BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 7/16/15**
SECTION: DRUGS	**LAST REVIEW DATE: 9/20/18**
	LAST CRITERIA REVISION DATE: 9/20/18
	ARCHIVE DATE:

LENVIMA™ (lenvatinib) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

LENVIMA™ (lenvatinib) oral capsule (cont.)

Criteria:

- **Criteria for initial therapy:** Lenvima (lenvatinib) is considered ***medically necessary*** with medical record documentation of **ALL** of the following:

  1. Prescriber is an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Papillary, follicular, & Hürthle cell thyroid cancer that is progressive and/or symptomatic radioactive iodine (RAI)-refractory and is either unresectable locoregional recurrent or persistent disease **or** distant metastatic disease
     - Medullary thyroid carcinoma that is recurrent or persistent distant metastases, symptomatic or progressive disease that progressed on Caprelsa (vandetanib) or Cometriq (cabozantinib)
     - Advanced renal cell carcinoma following one prior anti-angiogenic therapy and when approved will be used in combination with Afinitor (everolimus)
     - Hepatocellular Carcinoma (Child-Pugh Class A only) who are unresectable due to inadequate liver reserve or tumor location and not a transplant candidate; or are inoperable by performance status or comorbidity, local disease or local disease with minimal extrahepatic disease only; or have metastatic disease or have extensive liver tumor burden
     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Measurement of blood pressure **AND** initiate **OR** adjust blood pressure medication if abnormal
     - Liver enzymes
     - Urine dipstick for proteinuria
     - 24-hour urine protein if urine dipstick for proteinuria is $\geq$ 2+
     - Thyroid function tests

  5. Will not be used in a patient with end-stage renal disease

  6. Woman patient of child bearing potential should use effective contraception during and for at least 2 weeks after therapy

  7. Woman patient who is breast feeding an infant or child should stop breast feeding during therapy

  Initial approval duration: 6 months

LENVIMA™ (lenvatinib) oral capsule (cont.)

- **Criteria for continuation of coverage (renewal request):** Lenvima (lenvatinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by an Oncologist

  2. Individual's condition responded while on therapy
     - Response is defined as:
       - No evidence of disease progression
       - No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use
  3. Individual has been adherent with the medication

  4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
     - Significant adverse effect such as:
       - Uncontrolled or life-threatening hypertension
       - Severe and persistent cardiac dysfunction such as decreased left or right ventricular function, cardiac failure, or pulmonary edema
       - Arterial thromboembolic event
       - Hepatic failure or severe and persistent hepatotoxicity
       - Nephrotic syndrome
       - Severe and persistent renal impairment or renal failure
       - Severe and persistent vomiting and/or diarrhea despite medical management
       - Gastrointestinal perforation or life-threatening fistula
       - Reversible posterior leukoencephalopathy syndrome that does not resolve or recurs
       - Severe and persistent hemorrhage
       - Patient with wound healing complications

  5. There are no significant interacting drugs

  Renewal duration: 12 months

Description:

Lenvima (lenvatinib) is a kinase inhibitor indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) and when used in combination with everolimus for patients with advanced renal cell carcinoma following one prior anti-angiogenic therapy.

Thyroid cancer is the most common of the endocrine malignancies. The annual incidence of thyroid cancer varies considerably by geographic area, age and sex. The only recognized environmental risk factor for thyroid carcinoma is exposure to ionizing radiation.

Thyroid cancer can develop from follicular or non-follicular thyroid cells. Thyroid cancers from follicular cells include papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), Hurthle cell cancer (HCC, also known as oxyphil thyroid cancer, a subtype of FTC), and anaplastic thyroid cancer (ATC). PTC and FTC are often referred

to as differentiated thyroid cancer (DTC). There are several subtypes of DTC that includes tall cell, columnar and insular thyroid cancers. ATC is an undifferentiated thyroid cancer. Medullary thyroid cancer (MTC) arises from non-follicular thyroid cells called calcitonin-producing cells.

DTC is the least aggressive of the thyroid cancers with an excellent prognosis. However a small percentage of patients with DTC exhibit a more aggressive form of disease. Several factors are implicated in increasing the risk for the development of the more aggressive form. These include age greater than 45 years, male gender, radioactive iodine resistance, and a positive fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scan.

Initial treatment for DTC includes surgery (either total throidectony or lobectomy), radioactive iodine treatment, and thyroid hormone suppression therapy. Patients with progressive DTCs that are not responding to standard treatment require additional therapy. Additional therapy can include external beam radiation (EBRT) in select cases, chemotherapy (such as doxorubicin, cisplatin, oxaliplatin, gemcitabine), thalidomide derivatives (thalidomide, lenalidomide) and targeted therapy for advanced disease that block known pathways for thyroid cancer cell growth and differentiation. Tyrosine kinase inhibitors have activity against pathways that are implicated in DTC.

