FUSILEV - levoleucovorin injection, powder, lyophilized, for solution
FUSILEV - levoleucovorin injection, solution
Acrotech Biopharma LLC

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

Fusilev® (levoleucovorin) for injection, for intravenous use
Fusilev® (levoleucovorin) injection, for intravenous use
Initial U.S. Approval: 1952 (d,l-leucovorin)

RECENT MAJOR CHANGES

Indications and Usage (1)	01/2020
Dosage and Administration (2)	11/2020
Contraindications (4)	01/2020
Warnings and Precautions (5)	01/2020

INDICATIONS AND USAGE

Fusilev is a folate analog indicated for:
• Rescue after high-dose methotrexate therapy in adult and pediatric patients with osteosarcoma. (1)
• Diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients. (1)
• Treatment of adults with metastatic colorectal cancer in combination with fluorouracil. (1)

Limitations of Use:
Fusilev is not indicated for the treatment of pernicious anemia and megaloblastic anemia secondary to lack of vitamin B12, because of the risk of progression of neurologic manifestations despite hematologic remission. (1)

DOSAGE AND ADMINISTRATION

For intravenous administration only. Do not administer intrathecally. (2.1)

Rescue After High-Dose Methotrexate Therapy
• Rescue recommendations are based on methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Initiate rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours, 24 hours after the beginning of methotrexate infusion. (2.2)
• Continue until the 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)

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

Metastatic Colorectal Cancer in Combination with Fluorouracil
• The following regimens have been used for the treatment of colorectal cancer:
  o Fusilev 100 mg/m^2 by intravenous injection over a minimum of 3 minutes, followed by fluorouracil 370 mg/m^2 once daily for 5 consecutive days.(2.4)
  o Fusilev 10 mg/m^2 by intravenous injection followed by fluorouracil 425 mg/m^2 once daily for 5 consecutive days. (2.4)
• Administer Fluorouracil and Fusilev separately to avoid the formation of precipitate.
• The above five-day courses may be repeated every 4 weeks for 2 courses, then every 4 to 5 weeks, if the patient has recovered from toxicity from the prior course.
• Do not adjust Fusilev dosage for toxicity. (2.5)

DOSAGE FORMS AND STRENGTHS

• For Injection: 50 mg of levoleucovorin as a lyophilized powder in a single-dose vial for reconstitution (3)
• Injection: 175 mg/17.5 mL (10 mg/mL) or 250 mg/25 mL (10 mg/mL) in a single-dose vial

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

• Hypercalcemia: Due to calcium content, inject no more than 16 mL (160 mg) of levoleucovorin solution intravenously per minute. (5.1)
• Increased Gastrointestinal Toxicities with Fluorouracil: Do not initiate or continue therapy with Fusilev and fluorouracil in patients with symptoms of gastrointestinal toxicity until symptoms have resolved. Monitor patients with diarrhea until it has resolved as rapid deterioration leading to death can occur. (5.2,7)
• Drug Interaction with Trimethoprim-Sulfamethoxazole: Increased rates of treatment failure and morbidity 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 Fusilev rescue are stomatitis and vomiting. (6.1)
• The most common adverse reactions (>50%) in patients receiving Fusilev in combination with fluorouracil for metastatic colorectal cancer are stomatitis, diarrhea, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acrotech Biopharma LLC at 1-877-387-4538 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fusilev is indicated for:
• rescue after high-dose methotrexate therapy in adult and pediatric patients with osteosarcoma.
• diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients.
• the treatment of adults with metastatic colorectal cancer in combination with fluorouracil.

Limitations of Use
Fusilev is not indicated for pernicious anemia and megaloblastic anemia secondary to the 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

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

2.2 Co-adminstration of Fusilev with other agents

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

2.3 Recommended Dosage for Rescue After High-Dose Methotrexate Therapy

The recommended dosage for Fusilev is based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Twenty-four hours after starting the methotrexate infusion, initiate Fusilev at a dose of 7.5 mg (approximately 5 mg/m^2) as an intravenous infusion every 6 hours.
Monitor serum creatinine and methotrexate levels at least once daily. Continue Fusilev administration, hydration, and urinary alkalinization (pH of 7 or greater) until the methotrexate level is below 5×10^{-8} M (0.05 micromolar). Adjust the Fusilev dose or extend the duration as recommended in Table 1.

