

Medical Drug Clinical Criteria

Subject: Levoleucovorin Agents

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Overview

This document addresses the use of levoleucovorin agents (Khapzory). Levoleucovorin is a folate analogue primarily used to diminish the toxicity and counteract the effects of impaired folic acid antagonists (such as methotrexate) and to enhance the therapeutic effects of fluoropyrimidines (such as 5-fluorouracil) in the treatment of various types of cancer. Levoleucovorin (l-LV) is the l-isomer, or biologically active moiety of leucovorin and is dosed at one-half that of the racemic mixture d,l-leucovorin (d-LV).

The FDA approved indications for levoleucovorin agents (Khapzory) include rescue following high-dose methotrexate in osteosarcoma, to diminish the toxicity and counteract the effects of impaired methotrexate elimination or inadvertent overdosage of folic acid antagonists, and in combination chemotherapy with 5-fluorouracil for advanced metastatic colorectal cancer. The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the use in combination with high dose methotrexate or 5-fluorouracil in various types of cancer.

Definitions and Measures

Analogue: A drug or substance which is similar to, but not identical, to another drug or substance.

Antagonist: An agent which blocks the binding of an agonist (a substance that binds to a specific receptor and triggers a response in the cell) at a receptor site.

Adenocarcinoma: Cancer originating in cells that line specific internal organs and that have gland-like (secretory) properties.

Anal cancer: Cancer originating in the tissues of the anus; the anus is the opening of the rectum (last part of the large intestine) to the outside of the body.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Colon cancer: Cancer originating in the tissues of the colon (the longest part of the large intestine). Most colon cancers are adenocarcinomas that begin in cells that make and release mucus and other fluids.

Colorectal cancer: Cancer originating in the colon (the longest part of the large intestine) or the rectum (the last several inches of the large intestine before the anus).

Isomer: Drugs or substances that share the same chemical formula but have different molecular arrangements. l-LV and d-LV are stereoisomers that are non-superimposable mirror images of each other. Though some isomers show different chemical properties, l-LV and d-LV have been shown to have equivalent therapeutic effects.

Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.

Neuroendocrine Tumor (NET): A tumor that forms from cells that release hormones into the blood in response to a signal from the nervous system. NETs may make higher-than-normal amounts of hormones, which can cause many different symptoms. These tumors may be benign (not cancerous) or malignant (cancerous).

Rectal cancer: Cancer originating in tissues of the rectum (the last several inches of the large intestine closest to the anus).

Summary of FDA-Approved Indications or Indications Meeting Off-Label Use Policy for Leucovorin Agents:

Indications	Fusilev (levoleucovorin)	Khapzory (levoleucovorin)	Leucovorin	Levoleucovorin
Osteosarcoma; after high dose methotrexate therapy	X	X	X	X
Methotrexate; to diminish toxicity and counteract the effects of impaired elimination	X	X	X	X
Inadvertent over-dosage of folic acid antagonists	X	X	X	X
Colorectal cancer; in combination with fluorouracil	X	X	X	X
Megaloblastic anemia due to folic acid deficiency			X	Y
Acute lymphoblastic leukemia (ALL)	Y	Y	Y	Y
Acute Myeloid Leukemia <ul style="list-style-type: none"> Blastic Plasmacytoid Dendritic Cell Neoplasm 	Y	Y	Y	Y
Ampullary Adenocarcinoma	Y	Y	Y	Y
Anal Carcinoma	Y	Y	Y	Y
B-Cell Lymphoma <ul style="list-style-type: none"> Follicular Lymphoma (grade 1-2) Diffuse Large B-Cell Lymphoma High Grade B-Cell Lymphomas with Translocations Post Transplant Lymphoproliferative Disorders Mantle Cell Lymphoma AIDS-Related B-Cell Lymphomas Burkitt Lymphoma 	Y	Y	Y	Y
Bladder Cancer	Y	Y	Y	Y
Central nervous system (CNS) cancers <ul style="list-style-type: none"> Primary CNS Lymphoma Limited Brain Metastases Extensive Brain Metastases Leptomeningeal Metastases 	Y	Y	Y	Y
Cervical Cancer	Y	Y	Y	Y
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Y	Y	Y	Y
Esophageal and Esophagogastric Junction Cancers	Y	Y	Y	Y
Gastric Cancer	Y	Y	Y	Y
Gestational Trophoblastic Neoplasia	Y	Y	Y	Y
Hepatobiliary, Biliary Tract	Y	Y	Y	Y
Lymphoplasmacytic Lymphoma	Y	Y	Y	Y
Neuroendocrine and Adrenal Tumors, including Well Differentiated Grade 3, Poorly Differentiated (High Grade)/Large or Small Cell	Y	Y	Y	Y
Occult Primary	Y	Y	Y	Y
Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer, including Mucinous Carcinoma	Y	Y	Y	Y
Pancreatic Adenocarcinoma	Y	Y	Y	Y
Pediatric Aggressive Mature B-Cell Lymphomas	Y	Y	Y	Y

