

PHARMACY POLICY – 5.01.518

BCR-ABL Kinase Inhibitors


Effective Date: May 1, 2024
Last Revised: April 9, 2024
Replaces: N/A

RELATED MEDICAL POLICIES:

- 5.01.517 Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Treatment
- 5.01.534 Multiple Receptor Tyrosine Kinase Inhibitors
- 5.01.544 Prostate Cancer Targeted Therapies
- 5.01.603 Epidermal Growth Factor Receptor (EGFR) Inhibitors

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Introduction

BCR-ABL is an abnormal gene that is found in a specific chromosome in people who have chronic myelogenous leukemia (CML). The BCR-ABL gene makes a protein known as a tyrosine kinase. Tyrosine kinase acts as an “on/off switch” in a cell and causes certain types of cancer cells to grow uncontrollably, leading to specific types of blood cancer (leukemia). Newer types of chemotherapy attack cellular targets specifically involved in tumor growth. Drugs that target the BCR-ABL protein are known as BCR-ABL tyrosine kinase inhibitors. This policy describes when BCR-ABL kinase inhibitors may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
<p>Gleevec (imatinib)</p>	<p>Gleevec (imatinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib for:</p> <ul style="list-style-type: none"> • Treatment of adult and pediatric individuals with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase, accelerated phase or blast crisis • Treatment of pediatric individuals with Ph+ chronic phase CML whose disease has recurred after stem cell transplant • Treatment of adult and pediatric individuals with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy • Adult individuals with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements • Adult individuals with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown • Adult individuals with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for individuals with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown • Adult individuals with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) or aggressive desmoid tumors • Single-agent therapy or in combination with cisplatin or sirolimus for the treatment of recurrent chordoma • Single-agent therapy for the treatment of Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor • Treatment of individuals with Kit (CD117) positive GIST, melanoma and other tumors • Treatment of individuals with Ph+ NHL – Lymphoblastic lymphoma



Drug	Medical Necessity
	<p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy.</p>
<p>Generic imatinib</p>	<p>Generic imatinib may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Treatment of adult and pediatric individuals with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase, accelerated phase or blast crisis • Treatment of pediatric individuals with Ph+ chronic phase CML whose disease has recurred after stem cell transplant • Treatment of adult and pediatric individuals with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy • Adult individuals with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements • Adult individuals with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown • Adult individuals with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for individuals with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown • Adult individuals with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) or aggressive desmoid tumors • Single-agent therapy or in combination with cisplatin or sirolimus for the treatment of recurrent chordoma • Single-agent therapy for the treatment of Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor • Treatment of individuals with Kit (CD117) positive GIST, melanoma and other tumors • Treatment of individuals with Ph+ NHL – Lymphoblastic lymphoma



Drug	Medical Necessity
Phyrago (dasatinib)	<p>Phyrago (dasatinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib for:</p> <ul style="list-style-type: none"> • Treatment of newly diagnosed adults with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase • Treatment of adults with chronic, accelerated, or blast phase Ph+ CML • Treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) <p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy.</p>
Sprycel (dasatinib)	<p>Sprycel (dasatinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib for:</p> <ul style="list-style-type: none"> • Treatment of newly diagnosed adults with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase • Treatment of adults with chronic, accelerated, or blast phase Ph+ CML • Treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) • Treatment of individuals with gastrointestinal stromal tumor (GIST) • Treatment of pediatric individuals with Ph+ CML in chronic phase <p>Sprycel (dasatinib) may be considered medically necessary for the treatment of newly diagnosed pediatric and adult individuals with Ph+ ALL in combination with chemotherapy.</p> <p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy.</p>



Drug	Medical Necessity
Scemblix (asciminib)	<p>Scemblix (asciminib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib and an additional tyrosine kinase inhibitor (e.g., bosutinib, dasatinib, nilotinib) for:</p> <ul style="list-style-type: none"> • Treatment of adults with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase <p>Scemblix (asciminib) may be considered medically necessary for the treatment of adults with:</p> <ul style="list-style-type: none"> • T315I-positive Ph+ CML in chronic phase <p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy. Individuals that have not demonstrated objective response to bosutinib, dasatinib, or nilotinib therapy after three months are considered resistant for purposes of prescribing Scemblix (asciminib).</p>
Tasigna (nilotinib)	<p>Tasigna (nilotinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib for:</p> <ul style="list-style-type: none"> • Treatment of adults with chronic, accelerated, or blast phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) • Treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) • Treatment of pediatric individuals greater than or equal to 1 year of age with Ph+ CML in chronic phase <p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy.</p>
Bosulif (bosutinib)	<p>Bosulif (bosutinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy for:</p> <ul style="list-style-type: none"> • Treatment of adults with accelerated or blast phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML)



