CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208723Orig1s000

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LEVOLEUCOVORIN FOR INJECTION safely and effectively. See full prescribing information for LEVOLEUCOVORIN FOR INJECTION.

LEVOLEUCOVORIN for injection, for intravenous use
Initial U.S. Approval: 1952

----------INDICATIONS AND USAGE----------
Levoleucovorin for injection is a folate analog indicated for:
- Rescue after high-dose methotrexate therapy in osteosarcoma. (1 1)
- Diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination.

Limitation of Use
Levoleucovorin for injection is not indicated for the treatment of pernicious anemia or megaloblastic anemia secondary to lack of vitamin $B_{12,}$ because of the risk of progression of neurologic manifestations despite hematologic remission. (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Do not substitute Levoleucovorin for injection for racemic *d,l-leucovorin.* (2.1)
- For intravenous administration only. Do not administer intrathecally. (2.1)
- Administer intravenously at a rate of less than 16 mL per minute. (2.1, 5.1)

Rescue After High-Dose Methotrexate Therapy
- Rescue recommendations are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Initiate rescue at 7.5 mg (approximately 5 mg/m^2) every 6 hours, 24 hours after beginning methotrexate infusion. (2.2)
- Continue until methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). Adjust dose if necessary based on methotrexate elimination; refer to Full Prescribing Information. (2.2)

Methotrexate Overdosage or Impaired Methotrexate Elimination
- Start as soon as possible after methotrexate overdosage, or within 24 hours of delayed methotrexate elimination. (2.3)
- Administer Levoleucovorin for injection 7.5 mg (approximately 5 mg/m^2) intravenously every 6 hours until methotrexate level is less than 10^{-8} M (0.05 micromolar). (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 175 mg, lyophilized powder in single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------
Patients who have had severe hypersensitivity reactions to leucovorin products, folic acid, or folinic acid. (4)

----------WARNINGS AND PRECAUTIONS----------
Hypercalcemia: Limit rate of infusion due to calcium content. (2.1, 2.4, 5.1)

Increased gastrointestinal toxicities with fluorouracil (5.2, 7)

Drug interaction with trimethoprim-sulfamethoxazole: Increased rates of treatment failure with concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for Pneumocystis jiroveci pneumonia in patients with HIV. (5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 20%) in patients receiving high-dose methotrexate therapy with levoleucovorin rescue were stomatitis and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Revised: 9/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Levoleucovorin for injection is indicated for:

- rescue after high-dose methotrexate therapy in patients with osteosarcoma *[see Clinical Studies (14)]*.
- diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination.

Limitation of Use

Levoleucovorin for injection is not indicated for the treatment of pernicious anemia or megaloblastic anemia secondary to lack of vitamin B_{12}, because of the risk of progression of neurologic manifestations despite hematologic remission.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

- **Do not substitute** Levoleucovorin for injection for racemic *d,l*-leucovorin.
- Levoleucovorin for injection is indicated for intravenous administration only. **Do not administer intrathecally.**
- Administer intravenously at a rate less than 16 mL (160 mg of levoleucovorin) per minute *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosing for Rescue After High-Dose Methotrexate Therapy

The recommendations for Levoleucovorin for injection rescue are based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours (refer to methotrexate prescribing information that includes high-dose methotrexate regimens) in adult and pediatric patients. Twenty-four hours after starting the methotrexate infusion, initiate Levoleucovorin for injection rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours.

Monitor serum creatinine and methotrexate levels at least once daily. Continue Levoleucovorin for injection administration, hydration, and urinary alkalinization (pH 7.0 or greater) until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). Adjust dosage or extend duration based on the guidelines in Table 1.

Table 1 Guidelines for Levoleucovorin for Injection Dosage and Administration

Clinical Situation	Laboratory Findings	Recommendation
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.	Administer 7.5 mg by intravenous infusion every 6 hours for 60 hours (10 doses starting 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	Continue 7.5 mg by intravenous infusion every 6 hours, until methotrexate level is less than

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	administration.	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 • 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).	Administer 75 mg by intravenous infusion every 3 hours until methotrexate level is less than 1 micromolar; then 7.5 mg by intravenous infusion every 3 hours until methotrexate level is less than 0.05 micromolar.

