BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/15/18**
	LAST CRITERIA REVISION DATE: 11/15/18
	ARCHIVE DATE:

ICLUSIG® (ponatinib) 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.**

ICLUSIG® (ponatinib) oral tablet (cont.)

Criteria:

- **Criteria for initial therapy:** Iclusig (ponatinib) 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:
     - CML or Ph+ALL that is **ONE** of the following:
       - T315I mutation positive
       - Failure, contraindication or intolerance to at least **TWO** TKI (Tyrosine Kinase Inhibitors)
         - Gleevec (imatinib)
         - Sprycel (dasatinib)
         - Tasigna (nilotinib)
         - Bosulif (bosutinib)

     - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Complete blood count with differential
     - Liver function tests
     - Serum lipase
     - Evaluation of blood pressure, and if elevated is adequately controlled with medication
     - Eye exam
     - Pregnancy test in a woman of child bearing potential

  5. Will not be used with strong CYP3A4 inducers drugs known to lower Iclusig blood levels such as carbamazepine, phenytoin, rifampin, and St. John's wort

  6. Woman patient of child bearing potential should use effective contraception during and for at least 3 weeks after therapy

  7. Woman patient who is breast feeding an infant or child should stop breast feeding during and for at least 6 days after therapy

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Iclusig (ponatinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

ICLUSIG® (ponatinib) oral tablet (cont.)

1. Individual continues to be seen by an Oncologist

2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - ALL
       - Failed to achieve a complete response in blood and bone marrow
       - Failed to achieve a complete response with incomplete blood count
       - Progression of disease as increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
       - Relapsed disease as the reappearance of blasts in the blood or bone marrow (> 5 %) or in any extramedullary site after a complete response
     - CML
       - Failed to achieve or maintain a complete hematologic response (peripheral blood counts have not normalized)
       - Failure to achieve a complete cytogenetic response (there are > 1% Ph+ metaphases in the bone marrow) at 12 months
       - Failure to achieve an early molecular response (*BCR-ABL (IS)* $\geq$ 10% at 6 months)
       - Loss of response after a previous cytogenetic or hematologic response

3. Individual has been adherent with the medication

4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
   - Significant adverse effect such as:
     - Marrow suppression
     - Hepatic impairment
     - Pancreatitis
     - Arterial occlusion
     - Venous thromboembolism
     - Heart failure
     - Severe and persistent hypertension despite antihypertensive therapy
     - Neuropathy
     - Serious ocular toxicity
     - Hemorrhage
     - Fluid retention (pericardial effusion, pleural effusion, pulmonary edema, peripheral edema)
     - Tumor lysis syndrome
     - Posterior leukoencephalopathy syndrome

5. There are no significant interacting drugs

Renewal duration: 12 months

ICLUSIG® (ponatinib) oral tablet (cont.)

Description:

Iclusig (ponatinib) is indicated for the treatment of adults with T315I-positive chronic myeloid leukemia (CML) chronic phase, accelerated phase, or blast phase; for the treatment of adults with T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL); for the treatment of adults with CML chronic phase, accelerated phase, or blast phase for whom no other tyrosine kinase inhibitor therapy (TKI) is indicated; and for the treatment of adults with Philadelphia chromosome positive Ph+ ALL for whom no other TKI is indicated. Iclusig (ponatinib) is not indicated and is not recommended for the treatment of patients with newly diagnosed chronic phase CML.

Iclusig (ponatinib) is a kinase inhibitor of ABL and T315I mutant ABL. Ponatinib also inhibits the *in vitro* activity of additional kinases members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3. Ponatinib is a TKI with activity against all BCR-ABL1 mutations associated with resistance to all of the other TKIs including the T315I (the gate-keeper) mutation.

Use of Iclusig (ponatinib) is subject to a Risk Evaluation and Mitigation Strategies (REMS) program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks. The FDA approved REMS program consist of a communication plan and medication guide. Elements of the REMS include provision of a medication guide with each prescription as well as a communication plan consisting of letters to healthcare professionals and to professional societies.

The healthcare professional letter informs the provider of the approved indications and serious risk of vascular occlusion and thromboembolism associated with the drug. The letter includes the prescribing information and a fact sheet. The REMS also includes a journal information piece to be published in professional journals.

Chronic myeloid leukemia (CML)

- CML is a malignant clonal disorder of hematopoietic stem cells arising from a genetic mutation that results in increased myeloid cells, and occasionally in erythroid cells, and platelets in the peripheral blood along with myeloid hyperplasia in the bone marrow

- CML is associated with the Philadelphia chromosome
    - There is a translocation between chromosomes 8 and 22 that gives rise to a *BCR-ABL1* fusion gene that produces a protein with deregulated tyrosine kinase activity

- CML occurs in three phases:
    - Chronic phase (CP-CML)
    - Accelerated phase (AP-CML)
    - Blast phase (BP-CML).

