BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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GLEEVEC® (imatinib mesylate) oral tablet
IMATINIB MESYLATE 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.**

GLEEVEC® (imatinib mesylate) oral tablet
IMATINIB MESYLATE oral tablet (cont.)

Description:

Gleevec® (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 juxtamembrane 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-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.

Gleevec (imatinib)

Medication class:
Antineoplastic Agent, BCR-ABL Tyrosine Kinase Inhibitor

FDA-approved indication(s):
- Treatment of Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (newly diagnosed) in adults and children
- Treatment of Ph+ CML in blast crisis (BC), accelerated phase (AP), or chronic phase (CP) after failure of interferon-alfa therapy
- Treatment of relapsed or refractory Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in adults
- Treatment of newly diagnosed Ph+ ALL in children (in combination with chemotherapy)
- Treatment of myelodysplastic syndrome/myeloproliferative disease (MDS/MPD) associated with PDGF receptor gene rearrangements as determined by an approved test in adults
- Treatment of aggressive systemic mastocytosis (ASM) in adults without D816V c-kit mutation (as determined by an approved test) or with c-kit mutational status unknown
- Treatment of hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) in adult patients who have the FIP1L1-platelet-derived growth factor receptor (PDGFR) alpha fusion kinase (mutational analysis or fluorescent in situ hybridization [FISH] demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGF receptor alpha fusion kinase negative or unknown
- Treatment of unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP) in adults
- Treatment of Kit (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)
- Adjuvant treatment of Kit (CD117)-positive GIST following complete gross resection

Recommended Dose:
- Adults with Ph+ CML CP: 400 mg once daily
- Adults with Ph+ CML AP or BC: 600 mg once daily
- Pediatrics (1 year of age or older) with Ph+ CML CP: 340 mg/m^2/day, not to exceed 600 mg daily
- Adults with Ph+ ALL: 600 mg once daily
- Adults with MDS/MPD: 400 mg once daily
- Adults with ASM: 100 mg once daily or 400 mg once daily
- Adults with HES/CEL: 100 mg once daily or 400 mg once daily
- Adults with DFSP: 400 mg twice daily
- Adults with metastatic and/or unresectable GIST: 400 mg once daily
- Adjuvant treatment of adults with GIST: 400 mg once daily

Maximum dosage

GLEEVEC® (imatinib mesylate) oral tablet
IMATINIB MESYLATE oral tablet (cont.)

- Not stated, label states that experience with doses > 800 mg is limited & to increase dose when used with CYP3A4 inducers

Available Dosage Forms:
- 100 mg and 400 mg scored tablets

Warnings, Precautions, and other Clinical Information:
- Adjust the dose in patients with mild to moderate hepatic impairment to 400 mg once daily
- Adjust the dose in patients with severe hepatic impairment to 300 mg once daily
- Doses > 600 mg are not recommended in patients with mild renal impairment (CrCL 40-59 mL/min)
- Doses > 400 mg are not recommended in patients with moderate renal impairment (CrCL 20-39 mL/min)
- Dose reductions are necessary for patients with severe renal impairment, but the label does not provide information
- For drug-induced cytopenias (anemia, neutropenia, thrombocytopenia), mange with dose reduction, dose interruption or discontinuation of treatment
- Avoid concurrent use of strong CYP 450 3A4 inducers such as carbamazepine, dexamethasone, fosphenytoin, oxcarbazepine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifampicin, or St. John's Wort, if concurrent use is unavoidable, increase imatinib dose
- Woman of child bearing potential should have a pregnancy test before initiation of therapy
- Woman of child bearing potential should be warned against becoming pregnant
- Woman of child bearing potential should use effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding

Criteria:

- **Criteria for initial therapy:** Gleevec (imatinib mesylate) or Imatinib mesylate is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is an Oncologist

2. A diagnosis of **ONE** of the following:

   - Acute lymphoblastic leukemia (ALL) in **ONE** of the following:
     - Adult with relapsed or refractory Philadelphia chromosome positive (Ph+) ALL
     - Pediatric individual (age of 1 year or older) with newly diagnosed Ph+ ALL in combination with chemotherapy

