PHARMACY COVERAGE GUIDELINE

GLEEVEC® (imatinib mesylate) oral tablet
Imatinib Mesylate oral tablet
IMKELDI (imatinib mesylate) oral solution
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:** Gleevec (imatinib mesylate), Imkeldi (imatinib mesylate), or generic imatinib mesylate are 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, HIV/AIDS Specialist, or Gastroenterologist depending upon indication or use

2. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Newly diagnosed adult and pediatric (1 year of age or older) patient with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase

b. Philadelphia chromosome positive chronic myeloid leukemia in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy

c. Adult (18 years of age or older) patient with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

d. Pediatric (1 year of age or older) patient with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy

e. Adult patient (18 years of age or older) with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements

f. Adult patient (18 years of age or older) with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown

g. Adult patient (18 years of age or older) with hypereosinophilic syndrome and/or chronic eosinophilic leukemia (HES/CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or fluorescence *in situ* hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown

h. Adult patient (18 years of age or older) with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP)

i. Adult patient (18 years of age or older) with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

j. Adjuvant treatment of adult patient (18 years of age or older) following resection of Kit (CD117) positive GIST

k. 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

3. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Where applicable, genetic testing has been completed using an FDA approved test and the result of testing is submitted
   b. Other required testing as outlined by manufacturer and FDA labeling have been completed and/or are ongoing
   c. Liver function tests
   d. Assessment of hydration status and uric acid levels, with correction if abnormal
   e. Negative pregnancy test in a woman of childbearing age

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

5. There are no significant interacting drugs such as use with CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Gleevec (imatinib mesylate), Imkeldi (imatinib mesylate), or generic Imatinib mesylate are considered ***medically necessary*** and will be approved when **ALL** 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, HIV/AIDS Specialist, or Gastroenterologist depending upon indication or use

2. Individual's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **Request for Gleevec and Imkeldi:** Individual has failure after adequate trial, contraindication per FDA label, intolerance or is not a candidate for **generic imatinib mesylate** [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. Cytopenias (anemia, neutropenia, thrombocytopenia)
    b. Pleural effusions, pericardial effusions, pulmonary edema, ascites:
    c. Heart failure, left ventricular dysfunction, or cardiogenic shock
    d. Hepatotoxicity
    e. GI bleeding or perforation
    f. Erythema multiforme/Stevens-Johnson Syndrome
    g. Tumor lysis syndrome
    h. Renal toxicity

6. There are no significant interacting drugs such as use with CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

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:

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

Description:

Imatinib is used for the treatment of several malignancies: acute lymphoblastic leukemia, aggressive systemic mastocytosis, chronic myeloid leukemia, dermatofibrosarcoma protuberans, gastrointestinal stromal tumors, hypereosinophilic syndrome / chronic eosinophilic leukemia, and myelodysplastic / myeloproliferative disease. It is a small molecule tyrosine kinase inhibitor with several important actions on cellular function. It blocks tyrosine kinase activity of several key proteins involved the regulation of growth, differentiation, and apoptosis. Deregulation of tyrosine kinase activity has been shown to play an important role in development of various cancers.

Tyrosine kinase inhibitors (TKIs) are a class of agents designed to compete with adenosine triphosphate (ATP) for its binding pocket within the intracellular domain of wild type and/or mutated receptor. Binding of Imatinib within the pocket blocks downstream signaling important for tumor growth. All TKIs are designed to compete with ATP for the ATP binding pocket of similar or different tyrosine kinases that are mutated and/or over-expressed in specific tumors.

In the treatment of chronic myeloid leukemia (CML), Imatinib inhibits the breakpoint cluster region-Abelson (BCR-ABL) tyrosine kinase fusion protein created by the chromosomal abnormality known as the Philadelphia chromosome (Ph). BCR-ABL is uniquely expressed by leukemic cells and is essential for the survival of these cells. The fusion protein is present in 95% of individuals with CML. Philadelphia chromosome is also an abnormality seen in approximately 30% of newly diagnosed adults with acute lymphoblastic leukemia (ALL). Imatinib potently and specifically inhibits growth of BCR-ABL expressing cells leading to inhibition of proliferation and apoptosis in BCR-ABL positive cell lines as well as fresh leukemic cells.

Gastrointestinal stromal tumors (GISTs) are neoplasms of the gastrointestinal (GI) tract. They are thought to arise from the interstitial cells of Cajal. GISTs are defined by the expression of the tyrosine kinase c-KIT (CD117) receptor, the receptor for stem cell factor (SCF), in the tumor cells resulting in constitutive activation of the tyrosine kinase. The c-KIT is expressed in approximately 85% of GISTs. Imatinib inhibits proliferation and induces apoptosis in GISTs cells, which express an activating c-KIT mutation.