Table 1 Recommended Dosage for Fusilev based on Serum Methotrexate and Creatinine Levels

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 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 by intravenous infusion every 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 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 Fusilev therapy, continue hydration and urinary alkalinization and monitoring 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 the abnormalities described in Table 1 can occur following methotrexate administration. If toxicity associated with methotrexate is observed, in subsequent courses extend Fusilev rescue for an additional 24 hours (total of 14 doses over 84 hours).

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 delay methotrexate elimination. Under such circumstances, higher doses of Fusilev or prolonged administration may be indicated.

2.4 Recommended Dosage for Overdosage of Folic Acid Antagonists or Impaired Methotrexate Elimination

Start Fusilev as soon as possible after an overdosage of methotrexate or within 24 hours of methotrexate administration when methotrexate elimination is impaired. As the time interval between methotrexate administration and Fusilev increases, the effectiveness of Fusilev to diminish methotrexate toxicity may decrease. Administer Fusilev 7.5 mg (approximately 5 mg/m^2) by intravenous infusion every 6 hours until the serum methotrexate level is less than 5×10^{-8} M (0.05 micromolar).

Monitor serum creatinine and methotrexate levels at least every 24 hours. Increase the dosage of Fusilev to 50 mg/m2 intravenously every 3 hours and continue Fusilev at this dosage until the methotrexate level is less than 5×10^{-8} M for the following:

• if serum creatinine at 24-hours increases 50% or more compared to baseline
• if the methotrexate level at 24-hours is greater than 5×10^{-6} M
• if the methotrexate level at 48-hours is greater than 9×10^{-7} M,

Continue concomitant hydration (3 L per day) and urinary alkalinization with sodium bicarbonate. Adjust the sodium bicarbonate dose to maintain urine pH at 7 or greater.

2.5 Dosage in Combination with Fluorouracil for Metastatic Colorectal Cancer

The following regimens have been used for the treatment of colorectal cancer:

• Fusilev 100 mg/m^2 by intravenous injection over a minimum of 3 minutes, followed by fluorouracil at 370 mg/m^2 by intravenous injection, once daily for 5 consecutive days.
• Fusilev 10 mg/m^2 by intravenous injection, followed by fluorouracil 425 mg/m^2 by intravenous injection, once daily for 5 consecutive days.

Administer Fluorouracil and Fusilev separately to avoid the formation of a precipitate.

This five-day course may be repeated every 4 weeks for 2 courses, then every 4 to 5 weeks, if the patient has recovered from the toxicity from the prior course. Do not adjust Fusilev dosage for toxicity.

Refer to fluorouracil prescribing information for information on fluorouracil dosage and dosage

modifications for adverse reactions.

2.6 Preparation for Administration

Fusilev for Injection

• Prior to intravenous injection, reconstitute the 50 mg vial of Fusilev for Injection with 5.3 mL of 0.9% Sodium Chloride Injection, USP to yield a levoleucovorin concentration of 10 mg per mL. Reconstitution with Sodium Chloride solutions with preservatives (e.g. benzyl alcohol) has not been studied. The use of solutions other than 0.9% Sodium Chloride Injection, USP is not recommended.
• The reconstituted 10 mg per mL levoleucovorin contains no preservative. Observe strict aseptic technique during reconstitution of the drug product. Discard unused portion.
• Saline reconstituted levoleucovorin solutions may be further diluted, immediately, to concentrations of 0.5 mg/mL to 5 mg/mL in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Do not store the reconstituted product or reconstituted product dilutedusing 0.9% Sodium Chloride Injection, USP for more than 12 hours at room temperature. Do not store reconstituted product diluted using 5% Dextrose Injection, USP for more than 4 hours at room temperature.
• Visually inspect the reconstituted solution for particulate matter and discoloration prior to administration. Do not use if cloudiness or precipitate is observed.
• Do not intravenously inject more than 16 mL of reconstituted solutions (160 mg of levoleucovorin) per minute, because of the calcium content of the levoleucovorin solution.

Fusilev Injection

• Levoleucovorin contains no preservative. Observe strict aseptic technique during reconstitution of the drug product. Discard unused portion.
• 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. Do not store the product diluted using 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP for more than 4 hours at room temperature.
• Visually inspect the diluted solution for particulate matter and discoloration prior to administration. Do not use if cloudiness or precipitate is observed.
• Inject no more than 16 mL of Fusilev Injection (160 mg of levoleucovorin) intravenously per minute, because of the calcium content of the levoleucovorin solution.