* These patients are likely to develop reversible renal failure. In addition to appropriate levoleucovorin for injection therapy, continue hydration and urinary alkalinization, and monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Impaired Methotrexate Elimination or Renal Impairment
Decreased methotrexate elimination or renal impairment which are clinically important but less severe than abnormalities described in Table 1 can occur following methotrexate administration. If toxicity is observed, extend Levoleucovorin for injection rescue for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses.

Third-Space Fluid Collection and Other Causes of Delayed Methotrexate Elimination
Accumulation in a third-space fluid collection (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration can cause delayed methotrexate elimination. Under such circumstances, higher doses of Levoleucovorin for injection or prolonged administration may be indicated.

2.3 Recommended Dosing for Treatment of Methotrexate Overdosage or Impaired Methotrexate Elimination
Start Levoleucovorin for injection rescue in adult and pediatric patients as soon as possible after an overdosage of methotrexate or within 24 hours of methotrexate administration when there is impaired methotrexate elimination. As the time interval between methotrexate administration and Levoleucovorin for injection rescue increases, effectiveness of Levoleucovorin for injection in diminishing toxicity may decrease. Administer Levoleucovorin for injection 7.5 mg (approximately 5 mg/m^2) intravenously every 6 hours until the serum methotrexate level is less than 10^{-8} M (0.05 micromolar).

Monitor serum creatinine and methotrexate levels at least every 24 hours. If 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 48-hour level is greater than 9 x 10^{-7} M, increase the dose of Levoleucovorin for injection to 50 mg/m^2 intravenously every 3 hours until the methotrexate level is less than 10^{-8} M. Continue concomitant hydration (3 L per day) and urinary alkalinization with sodium bicarbonate. Adjust the bicarbonate dose to maintain urine pH at 7.0 or greater.

2.4 Preparation and Administration

Preparation
- Reconstitute vial contents with 17.7 mL of 0.9% Sodium Chloride Injection, USP, to obtain a clear, colorless to yellowish solution (resultant concentration 10 mg/mL levoleucovorin). Reconstitution with a sodium chloride solution with preservatives (e.g. benzyl alcohol) has not been studied.
- Discard vial if particulate matter or discoloration is observed.

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- Dilute reconstituted solution immediately, to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

Storage
- If necessary, store reconstituted solution for not more than 24 hours at room temperature.
- Do not store reconstituted solution diluted with 0.9% Sodium Chloride Injection, USP, for more than 24 hours at room temperature.
- Do not store reconstituted solution diluted with 5% Dextrose Injection, USP, for more than 4 hours at room temperature.

Administration
- Inspect reconstituted solution in the vial for particulate matter and discoloration prior to administration.
- Do not co-administer with other agents in the same admixture, due to risk of precipitation.
- Administer intravenously at a rate less than 16 mL (160 mg of levoleucovorin) per minute *[see Warnings and Precautions (5.1)]*.

3 DOSAGE FORMS AND STRENGTHS

For injection: 175 mg sterile, off-white to yellowish lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

Levoleucovorin is contraindicated in patients who have had severe hypersensitivity to leucovorin products, folic acid, or folinic acid *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia
Due to the calcium content of the levoleucovorin solution, inject no more than 16 mL (160 mg of levoleucovorin) intravenously per minute *[see Dosage and Administration (2.1 and 2.4)]*.

5.2 Increased Gastrointestinal Toxicities with Fluorouracil
Leucovorin products increase the toxicities of fluorouracil *[see Drug Interactions (7)]*. Gastrointestinal toxicities, (particularly stomatitis and diarrhea) occur more commonly, and may be of greater severity and prolonged duration. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly *d,l*-leucovorin and fluorouracil.

5.3 Drug-Interaction with Trimethoprim-Sulfamethoxazole
Concomitant use of *d,l*-leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis jiroveci pneumonia in patients with HIV infection was associated with increased rates of treatment failure and morbidity in a placebo-controlled study.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

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- Hypercalcemia *[see Warnings and Precautions (5.1)]*
- Increased gastrointestinal toxicities with fluorouracil *[see Warnings and Precautions (5.2)]*
- Drug-interaction with trimethoprim-sulfamethoxazole *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because 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.

