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:

INLYTA® (axitinib) 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.

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.**

INLYTA® (axitinib) oral tablet (cont.)

Description:

Inlyta (axitinib), a tyrosine kinase inhibitor, is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

Inlyta (axitinib) has been shown to inhibit receptor tyrosine kinases including vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3 at therapeutic plasma concentrations. These receptors are implicated in pathologic angiogenesis, tumor growth, and cancer progression. VEGF-mediated endothelial cell proliferation and survival were inhibited by axitinib *in vitro* and in animal models. Inlyta (axitinib) was shown to inhibit tumor growth and phosphorylation of VEGFR-2 in animal tumor models.

RCCs, which originate within the renal cortex, constitute 80-85% of primary renal neoplasms. Urothelial (or transitional cell) carcinomas of the renal pelvis account for about 8% of kidney tumors, and other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, are rare. RCC can be classified as localized RCC or advanced RCC. There are several subtypes of RCCs: clear cell, papillary (or chromophilic), chromophobe, oncoyte, and collecting duct. The most common histologic pattern of RCC is clear cell which accounts for 75-85% of tumors. Non-clear cell RCC includes papillary, chromophobe, collecting duct, translocation carcinomas, and unclassified types. Medullary renal carcinoma is a variant of collecting duct carcinoma.

Surgery, either radical nephrectomy or partial nephrectomy, is curative in the majority of patients with localized RCC who do not have metastases and for those with resectable primary tumor and a single metastasis. Cryotherapy, radiofrequency ablation may be an alternative for patients with small renal masses who are not surgical candidates.

Many RCCs are clinically silent and the diagnosis is frequently not made until disease is locally advanced (and unresectable) or has metastasized. Many patients who initially are resectable will eventually have a recurrence. Systemic therapy involving immunotherapy, molecularly targeted agents, surgery, and radiation may have a role depending upon the extent of disease, sites of involvement, and patient-specific comorbidities.

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

INLYTA® (axitinib) oral tablet (cont.)

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:

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)

Inlyta (axitinib)

Medication class:

Antineoplastic, tyrosine kinase inhibitor, vascular endothelial growth factor inhibitor

FDA-approved indication(s):

- Treatment of advanced renal cell carcinoma after failure of one prior systemic therapy

Recommended Dose:

- 5 mg twice daily, dose may be increased to 7mg twice daily after at least two consecutive weeks with no adverse reactions above grade 2, are normotensive, and not receiving antihypertensive medications and further to 10 mg twice daily following the same criteria

Maximum dosage

- Not stated

Available Dosage Forms:

- 1 mg and 5 mg tablets

INLYTA® (axitinib) oral tablet (cont.)

Warnings, Precautions, and other Clinical Information:

- Decrease starting dose by half for patients with moderate hepatic impairment (Child-Pugh class B)
- Inlyta has not been studied In patients with severe hepatic impairment (Child-Pugh class C)
- Thyroid function tests should be done before starting therapy, hypothyroidism occurs with use of Inlyta
- Blood pressure should be well controlled before starting therapy
- Discontinue if severe and persistent hypertension occurs despite antihypertensive therapy
- Consider discontinuation if hypertensive crisis occurs
- Inlyta should not be used in patients with untreated brain metastasis
- Inlyta causes hemorrhagic events such as cerebral hemorrhage, hematuria, hemoptysis, lower gastrointestinal bleed, and melana
- Inlyta should not be used in patients with recent active gastrointestinal bleeding
- Inlyta causes gastrointestinal perforation or fistulas
- Permanently discontinue if reversible posterior leukoencephalopathy syndrome (RPLS) occurs
- Inlyta has not been studied in patients who had an arterial thromboembolic event with in the previous 12 months (such as transient ischemic attack, cerebrovascular accident, myocardial infarction, and retinal artery occlusion)
- Inlyta has not been studied in patients who had a venous thromboembolic event within the previous 6 months (such as pulmonary embolism, deep vein thrombosis, retinal vein occlusion, and retinal vein thrombosis)
- Cardiac failure can occur with Inlyta and management of cardiac failure may require permanent discontinuation of Inlyta
- Woman of child bearing potential should use effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding
- Male on Inlyta with female partner of reproductive potential should use effective birth control
- Mean absolute bioavailability after a 5 mg dose is 58%
- Avoid use with strong CYPA3/4 inducers such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifabutin, rifampin, rifapentin, and St. John's wort
- Decrease dose by half if used with a strong CYPA3/4 inhibitors such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole

INLYTA® (axitinib) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Inlyta (axitinib) 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 advanced renal cell carcinoma (RCC) after failure of **one** prior systemic therapy
     - Systemic therapies include (alphabetically listed):
       - For Predominant Clear Cell Histology:
         - Avastin (bevacizumab) with interferon alpha-2b
         - Cabometyx (cabozantinib)
         - Opdivo (nivolumab)
         - Sutent (sunitinib)
         - Torisel (temsirolimus)
         - Votrient (pazopanib)
       - For Non-Clear Cell Histology:
         - Sutent (sunitinib)
         - Torisel (temsirolimus)

  4. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Liver function tests
     - Thyroid function test
     - Blood pressure, with hypertensive individuals showing good control on standard antihypertensive therapy

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

- **Criteria for continuation of coverage (renewal request):** Inlyta (axitinib) 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 Inlyta

  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:
     - Hypertension and Hypertensive Crisis
       - Signs and symptoms may include:

INLYTA® (axitinib) oral tablet (cont.)

- 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

- 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
- Venous thromboembolic events
  - Signs and symptoms may include:
    - Shortness of breath, chest pain, or arm or leg swelling, leg pain
- 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
- Cardiac failure
  - Signs and symptoms may include:
    - Edema, shortness of breath, weight gain, chest pain, shortness of breath
- 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
- Gastrointestinal perforation and fistula formation
  - Signs and symptoms may include:
    - Abdominal tenderness or severe pain in abdomen, nausea, vomiting
- 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

5. There are no significant interacting drugs

Renewal duration: 12 months

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.

Inlyta. Package Insert. Revised by manufacturer 8/2014. Accessed 09-04-2015, 10-20-2016

INLYTA® (axitinib) oral tablet (cont.)

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

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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.