3 DOSAGE FORMS AND STRENGTHS

• For Injection: 50 mg of levoleucovorin as a sterile white to pale yellow lyophilized powder in a single-dose vial for reconstitution.
• Injection: 175 mg/17.5 mL (10 mg/mL) or 250 mg/25 mL (10 mg/mL) of levoleucovorin sterile colorless to faint yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

Fusilev 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

Because of the calcium content of the levoleucovorin solution, inject no more than 16 mL (160 mg of levoleucovorin) intravenously per minute.

5.2 Increased Gastrointestinal Toxicities with Fluorouracil

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

Monitor patients for gastrointestinal toxicities. Do not initiate or continue therapy with Fusilev and fluorouracil in patients with symptoms of gastrointestinal toxicity until those symptoms have resolved. Monitor patients with diarrhea until resolved, as rapid deterioration leading to death can occur.

5.3 Drug Interaction with Trimethoprim-Sulfamethoxazole

The 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 [*see Drug Interactions* (7)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• Hypercalcemia [*see Warnings and Precautions (5.1)*]
• Increased gastrointestinal toxicities with fluorouracil [*see Warnings and Precautions (5.2)*]

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.

High-Dose Methotrexate Therapy

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 Fusilev rescue for osteosarcoma in 16 patients aged 6 to 21 years. Most patients received Fusilev 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

Adverse Reactions	**Fusilev n=16**	
	All Grades (%)	**Grade 3-4 (%)**
Gastrointestinal		
Stomatitis	38	6
Vomiting	38	0
Nausea	19	0
Diarrhea	6	0
Dyspepsia	6	0
Typhlitis	6	6
Respiratory		
Dyspnea	6	0
Skin and Appendages		
Dermatitis	6	0
Other		
Confusion	6	0
Neuropathy	6	0
Renal function abnormal	6	0
Taste perversion	6	0

Combination with Fluorouracil in Colorectal Cancer

Table 3 presents the frequency of adverse reaction which occurred in 2 arms of a randomized controlled trial conducted by the North Central Cancer Treatment Group (NCCTG) in patients with metastatic colorectal cancer. The trial failed to show superior overall survival with fluorouracil + levoleucovorin compared to fluorouracil + d,l-leucovorin. Patients were randomized to fluorouracil 370 mg/m^2 intravenously and levoleucovorin 100 mg/m^2 intravenously, both daily for 5 days, or to fluorouracil 370 mg/m^2 intravenously and d,l-leucovorin 200 mg/m^2 intravenously, both daily for 5 days. Treatment was repeated week 4 and week 8, and then every 5 weeks until disease progression or unacceptable toxicity.

Table 3 Adverse Reactions Occurring in ≥ 10% of Patients in Either Arm

Adverse Reaction	**Levoleucovorin/fluorouracil n=318**		***d,l*-Leucovorin/fluorouracil n=307**	
	Grades 1-4 (%)	**Grades 3-4 (%)**	**Grades 1-4 (%)**	**Grades 3-4 (%)**
Gastrointestinal Disorders				
Stomatitis	72	12	72	14
Diarrhea	70	19	65	17
Nausea	62	8	61	8
Vomiting	40	5	37	6
Abdominal Pain[1]	14	3	19	3
General Disorders				
Asthenia/Fatigue/Malaise	29	5	32	11
Skin Disorders				
Dermatitis	29	1	28	1
Alopecia	26	0.3	28	1
Metabolism and Nutrition				
Anorexia/Decreased Appetite	24	4	25	2

[1]Includes abdominal pain, upper abdominal pain, lower abdominal pain, and abdominal tenderness

6.2 Postmarketing Experience

The following adverse reaction have been identified during postapproval use of levoleucovorin

products. Because these reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Dermatologic: pruritus, rash
Respiratory: dyspnea
Other: temperature change, rigors, allergic reactions

7 DRUG INTERACTIONS

7.1 Effects of Leucovorin Products on Other Drugs

Antiepileptic Drugs
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. Monitor patients taking folinic acid in combination with antiepileptic drugs.

