09-J2000-31

Original Effective Date: 04/01/15

Reviewed: 02/13/19

Revised: 06/01/26

Subject: Levoleucovorin (Fusilev® and Khapzory™) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Levoleucovorin calcium (Fusilev®) is the pharmacologically active levoisomer of racemic leucovorin (also called folinic acid), a synthetic folate analogue. Folates are a group of vitamins that allow cells to reproduce by fueling the synthesis of purinic and pyrimidinic bases for DNA production. Levoleucovorin calcium was approved by the US Food and Drug Administration (FDA) in March 2008 for use after high-dose methotrexate therapy in osteosarcoma and to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. Methotrexate is a folic acid antagonist that prevents folates from being metabolized to their reduced active form by binding and inhibiting enzymes involved in the activation of folic acid to folinic acid, leading to cell death. The administration of levoleucovorin or leucovorin, therefore, bypasses the metabolic block affected by methotrexate. In May 2011, the FDA granted the additional indication of use in combination chemotherapy with 5-fluorouracil (5-FU) in the palliative treatment of patients with advanced metastatic colorectal cancer. Levoleucovorin enhances the binding of 5-FU to thymidylate synthase and is frequently administered concurrently with 5-FU for therapeutic advantage. A new brand formulation of levoleucovorin (Khapzory) was FDA approved for all uses of levoleucovorin calcium in October 2018.

In a bioequivalence study, 40 healthy volunteers received a 2-hour infusion of a single-dose of either levoleucovorin 200 mg/m^2 or racemic leucovorin 400 mg/m^2, which yielded similar mean Cmax values of the active metabolite 5-methyltetrahydrofolate of 4,930 nanograms/mL and 4,658 nanograms/mL, respectively. The safety and efficacy of levoleucovorin rescue following high-dose methotrexate was evaluated in 16 patients age 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 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. The NCCN guidelines for colon and rectal cancer recommend the use of levoleucovorin in combination with fluorouracil-based regimens for colorectal cancer when leucovorin is not available. NCCN guidelines also recommend use of levoleucovorin as a component of high-dose methotrexate regimens in osteosarcoma.

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

Levoleucovorin calcium (both brand Fusilev and generic formulations) meets the definition of **medical necessity** when **BOTH** of the following criteria are met:

1. Leucovorin injection is **NOT** available for use due to a national drug shortage.*†
2. Any **ONE** of the following indications:
    a) Used in combination with a systemic fluorouracil (5-FU)-based chemotherapy regimen administered for the treatment of cancer.
    b) Used in combination with a high-dose methotrexate regimen (to diminish toxicity) used for the treatment of cancer.
    c) To diminish the toxicity and counteract the effects of an overdosage of a folic acid antagonist (e.g., methotrexate, pemetrexed, proguanil, pyrimethamine, trimethoprim)

*To verify non-availability, the status of leucovorin injection must be listed as "Currently in Shortage" on the FDA Drug Shortages webpage (http://www.accessdata.fda.gov/scripts/drugshortages/) **AND** all listed manufactures must have all strengths unavailable.

†Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

Approval duration: 6 months.

Levoleucovorin (Khapzory) meets the definition of **medical necessity** when **BOTH** of the following criteria are met:

1. Both leucovorin injection and levoleucovorin calcium (both brand Fusilev and generic formulations) are **NOT** available for use due to a national drug shortage.*†
2. Any **ONE** of the following indications:
    a) Used in combination with a systemic fluorouracil (5-FU)-based chemotherapy regimen administered for the treatment of cancer.
    b) Used in combination with a high-dose methotrexate regimen (to diminish toxicity) used for the treatment of cancer.
    c) To diminish the toxicity and counteract the effects of an overdosage of a folic acid antagonist (e.g., methotrexate, pemetrexed, proguanil, pyrimethamine, trimethoprim)

*To verify non-availability, the status of leucovorin injection and levoleucovorin calcium must be listed as "Currently in Shortage" on the FDA Drug Shortages webpage (http://www.accessdata.fda.gov/scripts/drugshortages/) **AND** all listed manufactures must have all strengths unavailable.

†Step therapy requirement does not apply if a prior health plan paid for the medication - documentation of a paid claim within the past 90 days must be submitted

Approval duration: 6 months.

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: Levoleucovorin is indicated for: (1) rescue after high-dose methotrexate therapy in osteosarcoma, (2) diminishing the toxicity and counteracting the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists, and (3) use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer. It is **NOT** approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

For IV use only. Do **NOT** administer intrathecally. See prescribing information for dosing recommendations.

Rescue After High-Dose Methotrexate Therapy

Rescue recommendations are based on a methotrexate dose of 12 grams/m^2 administered IV over 4 hours. Provide levoleucovorin rescue at a dose of 7.5 mg (approximately 5 mg/m^2) every 6 hours for 10 doses starting 24 hours after the beginning of the methotrexate infusion. Determine serum creatinine and methotrexate levels at least once daily. Continue levoleucovorin administration, hydration, and urinary alkalinization (pH of 7or greater) until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). The dosage may need to be adjusted based on methotrexate levels. Refer to the prescribing information for dosing recommendations.