Table 2 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, ages 6-21 years. Most patients received levoleucovorin 7.5 mg every 6 hours for 60 hours or longer, beginning 24 hours after completion of methotrexate administration.

Table 2 Adverse Reactions with High-Dose Methotrexate Therapy

Body System/Adverse Reaction	**Number (%) of Patients (N = 16)**	
	All Grades	**≥ Grade 3**
Gastrointestinal		
Stomatitis	6 (37.5)	1 (6.3)
Vomiting	6 (37.5)	0
Nausea	3 (18.8)	0
Diarrhea	1 (6.3)	0
Dyspepsia	1 (6.3)	0
Typhlitis	1 (6.3)	1 (6.3)
Respiratory		
Dyspnea	1 (6.3)	0
Skin and Appendages		
Dermatitis	1 (6.3)	0
Other		
Confusion		
Neuropathy	1 (6.3)	0
Renal function abnormal	1 (6.3)	0
Taste perversion	1 (6.3)	0
	1 (6.3)	0
Total number of patients	9 (56.3)	

6.2 Postmarketing Experience

The following adverse reactions were identified during postapproval use of levoleucovorin, administered in combination with a methotrexate or other regimen. Because these reactions are reported 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. The following have been reported:

- *Respiratory*: dyspnea
- *Dermatologic*: pruritus, rash
- *Other Clinical Events*: temperature change, rigors, allergic reactions

7 DRUG INTERACTIONS

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Effect of leucovorin products on fluorouracil: Leucovorin products increase the toxicity of fluorouracil *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited data with levoleucovorin use in pregnant women. Animal reproduction studies have not been conducted with levoleucovorin.

Levoleucovorin is administered in combination with methotrexate, which can cause embryo-fetal harm. Refer to methotrexate prescribing information for additional information.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of levoleucovorin in human milk or its effects on the breastfed infant or on milk production.

Levoleucovorin is administered in combination with methotrexate. Refer to methotrexate prescribing information for additional information.

8.4 Pediatric Use

The safety and effectiveness of levoleucovorin have been established in pediatric patients. Use of levoleucovorin in pediatric patients is supported by open-label clinical trial data in 16 pediatric patients, 6 years of age and older and with additional supporting evidence from literature *[see Clinical Studies (14)]*.

8.5 Geriatric Use

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

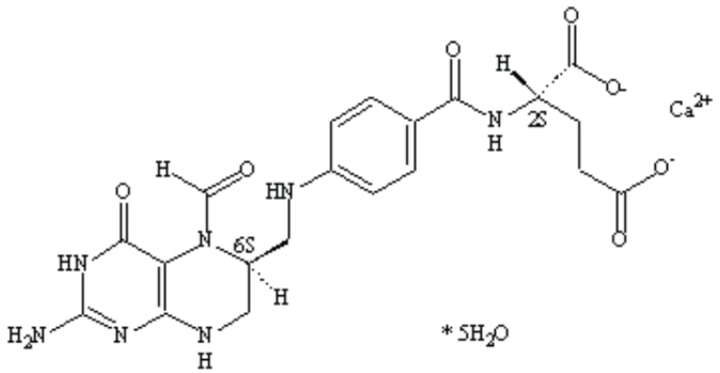
10 OVERDOSAGE

No data are available regarding overdosage with levoleucovorin.

11 DESCRIPTION

The active pharmaceutical ingredient in Levoleucovorin for injection is the calcium salt in a pentahydrate form of levoleucovorin. Levoleucovorin is a folate analog and the pharmacologically active levo-isomer of *d,l*-leucovorin. The chemical name of the salt is 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 formula is $C_{20}H_{21}CaN_7O_7 \cdot 5\ H_2O$ with molecular weight 601.6 amu. The molecular structure is:

Reference ID: 3992507



Levoleucovorin for injection is a sterile lyophilized powder consisting of 175 mg levoleucovorin (equivalent to 222 mg levoleucovorin calcium pentahydrate) and 175 mg mannitol per vial. Sodium hydroxide and/or hydrochloric acid are used to adjust pH during manufacturing. It is an intravenous infusion, after reconstitution with 17.7 mL of sterile 0.9% sodium chloride injection, USP *[see Dosage and Administration (2.4)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

