CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Lorlatinib (Lorbrena®)

Version: 1.0

EFFECTIVE DATE: 5/5/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Lorlatinib (Lorbrena®)

Discussion

Lorlatinib is a kinase inhibitor against ALK, ROS1, TYK1, FER, FPS, TRKA, TRKB, TRKC, FAK, FAK2, and ACK. It demonstrated in vitro activity against multiple mutant forms of the ALK enzyme, including some mutations detected in tumors at the time of disease progression on crizotinib and other ALK inhibitors. As ALK and ROS1 are related tyrosine kinases, several small-molecule tyrosine kinase inhibitors (TKIs) effectively target both ALK and ROS1.

Lorlatinib is a novel, oral, reversible, ATP-competitive macrocyclic TKI of ALK and ROS1. This potent and highly selective third-generation inhibitor was designed to penetrate the blood–brain barrier and to overcome known ALK resistance mutations.[1,2]

Adverse reactions associated with lorlatinib include the risk of serious hepatotoxicity when used concomitantly with strong CYP3A inducers, central nervous system effects, hyperlipidemia, atrioventricular block, interstitial lung disease/pneumonitis, hypertension, hyperglycemia, embryo-fetal toxicity, edema, peripheral neuropathy, weight gain, cognitive effects, fatigue, dyspnea, arthralgia, diarrhea, mood disturbances, hypercholesterolemia, hypertriglyceridemia, and cough.

Lorlatinib is approved by the Food and Drug Administration (FDA) for non-small cell lung cancer.[1] The National Comprehensive Cancer Network (NCCN) endorses lorlatinib for the following cancer types: B-cell lymphomas, central nervous system, histiocytic neoplasms, non-small cell lung, peripheral t-cell lymphomas, soft tissue, and uterine.[3,4,5,6,7,8,9,10]

Definitions

- **Anaplastic lymphoma kinase (ALK)** - A transmembrane tyrosine kinase receptor involved in the carcinogenesis of several human cancers through gene fusion, amplification, mutation, or protein overexpression.[11]
- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[12]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.[13]
- **Ros oncogene 1 (ROS)** - A proto-oncogene that encodes a receptor tyrosine kinase with an unknown physiological role in humans. Somatic chromosomal fusions involving ROS1 produce chimeric oncoproteins that drive a diverse range of cancers in adult and pediatric patients.[14]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

B-Cell Lymphomas - Diffuse Large B-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Relapsed or refractory ALK-positive disease.[3]

Central Nervous System Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Limited Brain Metastases

For **NCCN** required criteria coverage:

3. Single-agent treatment for disease metastases in ALK rearrangement-positive non-small cell lung cancer for one of the following:
   a) Initial treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent brain metastases
   c) Relapsed disease with either stable systemic disease or reasonable systemic treatment options; OR

Extensive Brain Metastases

For **NCCN** required criteria coverage:

4. Single-agent treatment for disease metastases in ALK rearrangement-positive non-small cell lung cancer for one of the following:
   a) Primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options.[4]

Histiocytic Neoplasms

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line or subsequent therapy for anaplastic lymphoma kinase (ALK)-fusion target as a single agent for one of the following:
   a) Erdheim-Chester Disease (ECD) with symptomatic disease
   b) Relapsed/refractory disease.[5]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Metastatic disease whose tumors are anaplastic lymphoma kinase (ALK)-positive[1]; OR

For **NCCN** required criteria coverage:

4. Single-agent therapy for ALK rearrangement positive recurrent, advanced, or metastatic disease for one of the following:
   a) First-line therapy
   b) Intolerant to crizotinib
   c) Following disease progression on first-line therapy with lorlatinib, as continuation of therapy except in cases of symptomatic systemic disease with multiple lesions
   d) Subsequent therapy option for resistant mutations, such as ALK G1202R, L1196M (except compound L1196M/G1202R), following disease progression on first-line therapy with either alectinib, brigatinib, or ceritinib
   e) Subsequent therapy (if not previously given) following disease progression on first-line therapy with either alectinib, brigatinib, or ceritinib for symptomatic systemic disease
   f) Subsequent therapy for further progression (if not previously given) following disease progression on first-line therapy with either alectinib, brigatinib, or ceritinib and subsequent therapy with continuation of either alectinib, brigatinib, or ceritinib except in cases of symptomatic systemic disease with multiple lesions
   g) Subsequent therapy (if not previously given) following disease progression on first-line therapy with crizotinib
   h) Subsequent therapy for further progression (if not previously given) following disease progression on first-line therapy with crizotinib and subsequent therapy with either alectinib, brigatinib, or ceritinib; OR
5. Single-agent therapy for recurrent, advanced, or metastatic disease in those with ROS1 rearrangement positive tumors as subsequent therapy following disease progression on entrectinib, crizotinib, or repotrectinib for one of the following:
   a) Asymptomatic progression
   b) Symptomatic progression in the brain
   c) Symptomatic systemic progression.[6]

