CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Lenvatinib Mesylate (Lenvima®)

Version: 1.0

EFFECTIVE DATE: 7/1/2024

NantHealth® | Eviti®

Please note the following:

Lenvatinib Mesylate (Lenvima®)

Note: 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.

Note: 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.

Lenvatinib Mesylate (Lenvima): Discussion

Lenvatinib mesylate inhibits proteins that promote cancer cell division and the growth of new blood vessels essential for tumor growth, thereby preventing cancer cells from proliferating.

Lenvatinib mesylate is a type of targeted therapy drug called a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1, VEGFR2, and VEGFR3. Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFRA), KIT proto-oncogene receptor tyrosine kinase (KIT), and rearranged during transfection (RET). It also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2 alpha (FRS2) phosphorylation.[1,2]

For patients with thymic carcinomas treated with lenvatinib, there is a high risk for side effects and frequent dose reductions may be needed.[3]

For advanced renal cell carcinoma (RCC) the combination of lenvatinib and everolimus showed increased antiangiogenic and antitumor activity as demonstrated by decreases in human endothelial cell proliferation, tube formation, and VEGF signaling in vitro, and by decreases in tumor volume.[1,4]

Despite common treatment-emergent adverse events (TEAEs), the benefits of lenvatinib in improving PFS, overall survival (OS), and response rates support its role as a preferred therapeutic option in this setting.[5]

Lenvatinib mesylate is associated with several adverse reactions including hypertension, cardiac dysfunction, hepatotoxicity, renal impairment or failure, gastrointestinal perforation, proteinuria, fistula formation, QT interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome (RPLS), hemorrhagic events, impaired wound healing,

osteonecrosis of the jaw, embryo-fetal toxicity. This may cause liver problems that may lead to liver failure and death. It is important to check liver function before and during treatment.

Lenvatinib mesylate is approved by the Food and Drug Administration (FDA) for differentiated thyroid cancer (DTC), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and endometrial carcinoma (EC).[1]

The National Comprehensive Cancer Network (NCCN) endorses lenvatinib mesylate in the following cancer types: thymomas and thymic, cutaneous melanoma, hepatocellular, salivary gland, kidney, endometrial, and thyroid.[3,4,5,6,7,8,9]

Lenvatinib Mesylate: Definitions

- **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.
- **National Comprehensive Cancer Network (NCCN)** - An alliance of at least 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.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** - A neurological disorder characterized by transient brain edema and white matter changes, typically affecting the posterior regions of the brain. It manifests with symptoms such as headaches, seizures, visual disturbances, and altered mental status, often associated with conditions like hypertension, eclampsia, renal disease, autoimmune disorders, or certain medications.[1]
- **Vascular endothelial growth factor (VEGF)** - Cell surface proteins that bind to vascular endothelial growth factors, essential for initiating blood vessel formation (angiogenesis) in processes like development, wound healing, and cancer progression.

Lenvatinib Mesylate: Policy

Note: Coverage of lenvatinib mesylate will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Lenvatinib mesylate will be considered for coverage when the following criteria are met:

Thymomas and Thymic Carcinomas

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

For **NCCN** required criteria coverage:

3. A single agent for those who cannot tolerate first-line combination regimens as preoperative systemic therapy for surgically resectable disease if R0 resection is considered uncertain; OR
4. Single agent for those who cannot tolerate first-line combination regimens for thymic carcinoma after R1 or R2 resection; OR
5. First-line therapy for recurrent, advanced, or metastatic disease as a single agent for those who cannot tolerate first-line combination regimens for one of the following:
   a) Resectable locally advanced disease and solitary metastasis or ipsilateral pleural metastasis
   c) Consideration following surgery for solitary metastasis or ipsilateral pleural metastasis
   d) Medically inoperable/unresectable solitary metastasis or ipsilateral pleural metastasis
   e) Extrathoracic metastatic disease; OR
6. Second-line therapy as a single agent for one of the following:
   a) Unresectable locally advanced disease
   b) Solitary metastasis or ipsilateral pleural metastasis
   c) Extrathoracic metastatic disease.[3]

Kidney 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. In combination with everolimus, in advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy[1]; OR

For **NCCN** required criteria coverage:

4. Used in combination with everolimus for relapse or stage IV disease for one of the following:
   a) Subsequent therapy for clear cell histology
   b) Systemic therapy for non-clear cell histology; OR
5. In combination with pembrolizumab for relapse or stage IV disease with clear cell histology as one of the following:
   a) First-line therapy
   b) Subsequent therapy if immuno-oncology therapy naive
   c) Subsequent therapy if prior history includes immuno-oncology therapy.[4]

