BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ICLUSIG® (ponatinib)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Iclusig (ponatinib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Chronic myeloid leukemia (CML) in chronic phase that is resistance or intolerance to at least two prior kinase inhibitors

b. Chronic myeloid leukemia (CML) in accelerated phase or blast phase where no other kinase inhibitors are indicated

c. Chronic myeloid leukemia (CML) in chronic phase, accelerated phase, or blast phase that is T315I-positive

d. Acute lymphoblastic leukemia (ALL) that is Philadelphia (Ph) chromosome positive where no other tyrosine kinase inhibitor (TKI) is indicated

e. Acute lymphoblastic leukemia (ALL) that is Philadelphia (Ph) chromosome positive that is T3151-positive

f. Acute lymphoblastic leukemia (ALL) that is Philadelphia (Ph) chromosome positive that is newly diagnosed in combination with chemotherapy

g. 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. Individual does not have newly diagnosed chronic phase chronic myeloid leukemia (CML)

5. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
   a. Serum lipase
   b. Blood pressure, and if elevated is adequately controlled with medication
   c. Eye exam
   d. Negative pregnancy test in a woman of childbearing potential
   e. Eastern Oncology Cooperative Group (ECOG) performance status 0 to 2
   f. Complete blood count
   g. Liver function tests

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label or intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Iclusig (ponatinib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition has not worsened while on therapy defined as:
   a. For **acute lymphoblastic leukemia (ALL)**: **ANY** of the following:
      i. Failed to achieve a complete response in blood and bone marrow

ii. Failed to achieve a complete response with incomplete blood count
iii. Progression of disease as increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
iv. Relapsed disease as the reappearance of blasts in the blood or bone marrow (> 5 %) or in any extramedullary site after a complete response

b. For **chronic myeloid leukemia (CML)**: **ANY** of the following:
i. Failed to achieve or maintain a complete hematologic response (peripheral blood counts have not normalized)
ii. Failure to achieve a complete cytogenetic response (there are > 1% Ph+ metaphases in the bone marrow) at 12 months
iii. Failure to achieve an early molecular response (*BCR-ABL (IS)* ≥ 10% at 6 months)
iv. Loss of response after a previous cytogenetic or hematologic response

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label or intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
a. Arterial occlusive event that is severe to life-threatening or has recurred after interruption and dose reduction
b. Cardiac arrhythmia that is severe or recurrent
c. Fluid retention (pericardial effusion, pleural effusion, pulmonary edema, peripheral edema) that is severe or recurrent
d. Gastrointestinal perforation or fistula
e. Heart failure that is life-threatening or has recurred after interruption and dose reduction
f. Hemorrhage that is severe or recurrent
g. Hepatotoxicity
h. Other non-hematologic adverse reactions that have recurred after interruption and dose reduction
i. Reversible posterior leukoencephalopathy syndrome
j. Serious ocular toxicity
k. Severe and persistent hypertension despite antihypertensive therapy or hypertensive crisis
l. Symptomatic pancreatitis or serum lipase is greater than five times the upper limit of normal
m. Venous thromboembolism that is life-threatening or has recurred after interruption and dose reduction

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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Description:

Iclusig (ponatinib) is indicated for the treatment of adult patients with a) chronic phase chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors; b) accelerated phase or blast phase CML or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated; and c) T315I-positive CML (chronic, accelerated, blast phases) or e) acute lymphoblastic leukemia (ALL) that is Philadelphia (Ph) chromosome positive that is T3151-positive or f) acute lymphoblastic leukemia (ALL) that is Philadelphia (Ph) chromosome positive that is newly diagnosed in combination with chemotherapy

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 gatekeeper) 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 consists 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) 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), and blast phase (BP-CML).

Tyrosine kinase inhibitors (TKI) are considered first-line therapy. 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.

Acute lymphoblastic leukemia (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. 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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation 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

HyperCVAD therapy:
- Hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine

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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

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

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***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
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 defined 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"
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

Resources:

Iclusig (ponatinib) product information, revised by Takeda Pharmaceutical America, Inc 03-2024. Available at DailyMed http://dailymed.nlm.nih.gov. July 24, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute lymphoblastic leukemia. Version 2.2025 – Updated June 27, 2025. Available at https://www.nccn.org. Accessed October 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic myeloid leukemia. Version 1.2026 – Updated July 16, 2025. Available at https://www.nccn.org. Accessed October 08, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes. Version 1.2026 – Updated October 03, 2025. Available at https://www.nccn.org. Accessed October 08, 2025.

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.