   - Aggressive systemic mastocytosis (ASM) in **ONE** of the following:
     - Adult with a negative D816V c-KIT mutation as determined with an FDA-approved test
     - Adult with an unknown D816V c-KIT mutation

   - Chronic myeloid leukemia (CML) in **ONE** of the following:
     - Newly diagnosed adult and pediatric individual (age of 1 year or older) with Ph+ CML in chronic phase

- Adult with Ph+ CML in blast crisis, accelerated phase or chronic phase after failure of interferon-alfa therapy

- Adult with Dermatofibrosarcoma protuberans (DFSP) that is unresectable, recurrent, and/or metastatic

- Gastrointestinal stromal tumors (GISTs) in **ONE** of the following:
  - Adult with c-KIT (CD117) positive unresectable and/or metastatic malignant tumors
  - Adjuvant treatment of adult with c-KIT (CD117) positive GISTs following complete gross resection

- Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) in **ONE** of the following:
  - Adult with HES and/or CEL who have the FIP1L1-PDGF alpha fusion kinase (mutational analysis or fluorescent in situ hybridization [FISH] demonstration of CHIC2 allele deletion)
  - Adult with HES and/or CEL who are FIP1L1-PDGF alpha fusion kinase negative or unknown

- Adult with Myelodisplastic syndrome / Myeloproliferative disease (MDS/MPD) associated with PDGFR gene rearrangements as determined with an FDA-approved test

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

4. Request for **brand** Gleevec: individual has failure, contraindication or intolerance to **generic imatinib mesylate**

Initial approval duration: 6 months

➢ **Criteria for continuation of coverage (renewal request):** Gleevec (imatinib mesylate) or Imatinib mesylate is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Individual continues to be seen by Prescriber is an Oncologist

2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - Cancer progression

3. Individual has been adherent with the medication

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4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
    - Contraindications as listed in the criteria for initial therapy section
    - Significant adverse effect such as:
        - Cytopenias (anemia, neutropenia, thrombocytopenia)
            - Signs and symptoms may include: fever, chills, infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath, bleeding and easy bruising, unusual bleeding or bruising, nose bleeds, red or purple spots on body
        - Pleural effusions, pericardial effusions, pulmonary edema, ascites:
            - Signs and symptoms may include: shortness of breath, cough, sharp chest pain
        - Heart failure, left ventricular dysfunction, or cardiogenic shock
            - Signs and symptoms may include: edema of ankles or feet, shortness of breath, weight gain, chest pain, shortness of breath, fatigue
        - Hepatotoxicity
            - 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
        - GI bleeding or perforation
            - Signs and symptoms may include: blood in stool, dark red or tar-like stools, coughing up blood, vomiting blood, or unusual bleeding, easy bruising, blood in urine, dizziness or feeling faint, abdominal tenderness or severe pain in abdomen, nausea, vomiting
        - Erythema multiforme/Stevens-Johnson Syndrome
            - Signs and symptoms may include: progressive skin rash, hives, blistering, oral ulcers
        - Tumor lysis syndrome
            - Signs and symptoms may include: nausea, vomiting, shortness of breath, irregular heartbeat, flank pain, blood in urine, weakness, lethargy, edema, seizure, labs: high K, uric acid, & phosphorous, low calcium
        - Renal toxicity
            - Signs and symptoms may include: rapid weight gain, unable to start urination, trouble emptying bladder, weak urine stream, painful urination

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.

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Imatinib mesylate. Package insert. Revised by manufacturer 10-2016. Accessed 12-14-2016

Gleevec®. Package Insert. Revised by the manufacturer 09/2016. Accessed 12-14-2016.

Gleevec®. Package Insert. Revised by the manufacturer 01/2015. Accessed 12-11-2015.

Gleevec®. Package Insert. Reference ID: 3511243. Revised by the manufacturer 05/2014. Accessed 12-05-2014.

Gleevec. Package Insert. Revised by the manufacturer 10/2017. Accessed 01-02-2018

Imatinib mesylate. Package insert. Revised by manufacturer 10/2017. Accessed 01-02-2018

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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.