Drug	Medical Necessity
	<ul style="list-style-type: none"> Treatment of individuals 1 year of age or older with chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) <p>Bosulif (bosutinib) may be considered medically necessary in individuals 1 year of age or older with newly diagnosed chronic phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+CML)</p> <p>Note: Individuals that have not demonstrated objective response to prior therapy after three months are considered resistant for purposes of prescribing an alternative therapy.</p>
Iclusig (ponatinib)	<p>Iclusig (ponatinib) may be considered medically necessary in individuals with resistance or intolerance to prior therapy with generic imatinib and an additional tyrosine kinase inhibitor (e.g., bosutinib, dasatinib, nilotinib) for:</p> <ul style="list-style-type: none"> Treatment of adults with chronic, accelerated, or blast phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) Treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) <p>Iclusig (ponatinib) may be considered medically necessary for the treatment of adults with:</p> <ul style="list-style-type: none"> T315I-positive chronic, accelerated, or blast phase Ph+ CML T315I-positive Ph+ ALL Newly diagnosed Ph+ ALL in combination with chemotherapy <p>Note: Individuals that have not demonstrated objective response to generic imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy. Individuals that have not demonstrated objective response to bosutinib, dasatinib, or nilotinib therapy after three months are considered resistant for purposes of prescribing Iclusig (ponatinib).</p>



Drug	Investigational
As listed	All other uses of the medications listed in this policy are considered investigational.

Length of Approval	
Approval	Criteria
Initial authorization	All drugs listed in policy may be approved up to 3 months.
Re-authorization criteria	Future re-authorization of all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Coding

N/A

Related Information

Benefit Application

This coverage is managed through the pharmacy benefit.

Evidence Review



Description

Cancer is characterized by the uncontrolled growth and spread of malignant cells. Nearly 1.4 million Americans will be diagnosed with cancer this year, and approximately 570,000 will die of the disease. The good news is, survival rates for cancer are on the rise, increasing from 50% to 64% over the last 30 years.

Conventional cytotoxic cancer chemotherapy has been one of the major medical advances realized in the last few decades. Although directed toward certain biologic targets thought to be involved in cellular growth and proliferation, typically they have not discriminated well between rapidly dividing normal cells (e.g., bone marrow, gastrointestinal tract) and tumor cells, frequently resulting in toxicities. In addition, tumor responses to traditional cytotoxic cancer chemotherapies can be unpredictable and brief.

"Targeted chemotherapies" (e.g., monoclonal antibodies, tyrosine kinase inhibitors, antisense inhibitors of growth factor receptors) are the newest therapeutic approach. These agents have been designed to interfere with molecular targets that have a role in tumor growth and progression (e.g., tyrosine kinase, vascular endothelial growth factor, epithelial growth factor, farnesyl transferase inhibition). There are typically more of these targets on or in tumor cells, thus these therapies are more attracted to tumor cells than to normal cells. The promise of these agents is that they will provide a broader therapeutic index with less toxicity. They may also be useful in combination with traditional cytotoxic chemotherapies, immunotherapies or radiation to produce additive or synergistic activity without overlap in toxicity profiles.

The Philadelphia Chromosome mutation was first described in 1960 as a translocation of parts of chromosomes 9 and 22. The result is that part of the BCR ("breakpoint cluster region") gene from chromosome 22 (region q11) is fused with part of the ABL gene on chromosome 9 (region q34). ABL stands for "Abelson", the name of a leukemia virus which carries a similar protein. The result of the translocation is a protein of p210 or sometimes p185 (p simply stands for "protein"; the numbers represent the apparent molecular weight of the mutant proteins in kDa [kilodaltons]). The fused "BCR-ABL" gene is located on the resulting, shorter chromosome 22. Because ABL carries a domain that can add phosphate groups to tyrosine residues (tyrosine kinase) the BCR-ABL fusion gene is also a tyrosine kinase. The BCR region is also a serine/threonine kinase.