Fluorouracil
Leucovorin products increase the toxicity of fluorouracil. Do not initiate or continue therapy with Fusilev and fluorouracil in patients with symptoms of gastrointestinal toxicity until those symptoms have resolved. Monitor patients with diarrhea until the diarrhea has resolved, as rapid deterioration leading to death can occur [*see Warningsand Precautions (5.2*)].

Trimethoprim-Sulfamethoxazole
The 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 [*see Warnings and Precautions (5.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 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 or fluorouracil. Refer to methotrexate and fluorouracil prescribing information for additional information.

8.4 Pediatric Use

The safety and effectiveness of Fusilev have been established in pediatric patients for rescue after high-dose methotrexate therapy in osteosarcoma and diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination. Use of levoleucovorin in pediatric patients is supported by open-label clinical trial data in 16 pediatric patients 6 years of age and older, with additional supporting evidence from literature [*see Clinical Studies (14.1)*].

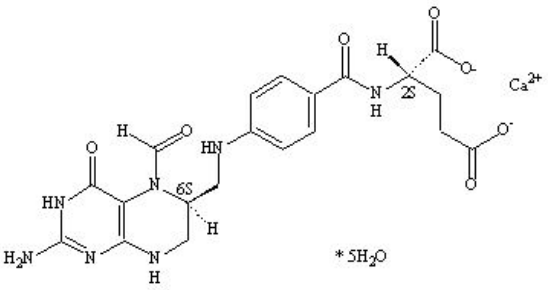
The safety and effectiveness of Fusilev have not been established for the treatment of pediatric patients with advanced metastatic colorectal cancer.

8.5 Geriatric Use

- Clinical studies of Fusilev in the treatment of osteosarcoma did not include patients aged 65 and over to determine whether they respond differently from younger patients.
- In the NCCTG clinical trial of Fusilev in combination with fluorouracil for the treatment of metastatic colorectal cancer, no overall differences in safety or effectiveness were observed between patients age 65 years and older and younger patients.

11 DESCRIPTION

Levoleucovorin is a folate analog and the pharmacologically active levo-isomer of d,l-leucovorin. The chemical name of levoleucovorin calcium 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 $C_{20}H_{21}CaN_7O_7 .5H_2O$ and the molecular weight is 601.6. The molecular structure is:



Fusilev (levoleucovorin) for injection, for intravenous use is supplied as a sterile white to pale yellow lyophilized powder consisting of 50 mg levoleucovorin (equivalent to 64 mg levoleucovorin calcium pentahydrate) and 50 mg mannitol per 50 mg single-dose vial. Sodium hydroxide and/or hydrocholoric acid are used to adjust the pH.

Fusilev (levoleucovorin) injection, for intravenous use is supplied as a sterile colorless to faint yellow solution of either 175 mg levoleucovorin in 17.5 mL or 250 mg levoleucovorin in 25 mL per single-dose vial. Each mL contains 10 mg levoleucovorin (equivalent to x mg levoleucovorin calcium pentahydrate) 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

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 counteracts the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

Combination with Fluorouracil in Colorectal Cancer

Levoleucovorin enhances the therapeutic and toxic effects of fluorouracil. Fluorouracil is metabolized to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which binds to and inhibits thymidylate synthase (an enzyme important in DNA repair and replication). Levoleucovorin is converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of FdUMP to thymidylate synthase and thereby enhancing the inhibition of thymidylate synthase.

12.3 Pharmacokinetics

The pharmacokinetics of levoleucovorin after intravenous administration of a 15 mg dose was studied in healthy subjects. The mean maximum serum total tetrahydrofolate (total-THF) concentrations was 1722 ng/mL (CV 39%) and the mean maximum serum (6S)-5-methyl-5,6,7,8-tetrahydrofolate concentrations was 275 ng/mL (CV 18%) observed around 0.9 hours post injection.

Distribution

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

Elimination

The mean terminal half-life was 5.1 hours for total-THF and 6.8 hours for (6S)-5-methyl-5,6,7,8-tetrahydrofolate.

Drug Interaction Studies

The mean dose-normalized steady-state plasma concentrations for both levoleucovorin and 5-methyl-THF were comparable whether fluorouracil (370 mg/m^2/day as an intravenous bolus) was given in combination with levoleucovorin (250 mg/m^2 and 1000 mg/m^2 as a continuous intravenous infusion for

5.5 days) or with d,l-leucovorin (500 mg/m^2 as a continuous intravenous infusion for 5.5 days).

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.