Thyroid Carcinoma

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

For **FDA** required criteria coverage:

3. For locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC)[1]; OR

For **NCCN** required criteria coverage:

4. For progressive and/or symptomatic disease including papillary carcinoma, follicular carcinoma, and oncocytic carcinoma for one of the following:
   a) Unresectable locoregional recurrent or persistent disease not amenable to radioactive iodine (RAI) therapy
   b) Distant metastatic disease not amenable to RAI therapy; OR
5. For medullary carcinoma of recurrent or persistent distant metastases if symptomatic disease or progression; OR
6. For anaplastic carcinoma used in combination with pembrolizumab for one of the following:
   a) First-line therapy for stage IVC disease
   b) Second-line therapy for stage IVC disease.[5]

Hepatocellular Carcinoma

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 treatment as a single agent for one of the following:
   a) Liver-confined, unresectable disease and are deemed ineligible for transplant
   b) Extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy; OR
4. Subsequent systemic therapy as a single agent if progression on or after systemic therapy for one of the following:
   a) Liver-confined, unresectable disease and are deemed ineligible for transplant
   b) Extrahepatic/metastatic disease and are deemed ineligible for resection, transplant, or locoregional therapy.[1,6]

Head and Neck Cancers - Salivary Gland Tumors

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 systemic therapy for recurrent adenoid cystic carcinoma for one of the following:
   a) Distant metastases in patients with a performance status (PS) of 0-3
   b) Unresectable locoregional recurrence or second primary with prior radiation therapy.[7]

Endometrial Carcinoma

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

For **FDA** required criteria coverage:

3. In combination with pembrolizumab for advanced endometrial carcinoma (EC) that is mismatch repair proficient (pMMR), or not microsatellite instability-high (MSI-H), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.[1]; OR

For **NCCN** required criteria coverage:

4. First-line therapy (useful in certain circumstances after prior platinum-based therapy), second-line or subsequent therapy in combination with pembrolizumab for recurrent disease that is mismatch repair proficient (pMMR) for one of the following:
   a) Isolated metastases
   b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
   c) Sequential EBRT is used with or without brachytherapy for locoregional recurrence in patients who have no prior RT to the site of recurrence, or who have only had previous vaginal brachytherapy
   d) After surgical exploration, sequential EBRT is used for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic or para-aortic lymph nodes
   e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
   f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to site of recurrence.[8]

Cutaneous Melanoma

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

For **NCCN** required criteria coverage:

3. Subsequent systemic therapy option in combination with pembrolizumab for metastatic or unresectable disease that has progressed following treatment with an anti-PD-1/PD-L1-based therapy, including in combination with anti-CTLA-4 for ≥2 doses.[9]

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

Lenvatinib Mesylate: References

1. Lenvatinib Mesylate (Lenvima) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/206947s031lbl.pdf. Accessed June 21, 2024.
2. Lenvatinib Mesylate – National Cancer Institute. https://www.cancer.gov/about-cancer/treatment/drugs/lenvatinibmesylate. Accessed June 21, 2024.
3. National Comprehensive Cancer Network. Thymomas and Thymic Carcinomas. https://www.nccn.org/professionals/physician_gls/pdf/thymic.pdf. Accessed June 21, 2024.
4. National Comprehensive Cancer Network. Kidney Cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed June 21, 2024.
5. National Comprehensive Cancer Network. Thyroid Cancer. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed June 21, 2024.
6. National Comprehensive Cancer Network. Hepatocellular Carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed June 21, 2024.
7. National Comprehensive Cancer Network. Head and Neck Cancers. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed June 21, 2024.
8. National Comprehensive Cancer Network. Uterine Neoplasms. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed June 21, 2024.
9. National Comprehensive Cancer Network. Melanoma: Cutaneous. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed June 21, 2024.

Lenvatinib Mesylate: 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
C06.9, C07, C08	Head and Neck Cancers - Salivary Gland Tumors
C22	Hepatocellular Carcinoma
C37, D15.0, D38.4	Thymomas and Thymic Carcinomas
C43	Melanoma: Cutaneous
C54, C55	Uterine Neoplasms - Endometrial Carcinoma
C64, C65	Kidney Cancer
C73	Thyroid Carcinoma
C9399, J8999	Lenvatinib mesylate

Lenvatinib Mesylate: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	7/1/2024
2	Policy Review Dates:	
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	10/29/2024
6	Revision Changes:	