Administration in Combination with 5-Fluorouracil (5-FU)

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

- Levoleucovorin 100 mg/m^2 by slow IV injection over a minimum of 3 minutes, followed by 5-FU 370 mg/m^2 IV.
- Levoleucovorin 10 mg/m^2 by IV injection followed by 5-FU 425 mg/m^2 IV.

Both treatments are repeated daily for five days. The 5-day treatment course may be repeated at 4 week (28-day) intervals, for two courses and then repeated at 4 to 5 week (28 to 35 day) intervals if the member has completely recovered from the toxic effects of the prior treatment course. In subsequent treatment courses, the dosage of 5-FU should be adjusted based on patient tolerance of the prior treatment course. 5-FU and levoleucovorin calcium (Fusilev) should be administered separately to avoid the formation of a precipitate.

Methotrexate Overdosage

Rescue should begin as soon as possible after overdosage and within 24 hours of methotrexate administration when there is delayed excretion. As the time interval between methotrexate and rescue increases, levoleucovorin's effectiveness in counteracting toxicity may decrease. Levoleucovorin 7.5 mg (approximately 5 mg/m^2) should be administered IV every 6 hours until the serum methotrexate level is less than 5 x 10^{-8} M. Serum creatinine and methotrexate levels should be determined at 24 hour intervals. The dosage may need to be adjusted based on methotrexate levels. Refer to the prescribing information for dosing recommendations.

PRECAUTIONS:

CONTRAINDICATION:

- Patients who have had previous allergic reactions attributed to leucovorin products, folic acid or folinic acid

WARNINGS:

- **Rate of Administration**: Due to the calcium ion (Ca^{2+}) content of levoleucovorin calcium (Fusilev), no more than 16 mL (160 mg) of levoleucovorin solution should be injected IV per minute.
- **Potential for Enhanced Toxicity with 5-Fluorouracil**: Levoleucovorin enhances the toxicity of 5-FU and deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and 5-FU. When administered concurrently, the dosage of 5-FU is typically lower than if administered alone. Compared to 5-FU alone,

gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be of greater severity and of prolonged duration in patients treated with the combination.

- **Potential for Interaction with Trimethoprim-Sulfamethoxazole**: Concomitant use of leucovorin with trimethoprim-sulfamethoxazole for Pneumocystis carinii pneumonia in HIV patients was associated with increased rates of treatment failure in a placebo-controlled study.
- **Pregnancy and Nursing:** Animal reproduction studies have not been conducted and it is unknown whether levoleucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Only give to a pregnant woman if clearly needed. It is not known whether this drug is excreted in human milk.

Drug Availability:

Fusilev brand: supplied in three different strengths: (1) 50 mg of freeze-dried powder for reconstitution in a single-use vial, (2) 175 mg per 17.5 mL solution (10 mg/mL) in a single-use vial, and (3) 250 mg per 25 mL solution (10 mg/mL) in a single-use vial. The unreconstituted powder may be stored at room temperature; however, the solution must be stored under refrigeration.

Generics also available in all strengths.

Khapzory: 175 mg and 300 mg lyophilized powder in a single dose vial for reconstitution for injection

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding (levoleucovorin calcium - both brand Fusilev and generic formulations)

J0641	Injection, levoleucovorin, 0.5 mg

HCPCS Coding (levoleucovorin – brand Khapzory)

J0642	Injection, levoleucovorin, 0.5 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

B20	Human immunodeficiency virus [HIV] disease
C15.3 – C15.5, C15.8, C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0 – C17.3, C17.8, C17.9	Malignant neoplasm of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0 - C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0 – C22.09	Malignant neoplasm of liver and bile duct
C23	Malignant neoplasm of gallbladder
C24.0 – C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C25.0 - C25.4, C25.7 – C25.9	Malignant neoplasm of pancreas
C37	Malignant neoplasm of thymus
C40.00 – C40.02	Malignant neoplasm of scapula and long bones of upper limb
C40.10 – C40.12	Malignant neoplasm of short bones of upper limb
C40.20 – C40.22	Malignant neoplasm of long bones of lower limb
C40.30 – C40.32	Malignant neoplasm of short bones of lower limb
C40.80 – C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of limb