14 CLINICAL STUDIES

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

The efficacy of levoleucovorin rescue following high-dose methotrexate was evaluated in 16 patients aged 6 to 21 years 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 grams/m2 as an intravenous infusion over 4 hours was administered to 13 patients, who received Fusilev 7.5 mg by intravenous infusion every 6 hours for 60 hours or longer beginning 24 hours after completion of methotrexate. Three patients received methotrexate 12.5 grams/m2 intravenously over 6 hours, followed by Fusilev 7.5 mg by intravenous infusion every 3 hours for 18 doses beginning 12 hours after completion of methotrexate. The mean number of Fusilev doses per course was 18.2 and the mean total dose per course was 350 mg. The efficacy of Fusilev rescue following high-dose methotrexate was based on the adverse reaction profile [*See Adverse Reactions (6.1)*].

14.2 Metastatic Colorectal Cancer

In a randomized clinical study conducted by Mayo Clinic and North Central Cancer Treatment Group (NCCTG) in patients with metastatic colorectal cancer comparing d,l leucovorin 200 mg/m^2 and fluorouracil 370 mg/m^2 versus d,l leucovorin 20 mg/m^2 and fluorouracil 425 mg/m^2 versus fluorouracil 500 mg/m^2, with all drugs administered by intravenous infusion daily for 5 days every 28 to 35 days, response rates were 26% (p=0.04 versus fluorouracil alone), 43% (p=0.001 versus fluorouracil alone) and 10%, respectively. Respective median survival times were 12.2 months (p=0.037), 12 months (p=0.050), and 7.7 months. The low dose d,l leucovorin regimen was associated with a statistically significant improvement in weight gain of more than 5%, relief of symptoms, and improvement in performance status. The high dose d,l leucovorin regimen was associated with a statistically significant improvement in performance status and trended toward improvement in weight gain and in relief of symptoms but these were not statistically significant.

In a second randomized clinical study conducted by Mayo Clinic and NCCTG, the fluorouracil alone arm was replaced by a regimen of sequentially administered methotrexate , fluorouracil, and d,l leucovorin. Response rates with d,l leucovorin 200 mg/m2 and fluorouracil 370 mg/m^2 versus d,l leucovorin 20 mg/m^2 and fluorouracil 425 mg/m^2 versus sequential methotrexate and fluorouracil and d,l leucovorin were respectively 31% (p≤0.01), 42% (p≤0.01), and 14%. Respective median survival times were 12.7 months (p≤0.04), 12.7 months (p≤0.01), and 8.4 months. There was no statistically significant difference in weight gain of more than 5% or in improvement in performance status was seen between the treatment arms.

A randomized controlled trial conducted by NCCTG in patients with metastatic colorectal cancer failed to show superiority of a regimen of fluorouracil + levoleucovorin to fluorouracil + d,l-leucovorin in overall survival. Patients were randomized to fluorouracil 370 mg/m^2 intravenously and levoleucovorin 100 mg/m^2 intravenously, both daily for 5 days, or to fluorouracil 370 mg/m^2 intravenously and d,l-leucovorin 200 mg/m^2 intravenously, both daily for 5 days. Treatment was repeated week 4 and week 8, and then every 5 weeks until disease progression or unacceptable toxicity.

16 HOW SUPPLIED/STORAGE AND HANDLING

Fusilev for Injection

Fusilev (levoleucovorin) for injection is a sterile white to pale yellow lyophilized powder in a single-dose vial available as:
50 mg vial – NDC 72893-009-01
Store at 20°C to 25°C (68°F to 77°F) in carton until contents are used. Excursions permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. Protect from light.

