09-J1000-49

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Reviewed: 01/08/20

Revised: 02/15/20

Subject: Pazopanib (Votrient™) Tablets

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DESCRIPTION:

Pazopanib (Votrient™) is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor (VEGFR) 1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptors (PDGFR) alpha and beta, and fibroblast growth factor receptor. Because pazopanib is a multikinase inhibitor, it may be able to overcome many of the signaling pathways and thus effectively inhibit the transduction of intracellular signals as well as angiogenesis. In October 2009, pazopanib received Food and Drug Administration (FDA) approval for the treatment of advanced renal cell carcinoma (RCC). The safety and efficacy of pazopanib was evaluated in a phase III open-label, international, multi-center study. A total of 435 subjects with clear cell advanced RCC and measurable disease with no prior treatment or one prior cytokine-based treatment were randomized 2:1 to pazopanib or placebo. The primary endpoint, progression-free survival (PFS), was significantly prolonged with pazopanib in the overall study population, averaging 9.2 months versus 4.2 months for subjects assigned to placebo. The treatment-naïve subpopulation of 233 subjects, which were also randomized 2:1 to pazopanib or placebo, had a median PFS of 11.1 months on pazopanib vs. 2.8 months on placebo. The National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer recommend pazopanib as first line treatment of individuals with relapsed or stage IV renal carcinoma with predominantly clear cell histology and indicate that it is also an appropriate option as subsequent therapy as a single agent. The use of pazopanib in relapsed or stage IV RCC with non-clear cell histology is also recommended by NCCN.

In April 2012, pazopanib received FDA approval for the treatment of advanced soft-tissue sarcoma (STS) in individuals who have received prior chemotherapy. In a phase III trial, 369 subjects with metastatic STS who failed at least one anthracycline-based chemotherapy regimen were randomized to either pazopanib or placebo. Pazopanib significantly prolonged median PFS (20 weeks vs. 7 weeks for placebo, $p<0.001$) and there was also a trend toward improved overall survival (OS) (11.9 months and 10.4 months,

respectively) although it was not statistically significant. The NCCN guidelines support the use of pazopanib in the treatment of soft tissue sarcomas and also provide recommendations for the use in kidney cancer, thyroid cancer, and uterine sarcomas.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

I. Initiation of pazopanib (Votrient®) **meets the definition of medical necessity** when used for an indication in Table 1, all indication specific criteria are met, and the dose does not exceed 800 mg/day:

Table 1

Indication	Specific Criteria
Dermatofibrosarcoma Protuberans (DFSP)	When used as a single agent as palliative therapy for metastatic disease
Kidney cancer	When used as a single agent for member's with relapsed or stage IV disease meeting **ONE** of the following: 1. Pazopanib is used as first line or subsequent therapy for disease with predominant clear cell histology 2. Pazopanib is used as treatment for disease with non-clear cell histology
Soft tissue sarcoma: Alveolar soft part sarcoma Angiosarcoma Extremity/superficial trunk/head/neck Gastrointestinal stromal tumors (GIST) Retroperitoneal/intraabdominal Rhabdomyosarcoma Solitary fibrous tumor/hemangiopericytoma	When used as a single agent for **ONE** of the following: 1. Pazopanib is used for the treatment of alveolar soft part sarcoma 2. Pazopanib is used as palliative therapy for angiosarcoma 3. Pazopanib is used as palliative therapy for sarcoma of the extremity/superficial trunk/head/neck 4. Pazopanib is used for the treatment of gastrointestinal stromal tumors after disease progression with imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga) 5. Pazopanib is used as palliative therapy for unresectable, recurrent, progressive, or metastatic retroperitoneal/intraabdominal sarcoma 6. Pazopanib is used as palliative therapy for pleomorphic rhabdomyosarcoma 7. Pazopanib is used for the treatment of solitary fibrous

	tumor/hemangiopericytoma
Thyroid cancer: Follicular carcinoma Hurthle cell carcinoma Papillary carcinoma Medullary carcinoma	When the member meets all criteria for treatment of **ONE** of the following: 1. Follicular carcinoma, Hurthle cell carcinoma, or Papillary carcinoma of the thyroid when used as a single agent for iodine-refractory symptomatic or progressive disease classified as **ONE** of the following: a. Unresectable locoregional disease that is recurrent or persistent b. Distant metastatic disease 2.Medullary carcinoma of the thyroid when used as a single agent for progressive or symptomatic distant metastatic disease and member meets **ONE** of the following: a. Member's disease progressed on vandetanib (Caprelsa) or cabozantinib (Cometriq) b. Member is unable to tolerate or has a contraindication to vandetanib (Caprelsa) or cabozantinib (Cometriq)
Uterine sarcoma	When used as a single agent and **ALL** of the following: 1. Member had disease progression on initial chemotherapy 2. Member has recurrent or metastatic disease
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	**ONE** of the following is met: 1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) 2. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

