09-J1000-50

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Reviewed: 01/08/20

Revised: 02/15/20

Next Review: 01/13/21

Subject: Sorafenib (Nexavar®) Tablets

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Sorafenib (Nexavar®) is an oral multikinase inhibitor that acts by inhibiting tumor growth and disrupting tumor microvasculature through antiproliferative, anti-angiogenic and proapoptotic effects. It exerts these effects via inhibition of multiple targets including Raf serine/threonine kinases, vascular endothelial growth factor receptor (VEGFR) tyrosine kinases; VEGFR-1, VEGRF-2, VEGRF-3 and platelet-derived growth factor receptor beta. Sorafenib as a single agent has shown promising activity in some cancers including renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), and thyroid cancers. The Food and Drug Administration (FDA) has approved sorafenib for the treatment of advanced renal cell carcinoma, unresectable hepatocellular carcinoma, and thyroid cancer. In addition to FDA approved indications, the National Comprehensive Cancer Network (NCCN) Guidelines recommend use of sorafenib for the treatment of Acute Myeloid Leukemia, ovarian cancer, and various types of bone cancers and soft tissue 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 sorafenib (Nexavar) **meets the definition of medical necessity** when the dose does not exceed 400 mg twice daily (800 mg/day), it is administered for treatment of an indication in Table I below, and all of the indication specific criteria are met:

Table 1

Indication	Specific Criteria
Acute Myeloid Leukemia (AML)	Member meets **ALL** of the following: 1. Sorafenib is used in combination with azacitidine (Vidaza) or decitabine (Dacogen) 2. FLT3-ITD mutation positive disease
Chordoma	When used as a single agent for the treatment of recurrent chordoma
Hepatocellular carcinoma	When used as a single agent for members with a Child-Pugh score less than or equal to 7 and **ONE** of the following: 1. Unresectable disease and is not a candidate for transplant 2. Metastatic disease 3. Inoperable due to performance status or comorbidities and has local disease 4. Extensive tumor burden 5. Member had disease progression on lenvatinib (Lenvima)
Kidney cancer	When used as a single agent in member's with relapsed or stage IV disease when used as subsequent therapy for disease with predominant clear cell histology
Osteosarcoma	When used as second-line therapy as a single agent and member has relapsed, refractory or metastatic disease
Ovarian cancer (includes epithelial ovarian, fallopian tube, or primary peritoneal cancer)	When the member has platinum resistant disease that is persistent or recurrent and sorafenib will be used in combination with topotecan
Soft tissue sarcoma: **Angiosarcoma** **Desmoid tumors** **Gastrointestinal stromal tumors (GIST)**	When used as a single agent and sorafenib is used for **ONE** of the following: 1. Angiosarcoma 2. Desmoid tumors (aggressive fibromatosis) 3. Gastrointestinal stromal tumors after disease progressed on imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga)

Solitary Fibrous Tumor/Hemangiopericytoma	4. Solitary Fibrous Tumor/Hemangiopericytoma
Thyroid cancer: **Follicular carcinoma** **Hurthle cell carcinoma** **Papillary carcinoma** **Medullary carcinoma**	When the member meets all criteria for **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)
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 (all indications)

II. Sorafenib (Nexavar®) **meets the definition of medical necessity** when used for the following designated Orphan Drug indication (http://www.fda.gov/orphan/designat/list.htm) when the dose does not exceed the maximum FDA-approved dosing:

1. Anaplastic thyroid cancer

III. Continuation of sorafenib (Nexavar®) **meets the definition of medical necessity** for the indications in Table 1 and orphan indications when the following criteria are met:

A. The member's disease has not progressed while receiving treatment with sorafenib

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 400 mg twice daily (800 mg/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: sorafenib is indicated for the treatment of unresectable hepatocellular carcinoma, advanced renal cell carcinoma, and locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to iodine treatment. The recommended dosage is 400 mg (2 tablets) orally twice daily without food (at least 1 hour before or 2 hour after a meal). Treatment should continue until the member is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

Dosage Adjustment

i. **Renal Impairment:** Dosage adjustments are not indicated for members with mild, moderate or severe renal impairment. Sorafenib has not been evaluated in individuals receiving dialysis.

ii. **Hepatic Impairment:** Dosage adjustments are not indicated for members with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Sorafenib has not been evaluated in individuals with severe (Child-Pugh C) hepatic impairment.

iii. **Adverse Reactions:** management of suspected adverse drug reactions may require temporary interruption, permanent discontinuation, and/or dose reduction. For renal cell carcinoma or hepatobiliary carcinoma, the dose may be initially reduced to 400 mg once daily; if additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day. For differentiated thyroid carcinomas, the dose may initially be reduced to 600 mg divided twice daily, further reduced to 400 mg divided twice daily, with additional reduction to 200 mg once daily if necessary.

iv. **Skin toxicity:** suggested dose adjustments for skin toxicity for renal cell carcinoma and hepatobiliary carcinoma are described in Table 1. See prescribing information for dose adjustments for skin toxicity with differentiated thyroid carcinomas.

