lenvatinib (Lenvima™), pazopanib (Votrient®), sorafenib (Nexavar®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO166

Description
Lenvatinib (Lenvima), pazopanib (Votrient), and sorafenib (Nexavar) are orally administered multi-tyrosine kinase inhibitors (multi-TKIs), which limit angiogenesis via inhibiting the binding of multiple tyrosine kinase enzymes to cell surface receptors (e.g. VEGF, FGFR, IL-2 receptor)

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lenvatinib (Lenvima)	4 mg tablets	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	90 tablets/30 days
	10 mg tablets		60 tablets/30 days
pazopanib (Votrient)	200 mg tablets	Advanced Renal Cell Carcinoma; Advanced Soft Tissue Sarcoma	120 tablets/30 days
sorafenib (Nexavar)	200 mg tablets	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	120 tablets/30 days

Initial Evaluation

I. Lenvatinib (Lenvima), pazopanib (Votrient), or sorafenib (Nexavar) may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The medication will be used as monotherapy unless outlined below [e.g. lenvatinib (Lenvima) in combination with everolimus (Afinitor) for Renal Cell Carcinoma]; **AND**

D. The member has not experienced disease progression while on other multi-TKIs [e.g. lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] unless outlined below (e.g. Renal Cell Carcinoma); **AND**

E. A diagnosis of one of the following:

1. **Renal Cell Carcinoma (RCC)**; **AND**
    i. The member has advanced (relapsed, stage III) OR metastatic (stage IV) disease; **AND**
    ii. The request is for pazopanib (Votrient) OR sorafenib (Nexavar); **OR**
    iii. The request is for lenvatinib (Lenvima); **AND**
        a. The member has had disease progression on, or intolerance to, **one** anti-angiogenic therapies unless all are contraindicated (e.g. sunitinib [Sutent], pazopanib [Votrient], axitinib [Inlyta], bevacizumab [Avastin]); **AND**
        b. Lenvatinib (Lenvima) will be used in combination with everolimus (Afinitor); **OR**
2. **Hepatocellular Carcinoma (HCC)**; **AND**
    i. The member has unresectable, advanced (stage III) or metastatic (stage IV) disease; **AND**
    ii. The request is for sorafenib (Nexavar); **OR**
    iii. The request is for lenvatinib (Lenvima); **AND**
        a. The request is for first-line systemic therapy (i.e. previously untreated with systemic chemotherapy); **OR**
3. **Thyroid Carcinoma; AND**
    i. The member has recurrent or metastatic (stage IV) disease; **AND**
    ii. The member has one of the following subtypes of differentiated thyroid carcinoma:
        a. Papillary thyroid carcinoma; **OR**
        b. Follicular thyroid carcinoma; **OR**
        c. Hurthle cell thyroid carcinoma; **AND**
    iii. The disease is refractory to radioactive iodine treatment (RAI)**; AND**
    iv. The request is for lenvatinib (Lenvima); **OR**
    v. The request is for sorafenib (Nexavar); **OR**
4. **Soft Tissue Sarcoma (STS); AND**
    i. The member has advanced (unresectable) or metastatic (stage IV) soft tissue sarcoma (STS); **AND**
    ii. The diagnosis of soft tissue sarcoma (STS) does not include the following histological subtypes:
        a. Gastrointestinal Stromal Tumors (GIST); **OR**
        b. Adipocytic Sarcoma (Liposarcoma); **AND**

iii. The request is for pazopanib (Votrient); **AND**
   a. The member has had disease progression on at least one anthracycline-based chemotherapy regimen unless all are contraindicated (e.g. doxorubicin, epirubicin, ifosfamide)

II. Sorafenib (Nexavar) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma

III. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) are considered investigational when used for all other conditions, including but not limited to:
   A. Gastrointestinal Stromal Tumor
   B. Adipocytic Sarcoma/Liposarcoma
   C. Advanced Endometrial Carcinoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Multi-kinase inhibitors [lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] exert their actions by inhibiting activities of multiple tyrosine kinases by depriving access to the Cdc37-Hsp90 molecular chaperone unit. This inhibitory activity leads to limiting angiogenesis via various cell surface receptors (e.g. VEGF, FGFR, IL-2 receptor). Multi-kinase inhibitors listed under this policy have received FDA-approval for patients 18 years and older. Efficacy and safety of these agents have not been established in the pediatric population.
II. Many treatment options exist for the conditions listed in this policy (e.g. renal cell carcinoma, hepatocellular carcinoma, thyroid carcinoma and soft tissue carcinoma). Initial and further line therapies in these settings are contingent upon patient specific characteristics. Given the

complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.

III. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety of these agents has not been studied in combination with other agents, except for lenvatinib in combination with everolimus for the treatment of renal cell carcinoma.

