Medical Drug Clinical Criteria

Subject:	Levoleucovorin and Leucovorin Agents		
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Table of Contents

Overview | Coding | References

Clinical criteria | Document history

Overview

This document addresses the use of injectable levoleucovorin and leucovorin agents.

Leucovorin is folinic acid, a derivative of folic acid. Levoleucovorin (l-LV), a folate analogue, 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).

Leucovorin and Levoleucovorin are 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.

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)	Levoleucovorin	Leucovorin	Vykoura (leucovorin calcium injection)
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		Y	X	X
Acute lymphoblastic leukemia (ALL)	Y	Y	Y	Y
Acute Myeloid Leukemia • Blastic Plasmacytoid Dendritic Cell Neoplasm	Y	Y	Y	Y
Ampullary Adenocarcinoma	Y	Y	Y	Y
Anal Carcinoma	Y	Y	Y	Y
Appendiceal neoplasms and cancers • Appendiceal adenocarcinoma • Undifferentiated carcinoma not otherwise specified • Goblet cell adenocarcinoma • Low-grade appendiceal mucinous neoplasm • High-grade appendiceal mucinous neoplasm	Y	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	Y
Bladder Cancer	Y	Y	Y	Y
Bone Cancer	Y	Y	Y	Y

Central nervous system (CNS) cancers • 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
Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma including Bing-Neel syndrome	Y	Y	Y	Y
Neuroendocrine and Adrenal Tumors, including Well Differentiated, 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 T-Cell Lymphoma	Y	Y	Y	Y
Thymomas and Thymic Carcinomas	Y	Y	Y	Y
Vaginal Cancer	Y	Y	Y	Y
Graft versus host disease in combination with methotrexate			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. Individual is under 19 years of age;

OR

II. Individual is using as a component of high-dose methotrexate therapy in osteosarcoma; **OR**
III. Individual is using as a treatment of impaired methotrexate elimination; **OR**
IV. Individual is using as a treatment of inadvertent over-dosage of folic acid antagonists; **OR**
V. Individual is using in combination chemotherapy with fluorouracil-based regimens to treat colorectal adenocarcinoma; **OR**
VI. Individual is using in combination with high-dose methotrexate when leucovorin is not available in pediatric acute lymphoblastic leukemia or pediatric aggressive mature B-cell lymphomas (including Burkitt lymphoma and diffuse B-cell lymphoma, primary mediastinal large B-cell lymphoma, and pediatric post-transplant lymphoproliferative disorders) (NCCN 2A); **OR**
VII. Individual is using in combination with high-dose methotrexate when leucovorin is not available for the management of symptomatic Bing-Neel syndrome in Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (NCCN 2A); **OR**
VIII. Individual is using in combination with 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. Appendiceal neoplasms and cancers including appendiceal adenocarcinoma, undifferentiated carcinoma not otherwise specified, goblet cell adenocarcinoma, low-grade appendiceal mucinous neoplasm, and high-grade appendiceal mucinous neoplasm; **OR**
    F. B-cell lymphoma, including, diffuse large B-cell lymphoma, high grade B-cell lymphomas, post-transplant lymphoproliferative disorders, HIV-related B-cell lymphomas or Burkitt lymphoma; **OR**
    G. Bladder cancer; **OR**
    H. Bone cancer including osteosarcoma, dedifferentiated chondrosarcoma, and high-grade undifferentiated pleomorphic sarcoma; **OR**
    I. Central nervous system (CNS) cancers, including primary CNS lymphoma, limited brain metastases, extensive brain metastases or leptomeningeal metastases; **OR**
    J. Cervical cancer; **OR**
    K. Chronic lymphocytic leukemia/small lymphocytic lymphoma; **OR**
    L. Esophageal and esophagogastric junction cancers; **OR**
    M. Gastric cancer; **OR**
    N. Gestational trophoblastic neoplasia; **OR**
    O. Biliary tract cancers including gallbladder cancer, intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma ; **OR**
    P. Neuroendocrine and adrenal tumors, including neuroendocrine tumors (NET) of the gastrointestinal tract (Well-differentiated grade 1/2), lung, and thymus, well differentiated grade 3 NET, Extrapulmonary poorly differentiated (neuroendocrine carcinoma/large or small cell carcinoma/mixed neuroendocrine-non-neuroendocrine neoplasm), or pancreas; **OR**
    Q. Occult primary; **OR**
    R. Ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, including mucinous carcinoma; **OR**
    S. Pancreatic adenocarcinoma; **OR**
    T. Small bowel adenocarcinoma; **OR**
    U. T-cell lymphomas, including hepatosplenic T-cell lymphoma, peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, or extranodal NK/T-cell lymphoma; **OR**
    V. Thymomas and thymic carcinomas; **OR**
    W. 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.

