09-J1000-67

Original Effective Date: 05/15/12

Reviewed: 01/08/20

Revised: 02/15/20

Subject: Axitinib (Inlyta®) 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:

Axitinib (Inlyta) is an oral multikinase inhibitor that exerts it chemotherapeutic effects via selective inhibition of vascular endothelial growth factor receptor (VEGFR) tyrosine kinases; VEGFR-1, VEGRF-2, and VEGRF-3.In January 2012 the US Food and Drug Administration approved axitinib for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Current National Comprehensive Cancer Network (NCCN) guidelines support the use of axitinib in relapsed or stage IV renal cell carcinoma (RCC) as a single agent or in combination with pembrolizumab (Keytruda) or avelumab (Bavencio). The NCCN guidelines also support the use of axitinib for differentiated thyroid cancer.

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 axitinib (Inlyta®) **meets the definition of medical necessity** when the dose does not exceed 20 mg/day using the fewest number of tablets per day for an indication in Table 1 and all indication specific criteria are met:

Table 1

Indication	Specific criteria
Kidney cancer	When used in member's with relapsed or stage IV disease meeting **ONE** of the following: 1. Axitinib is used in combination with pembrolizumab (Keytruda) for disease with predominant clear cell histology 2. Axitinib is used in combination with avelumab (Bavencio) as first line therapy for disease with predominant clear cell histology 3. Axitinib is used as a single agent as subsequent therapy for disease with predominant clear cell histology 4. Axitinib is used as a single agent as treatment for disease with non-clear histology
Thyroid cancer: Follicular carcinoma Hurthle cell carcinoma Papillary carcinoma	When used as a single agent in member's with iodine-refractory symptomatic or progressive disease classified as **ONE** of the following: 1. Unresectable locoregional disease that is recurrent or persistent 2. Distant metastatic disease
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	When **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: 6 months

II. Continuation of axitinib (Inlyta®) **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 treatment with axitinib
    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 20 mg per day and will be achieved using the fewest number of tablets.

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: axitinib is indicated for the treatment of advanced renal cell carcinoma following failure of one prior systemic therapy. The recommended starting dose is 5 mg twice daily and should be administered approximately 12 hours apart with or without food. The tablet should be swallowed whole with a glass of water.

Dose Modification

- **Hepatic Impairment:** reduce the starting dose by approximately 50% in persons with moderate hepatic impairment (Child-Pugh class B). Subsequent doses can be increased or decreased based on individual safety and tolerability. Axitinib has not been studied in persons with severe hepatic impairment (Child-Pugh class C).
- **Concomitant CYP3A4/5 Inhibitor:** if concomitant use is required, reduce the dose by approximately 50%.
- **Dose increase or reduction:** dose adjustment is recommended based on individual safety and tolerability. If treatment is tolerated for at least 2 consecutive weeks with no adverse reactions > Grade 2 (according to the Common Toxicity Criteria for Adverse Events [CTCAE]), are normotensive, and are not receiving anti-hypertension medication, their dose may be titrated up. Some adverse reactions require temporary interruption, dose reduction, or permanent discontinuation.

Drug Availability: axitinib is supplied as 1- and 5 mg film-coated tablet.

PRECAUTIONS:

- **Hypertension:** hypertension including hypertensive crisis has been observed. Blood pressure should be well-controlled prior to initiating axitinib. Monitor for hypertension and treat as needed. For persistent hypertension despite use of anti-hypertensive medications, reduce the axitinib dose.
- **Thrombosis:** arterial and venous thrombotic events have been observed and can be fatal. Use with caution in persons who are at increased risk for these events.
- **Hemorrhagic events:** hemorrhagic events, including fatal events, have been reported. Axitinib has not been studied in persons with evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in this population.
- **Cardiac failure:** Monitor for signs or symptoms of cardiac failure. Cardiac failure has been observed and can be fatal.
- **Gastrointestinal:** gastrointestinal perforation and fistula, including death, have occurred. Use with caution in persons at risk for gastrointestinal perforation or fistula.
- **Hypothyroidism:** hypothyroidism requiring thyroid hormone replacement has been reported. Monitor thyroid function before initiation of, and periodically throughout, treatment with axitinib.
- **Surgery:** discontinue axitinib at least 24 hours prior to scheduled surgery.
- **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** has been observed. Permanently discontinue axitinib if signs or symptoms of RPLS occur.

- **Proteinuria:** monitor for proteinuria before initiation of, and periodically throughout, treatment with axitinib. For moderate to severe proteinuria, reduce the dose or temporarily interrupt treatment with axitinib
- **Liver enzymes:** liver enzyme elevation has been observed during treatment with axitinib. Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with axitinib.
- **Pregnancy Category D:** axitinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while receiving axitinib.

BILLING/CODING INFORMATION:

HCPCS Coding:

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

ICD-10 Diagnosis Codes That Support Medical Necessity for:

C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C73	Malignant neoplasm of thyroid gland

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

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Pazopanib (Votrient TM) Tablets, 09-J1000-49

Sorafenib (Nexavar®) Tablets, 09-J1000-50

Sunitinib Malate (Sutent®) Capsules, 09-J1000-51

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: 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

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:

05/15/12	New Pharmacy Coverage Guideline.
11/15/13	Review and revision to guideline; consisting of revising position statement, description, dosage/administration and precautions section, adding related guidelines, updating program exceptions and references.
12/15/14	Review and revision to guideline; consisting of position statement, references, description
01/15/14	Revision to guideline; consisting of position statement.
12/15/15	Revision to guideline; consisting of updating position statement, dosage/administration, precautions, coding and references.
12/15/16	Review and revision to guideline; consisting of updating position statement, description, and references.
11/15/17	Review and revision to guideline; consisting of updating references.
01/15/19	Review and revision to guideline; consisting of updating position statement and references.
06/15/19	Revision to guideline; consisting of updating position statement and references.
07/15/19	Revision to guideline; consisting of updating position statement and references.
02/15/20	Review and revision to guideline; consisting of updating references.