



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

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.

BLUE CROSS®, BLUE SHIELD® and the Cross and Shield Symbols are registered service marks of the Blue Cross and Blue Shield Association, an association of independent Blue Cross and Blue Shield Plans. All other trademarks and service marks contained in this guideline are the property of their respective owners, which are not affiliated with BCBSAZ.

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.**



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

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 newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
 - b. Adult (18 years of age or older) with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) resistant or intolerant to prior therapy that included imatinib
 - c. Pediatric patient (1 year of age or older) with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase
 - d. Pediatric patient (1 year of age or older) with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior tyrosine-kinase inhibitor (TKI) therapy
 - e. 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. Comprehensive metabolic panel
 - b. Complete blood count with differential
 - c. Uric acid level
 - d. Amylase and lipase
 - e. Lipid profile
 - f. Electrocardiogram
 - g. Negative pregnancy test in a woman of child bearing potential
 4. There are **NO** contraindications.
 - a. Contraindications include:
 - i. Uncorrected hypokalemia
 - ii. Uncorrected hypomagnesemia
 - iii. Long QT syndrome

Initial approval duration: 6 months



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

TASIGNA® (nilotinib) oral capsule

- **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 not worsened while on therapy
 3. Individual has been adherent with the medication
 4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use, such as:
 - a. Any of the contraindication as listed above
 - b. Myelosuppression
 - c. QTcF prolongation of > 480 msec
 - d. Hepatotoxicity
 - e. Pancreatitis
 - f. Electrolyte abnormalities, such as uncorrected hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, hyperuricemia, and hyponatremia
 - g. Fluid retention with rapid weight gain or swelling, or effusions such as pleural effusion, pericardial effusion, pulmonary edema
 5. There are no significant interacting drugs

Renewal duration: 12 months

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.

**PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS**

**ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:**

TASIGNA® (nilotinib) oral capsule

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		2 nd line & subsequent treatment options	
Red	<ul style="list-style-type: none"> Evaluate compliance & drug interactions Mutational analysis 		<ul style="list-style-type: none"> Switch to alternate TKI Evaluate for HCT 	
Yellow	<ul style="list-style-type: none"> Evaluate compliance & drug interactions Mutational analysis 		<ul style="list-style-type: none"> Switch to alternate TKI or continue same TKI or dose escalation of imatinib (to max of 800 mg) Evaluate for HCT 	
Green	<ul style="list-style-type: none"> Monitor response & side effects 		<ul style="list-style-type: none"> 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	≥ 30% blasts in the blood, marrow, or both
Extramedullary blast proliferation	Extramedullary infiltrates or leukemic cells
Large foci or clusters of blasts in the bone marrow biopsy	
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

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

TASIGNA® (nilotinib) oral capsule

- 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 <i>BCR-ABL</i> (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+ metaphases
MR	Early MR (EMR) – <i>BCR-ABL</i> (IS) ≤ 10% at 3 and 6 months Major MR (MMR) – <i>BCR-ABL</i> (IS) ≤ 0.1% or ≥ 3 log reduction in <i>BCR-ABL1</i> 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 <i>BCR-ABL1</i> 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 <i>BCR-ABL1</i> transcriptions to <i>ABL1</i> 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 <i>ABL1</i> transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 10,000 normal <i>ABL1</i> 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 <i>ABL1</i> transcripts. This level of response requires that the assay being used is sensitive enough to detect a single abnormal transcript amongst 32,000 normal <i>ABL1</i> transcripts



An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 1/01/2016
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

TASIGNA® (nilotinib) oral capsule

Monitoring Response to TKI Therapy and Mutational Analysis:

Test	Recommendation
Bone marrow cytogenetic	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • At diagnosis • Every 3 months after initiating treatment. After <i>BCR-ABL1</i> (IS) $\leq 1\%$ ($> 0.1-1\%$) has been achieved, every 3 months x 2 y and every 3-6 months thereafter • If there is a 1-log increase in <i>BCR-ABL1</i> transcript levels with MMR, qPCR should be repeated in 1-3 months
BCR-ABL1 kinase domain mutation analysis	<ul style="list-style-type: none"> • Chronic phase <ul style="list-style-type: none"> ➢ Failure to reach response milestone ➢ Any signs of loss of response (defined as hematologic or cytogenetic relapse) ➢ 1-log increase in <i>BCR-ABL1</i> transcript levels and loss of MMR • Disease progression to accelerated or blast phase

Resources:

Tasigna (nilotinib) product information, revised by Novartis Pharmaceuticals Corporation 12-2020, at DailyMed <http://dailymed.nlm.nih.gov>. Accessed January 31, 2021.

Tasigna (nilotinib). National Comprehensive Cancer Network (NCCN). NCCN Drugs & Biologics Compendium. 2021; Available at: <http://www.nccn.org>. Accessed January 31, 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.