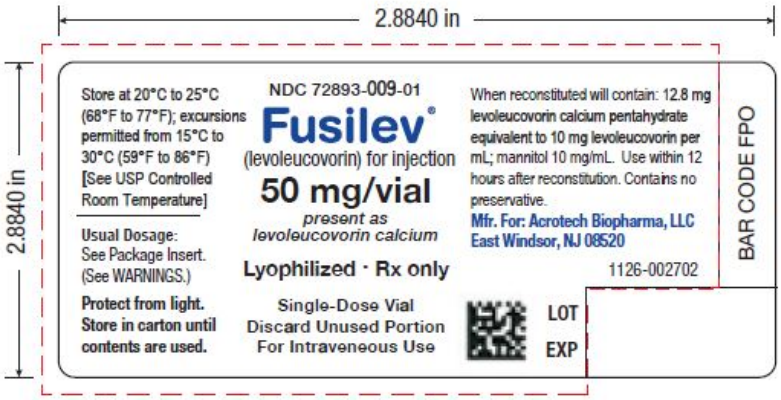
Fusilev Injection

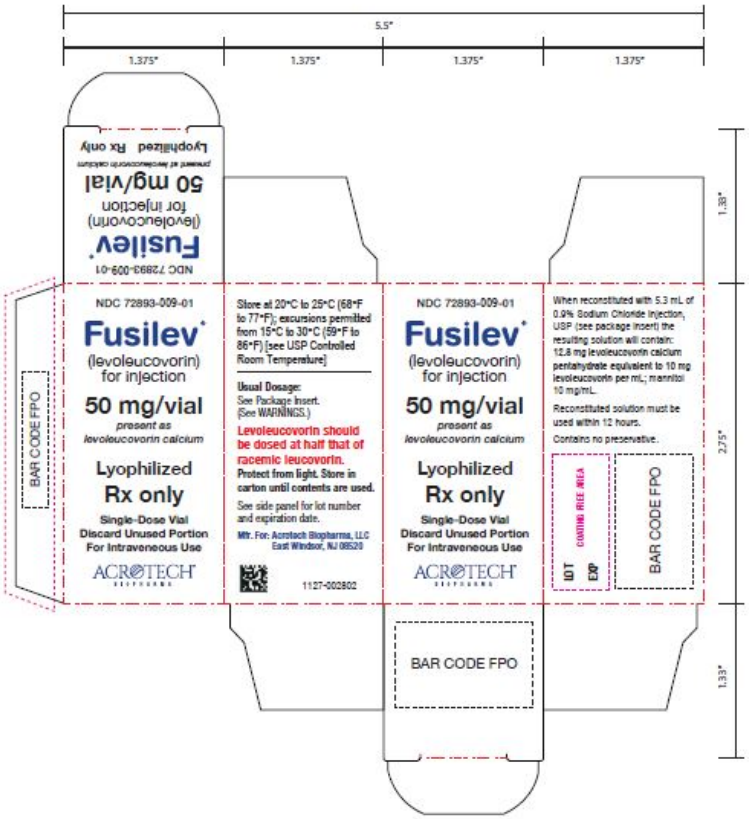
Fusilev (levoleucovorin) injection is a sterile colorless to faint yellow solution in a single-dose vial available as:
175 mg/17.5 mL solution – NDC 72893-013-01

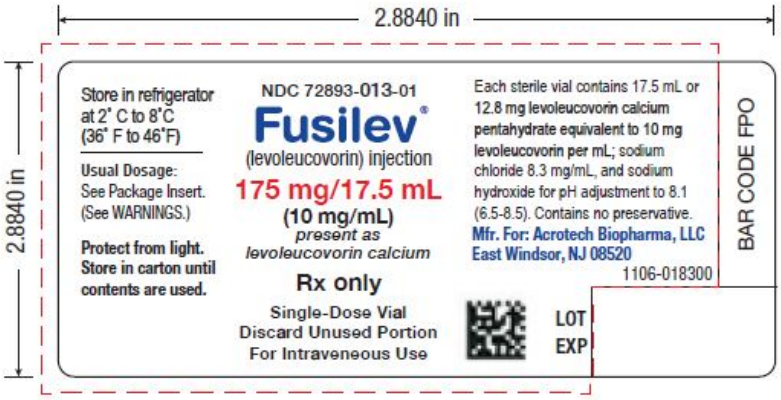
250 mg/25 mL solution – NDC 72893-014-01
Store in refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light. Store in carton until contents are used.