C40.90 – C40.92	Malignant neoplasm of unspecified bones and articular cartilage of limb
C41.0 – C41.4, C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C48.1 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C52	Malignant neoplasm of vagina
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C58	Malignant neoplasm of other and unspecified female genital organs
C67.0 – C67.9	Malignant neoplasm of bladder
C78.00 – C78.02	Secondary malignant neoplasm of lung
C78.1	Secondary malignant neoplasm of mediastinum
C78.2	Secondary malignant neoplasm of pleura
C78.30, C78.39	Secondary malignant neoplasm of other and unspecified respiratory organs
C78.4	Secondary malignant neoplasm of small intestine
C78.5	Secondary malignant neoplasm of large intestine and rectum
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C78.80, C78.89	Secondary malignant neoplasm of other and unspecified digestive organs
C79.31, C79.32	Secondary malignant neoplasm of brain and cerebral meninges
C79.40, C79.49	Secondary malignant neoplasm of other and unspecified parts of nervous system
C79.89, C79.9	Secondary malignant neoplasm of other specified and unspecified site
C7A.00 – C7.A8 C7B.00 – C7.B8	Malignant neuroendocrine tumors
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C81.00 – C83.99	Hodgkin, follicular and non-follicular lymphoma
C84.09– C84.99	Mature T/NK-cell lymphomas, Anaplastic large cell lymphomas
C85.10 – C85.99	Other specified types of non-hodgkin lymphoma
C86.00 - C86.60	Other specified types of T/NK-cell lymphoma
C88.00	Waldenstrom macroglobulinemia not having achieved remission
C91.00 – C91.02	Acute lymphoblastic leukemia [all]
C91.10 - C91.12	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.50 – C91.52	Adult T-cell lymphoma/leukemia
C91.Z0	Other lymphoid leukemia not having achieved remission
C91.Z2	Other lymphoid leukemia, in relapse
D09.0	Carcinoma in situ of bladder
D15.0	Benign neoplasm of thymus
D37.1 – D37.9	Neoplasm of uncertain behavior of oral cavity and digestive organs
D38.4	Neoplasm of uncertain behavior of thymus
D39.2	Neoplasm of uncertain behavior of placenta
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
O01.9	Hydatidiform mole, unspecified
T36.8X1A, T36.8X1D, T36.8X1S	Poisoning by other systemic antibiotics, accidental (unintentional)
T36.8X2A, T36.8X2D, T36.8X2S	Poisoning by other systemic antibiotics, intentional self-harm
T36.8X3A, T36.8X3D, T36.8X3S	Poisoning by other systemic antibiotics, assault

T36.8X4A, T36.8X4D, T36.8X4S	Poisoning by other systemic antibiotics, undetermined
T37.0X1A, T37.0X1D, T37.0X1S	Poisoning by sulfonamides, accidental (unintentional)
T37.0X2A, T37.0X2D, T37.0X2S	Poisoning by sulfonamides, intentional self-harm
T37.0X3A, T37.0X3D, T37.0X3S	Poisoning by sulfonamides, assault
T37.0X4A, T37.0X4D, T37.0X4S	Poisoning by sulfonamides, undetermined
T37.2X1A, T37.2X1D, T37.2X1S	Poisoning by antimalarials and drugs acting on other blood protozoa, accidental (unintentional)
T37.2X2A, T37.2X2D, T37.2X2S	Poisoning by antimalarials and drugs acting on other blood protozoa, intentional self-harm
T37.2X3A, T37.2X3D, T37.2X3S	Poisoning by antimalarials and drugs acting on other blood protozoa, assault
T37.2X4A, T37.2X4D, T37.2X4S	Poisoning by antimalarials and drugs acting on other blood protozoa, undetermined
T39.4X1A, T39.4X1D, T39.4X1S	Poisoning by antirheumatics, not elsewhere classified, accidental (unintentional)
T39.4X2A, T39.4X2D, T39.4X2S	Poisoning by antirheumatics, not elsewhere classified, intentional self-harm
T39.4X3A, T39.4X3D, T39.4X3S	Poisoning by antirheumatics, not elsewhere classified, assault
T39.4X4A, T39.4X4D, T39.4X4S	Poisoning by antirheumatics, not elsewhere classified, undetermined
T45.1X1A, T45.1X1D, T45.1X1S	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional)
T45.1X2A, T45.1X2D, T45.1X2S	Poisoning by antineoplastic and immunosuppressive drugs, intentional self-harm
T45.1X3A, T45.1X3D, T45.1X3S	Poisoning by antineoplastic and immunosuppressive drugs, assault
T45.1X4A, T45.1X4D, T45.1X4S	Poisoning by antineoplastic and immunosuppressive drugs, undetermined
T45.1X5A, T45.1X5D, T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage: Medical necessity is determined using any applicable NCD or LCD and then Step therapy Requirements for Medicare Outpatient (Part B) Medications outlined in Policy (09-J3000-39).

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

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leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. J Clin Oncol. 1997;15(11):3320-3329.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

04/01/15	New Medical Coverage Guideline.
11/01/15	Revision: ICD-9 Codes deleted.
04/15/16	Review and revision to guideline consisting of updating the description section, how supplied, and references.
10/01/16	Update to ICD-10 codes.
04/15/17	Review and revision to guideline consisting of updating description, drug availability, coding and references.
04/15/18	Review and revision to guideline consisting of updating references.
03/15/19	Review and revision to guideline consisting of updating description, position statement, dosing, coding and references.
04/01/19	Revision: added HCPCS code C9043.
07/15/19	Update to Program Exceptions.
10/01/19	Revision: Updated description for HCPCS J0641. Added HCPCS J0642 and removed HCPCS C9043 and J3490.
01/01/20	Revision to guideline consisting of updating the position statement.
10/01/21	ICD-10 coding update.
10/01/24	ICD-10 coding update.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.