Medical Policy:

Khapzory® (levoleucovorin) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.189	March 27, 2025	

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 overdosage
  - 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) † ‡ Φ, Dedifferentiated Chondrosarcoma ‡, High-Grade Undifferentiated Pleomorphic Sarcoma (UPS) ‡**
   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

1. Patient continues to meet INITIAL APPROVAL CRITERIA.; **AND**
2. 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**
3. 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; **AND**
4. Patient is responding to therapy.

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
C18.0	Malignant neoplasm of cecum
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
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
D37.4	Neoplasm of uncertain behavior of colon
T45.1X1A	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional) initial encounter
T45.1X1D	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional) subsequent encounter
T45.1X1S	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional) sequela

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	3/27/2025	Annual review: Initial Criteria: Added: “Dedifferentiated Chondrosarcoma ‡, High-Grade Undifferentiated Pleomorphic Sarcoma (UPS) ‡” to “Bone Cancer (Osteosarcoma) † ‡ Φ, Dedifferentiated Chondrosarcoma ‡, High-Grade Undifferentiated Pleomorphic Sarcoma (UPS) ‡” Renewal Criteria: Added: “Patient is responding to therapy.” Updated ICD-10 Codes.
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.