BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

VOTRIENT® (pazopanib) oral tablet

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.

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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.**

VOTRIENT® (pazopanib) oral tablet (cont.)

Description:

Votrient (pazopanib) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and it is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy. The efficacy of Votrient (pazopanib) for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors (GIST) has not been demonstrated.

Votrient (pazopanib) is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)-α and -β, fibroblast growth factor receptor (FGFR)-1 and -3, cytokine receptor (Kit), interleukin-2 receptor-inducible T-cell kinase (Itk), leukocyte-specific protein tyrosine kinase (Lck), and transmembrane glycoprotein receptor tyrosine kinase (c-Fms). In vitro, pazopanib inhibited ligand-induced autophosphorylation of VEGFR-2, Kit, and PDGFR-β receptors. In vivo, pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in mouse lungs, angiogenesis in a mouse model, and the growth of some human tumor xenografts in mice.

Definitions:

National Comprehensive Cancer Network (NCCN) version 1.2018 (Sep 7, 2017)
NCCN definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Relapse or Stage IV and surgically unresectable RCC:

Predominant Clear Cell Histology:

First-line therapy: (alphabetical by category and preference)

Category 1:
Clinical trial, pazopanib (preferred), sunitinib (preferred), bevacizumab + interferon alpha-2b, temsirolimus (for poor prognosis)

Category 2A:
Axitinib, cabozantinib (for poor and intermediate risk groups), high-dose aldesleukin [when excellent performance status (PS) and normal organ function]

Subsequent therapy: (alphabetical by category and preference)

Category 1:
Clinical trial, cabozantinib (preferred), nivolumab (preferred), axitinib, lenvatinib + everolimus,

Category 2A:
Everolimus, pazopanib, sorafenib, sunitinib

Non-Clear Cell Histology:

VOTRIENT® (pazopanib) oral tablet (cont.)

Systemic therapy: (alphabetical by category and preference)

Category 1:

Temsirolimus (poor prognosis patients)

Category 2A:

Clinical trial (preferred), sunitinib (preferred), axitinib, bevacizumab, bevacizumab + erlotinib (for selected patients with advanced papillary RCC including HLRCC), bevacizumab + everolimus (for selected patients with advanced papillary RCC including HLRCC), cabozantinib, erlotinib, everolimus, lenvatinib + everolimus, nivolumab, pazopanib, sorafenib temsirolimus (for risk groups other than poor-prognosis patients)

Votrient (pazopanib)

Medication class:
Antineoplastic agent, tyrosine kinase inhibitor, vascular endothelial growth factor (VEGF) inhibitor

FDA-approved indication(s):
- Treatment of patients with advanced renal cell carcinoma (RCC)
- Treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy

Limitations of use:
- The efficacy of pazopanib for the treatment of adipocytic STS or gastrointestinal stromal tumors (GIST) has not been demonstrated

Recommended Dose:
- 800 mg once daily

Maximum dosage
- Not stated

Available Dosage Forms:
- 200 mg tablets

Warnings, Precautions, and other Clinical Information:
- For patients with moderate hepatic impairment, reduce initial dose to 200 mg once daily
- It is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) or total bilirubin > 3x ULN with any level ALT
- Interrupt therapy for isolated ALT elevation of > 8x ULN, restart when resolves, if ALT increase > 3x ULN recurs, permanently discontinue Votrient
- ALT elevation > 3x ULN with bilirubin elevation > 2x ULN, permanently discontinue Votrient
- Use with caution in patients at risk for developing QT interval prolongation such as those using antiarrhythmic agents, or other drugs that prolong QT interval and in patients with relevant pre-existing cardiac disease
- Cardiac dysfunction such as congestive heart failure and decreased LVEF have occurred, consider baseline evaluation in patients at risk for cardiac dysfunction

VOTRIENT® (pazopanib) oral tablet (cont.)

- Votrient has not been studied in patients who have a history of hemoptysis, cerebral hemorrhage, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in these patients
- Votrient has not been studied in patients who has had an arterial thromboembolic event within the previous 6 months and should not be used in these patients
- Votrient can cause thrombotic microangiopathy (TMA) such as thrombotic thrombotcytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), permanently discontinue if TMA occurs
- Discontinue use in patients who develop interstitial lung disease (ILD) or pneumonitis
- Permanently discontinue if Reversible Posterior Leukoencephalopathy Syndrome (RPLS) occurs
- Blood pressure should be well controlled before starting therapy
- Discontinue if there is evidence of hypertensive crisis or if severe and persistent hypertension occurs despite antihypertensive therapy
- Interrupt treatment for 24-hour urine protein $\geq$ 3 grams and discontinue for repeated episodes despite dose reduction
- Interrupt or discontinue for severe infection with or without neutropenia
- Votrient is not indicated for use in combination with other cancer therapy agents
- Verify pregnancy status of a woman of child bearing potential before starting therapy
- Woman of child bearing potential should use effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding
- Males with female partners of reproductive potential should use condoms
- Avoid use with strong CYP3A4 inhibitors such as ketoconazole, ritonavir, clarithromycin, if unavoidable, reduce Votrient dose to 400 mg or less once daily
- Votrient should not be used in patients who cannot avoid chronic use of a strong CYP3A4 inducer
- Votrient is not recommended to be used with drugs that have narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8
- Votrient exhibits pH dependent solubility, avoid Votrient with drug that raise gastric pH, use short acting antacids in place of PPIs and H2 receptor antagonists, separate antacid and Votrient dose by several hours

