**Medication Policy Manual**

**Policy No:** dru398  
**Date of Origin:** May 8, 2015  
**Committee Approval Date:** September 9, 2016  
**Next Review Date:** May 2017  
**Effective Date:** October 1, 2016

**IMPORTANT REMINDER**
This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

_Benefit determinations should be based in all cases on the applicable contract language._ To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**
Lenvatinib (Lenvima) is an oral kinase inhibitor used in the treatment of local or metastatic differentiated thyroid cancer (DTC) that is refractory to radioactive iodine treatment. Lenvatinib (Lenvima) is also used in the treatment of advanced renal cell carcinoma (RCC). It works by blocking the production of specific proteins that cancer cells need to grow.
Policy/Criteria

I. Most contracts require prior authorization approval of lenvatinib prior to coverage. Lenvatinib (Lenvima) may be considered medically necessary when either criterion A or B below is met:

A. A diagnosis of locally recurrent or metastatic, radioactive iodine-refractory differentiated (papillary, follicular, and Hürthle) thyroid carcinoma (RAI-refractory DTC).

OR

B. A diagnosis of advanced renal cell carcinoma when criteria 1 and 2 below are met:

1. There has been progression of disease on or after antiangiogenic therapy with one of the following: bevacizumab (Avastin), sunitinib (Sutent), pazopanib (Votrient), axitinib (Inlyta), or sorafenib (Nexavar).

AND

2. Lenvatinib (Lenvima) will be used in combination with everolimus (Afinitor)

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx considers lenvatinib (Lenvima) to be a self-administered medication.

B. When prior authorization is approved, lenvatinib (Lenvima) may be authorized in quantities of up to one carton containing six, 5-day blister cards per month.

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Lenvatinib (Lenvima) is considered investigational when used for all other conditions, including but not limited to:

A. Anaplastic thyroid cancer
B. Endometrial cancer
C. Hepatocellular carcinoma
D. Malignant glioma
E. Melanoma

Position Statement

- Lenvatinib (Lenvima) is an oral cancer medication that blocks the activity of several different tyrosine kinase pathways, thereby preventing the synthesis of certain proteins necessary for tumor cell growth.
- Lenvatinib (Lenvima) is used for the treatment of locally recurrent or metastatic differentiated thyroid carcinoma (DTC) refractory to radioactive iodine (RAI) treatment. It is also used for the treatment of advanced renal cell carcinoma in patients who have progressed on or following treatment with a vascular endothelial growth factor (VEGF)-targeted therapy.

- Use of lenvatinib (Lenvima) in patients with asymptomatic or slowly progressing DTC is not recommended due to the potential for serious, life-threatening side effects.

- Lenvatinib (Lenvima) has not been shown to improve survival or quality of life in patients with DTC or advanced RCC.

- Lenvatinib (Lenvima) is currently being studied in a variety of other cancers. Well-designed, published clinical trials are needed to support the safety and efficacy of lenvatinib in these treatment settings.

**Clinical Efficacy**

**RADIOACTIVE IODINE-REFRACTORY DIFFERENTIATED THYROID CARCINOMA (RAI-REFRACTORY DTC)**

Lenvatinib (Lenvima) demonstrated improved progression-free survival (PFS) in patients with RAI-refractory DTC; however, there is currently no evidence that lenvatinib (Lenvima) improves overall survival.

- A single randomized controlled trial evaluated lenvatinib (Lenvima) in 382 patients with RAI-refractory DTC who had demonstrated progression of disease within the previous thirteen months. [1]
  
  * The primary endpoint was PFS. This endpoint has not been shown to correlate to more meaningful outcomes in DTC such as overall survival (OS) or quality of life.
  
  * Median PFS was significantly longer in patients treated with lenvatinib (Lenvima) compared to those patients in the placebo group (18.3 months vs 3.6 months, respectively).
  
  * OS results were not mature at the time of the analysis; however, future results may be potentially confounded by the crossover of 83% of patients in the placebo arm.

- The National Comprehensive Cancer Network (NCCN) thyroid carcinoma treatment guideline lists lenvatinib as a treatment option for progressive or symptomatic follicular, Hürthle cell, or papillary thyroid carcinomas as a category 2A recommendation. [2]

**ADVANCED RENAL CELL CARCINOMA (RCC)**

Lenvatinib (Lenvima) received accelerated approval based on a demonstrated improvement in PFS in patients with advanced RCC who had progressed on or following treatment with a VEGF-targeted therapy.