In a crossover-design pharmacokinetic comparability study, healthy subjects received a single 2-hour infusion of either levoleucovorin (200 mg/m^2) or racemic *d,l*-leucovorin (400 mg/m^2). The 90% confidence intervals for the geometric mean ratios for both $AUC_{0\text{-inf}}$ and C_{max} were within the standard limit of 80-125% for both *l*-leucovorin and *l*-5-methyl-THF. The exposure to *l*-leucovorin and 5-methyl-THF was comparable whether it was administered as levoleucovorin or as *d,l*-leucovorin as shown in Table 3:

Table 3 Geometric Mean Pharmacokinetic Parameters

Parameter	*l*-leucovorin	*d,l*-leucovorin	5-methyl-THF-*l*-leucovorin	5-methyl-THF-*d,l*-leucovorin
$AUC_{0\text{-inf}}$ (ng h/mL)	30719	31296	52105	50137
C_{MAX} (ng h/mL)	10895	11301	4930	4658

Distribution

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.

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Elimination
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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted to evaluate the potential of levoleucovorin in carcinogenesis, mutagenesis, and impairment of fertility.

14 CLINICAL STUDIES

14.1 Rescue after High-Dose Methotrexate Therapy in Patients with Osteosarcoma

The safety and efficacy of levoleucovorin rescue following high-dose methotrexate were evaluated in 16 patients, ages 6-21 years, who received 58 courses of chemotherapy 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 adverse reaction profile *[see Adverse Reactions (6)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Single-dose vial containing 175 mg of levoleucovorin formulated as a sterile, preservative-free, off-white to yellowish lyophilized powder. The vial stopper is not made with natural rubber latex.

NDC 0591-4130-54

Store at 25°C (77°F); excursions permitted from 15° to 30° C (59° to 86°F) [See USP Controlled Room Temperature]. Protect from light.

Made in Italy

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised – September 2016

Actavis

Reference ID: 3992507

NDC 0591-4130-54
Levoleucovorin
for Injection
175 mg/vial
Batch/Exp
Actavis
175 mg
vial
Rx Only
NDC 0591-4130-54
Levoleucovorin
for Injection
175 mg/vial
present as
levoleucovorin calcium
Lyophilized Powder
For Intravenous Use Only
Single-Dose Vial -
Discard Unused Portion
175 mg/vial
The vial stopper is not made
with natural rubber latex.
Sterile, Nonpyrogenic,
Preservative-free.
Made in Italy
Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA
Rev. 09/16
N 3 05914 13054 7
Rif. 5071ZP
N. 000000000.0
COUNTRY
Actavis
175 mg
vial
Rx Only
NDC 0591-4130-54
Levoleucovorin
for Injection
175 mg/vial
present as
levoleucovorin calcium
Lyophilized Powder
For Intravenous Use Only
Single-Dose Vial -
Discard Unused Portion
175 mg/vial
Levoleucovorin should be dosed
at half that of racemic leucovorin.
Each vial contains: levoleucovorin
calcium pentahydrate (equivalent
to 175 mg levoleucovorin) and
175 mg mannitol. Sodium
hydroxide and/or hydrochloric acid
are used to adjust the pH during
manufacture.
Usual Dosage: See Prescribing
Information. (See WARNINGS).
When reconstituted with 17.7 mL
of 0.9% sodium chloride injection,
USP (see package insert) the
resulting solution will contain:
levoleucovorin calcium equivalent
to 10 mg levoleucovorin per mL;
mannitol 10 mg per mL.
Reconstituted solution must be
used within 24 hours.
Store at 25°C (77°F); excursions
permitted between 15° to 30°C
(59° to 86°F). [See USP Controlled
Room Temperature.]
Protect from light. Store in carton
until contents are used.

(b) (4)

NDC 0591 4130 54
Rx Only
Levoleucovorin
for Injection
175 mg/vial
0591-4130-54
Actavis
Single-Dose Vial-
Discard Unused Portion
BATCH/EXP.

(b) (4)

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/s/

JOSEPH E GOOTENBERG
09/29/2016