Vykoura (leucovorin calcium)

Requests for Vykoura (leucovorin calcium) may be approved for the following:

I. Individual is under 19 years of age;

OR

II. Individual is using as a rescue after high-dose methotrexate therapy; **OR**

III. Individual is using to reduce the toxicity of one of the following:
   A. Methotrexate in individuals with impaired methotrexate elimination; **OR**
   B. Folic acid antagonists or dihydrofolate reductase (DHFR) inhibitors following an overdose; **OR**

IV. Individual is using in the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible; O**R**

V. Individual is using in combination with 5-fluorouracil in the treatment of metastatic colorectal cancer; **OR**

VI. Individual is using for the following oncology related indications:
   A. In combination with fluorouracil-based regimens for the following cancer diagnoses (NCCN 2A):
      1. Pancreatic adenocarcinoma, adenosquamus carcinoma, or squamous carcinoma; **OR**
      2. Biliary tract cancers including gallbladder cancer, intrahepatic cholangiocarinoma, and extrahepatic cholangiocarcinoma; **OR**
      3. Ovarian cancers including mucinous neoplasms of the ovary; **OR**
      4. Neuroendocrine and adrenal tumors including neuroendocrine tumors of the pancreas (well-differentiated grade 1/2),extrapulmonary poorly differentiated neuroendocrine carcinoma, large or small cell carcinoma, or mixed neuroendocrine-non-neuroendocrine neoplasm, neuroendocrine tumors of the gastrointestinal tract (well-differentiated grade 1/2), lung and thymus; **OR**
      5. Thymomas and thymic carcinomas; **OR**
      6. Occult primary tumors including squamous cell carcinoma, adenocarcinoma or carcinoma not otherwise specified; **OR**
      7. Cervical cancer including squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma; OR
      8. Bladder cancer including non-urothelial and urothelial with subtype histology, pure adenocarcinoma including urachal; **OR**
      9. Esophageal and Esophagogastric Junction Cancers; **OR**
      10. Gastric cancer; **OR**
      11. Vaginal cancer; **OR**
      12. Small bowel adenocarcinoma; **OR**
      13. Anal carcinoma; **OR**
      14. Appendiceal neoplasms and cancers including appendiceal adenocarcinoma, undifferentiated carcinoma not otherwise specified, goblet cell adenocarcinoma, low-grade appendiceal mucinous neoplasm, and high-grade appendiceal mucinous neoplasm; **OR**
      15. Ampullary adenocarcinoma; **OR**

   B. In combination with high-dose methotrexate for the following cancer diagnoses (NCCN 2A)
      1. Pediatric aggressive mature B-cell lymphomas including Burkitt lymphoma and diffuse B-cell lymphoma, primary mediastinal large B-cell lymphoma, and pediatric post-transplant lymphoproliferative disorders; **OR**
      2. Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma for the management of symptomatic Bing-Neel syndrome; **OR**
      3. Pediatric acute lymphoblastic leukemia; **OR**
      4. Pediatric Langerhans cell histiocytosis; **OR**
      5. Gestational trophoblastic neoplasia; **OR**
      6. Central nervous system (CNS) cancers including primary CNS lymphoma, brain metastases, and leptomeningeal metastases; **OR**
      7. Acute lymphoblastic leukemia (ALL); O**R**
      8. Bone cancer including osteosarcoma, dedifferentiated chondrosarcoma, and high-grade undifferentiated pleomorphic sarcoma; **OR**
      9. Acute Myeloid Leukemia (AML) including Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN); **OR**
      10. B-cell lymphomas including diffuse large B-cell lymphoma, high-grade b-cell lymphoma, Burkitt lymphoma, HIV-related B-cell lymphomas, and post-transplant lymphoproliferative disorders; **OR**

11. T-cell lymphomas including peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, hepatosplenic T-cell lymphoma, and extranodal NI/T-cell lymphomas; **OR**
12. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) including Richter transformation;

OR

VII. Individual is using as prophylaxis in combination with methotrexate for graft versus host disease (DrugDex BIIa).

Requests for Vykoura (leucovorin injection) 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.