- A small, open-label, randomized trial evaluated lenvatinib (Lenvima), everolimus (Afinitor), and the combination in 153 patients. [3]
* The primary endpoint was PFS. This endpoint has not been shown to correlate to more meaningful outcomes in RCC such as OS, symptom control, or quality of life.

* The combination of lenvatinib (Lenvima) plus everolimus (Afinitor) significantly prolonged median PFS compared with everolimus (Afinitor) alone (14.6 months vs 5.5 months, respectively).

* The study was not powered to detect a difference in OS between treatments.

- The NCCN kidney treatment guideline lists lenvatinib (Lenvima) plus everolimus (Afinitor) as a category 2A recommendation for subsequent therapy following anti-angiogenic therapy. [4]

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.**

**USE IN OTHER CONDITIONS**

- Lenvatinib (Lenvima) is under investigation for use in several other types of cancer, including endometrial carcinoma [5,6], anaplastic thyroid cancer [7], hepatocellular carcinoma [8-10], melanoma [11,12], and malignant glioma [13].

- The evidence for these indications is preliminary and limited to unpublished phase 2 studies or open-label phase 3 trials. Larger well-controlled trials are needed to demonstrate the safety and efficacy of lenvatinib in these conditions.

**Safety** [14]

- Similar to other tyrosine kinase inhibitors, lenvatinib (Lenvima) has a relatively toxic adverse events profile.

- Common adverse events associated with lenvatinib (Lenvima) include hypertension, diarrhea, nausea, stomatitis, vomiting, loss of appetite, headache, and hand-foot syndrome.

- Serious adverse events include myocardial dysfunction, prolonged QT interval, arterial thrombosis, proteinuria, and renal impairment.

**Dosing Considerations** [14]

- The recommended starting dose of lenvatinib (Lenvima) for RAI-refractory DTC is 24 mg (two 10 mg capsules and one 4 mg capsule) per day until disease progression or until unacceptable toxicity occurs.

- The recommended starting dose of lenvatinib (Lenvima) for advanced RCC is 18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg everolimus (Afinitor) per day until disease progression or until unacceptable toxicity.

- Lenvatinib (Lenvima) capsules are supplied in cartons of six, 5-day blister cards.

- Dose modifications or discontinuation of lenvatinib (Lenvima) may be necessary when adverse events such as hypertension, nephrotic syndrome, cardiac dysfunction, renal failure, gastrointestinal perforation, or QT prolongation occur.
### Cross References

<table>
<thead>
<tr>
<th>Cross-Referenced Products</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afinitor®, everolimus</td>
<td>Medication Policy Manual, Policy No. dru178</td>
</tr>
<tr>
<td>Avastin®, bevacizumab</td>
<td>Medication Policy Manual, Policy No. dru215</td>
</tr>
<tr>
<td>Cabometyxtm, cabozantinib</td>
<td>Medication Policy Manual, Policy No. dru290</td>
</tr>
<tr>
<td>Nexavar®, sorafenib</td>
<td>Medication Policy Manual, Policy No. dru134</td>
</tr>
<tr>
<td>Sutent®, sunitinib</td>
<td>Medication Policy Manual, Policy No. dru128</td>
</tr>
<tr>
<td>Votrient®, pazopanib</td>
<td>Medication Policy Manual, Policy No. dru199</td>
</tr>
</tbody>
</table>

### Codes

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>J8999</td>
<td>Prescription drug, oral, chemotherapeutic, Not otherwise specified</td>
</tr>
<tr>
<td>ICD-10</td>
<td>C73</td>
<td>Malignant neoplasm of the thyroid gland</td>
</tr>
<tr>
<td>ICD-10</td>
<td>C64.1</td>
<td>Malignant neoplasms of the kidney or renal pelvis</td>
</tr>
<tr>
<td></td>
<td>C64.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C64.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C65.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C65.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C65.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Z85.528</td>
<td></td>
</tr>
</tbody>
</table>

### References


13. Reardon DA, Pan E, Fan J, et al. A Phase 2 Trial of the Multitargeted Kinase Inhibitor Lenvatinib (E7080) in Patients (Pts) With Recurrent Glioblastoma (GBM) and Disease Progression Following Prior Bevacizumab Treatment. Presented at: ESMO; 2012; Vienna, Austria.


**Revision History**

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/9/2016</td>
<td>Addition of advanced renal cell carcinoma as a covered indication</td>
</tr>
<tr>
<td>05/13/2016</td>
<td>No changes to coverage criteria with this annual update</td>
</tr>
</tbody>
</table>