ca^{++} content, no more than 16 mL (160 mg) of levoleucovorin solution should be injected intravenously per minute. (5.1)

Concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in HIV patients was associated with increased rates of treatment failure in a placebo-controlled study. (5.3)

ADVERSE REACTIONS

Allergic reactions were reported in patients receiving levoleucovorin. (6.3)

Vomiting (38%), stomatitis (38%) and nausea (19%) were reported in patients receiving levoleucovorin as rescue after high dose methotrexate therapy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Levoleucovorin may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible patients. (7)

Rev: 11-2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Levoleucovorin injection is a folate analog.
- Levoleucovorin injection rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
- Levoleucovorin injection is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

1.1 Limitations of Use

- Levoleucovorin injection is not approved for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B_{12}. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Guidelines

Levoleucovorin injection is dosed at **one-half** the usual dose of racemic *d,l*-leucovorin.

Levoleucovorin injection is indicated for intravenous administration only. **Do not administer intrathecally.**

2.2 Co-administration of Levoleucovorin Injection with Other Agents

Due to the risk of precipitation, do not co-administer levoleucovorin injection with other agents in the same admixture.

2.3 Levoleucovorin Injection After High-Dose Methotrexate Therapy

The recommendations for levoleucovorin injection rescue are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). Levoleucovorin injection rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion.

Serum creatinine and methotrexate levels should be determined at least once daily. Levoleucovorin injection administration, hydration, and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The levoleucovorin injection dose should be adjusted or rescue extended based on the following guidelines.

Table 1 Guidelines for Levoleucovorin Injection Dosage and Administration

Clinical Situation	Laboratory Findings	Levoleucovorin Injection Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours	7.5 mg IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 7.5 mg IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5 micromolar or more at 48 hours after administration, OR; a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).	75 mg IV q 3 hours until methotrexate level is less than 1 micromolar; then 7.5 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate levoleucovorin injection therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than the abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, levoleucovorin injection rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g., medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Delayed methotrexate excretion may be caused by accumulation in a third space fluid collection (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. Under such circumstances, higher doses of levoleucovorin injection or prolonged administration may be indicated.

Although levoleucovorin injection may ameliorate the hematologic toxicity associated with high-dose methotrexate, levoleucovorin injection has no effect on other established toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

2.4 Dosing Recommendations for Inadvertent Methotrexate Overdosage

Levoleucovorin injection rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. As the time interval between antifolate administration [e.g., methotrexate] and levoleucovorin injection rescue increases, levoleucovorin injection effectiveness in counteracting toxicity may decrease. Levoleucovorin injection 7.5 mg (approximately 5 mg/m^2) should be administered IV every 6 hours until the serum methotrexate level is less than 10^{-8} M.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10^{-6} M or the 48 hour level is greater than 9 x 10^{-7} M, the dose of levoleucovorin injection should be increased to 50 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M. Hydration (3 L/day) and urinary alkalinization with $NaHCO_3$ should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

2.6 Reconstitution and Infusion Instructions

- Levoleucovorin contains no preservative. Observe strict aseptic technique during reconstitution of the drug product.
- Levoleucovorin solutions may be further diluted to concentrations of 0.5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. The diluted solution using 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP may be held at room temperature for not more than 4 hours.
- Visually inspect the diluted solution for particulate matter and discoloration, prior to administration. CAUTION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if cloudiness or precipitate is observed.
- No more than 16 mL of levoleucovorin injection (160 mg of levoleucovorin) should be injected intravenously per minute, because of the calcium content of the levoleucovorin solution.

3 DOSAGE FORMS AND STRENGTHS

Levoleucovorin injection, 175 mg is supplied in a single-use vial containing 17.5 mL sterile solution. Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

Levoleucovorin injection, 250 mg is supplied in a single-use vial containing 25 mL sterile solution. Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

4 CONTRAINDICATIONS

Levoleucovorin is contraindicated for patients who have had previous allergic reactions attributed to folic acid or folinic acid.

5 WARNINGS AND PRECAUTIONS

5.1 Rate of Administration

Because of the Ca^{++} content of the levoleucovorin solution, no more than 16 mL (160 mg of levoleucovorin) should be injected intravenously per minute.

5.3 Potential for Interaction with Trimethoprim-Sulfamethoxazole

The concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

6 ADVERSE REACTIONS

6.1 Clinical Studies in High-Dose Methotrexate Therapy

Since clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following table presents the frequency of adverse reactions which occurred during the administration of 58 courses of high-dose methotrexate 12 grams/m^2 followed by levoleucovorin rescue for osteosarcoma in 16 patients age 6 to 21. Most patients received levoleucovorin injection 7.5 mg every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate.