The fused BCR-ABL protein interacts with the interleukin-3 receptor beta(c) subunit. The BCR-ABL transcript is constitutively active. In turn, BCR-ABL activates a number of cell cycle-controlling proteins and enzymes, speeding up cell division. Moreover, it inhibits DNA repair, causing genomic instability and potentially causing blast crisis in CML.



The BCR-ABL kinase inhibiting agents currently available are as follows:

Drug Name	Pharmacology	How Given	FDA-approved Uses
Bosulif (bosutinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML
Gleevec (imatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL, PDGFR-associated MDS/MPD, KIT+ (CD117) cancers
Iclusig (ponatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL
Scemblix (asciminib)	BCR-ABL kinase inhibitor with binding to ABL myristoyl pocket	Oral (Rx)	Philadelphia chromosome +CML
Sprycel (dasatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL, KIT+ GIST
Synribo (omacetaxine mepesuccinate)	BCR-ABL kinase inhibitor	SC (Rx)	Philadelphia chromosome +CML
Tasigna (nilotinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, KIT+ GIST

Gleevec (imatinib) is a protein-tyrosine kinase inhibitor that inhibits the BCR-ABL tyrosine kinase, the abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myelogenous leukemia (CML). This inhibition prevents proliferation and induces apoptosis of the abnormal cells. Gleevec is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), and c-kit. In vitro, Gleevec inhibits proliferation and induces apoptosis in gastrointestinal stromal tumors (GIST) cells, which express an activating c-kit mutation.

Sprycel (dasatinib) and nilotinib are inhibitors of multiple protein-tyrosine kinases, including BCR-ABL, SRC family, c-KIT, EPHA2 and PDGFR-beta). Based on modeling studies, Sprycel is predicted to bind to multiple conformations of the ABL kinase.

Scemblix (asciminib) is an ABL/BCR-ABL1 tyrosine kinase inhibitor. Asciminib inhibits the ABL1 kinase activity of the BCR-ABL1 fusion protein, by binding to the ABL myristoyl pocket. In studies conducted in vitro or in animal models of CML, asciminib showed activity against wild-type BCR-ABL1 and several mutant forms of the kinase, including the T315I mutation.

Gleevec, approved in 2001, revolutionized treatment of CML. The imatinib molecule fits tightly into the ATP binding site of the BCR-ABL tyrosine kinase, interfering with function of the abnormal protein. Thus it is called a BCR-ABL tyrosine kinase inhibitor or BCR-ABL TKI. Long term follow-up of some of the first imatinib individuals shows an 8-year event-free survival of 81%. However, 17% of individuals do not respond to imatinib, and of those that do, 15% later



lose their response. Primary resistance (failure to achieve remission in 3-6 months) may be caused by excessive plasma protein binding, or reduced drug transport into the cell. Secondary resistance is thought to be most commonly due to acquired mutations in the drug binding site of the BCR-ABL TK protein. Mutations in imatinib-resistant individuals have been mapped and sequenced. Second and third generation TKI's – dasatinib, nilotinib, later bosutinib, and most recently ponatinib - have been developed to overcome imatinib-resistant mutations. In vitro binding and growth inhibition studies for these drugs are available for an ever-increasing number of mutations.

There is increasing evidence that mutations in the BCR-ABL gene correspond to success or failure of different TKI's. However, this information has limits on clinical usefulness. Over 80% of individuals do well on first-line agents and do not harbor mutations. Of individuals that fail imatinib therapy, Parker et al. were able to detect mutations in 28% of individuals by sequencing, and 32% by mass spectrometry. Soverini et al. estimated that 29% of individuals with imatinib failure harbor a detectible mutation in the BCR-ABL binding site. Branford et al. report a 10-20% mutation detection rate by sequencing, and of those for whom a mutation was detected, 43% had a mutation that was useful to guide clinical decisions. Mutations are now detected in about half of imatinib resistant individuals, and of those mutations that are detected, 20-25% are useful for guiding treatment choice. Differences in defining treatment failure, as well as increasing numbers of mutations in advancing disease, may account for variability in reported percentages.

New methods of mutation detection are developing. Mass spectrometry can be used to identify mutations that are at too low a clonal level to be detected by sequencing. Denaturing high-performance liquid chromatography (D-HPLC) is also more sensitive but does not characterize the mutation, and may be used to screen samples before sequencing. A rapid PCR method is available to detect the T315I mutation, which is resistant to all TKI's except ponatinib. Whether individuals could be screened for this single mutation to guide therapy has not been tested.