Levoleucovorin Agents

HCPCS

J0641	Injection, levoleucovorin, not otherwise specified, 0.5 mg. [levoleucovorin calcium]
J0642	Injection, levoleucovorin 0.5 mg [Khapzory]

ICD-10 Diagnosis

B20	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
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.1	Malignant neoplasm of ampulla of Vater
C24.0	Malignant neoplasm of extrahepatic bile duct
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
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
C79.31-C79.32	Secondary malignant neoplasm of brain and cerebral meninges
C7A.010-C7A.8	Malignant neuroendocrine tumors
C7B.00-C7B.09	Secondary carcinoid tumors
C7B.8	Other secondary neuroendocrine tumors
C80.0-C80.1	Malignant neoplasm without specification of site
C83.00-C83.09	Small cell B-cell lymphoma

C83.30-C83.398	Diffuse large B-cell lymphoma
C83.50-C83.59	Lymphoblastic (diffuse) lymphoma
C83.70-C83.79	Burkitt lymphoma
C83.80-C83.89	Other non-follicular lymphoma
C83.90-C83.99	Non-follicular (diffuse) lymphoma, unspecified
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
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.40	Blastic NK-cell lymphoma not having achieved remission
C86.50	Angioimmunoblastic T-cell lymphoma 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)
D09.0	Carcinoma in situ of bladder
D39.2	Neoplasm of uncertain behavior of placenta
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
E16.1	Other hypoglycemia
E16.3	Increased secretion of glucagon
E16.8	Other specified disorders of pancreatic internal secretion
T45.1X1A-T45.1X1S	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional)
T45.1X5A-T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs

Leucovorin Agents

HCPCS

J0644	Injection, leucovorin calcium (Avyxa), 1 mg [Vykoura]

ICD-10 Diagnosis

B20	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
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct

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
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
C79.31-C79.32	Secondary malignant neoplasm of brain and cerebral meninges
C7A.010-C7A.8	Malignant neuroendocrine tumors
C7B.00-C7B.09	Secondary carcinoid tumors
C7B.8	Other secondary neuroendocrine tumors
C80.0-C80.1	Malignant neoplasm without specification of site
C83.00-C83.09	Small cell B-cell lymphoma
C83.30-C83.398	Diffuse large B-cell lymphoma
C83.50-C83.59	Lymphoblastic (diffuse) lymphoma
C83.70-C83.79	Burkitt lymphoma
C83.80-C83.89	Other non-follicular lymphoma
C83.90-C83.99	Non-follicular (diffuse) lymphoma, unspecified
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
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.40	Blastic NK-cell lymphoma not having achieved remission
C86.50	Angioimmunoblastic T-cell lymphoma 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)
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis

C96.6	Unifocal Langerhans-cell histiocytosis
D09.0	Carcinoma in situ of bladder
D39.2	Neoplasm of uncertain behavior of placenta
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D52.0-D52.9	Folate deficiency anemia
D89.810-D89.813	Graft-versus-host disease
E16.1	Other hypoglycemia
E16.3	Increased secretion of glucagon
E16.8	Other specified disorders of pancreatic internal secretion
T45.1X1A-T45.1X1S	Poisoning by antineoplastic and immunosuppressive drugs, accidental (unintentional)
T45.1X5A-T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs

Document History

Revised: 08/14/2026
Document History:

