Medical Drug Clinical Criteria

Subject:	Levoleucovorin Agents		
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Table of Contents

Overview

This document addresses the use of levoleucovorin agents. 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 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	Khapzory (levoleucovorin)	Leucovorin	Levoleucovorin
Osteosarcoma; after high dose methotrexate therapy	X	X	X
Methotrexate; to diminish toxicity and counteract the effects of impaired elimination	X	X	X
Inadvertent over-dosage of folic acid antagonists	X	X	X
Colorectal cancer; in combination with fluorouracil	X	X	X
Megaloblastic anemia due to folic acid deficiency		X	Y
Acute lymphoblastic leukemia (ALL)	Y	Y	Y
Acute Myeloid Leukemia • Blastic Plasmacytoid Dendritic Cell Neoplasm	Y	Y	Y
Ampullary Adenocarcinoma	Y	Y	Y
Anal Carcinoma	Y	Y	Y
B-Cell Lymphoma • Follicular Lymphoma (grade 1-2) • Diffuse Large B-Cell Lymphoma • High Grade B-Cell Lymphomas with Translocations • Post Transplant Lymphoproliferative Disorders • Mantle Cell Lymphoma • HIV Related B-Cell Lymphomas • Burkitt Lymphoma	Y	Y	Y
Bladder Cancer	Y	Y	Y
Central nervous system (CNS) cancers • Primary CNS Lymphoma • Limited Brain Metastases • Extensive Brain Metastases • Leptomeningeal Metastases	Y	Y	Y
Cervical Cancer	Y	Y	Y
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Y	Y	Y
Esophageal and Esophagogastric Junction Cancers	Y	Y	Y
Gastric Cancer	Y	Y	Y

Gestational Trophoblastic Neoplasia	Y	Y	Y
Hepatobiliary, Biliary Tract	Y	Y	Y
Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma	Y	Y	Y
Neuroendocrine and Adrenal Tumors, including Well Differentiated ~~Grade 3~~, Poorly Differentiated (High Grade)/Large or Small Cell	Y	Y	Y
Occult Primary	Y	Y	Y
Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer, including Mucinous Carcinoma	Y	Y	Y
Pancreatic Adenocarcinoma	Y	Y	Y
Pediatric Aggressive Mature B-Cell Lymphomas	Y	Y	Y
Pediatric Acute Lymphoblastic Leukemia	Y	Y	Y
Rectal Cancer	Y	Y	Y
Small Bowel Adenocarcinoma	Y	Y	Y
T-Cell Lymphomas • Peripheral T-Cell Lymphomas • Adult T-Cell Leukemia/Lymphoma • Extranodal NK/T-Cell Lymphoma, nasal type • Hepatosplenic T-Cell • Lymphoma	Y	Y	Y
Thymomas and Thymic Carcinomas	Y	Y	Y
Vaginal Cancer	Y	Y	Y

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 (Levoleucovorin calcium, Khapzory)

Requests for levoleucovorin agents (Levoleucovorin calcium, 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 with high-dose methotrexate when leucovorin is not available in Pediatric Acute Lymphoblastic Leukemia or Pediatric Aggressive Mature B-Cell Lymphomas; **OR**
VI. In combination with high-dose methotrexate when leucovorin is not available for the management of symptomatic Bing-Neel syndrome in Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma; **OR**
~~V.~~VII. In combination chemotherapy for **any** of the following cancers (NCCN 2A):

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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~~HIV-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.~~J. Esophageal and Esophagogastric Junction Cancers; **OR**
~~L.~~K. Gastric Cancer; **OR**
~~M.~~L. Gestational Trophoblastic Neoplasia; **OR**
~~N.~~M. ~~Hepatobiliary Cancers,~~ Biliary Tract Cancers; **OR**
~~O.~~N. Neuroendocrine and Adrenal Tumors, Well Differentiated Grade 3 NET, including Poorly Differentiated (High Grade)/Large or Small Cell; **OR**
~~P.~~O. Occult Primary; **OR**
~~Q.~~P. Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer, including Mucinous Carcinoma; **OR**
~~R.~~Q. Pancreatic Adenocarcinoma; **OR**
~~S. Pediatric Aggressive Mature B-Cell Lymphomas; **OR**~~
~~T. Pediatric Acute Lymphoblastic Leukemia; **OR**~~
~~U. Rectal Cancer; **OR**~~
~~V.~~R. Small Bowel Adenocarcinoma; **OR**
~~W.~~S. T-Cell Lymphomas, including Hepatosplenic T-Cell Lymphoma~~Gamma-Delta~~, Peripheral T-Cell Lymphomas, Adult T-Cell Leukemia/Lymphoma, or Extranodal NK/T-Cell Lymphoma, nasal type; **OR**
~~X.~~**T.** Thymomas and Thymic Carcinomas; **OR**
~~Y.~~U. Vaginal Cancer.