Despite the wealth of information on mutations and in vitro sensitivity, there are no published prospective clinical trials on the clinical usefulness of mutational analysis to select a TKI. Studies to date are retrospective or observational. For example, in the phase II efficacy trial of Nilotinib in imatinib-resistant individuals, mutation data were collected at baseline and thereafter. Individuals who had no mutation detected, or mutations with high in vitro sensitivity to nilotinib, had a better response than those with mutations that were resistant to nilotinib in vitro (mutations Y253H, E255K/V, F359C/F). Omacetaxine, a protein translation inhibitor, has been approved by the FDA as second-line therapy, and other potential treatments for imatinib-resistant individuals are being tested.



As individuals who are successful on primary therapy are maintained for longer periods with molecular markers below the level of detection, the question has arisen as to whether they may actually be able to discontinue TKI therapy. In one pilot study, 100 individuals who had been on imatinib for >2 years with complete molecular response discontinued treatment. At one year, 41% remained in complete molecular response. All of the 69% that relapsed remained sensitive to imatinib.

Rationale

The effectiveness of Sprycel (dasatinib) is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. To date, Sprycel has been studied in four uncontrolled Phase II pivotal clinical trials and one Phase II pilot study in individuals in all phases of CML, as well as BCR-ABL+ (Ph+) ALL.

Two Phase II studies evaluated the efficacy and safety of Sprycel in individuals with chronic phase CML who were previously treated with Gleevec (imatinib). One randomized, non-comparative pilot study enrolled individuals (N=150) after failure of low-dose Gleevec (i.e., <600 mg/day). One other single-arm study enrolled individuals (N=186) who were resistant to or intolerant of Gleevec at any dose. The primary endpoint in both studies was the rate of major cytogenetic response (MCyR). In the pilot study, 35% of Sprycel-treated individuals achieved a MCyR at 12 weeks and 21% achieved a complete cytogenetic response (CCyR). In the single-arm study 39% of individuals achieved a MCyR.

Three single-arm Phase II studies were performed to evaluate the safety and efficacy of Sprycel in individuals with advanced stage CML and BCR-ABL+ (Ph+) ALL who were resistant to or intolerant of Gleevec. The primary endpoint in these studies was the rate of major hematologic response (MaHR) and overall hematologic response (OHR).

Sprycel was also evaluated in two pediatric studies which examined chronic phase CML in 97 total individuals. The first trial (N=51) examined newly diagnosed chronic phase CML individuals, while the 2nd trial (n=46) looked at individuals that were resistant or intolerant to imatinib. The studies both found increasing trends for CCyR, MCyR, and MMR across 3 to 24 months.

The safety and efficacy of nilotinib has been studied in one uncontrolled, open-label, phase II pivotal clinical trial in imatinib-resistant and -intolerant individuals with all phases of CML, as well as Ph+ ALL. Hematologic and cytogenetic response rates ranged from 16%-74%. In a preliminary report from another single-arm, open-label, phase II study, nilotinib has also shown activity in individuals with all phases of Ph+ CML and Ph+ ALL who were unresponsive or



intolerant to both imatinib and dasatinib. No controlled clinical trials for the agent are available at this time.

Although no head-to-head clinical trials between the second-generation TKIs nilotinib and dasatinib are available, their safety profiles appear to differ. Nilotinib notably carries a boxed warning for QT prolongation and sudden death and the need to take the drug on an empty stomach (avoid food two hours before and within one hour after dose). A greater incidence of grade 3/4 elevated serum lipase and electrolyte abnormalities were reported with nilotinib. While a greater incidence of grade 3/4 myelosuppression, bleeding-related events, and fluid retention were reported with dasatinib.

Management guidelines developed by the National Comprehensive Cancer Network (NCCN) recommend individuals with disease resistant to primary treatment with imatinib should be treated with bosutinib, dasatinib, or nilotinib in the second-line setting, taking into account BCR::ABL1 kinase domain mutation. For individual with disease resistant to primary treatment with bosutinib, dasatinib, or nilotinib can be treated with an alternative TKI (other than imatinib) in the second-line setting, taking into account BCR::ABL1 kinase domain mutation status.

NCCN Compendium and Other Practice Guidelines

The National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium is based directly on the NCCN Clinical Practice Guidelines in Oncology. The compendium lists specific panel recommendations for off-label uses of drugs, and each recommendation is supported by a level of evidence category.

The NCCN Categories of Evidence and Consensus used in the recommendations are:

- Category 1: The recommendation is based on high level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.
- Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.
- Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).
- Category 3: The recommendation is based on any level of evidence but reflects major disagreement.