- 08/14/2026 – Annual Review: Updated NCCN 2A indications for Khapzory/Levoleucovorin to clarify types of B-cell lymphomas and neuroendocrine tumors; Updated NCCN 2A indications for Vykoura/leucovorin to clarify types of neuroendocrine tumors; Updated step therapy to clarify application to injectable agents only and to include Levoleucovorin agents in criteria body. Coding Reviewed: Removed HCPCS J3490 and C9310 for Vykoura effective 9/30/26 and added J0644 effective 10/1/26. Added ICD-10-CM C7B.00-C7B.09, C7B.8, E16.1, E16.3, E16.8 to Vykoura, levoleucovorin, and Khapzory. Removed C82.00-C82.09, C82.10-C82.19 from levoleucovorin and Khapzory.
- 07/06/2026 – Coding Update: Removed HCPCS NOC C9399 and added C9310 for Vykoura.
- 04/15/2026 – Coding Update: Removed HCPCS J0640.
- 03/09/2026 – Select Review: Wording and formatting criteria updates; Added criteria for new agent Vykoura per label and NCCN; updated existing step therapy to include Vykoura; updated labeled and off-labeled indications in chart; Khapzoury/levoleucovorin – updated NCCN 2A indications: updated Pediatric Aggressive Mature B-Cell Lymphoma to include examples; added Appendiceal neoplasms, removed Mantle Cell Lymphoma, Added Bone cancer, added qualification for CLL/SLL to include Richter transformation, updated biliary tract cancers to include examples. Coding Reviewed: Added ICD-10-CM C22.1, C24.0, C79.31, C86.10, C86.20, C86.40, C86.50, D09.0, T45.1X1A-T45.1X1S, T45.1X5A-T45.1X5S to levoleucovorin agents. Separated range C83.00-C83.99 and removed C83.0A, C83.10-C83.1A, C83.3A, C83.5A, C83.7A, C83.8A, C83.9A from levoleucovorin agents. Added HCPCS J0640 and HCPCS NOC C9399 and J3490 for Vykoura. Added ICD-10-CM B20, C15.3-C17.9, C18.0-C21.8, C22.1, C23, C24.0, C24.1, C24.8, C24.9, C25.0-C25.9, C37, C40.00-C41.9, C48.1-C48.8, C52-C53.9, C56.1-C56.9, C57.00-C57.9, C58, C67.0-C67.9, C79.31-C79.32, C7A.010-C7A.8, C80.0-C80.1, C83.00-C83.09, C83.30-C83.398, C83.50-C83.59, C83.70-C83.79, C83.80-C83.89, C83.90-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, C86.10, C86.20, C86.40, C86.50, C88.00, C91.00-C91.02, C91.10-C91.12, C91.50-C91.52, C96.0, C96.5-C96.6, D09.0, D39.2, D47.Z1, D52.0-D52.9, D89.810-D89.813, T45.1X1A-T45.1X1S, T45.1X5A-T45.1X5S for leucovorin agents.
- 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

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    a. Acute Lymphoblastic Leukemia. V1.2026. Revised April 8, 2026.
    b. Acute Myeloid Leukemia. V3.2026. Revised November 24, 2025.
    c. Ampullary Adenocarcinoma. V2.2026. Revised February 10, 2026.
    d. Anal Carcinoma. V2.2026. Revised April 7, 2026.
    e. Appendiceal Neoplasms and Cancers. V2.2026. Revised April 10, 2026.
    f. B-Cell Lymphomas. V2.2026. Revised May 20, 2026.
    g. Biliary Tract Cancers. V1.2026. Revised March 10, 2026.
    h. Bladder Cancer. V2.2026. Revised June 22, 2026.
    i. Bone Cancer. V2.2026. Revised December 19, 2025.
    j. Central Nervous System Cancers. V2.2026. Revised June 10, 2026.
    k. Cervical Cancer. V2.2026. Revised November 11, 2025.
    l. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V2.2026. Revised December 22, 2025.
    m. Colon Cancer. V2.2026. Revised April 7, 2026.
    n. Esophageal and Esophagogastric Junction Cancers. V3.2026. Revised June 3, 2026.
    o. Gastric Cancer. V3.2026. Revised June 3, 2026.
    p. Gestational Trophoblastic Neoplasia. V2.2026. Revised November 21, 2025.
    q. Histocytic neoplasms. V1.2026. Revised May 8, 2026.
    r. Neuroendocrine and Adrenal Tumors. V1.2026. Revised April 21, 2026.
    s. Occult Primary (Cancer of Unknown Primary [CUP]). V2.2026. Revised May 4, 2026.
    t. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V4.2026, Revised April 10, 2026.
    u. Pancreatic Adenocarcinoma. V2.2026. Revised April 22, 2026.
    v. Pediatric Acute Lymphoblastic Leukemia. V1.2026. Revised August 11, 2025.
    w. Pediatric Aggressive Mature B-Cell Lymphomas. V1.2026. Revised March 20, 2026.
    x. Rectal Cancer. V2.2026. Revised April 7, 2026.
    y. Small Bowel Adenocarcioma. V2.2026. Revised April 7, 2026.
    z. T-Cell Lymphomas. V2.2026. Revised February 13, 2026.
    aa. Thymomas and Thymic Carcinomas. V2.2026. Revised April 10, 2026.
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