Approval duration: 180 days (for all indications)

II. Continuation of pazopanib (Votrient®) **meets the definition of medical necessity** for the indications in Table 1 when the following criteria are met:

A. The member's disease has not progressed while receiving therapy with pazopanib

B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage

C. The dose does not exceed 800 mg per day.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: pazopanib is approved for the treatment of members with advanced renal cell carcinoma or advanced soft tissue sarcoma who have received prior chemotherapy. The recommended dose is 800 mg once daily without food (at least 1 hour before or 2 hours after a meal). Tables should not be crushed due to the potential for increased rate of absorption which may affect systemic exposure.

Dosage Adjustments

- Prior to pazopanib initiation, hepatic function should be assessed; members with baseline moderate hepatic impairment should be considered for alternative therapy. If pazopanib is used, administer 200 mg once daily. Pazopanib is not recommended in members with severe hepatic impairment. Therapy should be continued for as long as the member derives clinical benefit from the drug or until unacceptable toxicity occurs.
- When dosage modification is necessary for renal cell carcinoma, dosage of pazopanib should be reduced by 400 mg daily initially; subsequent dosage adjustments should be made in increments of 200 mg daily, depending on individual member tolerability.
- For soft tissue sarcoma, a decrease or increase in 200 mg increments is recommended based on tolerability.
- Serum ALT 3-8 times upper limit of normal (ULN): Continue pazopanib; monitor liver function test (LFT) weekly until serum ALT concentration returns to grade 1 or baseline
- Serum ALT greater than 8 times ULN: Interrupt pazopanib therapy until serum ALT concentration returns to grade 1 or baseline. If benefit outweighs risk, reinitiate at a reduced dosage of 400 mg or less once daily. Following re-initiation, monitor LFTs weekly for 8 weeks, if serum ALT concentration rises to greater than 3 times ULN, discontinue pazopanib permanently.
- Serum ALT greater than 3 times ULN and mild, indirect hyperbilirubinemia in members with known Gilbert's syndrome: manage per recommendations above for isolated serum ALT elevations
- Serum ALT greater than 3 times ULN and serum bilirubin concentrations 2 times ULN: discontinue pazopanib permanently and monitor LFTs until hepatotoxicity resolves.
- Concomitant use with potent CYP3A4 inhibitors: if concomitant use with a potent CYP3A4 inhibitor cannot be avoided, the manufacturer recommends reducing the dosage of pazopanib to 400 mg daily
- Concomitant use with potent CYP3A4 inducers: avoid pazopanib therapy.
- Avoid use with agents that raise gastric pH

Drug Availability: pazopanib is available as a 200 mg film-coated tablet.

Missed dose: If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

PRECAUTIONS:

CONTRAINDICATIONS

At this time, there are no known contraindications to pazopanib therapy.

WARNINGS

Boxed Warning, Hepatotoxicity: Severe and fatal hepatotoxicity has been observed in clinical trials. Hepatic function should be monitored and pazopanib should be interrupted, discontinue or dosage reduced as recommended.

Cardiac effects: Prolonged QT intervals, torsades de pointes, congestive heart failure, and decreased left ventricular ejection fraction (LVEF) were observed in clinical trials. Monitoring should include assessment of electrocardiograms, electrolytes, blood pressure, and periodic assessment of LVEF in members at risk of cardiac dysfunction.

Endocrine: hypothyroidism may occur; monitor thyroid function tests.

Fatal Hemorrhagic Events: pazopanib has not been studied in individuals who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in these member populations.

Gastrointestinal: perforation of fistula, including fatal events, have occurred. Use with caution in individuals at risk.

Hypertension: Hypertensive crisis has occurred. Blood pressure should be well-controlled prior to pazopanib initiation; monitor blood pressure within one week after therapy initiation and frequently thereafter.

Infection: serious infections (with or without neutropenia) have been observed. Monitor for signs and symptoms and treat active infection promptly; consider discontinuation.

Liver chemistries: Increases in serum transaminase levels and bilirubin were observed. Measure liver chemistries prior to and regularly during treatment to monitor for hepatotoxicity.

Lung: Interstitial lung disease (ILD) or pneumonitis have occurred and can be fatal. Discontinue if this occurs.