Renal Cell Carcinoma (RCC) is a common type of kidney cancer with three major sub-types: clear cell renal carcinoma (the most common RCC), papillary renal cell carcinoma (second most common), and chromophobe renal cell carcinoma (third most common). There are other rare types of renal cell carcinoma that make up less than 1% of the RCC. RCC has a high mortality rate but if it is detected early, it is potentially curable by surgery. In localized disease, partial nephrectomy for small tumors and radical nephrectomy for large tumors continue to be the gold-standard treatments. Cytoreductive nephrectomy is often indicated before the start of systemic treatment in patients with metastatic disease as part of integrated management strategy. Targeted therapy is a treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment attempts to blocks the growth and spread of cancer cells while limiting damage to healthy cells. Anti-angiogenesis therapy is a type of treatment aimed at the process by which cancer cells make new blood vessels. Many of the anti-angiogenesis agents used attack the protein known as vascular endothelial growth factor (VEGF) that controls the formation of new blood vessels.

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, it accounts for more than 90% of all cases of primary liver cancer. Several of important risk factors for the development of HCC have been identified. Some of these include hepatitis B viral (HBV) infection, chronic hepatitis C virus (HCV) infection, hereditary hemochromatosis, cirrhosis of almost any cause, alcohol use, and nonalcoholic fatty liver disease. Other factors include environmental toxins, dietary factors, tobacco abuse, diabetes mellitus, and alpha-1 antitrypsin deficiency. HCC is an aggressive tumor, it is typically diagnosed late in its course, and the median survival following diagnosis is approximately 6-20 months. The mainstay of therapy is surgical resection, but the majority of patients are not eligible because of tumor extent or underlying liver dysfunction

Lenvima (lenvatinib) is a receptor tyrosine kinase (RTK) inhibitor of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4); and other RTK involved in pathogenic angiogenesis, tumor growth, and cancer progressions such as fibroblast growth factor receptors (FGFR-) 1, 2, 3, and 4, platelet derived growth factor receptor alpha (PDGFR-alfa), KIT, and rearranged during transfection (RET) proto-oncogene that encodes for tyrosine kinase receptor. Inhibition of these receptor tyrosine kinases leads to decreased tumor growth and slowing of cancer progression. The combination of lenvatinib and everolimus showed increased anti-angiogenic

LENVIMA™ (lenvatinib) oral capsule (cont.)

and antitumor activity in models of human renal cell cancer greater than each drug alone. Many of the anti-angiogenesis drugs used attack the VEGF pathway.

Recent recommendations from the National Comprehensive Cancer Network (NCCN) on the treatment of thyroid carcinoma and treatment of renal cell carcinoma are as follows:

Thyroid Carcinoma – NCCN version 1.2018, May 22, 2018

Papillary, follicular, & Hürthle Cell thyroid carcinomas:

Consider Lenvima (lenvatinib) for treatment of progressive and/or symptomatic iodine-refractory disease as the preferred agent for:

- unresectable locoregional recurrent or persistent disease
- distant metastatic disease

Medullary carcinoma

Consider Lenvima (lenvatinib) for treatment of recurrent or persistent distant metastases if symptomatic disease or progression **if:**

- clinical trials, vandetanib, or cabozantinib are not available or appropriate
- there is progression on vandetanib or cabozantinib

Kidney Cancer – NCCN version 4.2018, Apr 23, 2018

Use Lenvima (lenvatinib) in combination with everolimus for relapse or surgically unresectable stage IV disease:

- as subsequent therapy for predominant clear cell histology – Category 1
- as systemic therapy for non-clear cell histology – Category 2A

Hepatocellular Carcinoma – NCCN version 3.2018, Aug 29, 2018

Treatment as a single agent for patients (Child-Pugh Class A only) who

- have unresectable disease and are not a transplant candidate
- are inoperable by performance status or comorbidity, or have local disease or local disease with minimal extrahepatic disease only
- have metastatic disease or extensive liver tumor burden

Resources:

Lenvima. Package Insert. Revised by manufacturer 08/2018. Accessed 09-04-2018.

Lenvima. Package Insert. Revised by manufacturer 02/2017. Accessed 06-24-2017.

Lenvima. Package Insert. Revised by manufacturer 05/2016. Accessed 05-23-2016.

Lenvima. Package Insert. Revised by manufacturer 02/2015. Accessed 05-08-2015.

Pacini P, Castagna MG, Brill L, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncology 2012 23 (Sup 7 Oct): vii 110-vii 119.

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Brown RL, de Souza JA, Cohen EEW. Thyroid cancer: Burden of illness and management of disease. J Cancer 2011; 2:193-199.

National Comprehensive Cancer Network Clinical Guidelines in Oncology 2015 version 1

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

Lenvima (lenvatinib) product information accessed 07-16-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f4bedd21-efde-44c6-9d9c-b48b78d7ed1e

NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Version 1.2018, May 22, 2018. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Version 4.2018, Apr 23, 2018. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

NCCN Clinical Practice Guidelines in Oncology: Hepatocellular Carcinoma. Version 3.2018, Aug 29, 2018. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

UpToDate: Overview of treatment approaches for hepatocellular carcinoma. Current through Aug 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-treatment-approaches-for-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

UpToDate: Epidemiology and etiologic associations of hepatocellular carcinoma. Current through Aug 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/epidemiology-and-etiologic-associations-of-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

UpToDate: Clinical features aand diagnosis of hepatocellular carcinoma. Current through Aug 2018. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-features-and-diagnosis-of-hepatocellular-carcinoma?search=hepatocellular%20carcinoma&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.