- It often presents in the chronic phase but it can progress to accelerated and ultimately to the blast phase or blast crisis
    - The prognosis for AP-CML or BP-CML is considered poor as they tend to be relatively resistant to most treatments, even after successful TKI treatment
    - Transplantation may need to be considered in such patients
- Tyrosine kinase inhibitors (TKI) are considered first-line therapy

- Choices include imatinib, dasatinib, and nilotinib
- Bosutinib is currently recommended for after failure of imatinib or dasatinib or nilotinib
- TKI target the constitutively active tyrosine kinase implicated in the pathogenesis of CML
- TKIs are the initial treatment of choice for the majority of patients with CML
- There are no clinical trials that compare TKI to help recommend one TKI over another for individual patients

- Selection on which agent to use may be dependent on patient age and co-morbidities, risk evaluation, toxicity profile of TKI, disease phase, response to previous therapy, and Breakpoint Cluster Region Abelson Murine Leukemia (BCR-ABL) mutation profile status

- In patients with disease progression to either AP-CML or BP-CML on prior TKI therapy, treatment with a course of an alternative TKI (one not received before) is helpful as a bridge to hematopoietic cell transplantation (HCT)

- Response during TKI therapy is the most important prognostic factor for long-term outcome in CML
  - Response is determined by
    - Measuring hematologic – normalization of peripheral blood counts
    - Cytogenetics – decrease in the number of Ph+ metaphases using bone marrow
    - Molecular responses – decrease in the amount of *BCR-ABL1* chimeric mRNA using QPCR
  - Primary resistance is when a TKI fails to achieve a desired response
  - Secondary resistance is a relapse following an initial response to a TKI

- The goal of TKI therapy is to achieve a complete cytogenetic response within 12 months of therapy and to prevent disease progression from CP-CML to accelerated or blast phase CML

Acute lymphoblastic leukemia (ALL)

- ALL is a heterogeneous hematologic disease characterized by proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs

- Chromosomal and molecular abnormalities categorize ALL subtypes in adults and children

- The frequency of subtypes differs between adults and children

- The cytogenetic abnormality for the Philadelphia chromosome is t(9;22)(q34;q11) with molecular abnormality in the *BCR-ABL1* gene that produces a fusion protein

- The chromosomal and molecular abnormalities provide prognostic information
  - Philadelphia-positive (Ph+) ALL is associated with a poor prognosis is uncommon in children but it is the most common subtype in adults
  - The frequency of Ph+ALL increases with age

- The emergence of targeted therapies for the treatment of Philadelphia-positive disease with TKIs has represented an advancement in treating this disorder

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- Induction therapy includes a BCR-ABL TKI in combination with chemotherapy regimen (such as hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD) alternating with high-dose methotrexate and cytarabine among others)
- Consolidation includes allogeneic hematopoietic cell transplantation
- If the patient is not a candidate for transplantation, consolidation chemotherapy incorporates a BCR-ABL TKI
- Maintenance includes a BCR-ABL TKI for two years after allogeneic hematopoietic cell transplantation or indefinitely if a transplantation is not performed
- Regimens for relapsed or refractory ALL includes use of TKIs based on mutations that are observed either alone or in combination with any of the induction regimens that were not used previously

Definitions:

Chronic myeloid leukemia (CML):

***Accelerated Phase CML*:**

Modified Criteria used at MD Anderson Cancer Center (most commonly used in clinical trials)
Peripheral blood blasts ≥ 15% and < 30% Peripheral blood blasts and promyelocytes combined ≥ 30% Peripheral blood basophils ≥ 20% Platelet count ≤ 100 x 10^9/L Additional clonal cytogenetic abnormalities in Ph+ cells
Semin Hematol 1988;25:49-61 Br J Haematol 1997;99:30-35 Blood 1993;82:691-703 Blood 2002;99:1928-1937

***Blast Phase CML*:**

World Health Organization Criteria	International Bone Marrow Transplant Registry
Blasts ≥ 20% of peripheral white blood cells or of nucleated bone marrow cells Extramedullary blast proliferation Large foci or clusters of blasts in the bone marrow biopsy	≥ 30% blasts in the blood, marrow, or both Extramedularry infiltrates or leukemic cells
NCCN Chronic myeloid leukemia. Version 1.2018, July 26, 2017	

***Treatment options based on BCR-ABL1 mutation profile*: (NCCN: CML, v 1.2018)**

Mutation	Treatment recommendations
E255K/V, F359V/C/I or Y253H	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib

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E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib, Omacetaxine, allogeneic HCT, or clinical trial

- Patients with disease that is resistant to primary treatment with imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting.
- Patients with disease that is resistant to primary treatment with nilotinib or dasatinib could be treated with an alternative TKI (other than imatinib) in the second-line setting.
- Ponatinib is also a treatment option for patients for whom no other TKI is indicated.
- Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