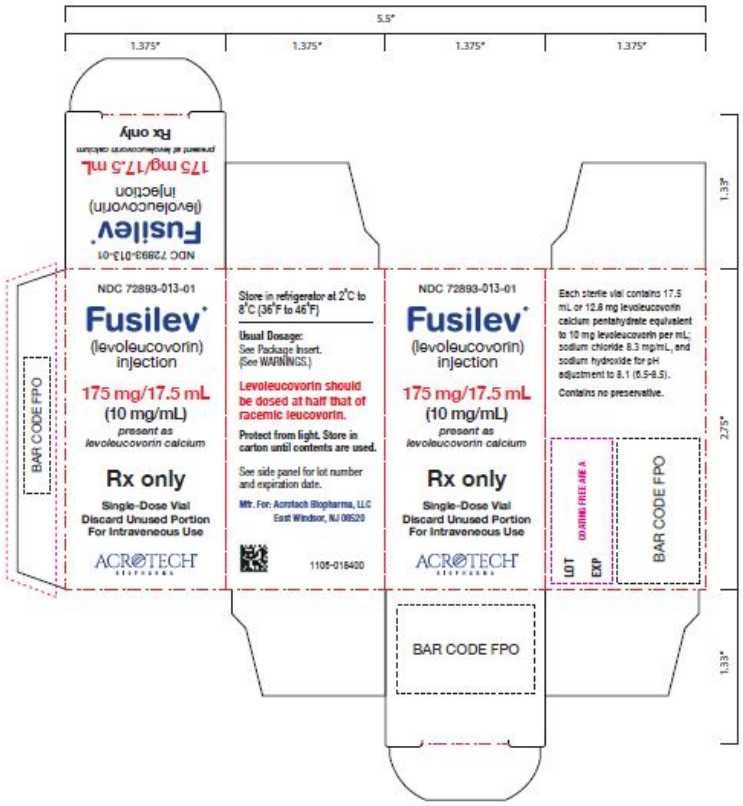
Manufactured for Acrotech Biopharma LLC.
East Windsor, NJ 08520
Fusilev® is a registered trademark of Acrotech Biopharma LLC.

