PHARMACY COVERAGE GUIDELINE

DANZITEN™ (nilotinib) oral tablet
TASIGNA® (nilotinib) oral capsule
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:** Danziten (nilotinib) tablets, Tasigna (nilotinib) capsules, and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Gastroenterologist depending upon indication or use

  2. Individual is **ONE** of the following:
     a. For Danziten (nilotinib) **tablets**:
        i. Adult (18 years of age or older) with:

1. Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
2. Chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib

b. For Tasigna (nilotinib) **capsules**:
   i. Adult (18 years of age or older) with:
      1. Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
      2. Chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib
   ii. Individual is a pediatric patient (1 year of age or older) with:
      1. Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
      2. Chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy

c. 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 treatment and with continued monitoring of the individual as clinically appropriate:
   a. Electrocardiogram
   b. Electrolytes, calcium, and magnesium
   c. Liver enzymes
   d. Glucose
   e. Amylase and lipase
   f. Uric acid level
   g. Negative pregnancy test in a woman of childbearing potential

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, 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. There are **NO** contraindications such as:
   a. Uncorrected hypokalemia
   b. Uncorrected hypomagnesemia
   c. Long QT syndrome

6. Individual has not had a recent myocardial infarction, does not have congestive heart failure, unstable angina, or clinically significant bradycardia

7. Individual is not using strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, others)

8. Individual is not using proton pump inhibitors (e.g., omeprazole, lansoprazole, etc.)

9. Individual is not using drugs that prolong QT interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Danziten (nilotinib) tablets, Tasigna (nilotinib) capsules, and/or generic equivalent (if available) 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 or Gastroenterologist depending upon indication or use

2. Individual's condition has responded while on therapy with response defined as the following:
    a. Documented evidence of efficacy, disease stability and/or improvement
    b. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, 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 contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindication as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Recurrence of QTcF prolongation of > 480 msec after dose modification
        ii. Recurrence of myelosuppression (neutropenia or thrombocytopenia) after dose modification
        iii. Recurrence of severe elevations of amylase, bilirubin, or transaminases after dose modification
        iv. Pancreatitis
        v. Fluid retention with rapid weight gain or swelling, or effusions such as pleural effusion, pericardial effusion, pulmonary edema, shortness of breath
        vi. Growth retardation or deceleration in a pediatric patient
        vii. Any moderate or severe reaction that does not improve after dose modification

6. Individual has not had a recent myocardial infarction, does not have congestive heart failure, unstable angina, or clinically significant bradycardia

7. Individual is not using strong CYP3A inducers (e.g.., rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, others)

8. Individual is not using proton pump inhibitors (e.g., omeprazole, lansoprazole, etc.)

9. Individual is not using drugs that prolong QT interval (e.g., amiodarone, sotalol, quinidine, procainamide, levofloxacin, 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:

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

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

Description:

Danziten (nilotinib) tablet is a kinase inhibitor is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) and for adults and for adult patients with chronic phase and accelerated phase Philadelphia chromosome positive myeloid leukemia (Ph+ CML-CP and Ph+CML-AP) resistant to or intolerant to prior therapy that included imatinib.

Tasigna (nilotinib) capsule is a kinase inhibitor is indicated for the treatment of adult and pediatric patients greater than or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) and for adult patients with chronic phase and accelerated phase Philadelphia chromosome positive myeloid leukemia (Ph+ CML-CP and Ph+CML-AP) resistant to or intolerant to prior therapy that included imatinib, and for pediatric patients greater than or equal to 1 year of age with chronic phase Philadelphia chromosome positive myeloid leukemia (Ph+ CML-CP) resistant to or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Nilotinib is an inhibitor of the BCR-ABL kinase. It binds to and stabilizes the inactive conformation of the kinase domain of the ABL protein. *In vitro*, nilotinib inhibited BCR-ABL mediated proliferation of leukemic cell lines derived from patients with Ph+ CML. Under the conditions of the assays, nilotinib was able to overcome imatinib resistance resulting from BCR-ABL kinase mutations. *In vivo*, nilotinib reduced the tumor size in a murine BCR-ABL xenograft model. Nilotinib inhibited the autophosphorylation of the following kinases: BCR-ABL), PDGFR, c-KIT, CSF-1R, and DDR1.

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Definitions:

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

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 Extramedullary infiltrates or leukemic cells
NCCN Chronic myeloid leukemia. Version 1.2018, July 26, 2017	

Treatment options based on BCR-ABL1 mutation profile:

Contraindicated Mutations	Therapy
AA337T, P465S	Asciminib
T315I/A, F317L/V/I/C, V299L	Dasatinib
T315A, Y253H, E255K/V, F359V/C/I	Nilotinib
T315A, V299L, G250E, F317L	Bosutinib
None	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, taking into account BCR-ABL1 kinase domain mutation status
- Patients with disease that is resistant to primary treatment with bosutinib, nilotinib, or dasatinib could be treated with an alternative TKI (other than imatinib) in the second line setting.

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%)) Major CyR (MCyR): 0-35% Ph+ metaphases Partial CyR (PCyR): 1-35% Ph+ metaphases Minor CyR: > 35%-65% Ph+ metaphases
MR	Early MR (EMR) – *BCR-ABL1 (IS)* ≤ 10% at 3 and 6 months Major MR (MMR) – *BCR-AB1L (IS)* ≤ 0.1% or ≥ 3 log reduction in *BCR-ABL1* mRNA from the standardized baseline, if qPCR (IS) is not available

	Deep molecular response (DMR): MR4.0: *BCR-ABL1 (IS)* ≤ 0.01% or MR4.5: *BCR-ABL1 (IS)* ≤ 0.0032%
Relapse	Any sign of loss of response defined as hematologic or cytogenetic Any sign of loss of CCyR or its molecular response corelate defined as an increase in *BCR-ABL1* transcript >1% 1 log increase in *BCR-ABL1* transcript levels with loss of MMR
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

Resources:

Danziten (nilotinib) tabs product information, revised by Azurity Pharmaceuticals, Inc. 11-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 16, 2024.

Tasigna (nilotinib) cap product information, revised by Novartis Pharmaceuticals Corporation 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 25, 2024.

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 December 16, 2024.

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.