Table 2 Adverse Reactions with High-Dose Methotrexate Therapy

Body System/Adverse Reactions	Number (%) of Patients with Adverse Reactions		Number (%) of Courses with Adverse Reactions	
	(N =16)		(N = 58)	
	All	Grade 3+	All	Grade 3+
Gastrointestinal				
Stomatitis	6 (37.5)	1 (6.3)	10 (17.2)	1 (1.7)
Vomiting	6 (37.5)	0	14 (24.1)	0
Nausea	3 (18.8)	0	3 (5.2)	0
Diarrhea	1 (6.3)	0	1 (1.7)	0
Dyspepsia	1 (6.3)	0	1 (1.7)	0
Typhlitis	1 (6.3)	1 (6.3)	1 (1.7)	1 (1.7)
Respiratory				
Dyspnea	1 (6.3)	0	1 (1.7)	0
Skin and Appendages				
Dermatitis	1 (6.3)	0	1 (1.7)	0
Other				
Confusion	1 (6.3)	0	1 (1.7)	0
Neuropathy	1 (6.3)	0	1 (1.7)	0
Renal function abnormal	1 (6.3)	0	3 (5.2)	0
Taste perversion	1 (6.3)	0	1 (1.7)	0
Total number of patients	9 (56.3)		2 (12.5)	
Total number of courses	25 (43.1)		2 (3.4)	

The incidence of adverse reactions may be underestimated because not all patients were fully evaluable for toxicity for all cycles in the clinical trials. Leukopenia and thrombocytopenia were observed, but could not be attributed to high-dose methotrexate with levoleucovorin rescue because patients were receiving other myelosuppressive chemotherapy.

6.3 Postmarketing Experience

Since adverse reactions from spontaneous reports are provided voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Spontaneously reported adverse reactions collected by the WHO Collaborating Center for International Drug Monitoring in Uppsala Sweden have yielded seven cases where levoleucovorin was administered with a regimen of methotrexate. The events were dyspnea, pruritus, rash, temperature change and rigors. For 217 adverse reactions (108 reports) where levoleucovorin was a suspected or interacting medication, there were 40 occurrences of "possible allergic reactions."

7 DRUG INTERACTIONS

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, both folic and folinic acids share some common metabolic pathways. Caution should be taken when taking folinic acid in combination with anticonvulsant drugs.

Preliminary human studies have shown that small quantities of systemically administered leucovorin enter the CSF, primarily as its major metabolite, 5-methyltetrahydrofolate (5-MTHFA). In humans, the CSF levels of 5-MTHFA remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with levoleucovorin. It is not known whether levoleucovorin can cause fetal harm when administered to a pregnant woman or if it can affect reproduction capacity. Levoleucovorin should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from levoleucovorin, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

[See CL**INICAL STUDIES (14)**].

8.5 Geriatric Use

Clinical studies of levoleucovorin in the treatment of osteosarcoma did not include subjects aged 65 and over to determine whether they respond differently from younger subjects.

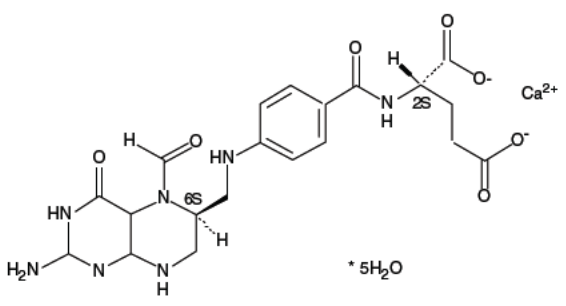
10 OVERDOSAGE

No data are available for overdosage with levoleucovorin.

11 DESCRIPTION

Levoleucovorin is the levo isomeric form of racemic *d,l*-leucovorin, present as the calcium salt. Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin].

Levoleucovorin injection contains levoleucovorin calcium, which is one of several active, chemically reduced derivatives of folic acid. It is useful as antidote to the inhibition of dihydrofolate reductase by methotrexate. This compound has the chemical designation calcium (6S)-N-{4-[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridinyl)methyl] amino]benzoyl}-L-glutamate pentahydrate. The molecular weight is 601.6 and the structural formula is:



Its molecular formula is: $C_{20}H_{21}CaN_7O_7$. 5 H_2O.