IV. Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial, and one randomized, Phase 2 discontinuation trial. The Phase 2 trial enrolled 202 patients with advanced RCC and included patients with no prior therapy and tumor histology other than clear cell carcinoma. Patients were on therapy for 12 weeks and then randomized to continue sorafenib (Nexavar) or switch to placebo. Sorafenib (Nexavar) had a PFS of 163 days compared to 41 days for placebo (p=0.0001). The Phase 3 trial included 769 patients with advanced RCC who had received on prior systemic therapy. The primary endpoints included OS and PFS. The median PFS was 167 days for sorafenib (Nexavar) compared to 84 days for placebo with a HR of 0.44 (95% CI 0.35, 0.55).

V. Lenvatinib (Lenvima) was studied in combination with everolimus (Afinitor) in one randomized, open-label, active-controlled, multicenter, Phase 1b/2 trial with 153 patients with advanced or metastatic RCC who had previously received anti-angiogenic therapy. The PFS for lenvatinib (Lenvima) in combination with everolimus (Afinitor) was 14.6 months compared to 5.5 months for everolimus (Afinitor) alone with a HR of 0.37 (95% CI 0.22, 0.62).

VI. Pazopanib (Votrient) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial with 435 patients with locally advanced and/or metastatic RCC who had received no prior therapy or one prior cytokine-based systemic therapy. The primary endpoint was PFS. Pazopanib (Votrient) had a PFS of 9.2 months compared to 4.2 months for placebo, with a HR of 0.46 (95% CI 0.34, 0.62).

VII. It is notable that NCCN guidelines recommend pazopanib (Votrient) as a preferred first-line therapy for clear cell histology stage IV renal cell carcinoma with a category 1 recommendation. Lenvatinib (Lenvima) in combination with everolimus (Afinitor), and sorafenib (Nexavar) are other recommended regimens for subsequent therapy with Category 1 and 2B recommendations, respectively. NCCN no longer recommends sorafenib (Nexavar) as a first-line treatment due to multiple alternative options and lack of current clinical use as a first-line treatment. Meta-analysis of clinical trials involving head-to-head comparison between multi-TKI shows that newer multi-TKI have better efficacy profile compared to sorafenib (Nexavar). Clinical trial for sorafenib (Nexavar) included patients with previous trials of interferon or cytokine-based regimens only, which are no longer used in the first-line setting.

VIII. Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial in 602 patients with unresectable hepatocellular carcinoma (HCC). The primary endpoint was overall survival (OS). Sorafenib (Nexavar) had an OS of 10.7 months compared to 7.9 months for placebo with a hazard ratio (HR) of 0.69 (95% CI 0.55, 0.87). The median time to

progression was 5.5 months for sorafenib (Nexavar) and 2.8 months for placebo with a HR of 0.58 (95% CI 0.45, 0.74).

IX. Lenvatinib (Lenvima) was studied in one randomized, open-label, active-controlled, non-inferiority, Phase 3 trial in patients with previously untreated unresectable HCC (N=954). The primary efficacy endpoint was OS. Lenvatinib (Lenvima) had a median OS of 13.6 months compared to 12.3 months for sorafenib (Nexavar) with a HR of 0.92 (95% CI 0.79, 1.06). Lenvatinib (Lenvima) had a median PFS of 7.3 months compared to 3.6 months for sorafenib (Nexavar) with a HR of 0.64 (95% CI 0.55, 0.75).

X. NCCN guidelines recommend sorafenib (Nexavar) and lenvatinib (Lenvima) as preferred regimens for first-line therapy as category 1 recommendations in patients with a Child-Pugh Class A score. Both therapies are also listed as subsequent therapy with category 2A recommendations. NCCN guidelines note that sorafenib (Nexavar) can be used after disease progression on lenvatinib (Lenvima); however, there is no clinical data to support the use of lenvatinib (Lenvima) after disease progression with sorafenib (Nexavar). Neither of these therapies have been studied in large scale clinical trials to support the use of either after progression of the other. NCCN guidelines for HCC advise caution while using sorafenib (Nexavar) in patients with Child-Pugh Class B7. More than 95% of participants enrolled in the studies on sorafenib (Nexavar) as well as lenvatinib (Lenvima) had Child-Pugh score class A liver function. safety data for patients with Child-Pugh score classes B or C are limited, and the recommended dose is uncertain.

XI. In the setting of thyroid carcinoma, sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial with 417 patients, who had locally recurrent or metastatic, progressively differentiated thyroid carcinoma. All participants were refractory to radioactive iodine (RAI) regimen. The primary efficacy outcome was PFS. Sorafenib (Nexavar) had a median PFS of 10.8 months compared to 5.8 months for placebo with a HR of 0.59 (95% CI 0.46, 0.76).

