

Drug Policy:

Fusilev™/Khapzory™ (levoleucovorin)

POLICY NUMBER UM ONC_1288	SUBJECT Fusilev™/Khapzory™ (levoleucovorin)		DEPT/PROGRAM UM Dept	PAGE 1 of 4
DATES COMMITTEE REVIEWED 04/13/16, 02/06/17, 02/01/18, 02/13/19, 12/11/19, 02/12/20, 11/11/20, 10/13/21, 11/15/21, 05/11/22, 10/12/22	APPROVAL DATE October 12, 2022	EFFECTIVE DATE October 28, 2022	COMMITTEE APPROVAL DATES 04/13/16, 02/06/17, 02/01/18, 02/13/19, 12/11/19, 02/12/20, 11/11/20, 10/13/21, 11/15/21, 05/11/22, 10/12/22	
PRIMARY BUSINESS OWNER: UM		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS HUM v8: UM 1-2; UM 2-1	NCQA STANDARDS UM 2		ADDITIONAL AREAS OF IMPACT	
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS Commercial, Exchange, Medicaid	

I. PURPOSE

To define and describe the accepted indications for Fusilev/Khapzory (levoleucovorin) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

New Century Health (NCH) is responsible for processing all medication requests from network ordering providers. Medications not authorized by NCH may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. PREFERRED MEDICATION GUIDANCE FOR INITIAL REQUEST:

1. When health plan Medicaid coverage provisions—including any applicable PDLs (Preferred Drug Lists)—conflict with the coverage provisions in this drug policy, health plan Medicaid coverage provisions take precedence per the [Preferred Drug Guidelines OR](#)
2. When health plan Exchange coverage provisions-including any applicable PDLs (Preferred Drug Lists)-conflict with the coverage provisions in this drug policy, health plan Exchange coverage provisions take precedence per the [Preferred Drug Guidelines OR](#)

3. For Health Plans that utilize NCH UM Oncology Clinical Policies as the initial clinical criteria, the Preferred Drug Guidelines shall follow NCH L1 Pathways (<http://pathways.newcenturyhealth.com>) when applicable, otherwise shall follow NCH drug policies AND
4. Continuation requests of previously approved, non-preferred medication are not subject to this provision AND
5. When applicable, generic alternatives are preferred over brand-name drugs AND
6. When there is a documented drug shortage, disease progression, contraindication, or confirmed intolerance to a Preferred drug/regimen, per NCH Policy and Pathway, the available alternative product may be used if deemed medically appropriate and the indication is listed in a standard reference compendia or accepted peer review literature. For a list of current drug shortages, please refer to FDA drug shortage website in the reference section.

B. Osteosarcoma

1. NOTE: Per NCH policy, J0642 Khapzory (levoleucovorin) is a non-Preferred drug, except when J9040 Leucovorin and J9041 Levoleucovorin are not available at the office and the drug shortage is reported by the FDA. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support that Khapzory is superior to Leucovorin/Fusilev.
2. The member has osteosarcoma or dedifferentiated chondrosarcoma and Khapzory is being used only when J9040 Leucovorin and J9041 Levoleucovorin are not available at the office and the shortage is reported on FDA drug shortage website ^A AND
3. Fusilev/Khapzory is being used following administration of high-dose methotrexate greater than 500 mg/m² over less than 4 hours OR greater than 1 g/m² over less than 4 hours AND
4. Is administered 24 hours after start of methotrexate infusion so that it does not interfere with the therapeutic effect of methotrexate.

C. Colorectal Cancer

1. NOTE: Per NCH policy, J0642 Khapzory (levoleucovorin) is a non-Preferred drug, except when J9040 Leucovorin and J9041 Levoleucovorin are not available at the office and the drug shortage is reported by the FDA. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support that Khapzory is superior to Leucovorin/Fusilev.
2. The member has colorectal cancer and Khapzory is being used only when J0640 Leucovorin and J0641 Levoleucovorin are not available at the office and the shortage is reported on FDA drug shortage website ^A AND
3. Fusilev/Khapzory is being used in combination with fluorouracil-based regimens in ONE of the following conditions:
 - a. For potentiation of fluorouracil therapy in the treatment of colorectal cancer
 - b. For treatment of colorectal cancer in combination regimen consisting of fluorouracil, leucovorin, and either irinotecan and/or oxaliplatin.

D. Overdosages of Folic Acid Antagonists

1. Note: Per NCH policy, J0642 Khapzory (levoleucovorin) is a non-Preferred drug, except when J9040 Leucovorin and J9041 Levoleucovorin are not available at the office and the drug shortage is reported by the FDA. This recommendation is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to support that Khapzory is superior to Leucovorin/Fusilev.
2. Khapzory is being used only when J9040 Leucovorin and J0641 Levoleucovorin are not available at the office and the shortage is reported on FDA drug shortage website ^A AND

3. Fusilev/Khazory is being used to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdoses of methotrexate in **ONE** of the following conditions:
 - a. Used in combination with cerebral spinal fluid (CSF) exchange and dexamethasone for intrathecal methotrexate overdose
 - b. Used in combination with forced diuresis and alkalization of urine to prevent potentially toxic blood levels of methotrexate
 - c. Used as high dose for methotrexate-induced nephrotoxicity.

III. EXCLUSION CRITERIA

- A. Fusilev/Khazory (levoleucovorin) is being used in member with pernicious or megaloblastic anemia.
- B. Dosing exceeds single dose limit of Fusilev/Khazory (levoleucovorin) 400 mg/m².
- C. Treatment in colorectal cancer exceeds the maximum 24 weeks duration limit.
- D. Investigational use of Fusilev/Khazory (levoleucovorin) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
 1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
 2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
 3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definition of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
 4. Whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
 5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
 6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
 7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

- A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

- A. Review – Utilization Management Department
- B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

- A. None

VII. REFERENCES

- A. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA:
<http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>
- B. Fusilev prescribing information. Acrotech Biopharma LLC. Irvine, CA. 2020.
- C. Khapzory prescribing information. Acrotech Biopharma LLC. Irvine, CA. 2020.
- D. Leucovorin prescribing information. Fresenius Kabi USA, LLC Lake Zurich, IL 2018
- E. Clinical Pharmacology Elsevier Gold Standard 2022.
- F. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, CO 2022.
- G. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2022.
- H. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2022.
- I. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.
- J. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services:
<https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf>.
- K. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA:
<http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.
- L. NCQA UM 2022 Standards and Elements.