

Medical Policy: Khapzory® (levoleucovorin)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.189	February 14, 2024	

Medical Guideline Disclaimer Property of EmblemHealth. All rights reserved.

The treating physician or primary care provider must submit to EmblemHealth, or ConnectiCare, as applicable (hereinafter jointly referred to as “EmblemHealth”), the clinical evidence that the member meets the criteria for the treatment or surgical procedure. Without this documentation and information, EmblemHealth will not be able to properly review the request preauthorization or post-payment review. The clinical review criteria expressed below reflects how EmblemHealth determines whether certain services or supplies are medically necessary. This clinical policy is not intended to pre-empt the judgment of the reviewing medical director or dictate to health care providers how to practice medicine. Health care providers are expected to exercise their medical judgment in rendering appropriate care. Health care providers are expected to exercise their medical judgment in rendering appropriate care.

EmblemHealth established the clinical review criteria based upon a review of currently available clinical information (including clinical outcome studies in the peer reviewed published medical literature, regulatory status of the technology, evidence-based guidelines of public health and health research agencies, evidence-based guidelines and positions of leading national health professional organizations, views of physicians practicing in relevant clinical areas, and other relevant factors). EmblemHealth expressly reserves the right to revise these conclusions as clinical information changes and welcomes further relevant information. Each benefit program defines which services are covered. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered and/or paid for by EmblemHealth, as some programs exclude coverage for services or supplies that EmblemHealth considers medically necessary.

If there is a discrepancy between this guideline and a member's benefits program, the benefits program will govern. Identification of selected brand names of devices, tests and procedures in a medical coverage policy is for reference only and is not an endorsement of any one device, test or procedure over another. In addition, coverage may be mandated by applicable legal requirements of a state, the Federal Government or the Centers for Medicare & Medicaid Services (CMS) for Medicare and Medicaid members. All coding and web site links are accurate at time of publication.

EmblemHealth may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. EmblemHealth Services Company, LLC, has adopted this policy in providing management, administrative and other services to EmblemHealth Plan, Inc., EmblemHealth Insurance Company, EmblemHealth Services Company, LLC, and Health Insurance Plan of Greater New York (HIP) related to health benefit plans offered by these entities. ConnectiCare, an EmblemHealth company, has also adopted this policy. All of the aforementioned entities are affiliated companies under common control of EmblemHealth Inc.

Definitions

Khapzory is a folate analog and the active isomer of 5-formyl tetrahydrofolic acid (THF). It counteracts the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In colorectal cancer, levoleucovorin enhances the therapeutic and toxic effects of fluorouracil, which is metabolized to 5-fluoro-2'- deoxyuridine-5'-monophosphate (FdUMP). Levoleucovorin stabilizes the binding of FdUMP to thymidylate synthase, thereby enhancing the inhibition of thymidylate synthase

Length of Authorization

Coverage will be provided for ninety days and it may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

- In combination with methotrexate or for inadvertent overdose

- 1,200 billable units every 28 days
- In combination with fluorouracil
 - 2,500 billable units every 28 days

Guideline

I. Initial Approval Criteria

Khapzory may be considered medically necessary if any of the below conditions are met **AND** use is consistent with the medical necessity criteria that follows:

Coverage is provided in the following conditions:

- Patient is at least 6 years old; **AND**
- Patient does not have pernicious anemia or vitamin B12 deficiency megaloblastic anemia; **AND**
- Racemic *d,l*-leucovorin calcium is not obtainable (in any dosage strength) as confirmed by FDA Drug shortage website located at: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>; **AND**
- Patient had an inadequate response, or has a contraindication or intolerance, to Fusilev™ (levoleucovorin); **AND**

1. **Bone Cancer (Osteosarcoma)**

- A. Patient is undergoing high-dose methotrexate chemotherapy treatment; **OR**
- B. Must be used as rescue therapy in combination with chemotherapy regimen containing high dose methotrexate.

2. **Reduction of toxicity due to impaired elimination or inadvertent overdose with folic acid antagonists**

- A. Patient is undergoing treatment with a folic acid antagonist, such as methotrexate; **AND**
- B. Patient has developed toxicity due to impaired elimination or inadvertent overdosage of the folic acid antagonist (i.e., methotrexate)

3. **Colorectal cancer**

- A. Must be used in combination with fluorouracil-based regimens

Limitations/Exclusions

Khapzory is considered investigational when used for any indication not listed above.

II. Renewal Criteria

- Patient continues to meet INITIAL APPROVAL CRITERIA.; **AND**
- Racemic *d,l*-leucovorin calcium is not obtainable (in any dosage strength) as confirmed by FDA Drug shortage website located at: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>; **AND**
- Absence of unacceptable toxicity from the drug including hypersensitivity reactions, seizures, and severe gastrointestinal disorders such as stomatitis, severe diarrhea, and severe nausea and vomiting.

Dosing and Administration

Please see Package Insert

Applicable Procedure Codes

Code	Description
J0642	Khapzory (levoleucovorin), for injection

Applicable NDCs

Code	Description
72893-0004-xx	Khapzory 175 mg single-use vial powder for injection
72893-0006-xx	Khapzory 300 mg single-use vial powder for injection

ICD-10 Diagnoses

Code	Description
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb

C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
Z85.038	Personal history of other malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.830	Personal history of malignant neoplasm of bone

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	2/14/2024	Annual Review: Updated dosing limits Initial Criteria: Added: "Patient had an inadequate response, or has a contraindication or intolerance, to Fusilev™ (levoleucovorin); AND" Bone Cancer (Osteosarcoma) Updated the following from and "AND" statement to and "OR" statement:"Patient is undergoing high-dose methotrexate chemotherapy treatment; OR Must be used as rescue therapy in combination with chemotherapy regimen containing high dose methotrexate."
EmblemHealth & ConnectiCare	6//14/2023	Annual Review: Removed NDCs 68152-0112-xx and 68152-0114-xx, added: 72893.0004-xx and 72893-0006-xx
EmblemHealth & ConnectiCare	09/01/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	07/05/2022	Annual Review. Multiple Myeloma: Added "or plan to receive" to the requirement that the patient has received lymphodepleting chemotherapy prior to infusion of Abcema
EmblemHealth & ConnectiCare	10/01/2019	Removed J3490, Unclassified Drug and replaced it with J0642, Khapzory (levoleucovorin), for injection.

References

1. Khapzory [package insert]. Irvine, CA; Spectrum Pharmaceuticals, Inc ; October 2018. Accessed October 2019.
2. Clinical Pharmacology Elsevier Gold Standard. 2018.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2018.

4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2018.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD. 2018.