Levoleucovorin injection is supplied as a sterile solution of either 175 mg levoleucovorin in 17.5 mL or 250 mg levoleucovorin in 25 mL. Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride. Sodium hydroxide is used for pH adjustment to pH 8.0 (6.5 to 8.5).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.1.1 Levoleucovorin effects during high-dose methotrexate therapy

Levoleucovorin is the pharmacologically active isomer of 5-formyl tetrahydrofolic acid. Levoleucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of levoleucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

12.2 Pharmacodynamics

Levoleucovorin is actively and passively transported across cell membranes. *In vivo*, levoleucovorin is converted to 5-methyltetrahydrofolic acid (5-methyl-THF), the primary circulating form of active reduced folate. Levoleucovorin and 5-methyl-THF are polyglutamated intracellularly by the enzyme folylpolyglutamate synthetase. Folylpolyglutamates are active and participate in biochemical pathways that require reduced folate.

12.3 Pharmacokinetics

The pharmacokinetics of levoleucovorin after intravenous administration of a 15 mg dose was studied in healthy male volunteers. After rapid intravenous administration, serum total tetrahydrofolate (total-THF) concentrations reached a mean peak of 1722 ng/mL. Serum (6S)-5-methyl-5,6,7,8-tetrahydrofolate concentrations reached a mean peak of 275 ng/mL and the mean time to peak was 0.9 hours. The mean terminal half-life for total-THF and (6S)-5-methyl-5,6,7,8-tetrahydrofolate was 5.1 and 6.8 hours, respectively.

A pharmacokinetic study was conducted in 40 healthy subjects who received a single intravenous dose of either levoleucovorin (200 mg/m^2) or racemic *d,l*-leucovorin (400 mg/m^2), each administered as a 2-hour infusion in a crossover design. Results indicate that the 90% confidence interval for the geometric mean ratios for both $AUC_{0\text{-}inf}$ and C_{max} were within the standard limit of 80 to 125% for both *l*-leucovorin and *l*-5-methyl-THF. Therefore, the exposure to *l*-leucovorin and 5-methyl-THF ($AUC_{0\text{-}inf}$ and C_{max}) was comparable whether it was administered as levoleucovorin or as *d,l*-leucovorin. The geometric mean $AUC_{0\text{-}inf}$ values for levoleucovorin were 30719 ng.h/mL and 31296 ng.h/mL for levoleucovorin and *d,l*-leucovorin, respectively. The geometric mean C_{max} values for levoleucovorin were 10895 ng/mL and 11301 ng/ mL for levoleucovorin and *d,l*-leucovorin, respectively. The geometric mean $AUC_{0\text{-}inf}$ values for 5-methyl-THF were 52105 ng.h/mL and 50137 ng.h/mL for levoleucovorin and *d,l*-leucovorin, respectively. The geometric mean C_{max} values for 5-methyl-THF were 4930 ng/mL and 4658 ng/mL for levoleucovorin and *d,l*-leucovorin, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the potential of levoleucovorin for carcinogenesis, mutagenesis and impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

The acute intravenous LD_{50} values in adult mice and rats were 575 mg/kg (1725 mg/m^2) and 378 mg/kg (2268 mg/m^2), respectively. Signs of sedation, tremors, reduced motor activity, prostration, labored breathing, and/or convulsion were observed in these studies. Anticipated human dose for each administration is approximately 5 mg/m^2 for high-dose methotrexate therapy which represents a 3-log safety margin.

14 CLINICAL STUDIES

14.1 High-Dose Methotrexate Therapy

The safety and efficacy of levoleucovorin rescue following high-dose methotrexate were evaluated in 16 patients age 6 to 21 who received 58 courses of therapy for osteogenic sarcoma. High-dose methotrexate was one component of several different combination chemotherapy regimens evaluated across several trials. Methotrexate 12 g/m^2 IV over 4 hours was administered to 13 patients, who received levoleucovorin 7.5 mg every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate. Three patients received methotrexate 12.5 g/m^2 IV over 6 hours, followed by levoleucovorin 7.5 mg every 3 hours for 18 doses beginning 12 hours after completion of methotrexate. The mean number of levoleucovorin doses per course was 18.2 and the mean total dose per course was 350 mg. The efficacy of levoleucovorin rescue following high-dose methotrexate was based on the adverse reaction profile. **[See ADVERSE REACTIONS (6)]**

16 HOW SUPPLIED/STORAGE AND HANDLING

Levoleucovorin injection, 175 mg contains 17.5 mL sterile solution in a single-use vial. Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

175 mg/17.5 mL solution – NDC 0781-3201-94

Levoleucovorin injection, 250 mg contains 25 mL sterile solution in a single-use vial. Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

250 mg/25 mL solution – NDC 0781-3203-94

Store in refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light. Store in carton until contents are used.

Manufactured in Germany by Haupt Pharma Wolfratshausen GmbH
Pfaffenrieder Str.5, 82515 Wolfratshausen,
for Sandoz Inc., Princeton , NJ 08540

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