Pediatric Acute Lymphoblastic Leukemia	Y	Y	Y	Y
Rectal Cancer	Y	Y	Y	Y
Small Bowel Adenocarcinoma	Y	Y	Y	Y
T-Cell Lymphomas				
• Peripheral T-Cell Lymphomas				
• Adult T-Cell Leukemia/Lymphoma				
• Extranodal NK/T-Cell Lymphoma, nasal type				
• Hepatosplenic Gamma-Delta				
Thymomas and Thymic Carcinomas	Y	Y	Y	Y
<u>Vaginal Cancer</u>	<u>Y</u>	<u>Y</u>	<u>Y</u>	<u>Y</u>

Y = off-label use

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Levoleucovorin agents (~~Fusilev~~, Khapzory)

Requests for levoleucovorin agents (~~Fusilev~~, Khapzory) may be approved for the following:

- I. As a component of high-dose methotrexate therapy in osteosarcoma; **OR**
- II. As a treatment of impaired methotrexate elimination; **OR**
- III. As a treatment of inadvertent over-dosage of folic acid antagonists; **OR**
- IV. In combination chemotherapy with fluorouracil-based regimens to treat colorectal adenocarcinoma; **OR**
- V. In combination chemotherapy for **any** of the following cancers (NCCN 2A):
 - A. Acute lymphoblastic leukemia (ALL); **OR**
 - B. Acute Myeloid Leukemia (AML) including Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN); **OR**
 - C. Anal Carcinoma; **OR**
 - D. Ampullary adenocarcinoma; **OR**
 - E. B-Cell Lymphoma, including Follicular Lymphoma (grade 1-2), Diffuse Large B-Cell Lymphoma, High Grade B-Cell Lymphomas High-Grade B-Cell Lymphomas (NOS), Post-Transplant Lymphoproliferative Disorders, Mantle Cell Lymphoma, AIDS-Related B-Cell Lymphomas or Burkitt Lymphoma; **OR**
 - F. Bladder Cancer; **OR**
 - G. Central nervous system (CNS) cancers, including Primary CNS Lymphoma, Limited Brain Metastases, Extensive Brain Metastases or Leptomeningeal Metastases; **OR**
 - H. Cervical Cancer; **OR**
 - I. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; **OR**
 - J. Lymphoplasmacytic Lymphoma; **OR**
 - K. Esophageal and Esophagogastric Junction Cancers; **OR**
 - L. Gastric Cancer; **OR**
 - M. Gestational Trophoblastic Neoplasia; **OR**
 - N. Hepatobiliary Cancers, Biliary Tract Cancers; **OR**
 - O. Neuroendocrine and Adrenal Tumors, Well Differentiated Grade 3 NET, including Poorly Differentiated (High Grade)/Large or Small Cell; **OR**
 - P. Occult Primary; **OR**
 - Q. Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer, including Mucinous Carcinoma; **OR**
 - R. Pancreatic Adenocarcinoma; **OR**
 - S. Pediatric Aggressive Mature B-Cell Lymphomas; **OR**
 - T. Pediatric Acute Lymphoblastic Leukemia; **OR**
 - U. Rectal Cancer; **OR**
 - V. Small Bowel Adenocarcinoma; **OR**
 - W. T-Cell Lymphomas, including Hepatosplenic Gamma-Delta, Peripheral T-Cell Lymphomas, Adult T-Cell Leukemia/Lymphoma, or Extranodal NK/T-Cell Lymphoma, nasal type; **OR**
 - X. Thymomas and Thymic Carcinomas; **OR**
 - X.Y. Vaginal Cancer.