Table 1

Skin toxicity dose modifications (renal cell carcinoma or hepatobiliary carcinoma)		
Skin Toxicity Grade	**Occurrence**	**Dose Modification**
Grade 1	Any occurrence	Continue treatment, consider topical therapy for symptomatic relief
Grade 2	1st occurrence	Continue treatment, consider topical therapy for symptomatic relief; if no relief within 7 days, see below
	No relief within 7 days or 2nd/3rd occurrence	Interrupt treatment until toxicity resolves to Grade 0-1 When resuming treatment, reduce dose by one dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue treatment

Grade 3	1st or 2nd occurrence	Interrupt treatment until toxicity resolves to Grade 0-1 When resuming treatment, reduce dose by one dose level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue treatment

Drug Availability: sorafenib is available as a 200 mg tablet.

PRECAUTIONS:

CONTRAINDICATIONS

Sorafenib is contraindicated in members with known severe hypersensitivity to sorafenib or any other component of the product. Additionally, sorafenib in combination with carboplatin and paclitaxel is contraindicated in members with squamous cell lung cancer.

WARNINGS

Bleeding: if bleeding necessitates medical intervention, discontinue therapy. Temporarily interrupt therapy in members undergoing major surgical procedures

Cardiovascular: cardiac ischemia and/or infarction may occur; consider temporary or permanent discontinuation.

Dermatologic: Interrupt and/or decrease dose. Discontinue for severe reactions or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected.

Drug-induced hepatitis: Monitor liver function tests regularly; discontinue therapy if there is no alternative explanation for elevated transaminase levels.

Gastrointestinal: discontinue if perforation occurs.

Hypertension: Typically occurs early in the course of treatment and can be managed with antihypertensive therapy. Monitor blood pressure weekly during the first 6 weeks of therapy and periodically thereafter. Treat as required.

Impairment of TSH suppression: Monitor TSH monthly and adjust thyroid replacement in individuals with thyroid carcinoma.

Pregnancy and Lactation: Sorafenib is classified as pregnancy category D. Although there are no adequate and well-controlled studies in pregnant women, pre-clinical studies demonstrated fetal harm. It is unknown if sorafenib is excreted in human milk. A careful risk vs. benefit analysis should be considered prior to sorafenib administration in women who are breastfeeding.

QT Prolongation: Monitor for prolonged QT in members with congestive heart failure, bradyarrhythmias, drugs known to prolong the QT, and electrolyte abnormalities. Avoid in members with congenital prolonged QT syndrome.

BILLING/CODING INFORMATION:

HCPCS Coding

C9399	Unclassified drugs or biologicals

J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

C22.0	Liver cell carcinoma
C22.2	Hepatoblastoma
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C40.00 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0 – C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C47.8	Malignant neoplasm of overlapping sites 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 soft tissue
C49.A0 – C49.A9	Gastrointestinal stromal tumor
C56.1 – C56.9	Malignant neoplasm of ovary
C57.1 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C64.1– C65.9	Malignant neoplasm of kidney
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C73	Malignant neoplasm of thyroid gland
C92.00 – C92.92	Myeloid leukemia
C93.00 – C93.02	Acute monoblastic/monocytic leukemia
C94.00 – C94.22	Other acute leukemias
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue

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:

FLT3-ITD mutation: a mutation of the FMS-like tyrosine kinase 3 (FLT3) gene that includes internal tandem duplication (ITDs). ITDs of the FLT3 gene are present in approximately 30% of individuals with acute myeloid leukemia and are associated with a poor prognosis.

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

Cryoablation of Liver Tumors, 02-40000-22

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

Erythropoiesis Stimulating Agents, 09-J0000-31

External Infusion Pumps (non-insulin), 09-E0000-10

Gemcitabine (Gemzar®), 09-J0000-96

Imatinib Mesylate (Gleevec) Tablets 09-J1000-46

Intensity-Modulated Radiation Therapy (IMRT), 04-77260-22

Kidney Transplantation, 02-50300-01

Liver Transplant, 02-40000-20

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

Proton Beam Therapy, 04-77260-18

Radiofrequency Ablation of Liver Tumors, 02-40000-23

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

Selective Internal Radiation Therapy, 04-77260-21

Stereotactic Body Radiotherapy, 02-77371-02

Sunitinib Maleate (Sutent) Capsules 09-J1000-51

Zoledronic Acid IV (Reclast®; Zometa®), 09-J0000-72

OTHER:

TABLE 2: 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 3: Child-Pugh Score and Classification

	1 point	2 points	3 points
Total bilirubin	< 2	2-3	> 3
Serum albumin	> 3.5	2.8-3.5	< 2.8
INR	> 1.7	1.71-2.20	< 2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV
Classification of Result: Class A: 5-6 points Class B: 7-9 points Class C: 10-15 points			

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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.
12/15/12	Review and revision to guideline; consisting of reformatting and revising position statement; revising description, dosage/administration, precaution sections; updating references, coding and related guidelines.
12/15/13	Review and revision to guideline; consisting of updating the position statement to include treatment of osteosarcoma and adding approval duration, updating references and coding.
12/15/14	Review and revision to guideline; consisting of reformatting position statement, updating references and coding.
12/15/15	Review and revision to guideline; consisting of updating the position statement, description, dosage, precautions, references and coding.
12/15/16	Review and revision to guideline; consisting of updating the position statement, coding and references.
11/15/17	Review and revision to guideline; consisting of updating the position statement and references.
01/15/19	Review and revision to guideline; consisting of updating the position statement, description, coding, and references.
02/15/20	Review and revision to guideline; consisting of updating the position statement, description, coding, and references.