XII. Lenvatinib (Lenvima) was studied in one randomized, double-blind, placebo-controlled Phase 3 trial in patients with locally recurrent or metastatic differentiated thyroid cancer refractory to RAI (N=392). The primary efficacy endpoint was PFS. Lenvatinib (Lenvima) had a median PFS of 18.3 months compared to 3.6 months for placebo with a HR of 0.21 (95% CI 0.16, 0.28).

XIII. NCCN guidelines recommend lenvatinib (Lenvima) as the preferred regimen and sorafenib (Nexavar) as other recommended regimen for advanced and metastatic thyroid carcinoma (category 2A recommendations). NCCN considers lenvatinib (Lenvima) to be the preferred agent due to its response rate of 65% compared to 12% for sorafenib (Nexavar), although these agents have never been compared in head-to-head trials. Additionally, lenvatinib (Lenvima) and sorafenib (Nexavar) have not been studied in the settings of medullary and anaplastic thyroid carcinomas.

XIV. Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma)

were excluded (of note, there are around 50 histological subtypes of STS). Histological subtype patient distribution for this trial consisted of 47% leiomyosarcoma, 10% synovial sarcoma, and 47% other soft tissue sarcomas. The primary endpoint was PFS. Pazopanib (Votrient) significantly prolonged PFS at 4.6 months vs 1.6 months for placebo ($p<0.0001$). There was no statistical difference between pazopanib (Votrient) and placebo for OS. NCCN guidelines recommend pazopanib (Votrient) as an option for palliative therapy for patients with progressive, unresectable, or metastatic STS with a category 2A recommendation.

XV. For lenvatinib (Lenvima), 68% of patients required dose reductions, and 18% discontinued therapy due to AEs. Sorafenib (Nexavar) had a 32% discontinuation rate due to AEs, and in another study, there were 66% of patients requiring a dose interruption, and 64% required a dose reduction. For pazopanib (Votrient), 42% of patients required a dose interruption, and 36% of patients required a dose reduction.

Investigational or Not Medically Necessary Uses

I. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Advanced Endometrial Cancer
      i. Lenvatinib (Lenvima) was studied in combination with pembrolizumab (Keytruda) in one single-arm, open-label, multicenter, Phase 1b/2 trial with 108 patients with metastatic endometrial carcinoma that had progressed on one prior systemic therapy. The primary efficacy outcome was overall response rate (ORR). The ORR was 38.3% (95% CI 29%, 49%). Of the responders to therapy there were 25 patients (69%) with a duration of response greater than six months. This indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
   B. Gastrointestinal Stromal Tumor
   C. Adipocytic Sarcoma/Liposarcoma
      i. Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma) were excluded.
   D. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma

i. Sorafenib (Nexavar) in combination with erlotinib, was studied in a randomized, placebo-controlled, Phase 3 trial in 720 patients with advanced HCC. Results found that the combination did not significantly improve survival relative to sorafenib (Nexavar) in combination with placebo. The combination had a significantly lower disease control rate (p=0.021) and a shorter treatment duration of 86 days compared to 123 days for sorafenib/erlotinib and sorafenib/placebo, respectively.

References

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4. Makker V, Rasco D et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicenter, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):711-718.
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7. Olivier Mir MD et al. PAZOGIST trial, Lancet Oncology; 2016; 17 (55) 632-641.
8. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Version 2.2020. Updated May 28, 2020.
9. National Comprehensive Cancer Network. NCCN Guidelines: Kidney Cancer. Version 1.2021. Updated July 15, 2020.
10. National Comprehensive Cancer Network. NCCN Guidelines: Hepatobiliary Cancers. Version 5.2020. Updated August 4, 2020.
11. National Comprehensive Cancer Network. NCCN Guidelines: Thyroid Carcinoma. Version 2.2020. Updated July 15, 2020.
12. National Comprehensive Cancer Network. NCCN Guidelines: Uterine Neoplasms. Version 2.2020. Updated July 24, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned criteria to policy format and merged into one policy; Updated criteria to include lenvatinib (Lenvima) requires failure of at least one anti-angiogenic therapy and combination therapy of lenvatinib (Lenvima) with everolimus (Afinitor); Updated disease staging requirements for most indications; Updated information on endometrial cancer for lenvatinib (Lenvima); and Updated supporting evidence section to align with policy changes	10/2020
Previous reviews • Lenvima: Updated indication to include advanced renal cell carcinoma (2017), updated indication to include unresectable hepatocellular carcinoma (2018) • Votrient: Updated to reflect FDA approved indications and quantity limits (2016) • Nexavar: Updated to reflect FDA approved indications (2016)	10/2018, 06/2017, 03/2016, 03/2016

Criteria created • Lenvima: 2015 • Votrient: 2012 • Nexavar: 2012	03/2015 02/2012 03/2012