Mutation of c-KIT is also found in the myeloproliferative disorder systemic mastocytosis. In GISTs, mutations and deletions of c-KIT are typically found in the juxta membrane domain, resulting in constitutive activation of the tyrosine kinase. With systemic mastocytosis, the characteristic D816V activating c-KIT mutation is within the kinase domain itself. While Imatinib has significant activity in advanced GISTs, it has proven largely unsuccessful in the treatment of systemic mastocytosis due to ineffective targeting of c-KIT kinases with the D816V mutation. All responses in patients with systemic mastocytosis were seen in those who were negative for D816V c-KIT mutation.

The idiopathic hypereosinophilic syndrome (HES), now reclassified as chronic eosinophilic leukemia (CEL), is characterized by the expression of the FIP1-like-1–platelet-derived growth factor receptor alpha (FIP1L1-

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PDGFRA) fusion protein, which is generated by an interstitial chromosomal deletion and results in constitutive signaling through PDGFRA. Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue tumor characterized by the presence of a distinctive, reciprocal rearrangement of certain chromosomes. The rearrangement leads to the fusion of collagen type 1 alpha-1 (COL1A1) chain to platelet-derived growth factor beta (PDGFB). The formation of COL1A1-PDGFB fusion gene results in constitutional up-regulation of PDGFB expression, leading to continuous autocrine activation of the receptor. Imatinib is an inhibitor specific for platelet derived growth factor receptor and is effect for HES/CEL and DFSP.

Definitions:

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

BCR-ABL1 (IS) Response Milestones:

BCR-ABL1 (IS)	3 months	6 months	12 months	> 12 months
> 10%	**YELLOW**	**RED**		
>1-10%	**GREEN**		**YELLOW**	**RED**
>0.1-1%	**GREEN**			**YELLOW**
≤ 0.1%	**GREEN**			

	Clinical considerations	2nd line & subsequent treatment options
Red	• Evaluate compliance & drug interactions • Mutational analysis	• Switch to alternate TKI • Evaluate for HCT
Yellow	• Evaluate compliance & drug interactions • Mutational analysis	• Switch to alternate TKI or continue same TKI or dose escalation of imatinib (to max of 800 mg) • Evaluate for HCT
Green	• Monitor response & side effects	• Continue same TKI

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 unrelated to therapy 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:

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 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 disappearance of palpable splenomegaly
CyR	Complete CyR (CCyR): no Ph+ metaphases (correlates to *BCR-ABL (IS)* ≤ 1% (> 0.1-1%)) Partial CyR (PCyR): 1-35% Ph+ metaphases Major CyR: 0-35% Ph+ metaphases Minor CyR: > 35% Ph+ metaphases No response: > 95% Ph+ metaphasese
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 CCyR but is not itself defined as relapse (hematologic or cytogenetic relapse)
CHR: complete hematologic response CyR: cytogenetic response MR: molecular response IS: International scale – the ratio of the BCR-ABL1 transcriptions to ABL1 transcripts	

Molecular response International Scale:

	International Scale (IS)
MR 2	Detectable disease at a level of ≤ 1% 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% 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% 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% 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

Monitoring Response to TKI Therapy and Mutational Analysis:

Test	Recommendation
Bone marrow cytogenetic	• At diagnosis • Failure to reach response milestone • Any signs of loss of response (defined as hematologic or cytogenetic relapse
Quantitative RT-PCT (qPCR) using IS	• At diagnosis • Every 3 months after initiating treatment. After *BCR-ABL1* (IS) ≤ 1 % (> 0.1-1%) has been achieved, every 3 months x 2 y and every 3-6 months thereafter • If there is a 1-log increase in *BCR-ABL1* transcript levels with MMR, qPCR should be repeated in 1-3 months
BCR-ABL1 kinase domain mutation analysis	• Chronic phase ➢ Failure to reach response milestone ➢ Any signs of loss of response (defined as hematologic or cytogenetic relapse ➢ 1-log increase in *BCR-ABL1* transcript levels and loss of MMR • Disease progression to accelerated or blast phase

Eastern Co-operative Oncology Group (ECGO) Performance Status:

Grade	**ECOG description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, 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, MM, Creech, RH, Tormey, DC, et al.: 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:

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Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Gleevec (imatinib mesylate) product information, revised by Novartis Pharmaceuticals Corporation 03-2024 Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 05, 2024.

Imatinib mesylate product information, revised by Mylan Pharmaceuticals, Inc. 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 05, 2024.

Imkeldi mesylate product information, revised by Shorla Oncology, Inc. 11-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Acute Lymphoblastic Leukemia Version 3.2024 – Updated December 20, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Pediatric Acute Lymphoblastic Leukemia Version 2.2025 – Updated December 16, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia Version 3.2025 – Updated November 27, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Dermatofibrosarcoma Protuberans Version 1.2025 – Updated October 11, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Soft Tissue Sarcoma Version 4.2024 – Updated November 21, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Gastrointestinal Stromal Tumors Version 2.2024 – Updated July 31, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myelodysplastic Syndromes Version 2.2025 – Updated January 17, 2025. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 2.2024 – Updated June 19, 2024. Available at https://www.nccn.org. Accessed February 02, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Systemic Mastocytosis Version 3.2024 – Updated April 24, 2024. Available at https://www.nccn.org. Accessed February 02, 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.

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