BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
ORIGINAL EFFECTIVE DATE:	**1/01/2016**
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TASIGNA® (nilotinib) oral capsule

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.**

TASIGNA® (nilotinib) oral capsule

Criteria:

- **Criteria for initial therapy:** Tasigna (nilotinib) 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 or Gastroenterologist depending upon indication or use

2. **ONE** of the following:
    a. Adult (18 years of age or older) with:
        i. Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
        ii. Chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib

    b. Pediatric patient (1 year of age or older) with:
        i. Newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
        ii. Chronic phase and accelerated phase 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. **ALL** of the following baseline tests have been completed before initiation of treatment:
    a. Electrocardiogram
    b. Electrolytes, calcium, and magnesium
    c. Amylase and lipase
    d. Uric acid level
    e. Negative pregnancy test in a woman of childbearing potential

4. There are **NO** contraindications.
    a. Contraindications include:
        i. Uncorrected hypokalemia
        ii. Uncorrected hypomagnesemia
        iii. Long QT syndrome

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

6. There are no significant interacting drugs

Initial approval duration: 6 months

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

  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. The condition has responded while on therapy
     a. Response is defined as:
        i. Documented evidence of efficacy, disease stability and/or improvement
        ii. 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. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
     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

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

  6. There are no significant interacting drugs

  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:

Tasigna (nilotinib) 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.

Definitions:

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

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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:

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 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 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	

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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:

Tasigna (nilotinib) product information, revised by Novartis Pharmaceuticals Corporation 09-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 06, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia Version 2.2022 – Updated November 15, 2021. Available at https://www.nccn.org. Accessed December 06, 2021.

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.