VOTRIENT® (pazopanib) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Votrient (pazopanib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Advanced renal cell carcinoma (RCC) that has relapsed **or** is Stage IV and unresectable
     - Advanced soft tissue sarcoma (STS) in an individual who has received prior chemotherapy
       - Prior chemotherapy includes:
         1. A doxorubicin combination regimen
         2. A gemcitabine combination regimen
         3. Ifosfamide-epirubicin-mesna
         4. Single agent therapy with:
            a. Dacarbazine
            b. Doxorubicin or liposomal doxorubicin
            c. Epirubicin
            d. Eribulin
            e. Gemcitabine
            f. Ifosfamide
            g. Temozolamide
            h. Trabectedin
            i. Vinorelbine

  4. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Liver function tests

  Initial approval duration: 6 months with initial fills of 14 days per fill for first 3 months

- **Criteria for continuation of coverage (renewal request):** Votrient (pazopanib) 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 has not worsened while on therapy
     - Worsening is defined as:
       - Disease progressed while on Votrient

  3. Individual has been adherent with the medication

  4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use such as:

VOTRIENT® (pazopanib) oral tablet (cont.)

- Hepatic impairment
  - Signs and symptoms may include:
    - Right sided abdominal pain, bruising, yellow skin or eyes, dark brown urine, severe nausea or vomiting, fatigue, light colored pale stools, itching, confusion
- Cardiac failure
  - Signs and symptoms may include:
    - Edema, shortness of breath, weight gain, chest pain, shortness of breath
- Hemorrhage
  - Signs and symptoms may include:
    - Blood in stool, coughing up blood, vomiting blood, or unusual bleeding, easy bruising, dark red or tar-like stools
- Arterial thromboembolic events
  - Signs and symptoms may include:
    - Chest pain that spreads to arms, neck, jaw, back, or stomach, sweating, sudden weakness or numbness on one side of body, headache, confusion, difficulty with speech, vision, or balance, fatigue
- Reversible Posterior Leukoencephalopathy Syndrome
  - Signs and symptoms may include:
    - Rapidly onset of seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension
- Hypertension and Hypertensive Crisis
  - Signs and symptoms may include:
    - Elevated blood pressure, severe headache, change in vision, difficulty in thinking, anxiety, nausea or vomiting, numbness or weakness of arms, legs, or face, shortness of breath, dizziness, chest pain
- Proteinuria
  - Signs and symptoms may include:
    - Despite dose reduction, repeated episodes of a 24-hour urine protein of $\geq$ 3 grams
- Interstitial lung disease
  - Signs and symptoms may include:
    - chest pain, palpitations, tachycardia, shortness of breath at rest dyspnea on exertion, dry cough, fatigue, weakness
- Thrombotic microangiopathy (TMA), hemolytic uremia syndrome (HUS), and thrombocytopenic purpura (TTP)
  - Signs and symptoms may include:
    - fever, decreased urine, kidney failure, thrombocytopenia, seizures, fatigue, dizziness, confusion, shortness of breath, bruising, easy bleeding of gums, nose bleeds, swollen legs, visual disturbances

5. There are no significant interacting drugs

Renewal duration: 12 months

VOTRIENT® (pazopanib) oral tablet (cont.)

Resources:

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.

Votrient. Package Insert. Revised by manufacturer 4/2015. Accessed 09-04-2015.

Votrient. Package Insert. Revised by manufacturer 08/2016. Accessed 10-20-2016

NCCN Clinical Practice Guidelines in Oncology: Kidney cancer. Version 1.2018, Sep 7, 2017. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

UpToDate: Overview of the treatment of renal cell carcinoma. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-the-treatment-of-renal-cell-carcinoma?source=search_result&search=renal%20cell%20carcinoma&selectedTitle=2~150#H1056311611

UpToDate: The treatment approach to non-clear cell renal carcinoma. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/the-treatment-approach-to-non-clear-cell-renal-carcinoma?source=search_result&search=renal%20cell%20carcinoma&selectedTitle=4~150

UpToDate: Anti-angiogenic and molecularly targeted therapy for advanced or metastatic clear-cell renal cell carcinoma. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/anti-angiogenic-and-molecularly-targeted-therapy-for-advanced-or-metastatic-clear-cell-renal-cell-carcinoma?source=search_result&search=renal%20cell%20carcinoma&selectedTitle=8~150#H38

NCCN Clinical Practice Guidelines in Oncology: Soft tissue sarcoma. Version 1.2018, Oct 31, 2017. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf

UpToDate: Systemic treatment of metastatic soft tissue sarcoma. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/systemic-treatment-of-metastatic-soft-tissue-sarcoma?source=search_result&search=soft%20tissue%20sarcoma&selectedTitle=2~150

UpToDate: Clinical presentation, histopathology, diagnostic evaluation, and staging of soft tissue sarcoma. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-presentation-histopathology-diagnostic-evaluation-and-staging-of-soft-tissue-sarcoma?source=search_result&search=soft%20tissue%20sarcoma&selectedTitle=1~150

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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.