Clinical Criteria

Subject:	Levoleucovorin Agents		
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Overview

This document addresses the use of levoleucovorin agents (Fusilev, 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 (Fusilev, 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.

Other Uses

While NCCN also provides 2A recommendations for levoleucovorin agents (Fusilev, Khapzory) in chronic lymphocytic leukemia and rhabdomyosarcoma, the evidence behind these recommendations is weak. Recommendations for methotrexate/levoleucovorin in chronic lymphocytic leukemia are based on one trial (Tsimberidou 2003) which showed significant toxicity and was not more effective than a modified chemotherapy regimen not containing methotrexate in a previous study. Recommendations for methotrexate/ levoleucovorin in rhabdomyosarcoma are based on one trial (Pappo 1997) in pediatric and adolescent individuals.

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
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
Acute lymphoblastic leukemia (ALL)	Y	Y	Y
Anal Carcinoma	Y	Y	Y
B-Cell Lymphoma • Mantle Cell Lymphoma • AIDS-Related B-Cell Lymphomas • Burkitt Lymphoma	Y	Y	Y
Bladder Cancer	Y	Y	Y
Bone 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
Colon Cancer	Y	Y	Y
Esophageal and Esophagogastric Junction Cancers	Y	Y	Y
Gastric Cancer	Y	Y	Y
Gestational Trophoblastic Neoplasia	Y	Y	Y
Neuroendocrine and Adrenal Tumors, including 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
Rectal Cancer	Y	Y	Y
T-Cell Lymphomas • Peripheral T-Cell Lymphomas • Adult T-Cell Leukemia/Lymphoma • Extranodal NK/T-Cell Lymphoma, nasal type	Y	Y	Y
Thymomas and Thymic Carcinomas	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 (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. B-Cell Lymphoma, including 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, Mantle Cell Lymphoma, AIDS-Related B-Cell Lymphomas or Burkitt Lymphoma; **OR**
E. Bladder Cancer; **OR**
F. Central nervous system (CNS) cancers, including Primary CNS Lymphoma, Limited Brain Metastases, Extensive Brain Metastases or Leptomeningeal Metastases; **OR**
G. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; **OR**
H. Esophageal and Esophagogastric Junction Cancers; **OR**
I. Gastric Cancer; **OR**
J. Gestational Trophoblastic Neoplasia; **OR**
K. Hepatobiliary Cancers, Biliary Tract Cancers; **OR**
L. Neuroendocrine and Adrenal Tumors, Well Differentiated Grade 3 NET, including Poorly Differentiated (High Grade)/Large or Small Cell; **OR**
M. Occult Primary; **OR**
N. Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer, including Mucinous Carcinoma; **OR**
O. Pancreatic Adenocarcinoma; **OR**
P. Pediatric Aggressive Mature B-Cell Lymphomas; **OR**
Q. Rectal Cancer; **OR**
R. Small Bowel Adenocarcinoma; **OR**
S. 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**
T. Thymomas and Thymic Carcinomas.

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. [Fusilev] (Effective 10/1/19)
J0642	Injection, levoleucovorin 0.5 mg [Khapzory] (Effective 10/1/2019)
ICD-10 Diagnosis	
ALL DIAGNOSES	

Document History

Revised: 08/20/2021
Document History:

- 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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2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: June 16, 2021.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2021; Updated periodically.
5. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on June 16, 2021.
    a. Acute Lymphoblastic Leukemia. V1.2021. Revised April 6, 2021.
    b. Acute Myeloid Leukemia. V3.2021. Revised March 2, 2021.
    c. Anal Carcinoma. V1.2021. Revised February 16, 2021.
    d. B-Cell Lymphomas. V4.2021. Revised May 5, 2021.
    e. Bladder Cancer. V3.2021. Revised April 22, 2021.
    f. Bone Cancer. V1.2021. Revised November 20, 2020.
    g. Central Nervous System Cancers. V1.2021. Revised June 4, 2021.
    h. Cervical Cancer. V1.2021. Revised October 2, 2020.
    i. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. V4.2021. Revised April 29, 2021,
    j. Colon Cancer. V2.2021. Revised January 21, 2021.
    k. Esophageal and Esophagogastric Junction Cancers. V2.2021. Revised March 9, 2021.
    l. Gastric Cancer. V2.2021. Revised March 9, 2021.
    m. Gestational Trophoblastic Neoplasia. V2.2021. Revised March 31, 2021.
    n. Hepatobiliary Cancers. V3.2021. Revised June 15, 2021.
    o. Neuroendocrine and Adrenal Tumors. V1.2021. Revised April 14, 2021.
    p. Occult Primary. V2.2021. Revised February 8, 2021.
    q. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. V1.2021. Revised February 26, 2021.
    r. Pancreatic Adenocarcinoma. V2.2021. Revised February 25, 2021.
    s. Pediatric Acute Lymphoblastic Leukemia. V2.2021. Revised October 22, 2020.
    t. Pediatric Aggressive Mature B-Cell Lymphomas. V2.2021. Revised June 7, 2021.
    u. Rectal Cancer. V1.2021. Revised December 22, 2020..
    v. Small Bowel Adenocarcioma. V1.2021. Revised Fer
    w. T-Cell Lymphomas. V1.2021. Revised October 5, 2020.
    x. Thymomas and Thymic Carcinomas. V1.2021. Revised December 4, 2020.
6. Tsimberidou AM, Kantarjian HM, et al. Fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone plus rituximab and granulocyte-macrophage-colony stimulating factor (GM-CSF) alternating with methotrexate and cytarabine plus rituximab and GM-CSF in patients with Richter syndrome or fludarabine-refractory chronic lymphocytic leukemia. Cancer 2003; 97:1711-20.
7. 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.