

Clinical Policy: Levoleucovorin (Fusilev)

Reference Number: CP.PHAR.151

Effective Date: 02/16

Last Review Date: 02/17

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene[®] clinical policy for levoleucovorin (Fusilev[®]).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation[®] that Fusilev is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria:

A. Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis (must meet all)

1. Meets a or b:
 - a. FDA approved use, one of the following:
 - i. Following high dose (12 grams/m² IV over 4 hours) methotrexate therapy as part of a treatment regimen for osteosarcoma;
 - ii. For impaired methotrexate elimination;
 - iii. After accidental folic acid antagonist overdose (including methotrexate);
 - b. Off-label NCCN recommended use,
 - i. Following high dose (12 grams/m² IV over 4 hours) methotrexate therapy as part of a treatment regimen for one of the following:
 - a) Dedifferentiated chondrosarcoma;
 - b) High-grade undifferentiated pleomorphic sarcoma;
2. No history of allergic reaction to folic acid or folinic acid;
3. Documented contraindication to leucovorin or leucovorin is not available for use due to a national drug shortage documented on the U.S. Food and Drug Administration's Drug Shortages Index (<http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>).

Approval duration: 1 month

B. Colorectal Cancer (must meet all)

1. Diagnosis of advanced metastatic colorectal cancer;
2. Will be used in combination with 5-fluorouracil for palliative treatment;
3. No history of allergic reaction to folic acid or folinic acid;
4. Documented contraindication to leucovorin or leucovorin is not available for use due to a national drug shortage documented on the U.S. Food and Drug Administration's Drug Shortages Index (www.accessdata.fda.gov/scripts/drugshortages/default.cfm).

Approval duration: 3 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy

II. Continued Approval

A. Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis (must meet all) :

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Responding positively to therapy;
3. No history of allergic reaction to folic acid or folinic acid;
4. Documentation supports contraindication to leucovorin or leucovorin continues to be unavailable due to national drug shortage.

Approval duration: 3 months

B. Colorectal Cancer (must meet all)

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. No disease progression or unacceptable toxicity;
3. No history of allergic reaction to folic acid or folinic acid;
4. Documentation supports contraindication to leucovorin or leucovorin continues to be unavailable due to national drug shortage.

Approval duration: 6 months

C. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy

Background

Description/Mechanism of Action:

Fusilev (levoleucovorin) is a folate analog. 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 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.
- Levoleucovorin effects in combination with 5-fluorouracil
Levoleucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy such as 5-fluorouracil. 5-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 readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to

stabilize the binding of FdUMP to thymidylate synthase and thereby enhances the inhibition of this enzyme.

Formulations:

Fusilev for Injection

- 50 mg single use vial of freeze dried powder:
 - Each 50 mg vial of Fusilev for Injection contains a sterile lyophilized powder consisting of 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol.

Fusilev Injection

- 175 mg/17.5 mL solution; 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; single-use vial:
 - Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

FDA Approved Indications:

Levoleucovorin is a folate analog/intravenous formulation 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.
- Use in combination chemotherapy with 5-fluorouracil in the palliative treatment of patients with advanced metastatic colorectal cancer.

Limitations of Use:

Levoleucovorin is not approved for:

- Pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B12. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0641	Injection, levoleucovorin calcium, 0.5 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed	01/16	2/16
Removed oncologist requirement.	02/17	2/17

Reviews, Revisions, and Approvals	Date	Approval Date
Added contraindication (allergy). Added “responding positively to therapy” under “Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis” continuation criteria. Removed detailed language under CRC continuation criteria regarding whether member has recovered between successive regimens and replaced it with “no disease progression or unacceptable toxicity”. NCCN recommended uses added. Added formulations		

References

1. Fusilev prescribing information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; April 2011. Available at <http://www.fusilev.com/downloads/m1-14-1-3-1125-000503-clean.pdf>. Accessed January 20, 2016.
2. Levoleucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 13, 2017.

Important reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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