***Definitions for response and relapse in CML*:**

CHR	Complete normalization of peripheral blood counts with leukocyte count < 10 x 10^9/L Basophils < 5% Platelet count < 450 x 10^9/L No immature cells (such as myelocytes, promyelocytes, or blasts) in peripheral blood No signs & symptoms of disease, with a non-palpable spleen
CyR	Complete CyR (CCyR): no Ph+ metaphases (correlates to *BCR-ABL (IS)* 0.1-1%) Partial CyR (PCyR): 1-35% Ph+ metaphases Minor CyR: 36-65% Ph+ metaphases Minimal CyR: 66-95% Ph+ metaphases No response: > 95% Ph+ metaphases
MR	Early MR (EMR) – *BCR-ABL (IS)* ≤ 10% at 3 and 6 months Major MR (MMR) – *BCR-ABL (IS)* < 0.1% or ≥ 3 log reduction in *BCR-ABL1* mRNA from the standardized baseline, if QPCR (IS) is not available Complete MR (CMR) – is variably described, and is best defined by the assay's level of sensitivity (such as MR 4.5)
Relapse	Any sign of loss of response define as hematologic or cytogenetic 1 log increase in *BCR-ABL1* transcript levels with loss of MMR should prompt bone marrow evaluation for loss of complete CyR but is not itself defined as relapse (hematologic or cytogenetic)
CHR: complete hematologic response CyR: cytogenetic response MR: molecular response IS: International scale – the ratio of the BCR-ABL1 transcriptions to ABL1 transcripts	

International Scale (IS)	
MR 2	Detectable disease at a level of ≤1 percent on the IS (≥2 log reduction from the standardized baseline). This level of response roughly corresponds to a "complete cytogenetic response"
MR 3	Detectable disease at a level of ≤0.1 percent on the IS (≥3 log reduction from the standardized baseline). This level of response has been termed a "major molecular response"

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MR 4	Either detectable disease at a level of ≤0.01 percent on the IS (≥4 log reduction) **or** undetectable disease in cDNA with ≥10,000 ABL1 transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 10,000 normal ABL1 transcripts
MR 4.5	Either detectable disease at a level of ≤0.0032 percent on the IS (≥4.4 log reduction) **or** undetectable disease in cDNA with ≥32,000 ABL1 transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 32,000 normal ABL1 transcripts

Acute lymphoblastic leukemia:

***Treatment options based on BCR-ABL1 mutation profile*: (NCCN: ALL, v 3.2017)**

Mutation	Treatment recommendations
E255K/V, F359V/C/I or Y253H	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib
• Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. It is indicated for patients with T315I positive Philadelphia chromosome positive ALL and for patients with T315I positive Philadelphia chromosome positive ALL for whom no other TKI is indicated. • The TKIs noted above may also be used in combination with any induction regimen that was not previously given.	

***Definitions for response blood and bone marrow in ALL*:**

CR	No circulating blasts or extramedullary disease No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement Trilineage hematopoiesis (TLH) and < 5% blasts ANC > 1,000/microL Platelets > 100,000/microL No recurrence for 4 weeks
CRi	Same as CR except platelet count and/or ANC
ORR	CR + CRi
Refractory	Failure to reach CR at end of induction
Progressive	Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
Relapse	Reappearance of blasts in the blood or bone marrow (> 5%) or in any extramedullary site after a CR
CR = complete response CRi = complete response with incomplete blood count recovery ORR = overall response rate TLH = red cells, white cells, and platelets maturing	

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Resources:

Iclusig. Package Insert. Revised by manufacturer 9/2014. Accessed 09-04-2015.

Iclusig. Package Insert. Revised by manufacturer 06/2016. Accessed 10-22-2016.

Iclusig REMS. 12-20-2013.

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.

NCCN Clinical Practice Guidelines in Oncology: Chronic myeloid leukemia. Version 02.2018, Oct 19, 2017. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf

NCCN Clinical Practice Guidelines in Oncology: Acute lymphoblastic leukemia. Version 3.2017, Sep 13, 2017. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf

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

UpToDate: Initial treatment of chronic myeloid leukemia in chronic phase. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/initial-treatment-of-chronic-myeloid-leukemia-in-chronic-phase?source=see_link#H15

UpToDate: Treatment of chronic myeloid leukemia in chronic phase after failure of initial therapy. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-chronic-myeloid-leukemia-in-chronic-phase-after-failure-of-initial-therapy?source=search_result&search=chronic%20myeloid%20leukemia&selectedTitle=4~150

UpToDate: Induction therapy for Philadelphia chromosome positive acute lymphoblastic leukemia. Current through Aug 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/induction-therapy-for-philadelphia-chromosome-positive-acute-lymphoblastic-leukemia-in-adults?source=search_result&search=all&selectedTitle=9~150

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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.