Requests for levoleucovorin agents (Levoleucovorin calcium, 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]
J0642	Injection, levoleucovorin 0.5 mg [Khapzory]
ICD-10 Diagnosis	
B20~~ALL DIAGNOSES~~	Human immunodeficiency virus [HIV] disease
C15.3-C17.9	Malignant neoplasm of esophagus, stomach, small intestine
C18.0-C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal
C23	Malignant neoplasm of gallbladder
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0-C25.9	Malignant neoplasm of pancreas
C37	Malignant neoplasm of thymus

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C40.00-C41.9	Malignant neoplasm of bone and articular cartilage of limbs, other and unspecified sites
C48.1-C48.8	Malignant neoplasm of peritoneum, overlapping sites of retroperitoneum and peritoneum
C52-C53.9	Malignant neoplasm of vagina, cervix uteri
C56.1-C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C67.0-C67.9	Malignant neoplasm of bladder
C79.32	Secondary malignant neoplasm of cerebral meninges
C7A.010-C7A.8	Malignant neuroendocrine tumors
C80.0-C80.1	Malignant neoplasm without specification of site
C82.00-C82.09	Follicular lymphoma grade I
C82.10-C82.19	Follicular lymphoma grade II
C83.00-C83.99	Non-follicular lymphoma
C84.40-C84.49	Peripheral T-cell lymphoma, not elsewhere classified
C84.60-C84.79	Anaplastic large cell lymphoma
C84.Z0-C84.Z9	Other mature T/NK-cell lymphomas
C84.90-C84.99	Mature T/NK-cell lymphomas, unspecified
C85.10-C85.19	Unspecified B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80-C85.89	Other specified types of non-Hodgkin lymphoma
C85.99	Non-Hodgkin lymphoma, unspecified, extranodal and solid organ sites
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
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
C91.50-C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated)
D39.2	Neoplasm of uncertain behavior of placenta
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Document History

Revised: 08/15/2025
Document History:

- 08/15/2025 – Annual Review: Clarify products for generic levoleucovorin calcium. Update NCCN 2A recommendations for use in Pediatric ALL, Pediatric Aggressive Mature B-cell lymphomas, B-cell Lymphomas, T-cell lymphomas, and Waldenström Macroglobulinemia. Update NCCN nomenclature for Biliary tract cancers. Coding Reviewed: Updated description for HCPCS J0642. Removed All Diagnoses and added ICD-10-CM B20, C15.3-C21.8, C23, C24.1, C24.8-C25.9, C37, C40.00-C41.9, C48.1-C48.8, C52-C53.9, C56.1-C56.9, C58, C67.0-C67.9, C79.32, C7A.010-C7A.8, C80.0-C80.1, C82.00-C82.09, C82.10-C82.19, C83.00-C83.99, C84.40-C84.49, C84.60-C84.79, C84.Z0-C84.Z9, C84.90-C84.99, C85.10-C85.19, C85.20-C85.29, C85.80-C85.89, C85.99, C86.00, C88.00, C91.00-C91.02, C91.10-C91.12, C91.50-C91.52, D39.2, D47.Z1. 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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3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2025; Updated periodically.
4. NCCN Clinical Practice Guidelines in Oncology™. © 2025 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on June 3, 2025.
    a. Acute Lymphoblastic Leukemia. V1.2025. Revised May 15, 2025.
    b. Acute Myeloid Leukemia. V2.2025. Revised January 27,2025.
    c. Ampullary Adenocarcinoma. V2.2025. Revised January 10, 2025.
    d. Anal Carcinoma. V4.2025. Revised May 30, 2025.
    e. B-Cell Lymphomas. V2.2025. Revised February 10, 2025.
    f. Bladder Cancer. V1.2025. Revised March 25, 2025.
    g. Biliary Tract Cancers. V1.2025. Revised March 20, 2025.
    h. Bone Cancer. V2.2025. Revised February 28, 2025.
    i. Central Nervous System Cancers. V1.2025. Revised June 3, 2025.
    j. Cervical Cancer. V4.2025. Revised March 24, 2025.
    k. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V3.2025. Revised April 2,2025.
    l. Colon Cancer. V3.2025. Revised April 24, 2025.
    m. Esophageal and Esophagogastric Junction Cancers. V3.2025. Revised April 22, 2025.
    n. Gastric Cancer. V2.2025. Revised April 4, 2025.
    o. Gestational Trophoblastic Neoplasia. V3.2025. Revised May 28, 2025.
    p. Neuroendocrine and Adrenal Tumors. V2.2025. Revised May 28, 205.
    q. Occult Primary (Cancer of Unknown Primary [CUP]). V2.2025. Revised September 11, 2024.
    r. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V2.2025. Revised May 23, 2025.
    s. Pancreatic Adenocarcinoma. V2.2025. Revised February 3, 2025.
    t. Pediatric Acute Lymphoblastic Leukemia. V3.2025. Revised March 17, 2025.
    u. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2025. Revised April 28, 2025.
    v. Rectal Cancer. V2.2025. Revised March 31, 2025.
    w. Small Bowel Adenocarcioma. V3.2025. Revised March 31, 2025.
    x. T-Cell Lymphomas. V2.2025. Revised May 28, 2025.
    y. Thymomas and Thymic Carcinomas. V2.2025. Revised May 19, 2025.
    z. Vaginal Cancer. V5.2025. Revised February 28, 2025.
    aa. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma. V3.2025. Revised February 6, 2025.
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6. Pappo AS, Bowman LC, et al. A phase II trial of high-dose methotrexate in previously untreated children and adolescents with high-risk unresectable or metastatic rhabdomyosarcoma. J Pediatr Hematol Oncol 1997;19:438-42.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.