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Requests for levoleucovorin agents (Fusilev, Khapzory) may not be approved when the above criteria are not met and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

- J0641 Injection, levoleucovorin, not otherwise specified, 0.5 mg. [~~levoleucovorin calcium~~][~~Fusilev~~]
(~~Effective 10/1/19~~)
- J0642 Injection, levoleucovorin 0.5 mg [Khapzory] (~~Effective 10/1/2019~~)

ICD-10 Diagnosis

ALL DIAGNOSES

Document History

Revised: 08/16/2024

Document History:

- 08/16/2024 – Annual Review: Add Vaginal Cancer criteria and Summary of FDA-Approved Indications or Indications Meeting Off-Label Use Policy for Leucovorin Agents, remove Fusilev discontinued product. Coding Reviewed: Changed description for J0641 to generic levoleucovorin calcium.
- 08/18/2023 – Annual Review: Add cervical cancer, pediatric acute lymphoblastic leukemia, Lymphoplasmacytic Lymphoma, levoleucovorin to step. Coding Reviewed: No changes.
- 08/19/2022 – Annual Review: Remove Translocations in high grade B-cell lymphomas, add ampullary adenocarcinoma.
- 08/20/2021 – Annual Review: Add new criteria for Levoleucovorin for Acute Myeloid Leukemia (BPDCN), Follicular Lymphoma (grade 1-2), Diffuse Large B-Cell Lymphoma, High Grade B-Cell Lymphomas with Translocations of MYC and BCL2 and/or BCL6, High Grade B-Cell Lymphomas (NOS), Post-Transplant Lymphoproliferative Disorders, Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Well-Differentiated Grade 3 NET, Pediatric Aggressive Mature B-Cell Lymphomas. Remove criteria for cervical cancer, as NCCN updated to a level 2B recommendation. Removed clinical criteria for Bone Cancer, as already represented in in RN 1. Removed Colon Cancer as already represented within RN 4. Coding reviewed: No changes.
- 08/21/2020 – Annual Review: Update existing NCCN 2A recommendation criteria for use T-cell lymphocytes with Hepatosplenic, Gamma-Delta. Add NCCN 2A recommendation to criteria for use in Hepatobiliary cancer, Biliary Tract Cancer, and Small Bowel Adenocarcinoma. Coding Review: No changes.
- 08/16/2019 – Annual Review: No changes. Coding Reviewed: Added HCPCS code J0641, J0642 (Effective 10/1/19), Delete HCPCS code J3490(Effective 10/1/19), Delete C9043 (Effective 1/1/2020)
- 05/17/2019 – Annual Review: Wording and formatting changes for clarity. Update summary table of FDA and off-label uses to include all approvable indications as well as off-label indications for Khapzory. Coding Reviewed: Added C9043, Injection, levoleucovorin

References

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- DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Updated periodically.
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- Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2024; Updated periodically.
- NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on June 20, 2024.
 - Acute Lymphoblastic Leukemia. V1.2024. Revised June 14, 2024.
 - Acute Myeloid Leukemia. V3.2024. Revised May 17, 2024.
 - Ampullary Adenocarcinoma. V1.2024. Revised December 13, 2023.
 - Anal Carcinoma. V1.2024. Revised December 20, 2023.

- e. B-Cell Lymphomas. V2.2024. Revised April 30, 2024.
 - f. Bladder Cancer. V4.2024. Revised May 9, 2024.
 - g. Biliary Tract Cancers. V2.2024. Revised April 19, 2024.
 - h. Bone Cancer. V2.2024. Revised March 12, 2024.
 - i. Central Nervous System Cancers. V1.2024. Revised May 31, 2024.
 - j. Cervical Cancer. V3.2024. Revised May 6, 2024.
 - k. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V3.2024. Revised March 26, 2024.
 - l. Colon Cancer. V3.2024. Revised April 24, 2024.
 - m. Esophageal and Esophagogastric Junction Cancers. V3.2024. Revised April 26, 2024.
 - n. Gastric Cancer. V2.2024. Revised May 29, 2024.
 - o. Gestational Trophoblastic Neoplasia. V1.2024. Revised March 8, 2024.
 - p. Neuroendocrine and Adrenal Tumors. V1.2023. Revised August 2, 2023.
 - q. Occult Primary. V2.2024. Revised April 29, 2024.
 - r. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V2.2024. Revised May 13, 2024.
 - s. Pancreatic Adenocarcinoma. V2.2024. Revised April 30, 2024.
 - t. Pediatric Acute Lymphoblastic Leukemia. V2.2024. Revised April 3, 2024.
 - u. Pediatric Aggressive Mature B-Cell Lymphomas. V1.2024. Revised April 8, 2024.
 - v. Rectal Cancer. V2.2024. Revised April 30, 2024.
 - w. Small Bowel Adenocarcinoma. V3.2024. Revised April 30, 2024.
 - x. T-Cell Lymphomas. V4.2024. Revised May 28, 2024.
 - y. Thymomas and Thymic Carcinomas. V1.2024. Revised November 21, 2023.
 - z. Vaginal Cancer. V1.2025. Revised March 26, 2024.
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