Pediatric Central Nervous System Cancers

1. Less than or equal to 21 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Diffuse High-Grade Gliomas

For **NCCN** required criteria coverage:

3. Adjuvant treatment for ALK-rearrangement positive disease for one of the following:
   a) Following standard brain radiation therapy (RT) with or without concurrent temozolomide in patients ≥3 years of age
   b) Patients <3 years of age

   Note: Except diffuse midline glioma, H3 K27-altered or pontine location; OR

4. Recurrent or progressive disease for ALK-rearrangement positive disease

   Note: Except oligodendroglioma, IDH-mutant and 1p/19q co-deleted or astrocytoma IDH-mutant.[7]

Soft Tissue Sarcoma - Inflammatory Myofibroblastic Tumor (IMT) with ALK Translocation

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single-agent therapy for the treatment of inflammatory myofibroblastic tumor (IMT) with ALK translocation.[8]

T-Cell Lymphomas - Peripheral T-Cell Lymphomas

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy for single agent relapsed/refractory ALK-positive anaplastic large cell lymphoma (ALCL).[9]

Uterine Neoplasms - Uterine Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line therapy for advanced, recurrent/metastatic, or inoperable disease (or second-line or subsequent therapy as clinically appropriate if not used previously) as a single agent for inflammatory myofibroblastic tumor (IMT) with ALK translocation for one of the following:
   a) Primary treatment of known or suspected extrauterine disease, diagnosed by biopsy or myomectomy
   b) Primary treatment of disease that is not suitable for primary surgery (disease is not amenable to resection, or the patient is not suitable for surgery based on comorbidities)

c) Additional therapy following total hysterectomy ± bilateral salpingo-oophorectomy (TH ± BSO) for stage II-III IMT with ALK translocation
d) Additional therapy following TH ± BSO for stage IV IMT with ALK translocation
e) Preoperatively or postoperatively for recurrent disease with resectable isolated metastases
f) Recurrent disease with unresectable isolated metastases or disseminated disease
g) Radiologically isolated vaginal/pelvic recurrence if no prior radiation therapy (RT), given in combination with RT
h) Radiologically isolated vaginal/pelvic recurrence if prior RT, given with or without RT.[10]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD-10, and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C34	Malignant neoplasm of bronchus and lung
C49	Malignant neoplasm of connective and soft tissue
C55	Malignant neoplasm of uterus, part unspecified
C71	Malignant neoplasm of brain
C79.31	Secondary malignant neoplasm of brain
C83.3	Diffuse large B-cell lymphoma
C84.6	Anaplastic large cell lymphoma, ALK-positive
D76.3	Other histiocytosis syndromes
J8999	Prescription drug, oral, chemotherapeutic, not otherwise specified

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	5/5/2025
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee:	5/5/2025
6	Revision Changes:	

References

[1] Lorlatinib (Lorbrena) [Package Insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210868s004lbl.pdf. Accessed March 27, 2025.

[2] Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol*. 2017;18(12):1590-1599. https://pubmed.ncbi.nlm.nih.gov/29074098/. Accessed March 27, 2025.

[3] National Comprehensive Cancer Network. NCCN Guidelines: B-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed March 27, 2025.

[4] National Comprehensive Cancer Network. NCCN Guidelines: Central Nervous System Cancers. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed March 27, 2025.

[5] National Comprehensive Cancer Network. NCCN Guidelines: Histiocytic Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed March 27, 2025.

[6] National Comprehensive Cancer Network. NCCN Guidelines: Non-Small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 27, 2025.

[7] National Comprehensive Cancer Network. NCCN Guidelines: Pediatric Central Nervous System Cancers. https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf. Accessed March 27, 2025.

[8] National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed March 27, 2025.

[9] National Comprehensive Cancer Network. NCCN Guidelines: T-Cell Lymphomas. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed March 27, 2025.

[10] National Comprehensive Cancer Network. NCCN Guidelines: Uterine Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed March 27, 2025.

[11] Della Corte CM, Viscardi G, Di Liello R, et al. Role and targeting of anaplastic lymphoma kinase in cancer. *Mol Cancer*. 2018;17(1):30. Published 2018 Feb 19. https://pmc.ncbi.nlm.nih.gov/articles/PMC5817803/. Accessed March 27, 2025.

[12] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed April 23, 2025.

[13] National Comprehensive National Cancer Network. https://www.nccn.org/home. Accessed April 23, 2025.

[14] Drilon A, Jenkins C, Iyer S, Schoenfeld A, Keddy C, Davare MA. ROS1-dependent cancers - biology, diagnostics and therapeutics. *Nat Rev Clin Oncol*. 2021;18(1):35-55. https://pubmed.ncbi.nlm.nih.gov/32760015/. Accessed March 27, 2025.