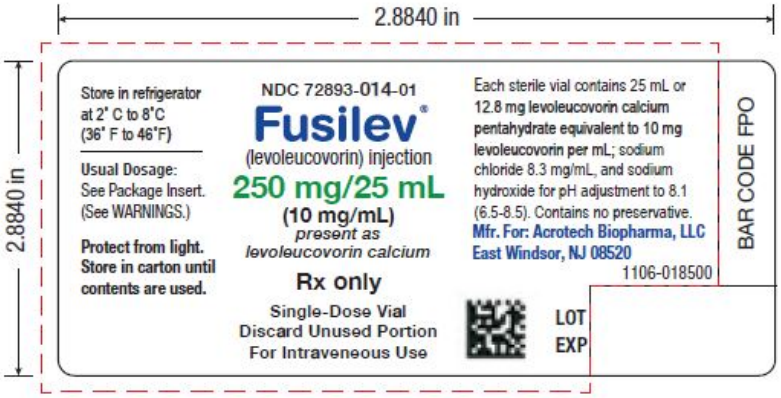
18. Principal Display Panel

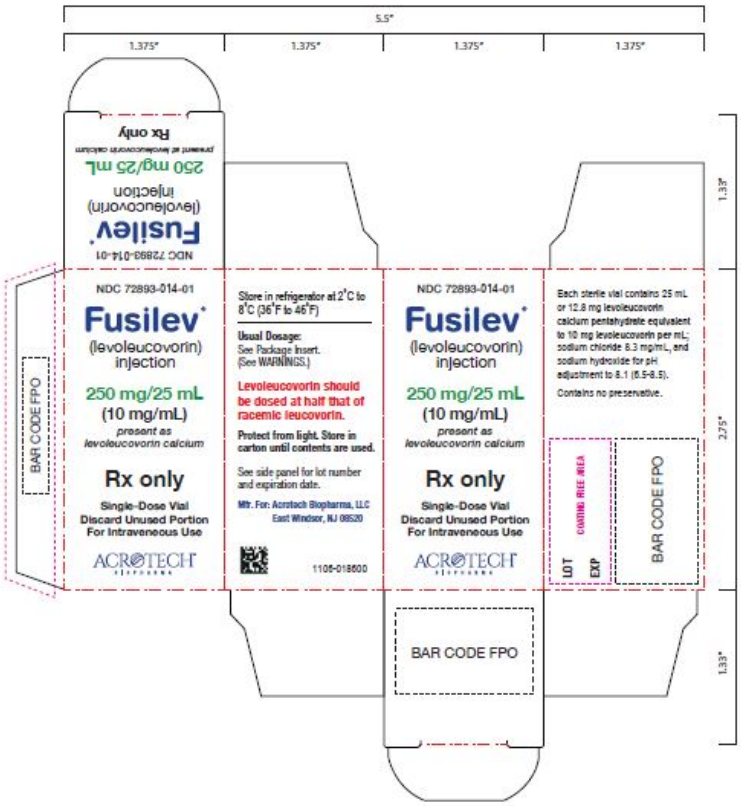





2.8840 in
2.8840 in
Store in refrigerator at 2° C to 8°C (36° F to 46°F)
Usual Dosage: See Package Insert. (See WARNINGS.)
Protect from light. Store in carton until contents are used.
NDC 72893-013-01
Fusilev®
(levoleucovorin) injection
175 mg/17.5 mL
(10 mg/mL)
present as levoleucovorin calcium
Rx only
Single-Dose Vial
Discard Unused Portion
For Intraveneous Use
Each sterile vial contains 17.5 mL or 12.8 mg levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin per mL; sodium chloride 8.3 mg/mL, and sodium hydroxide for pH adjustment to 8.1 (6.5-8.5). Contains no preservative.
Mfr. For: Acrotech Biopharma, LLC
East Windsor, NJ 08520
1106-018300
LOT
EXP
BAR CODE FPO


5.5"
1.375"
1.375"
1.375"
1.375"
1.35"
2.75"
1.35"
BAR CODE FPO
NDC 72893-013-01
Fusilev®
(levoleucovorin) injection
175 mg/17.5 mL
(10 mg/mL)
present as levoleucovorin calcium
Rx only
Single-Dose Vial
Discard Unused Portion
For Intraveneous Use
ACROTECH BIOPHARMA
Store in refrigerator at 2°C to 8°C (36°F to 46°F)
Usual Dosage: See Package Insert. (See WARNINGS.)
Levoleucovorin should be dosed at half that of racemic leucovorin.
Protect from light. Store in carton until contents are used.
See side panel for lot number and expiration date.
Mfr. For: Acrotech Biopharma, LLC
East Windsor, NJ 08520
1106-018400
NDC 72893-013-01
Fusilev®
(levoleucovorin) injection
175 mg/17.5 mL
(10 mg/mL)
present as levoleucovorin calcium
Rx only
Single-Dose Vial
Discard Unused Portion
For Intraveneous Use
ACROTECH BIOPHARMA
Each sterile vial contains 17.5 mL or 12.8 mg levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin per mL; sodium chloride 8.3 mg/mL, and sodium hydroxide for pH adjustment to 8.1 (6.5-8.5).
Contains no preservative.
LOT
EXP
BAR CODE FPO
BAR CODE FPO





FUSILEV

levoleucovorin injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72893-009
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVOLEUCOVORIN CALCIUM (UNII: 778XL6VBS8) (LEVOLEUCOVORIN - UNII:990S25980Y)	LEVOLEUCOVORIN	50 mg in 5 mL

Inactive Ingredients	
Ingredient Name	Strength
HYDROCHLORIC ACID (UNII: QTT17582CB)	
MANNITOL (UNII: 3OWL53L36A)	50 mg in 5 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72893-009-01	1 in 1 CARTON	08/15/2008	
1		5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020140	08/15/2008	

FUSILEV

levoleucovorin injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72893-013
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
LEVOLEUCOVORIN CALCIUM (UNII: 778XL6VBS8) (LEVOLEUCOVORIN - UNII:990S25980Y)	LEVOLEUCOVORIN	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	1 mL in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.3 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72893-013-01	1 in 1 CARTON	09/15/2011	
1		17.5 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020140	09/15/2011	

FUSILEV

levoleucovorin injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72893-014
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of	Strength

Ingredient Name	Strength	Strength
LEVOLEUCOVORIN CALCIUM (UNII: 778XL6VBS8) (LEVOLEUCOVORIN - UNII:990S25980Y)	LEVOLEUCOVORIN	10 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	1 mL in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	8.3 mg in 1 mL
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:72893-014-01	1 in 1 CARTON	09/15/2011	
1		25 mL in 1 VIAL; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020140	09/15/2011	

Labeler - Acrotech Biopharma LLC (116965616)

Registrant - Acrotech Biopharma LLC (116965616)

Establishment

Name	Address	ID/FEI	Business Operations
Cangene BioPharma, LLC		050783398	MANUFACTURE(72893-009, 72893-013, 72893-014)

Revised: 11/2020 Acrotech Biopharma LLC