Pediatrics: animal studies show severe effects on organ growth and maturation postnatally. The safety and effectiveness is not established in pediatrics.

Pregnancy and Lactation: Pazopanib is classified as pregnancy category D; although there are no adequate and well-controlled studies of pazopanib in pregnant women, pre-clinical studies in rats and rabbits demonstrated evidence of fetal harm. It is not known whether pazopanib is excreted in human milk. Pazopanib should be avoided in women who are breastfeeding.

Proteinuria: Monitor urine protein; interrupt treatment for 24-hour urine protein of 3 grams or greater and discontinue for repeat episodes despite dosage reduction.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS has occurred and can be fatal. Permanently discontinue pazopanib in members exhibiting signs or symptoms of RPLS.

Surgery: Interruption of therapy is recommended in individuals undergoing surgical procedures due to possible impairment of wound healing.

Thromboembolism: arterial and venous thrombotic events have been observed; use pazopanib with caution in members at risk for these events and monitor for signs and symptoms of these events.

Thrombotic microangiopathy (TMA): TMA including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) have been observed. Permanently discontinue if TMA occurs.

BILLING/CODING INFORMATION:

HCPCS Coding

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of connective and other soft tissue
C49.A0 – C49.A9	Gastrointestinal stromal tumor
C53.0	Malignant neoplasm of endocervix
C54.0– C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C64.1 – C65.9	Malignant neoplasm of kidney
C73	Malignant neoplasm of thyroid gland
C78.00 – C78.02	Secondary malignant neoplasm of unspecified lung

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Advantage: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline

DEFINITIONS:

None

RELATED GUIDELINES:

Adoptive Immunotherapy, 01-96400-01

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bevacizumab (Avastin®) Injection, 09-J0000-66

Carboplatin (Paraplatin®) IV, 09-J0000-93

Cryosurgical Ablation of Solid Tumors Other Than Liver or Prostate Tumors, 02-99221-12

Erythropoiesis Stimulating Agents, 09-J0000-31

Gemcitabine (Gemzar®), 09-J0000-96

Kidney Transplantation, 02-50300-01

Positron Emission Tomography (PET Scans) Oncologic Applications, 04-78000-17

Radiofrequency Ablation of Solid Tumors Other Than Liver Tumors, 02-99221-13

OTHER:

TABLE 1: Stages of Renal Cell Cancer

Stage I	The tumor is 7 centimeters or smaller and is found only in the kidney.
Stage II	The tumor is larger than 7 centimeters and is found only in the kidney.
Stage III	The tumor is any size and cancer is found only in the kidney and in 1 or more nearby lymph nodes; or cancer is found in the main blood vessels of the kidney or in the layer of fatty tissue around the kidney. Cancer may be found in 1 or more nearby lymph nodes.
Stage IV	Cancer has spread beyond the layer of fatty tissue around the kidney and may be found in the adrenal gland above the kidney with cancer, or in nearby lymph nodes; or to other organs, such as the lungs, liver, bones, or brain, and may have spread to lymph nodes.

TABLE 2: International Federation of Obstetrics and Gynecology (FIGO) Surgical Staging System of Uterine Sarcoma

Stage I	The tumor is found only in the uterus
Stage II	The tumor extends beyond the uterus, within the pelvis (adenexa and other pelvic tissues may be involved)
Stage III	The tumor infiltrates abdominal tissues in one or more sites (not just protruding into the abdomen) and regional lymph node metastasis may be present
Stage IV	The tumor invades the bladder or rectum and other distant metastasis may be present (excluding adnexa, pelvic, and abdominal tissues)

TABLE 3: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description

1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/08/20.

GUIDELINE UPDATE INFORMATION:

01/01/12	New Medical Coverage Guideline.
07/15/12	Revision to guideline consisting of adding 2 new indications and updating references.
12/15/12	Review and revision to guideline; consisting of reformatting and revising position statement; revising and reformatting description, dosage/administration, precaution section; updating references, adding contraindications section.
12/15/13	Review and revision to guideline; consisting of revising position statement, updating references, updating coding.
12/15/14	Review and revision to guideline; consisting of revising position statement, updating coding and references.
12/15/15	Review and revision to guideline; consisting of revising position statement, updating description, dosage, warnings, coding and references.
12/15/16	Review and revision to guideline; consisting of updating position statement, description, coding and references.
11/15/17	Review and revision to guideline; consisting of updating position statement, coding and references.
01/15/19	Review and revision to guideline; consisting of updating position statement, coding and references.
02/15/20	Review and revision to guideline; consisting of updating position statement and references.