In June 2008, the NCCN Compendium became one of four references for Centers for Medicare and Medicaid Services (CMS) for oncology coverage policy. In its national coverage decision CMS states that, in general, a use identified by the NCCN Compendium is medically accepted if the indication is a Category 1 or 2A as defined by NCCN. A use is not medically accepted if the indication is a Category 3 in NCCN. The local CMS contractor, Noridian Administrative Services (NAS), has issued an additional coverage statement regarding Category 2B:

NAS recognizes NCCN Categories of Evidence Levels Category 1 and Category 2A ONLY as medically accepted indications. If a provider chooses to use NCCN level 2B in support of a chemotherapeutic drug used off-label in an anti-cancer chemotherapeutic regimen, NAS expects that the provider will make available to NAS significant peer-reviewed Phase II or Phase III studies demonstrating such support. In the absence of such studies, level 2B evidence does not support such use.

2010 Update - The NCCN Drug Compendium

The Company recognizes indications and uses of drugs listed in the NCCN Drugs and Biologics Compendium with Categories of Evidence and consensus of 1 and 2A as proven and Categories of Evidence and Consensus of 2B and 3 as unproven. However, Category 2B uses may be considered for coverage if they are substantiated by provider submission of significant peer-reviewed Phase II or Phase III studies demonstrating treatment effectiveness.

This policy agrees with July 2010 NCCN Drugs and Biologics Compendium recommendations of 1 and 2A.

2011 Update

A literature search was conducted from October 2010 to September 2011. No major new developments were found.

Emerging evidence in CML individuals suggests that response rates can be increased by careful attention to therapeutic drug monitoring. Hehlmann and colleagues randomized 1014 newly-diagnosed CML individuals to receive 400mg/day, 800mg/day tolerability adjusted or 400mg/day plus alpha interferon. Individuals receiving the higher dose imatinib had a higher rate of MMR at 12 months than with imatinib 400 mg/d (59% [95% CI: 53% to 65%] v 44% [95% CI: 37% to 50%]; $P < .001$) or imatinib 400 mg/d plus IFN- α (59% v 46% [95% CI: 40% to 52%]; $P = .002$). Median dose in the 800-mg/d arm was 628 mg/d with a maximum dose of 737 mg/d



during months 4 to 6 and a maintenance dose of 600 mg/d. All three treatment approaches were well tolerated with similar grade 3 and 4 adverse events. The authors concluded that treatment of early-phase CML with imatinib can be optimized by giving early high-dose therapy followed by rapid adaptation to good tolerability. MMR at 12 months was strongly correlated with survival at 1 and 3 years.

2012 Update

A literature search was conducted from October 2011 to October 2012. No major new developments were found.

The TOPS trial published this year further elucidated the relationship between Imatinib trough plasma levels and achievement of complete cytogenetic response (CCyR) and major molecular response (MMR). The clinical significance of this in terms of practice changes remains to be assessed.

Ibrahim et al. demonstrated an incremental benefit from sequential administration of imatinib followed by one of the newer tyrosine kinase inhibitors after imatinib failure.

2013 Update

A complete review was prepared for the Pharmacy and Therapeutics Committee in January 2013. Focus was on the role of the newer agents in this class and the possibility of using genetic testing to predict resistance to imatinib or some of the other drugs in this class. Unfortunately, the technology was not sufficiently developed for use in routine clinical practice.

The medical necessity criteria for imatinib, dasatinib and nilotinib were updated to include currently labeled indications, and indications were added for bosutinib and ponatinib. These were also compared with current NCCN Compendium listings.

The European Leukemia Net (ELN) guidelines recommend imatinib as first-line therapy, with nilotinib or dasatinib as second line. Bosutinib and ponatinib have now also been approved as second-line agents.



2014 Update

A literature search was conducted from January 2013 to June 2014. No major new developments were found.

2015 Update

A literature search was conducted from June 2014 to May 2015. No major new developments were found. Reference list updated.

2016 Update

A literature search was conducted from July 1, 2015, to December 5, 2016,. No major new developments were found. Reference list updated.

2018 Update

Annual review, literature search from 5/1/2017 to 3/6/2018. Updated pediatric indication on dasatinib and revised wording in tables.

2019 Update

Reviewed prescribing information for all drugs and updated criteria for Tasigna (nilotinib) for use in pediatric individuals greater than or equal to 1 year of age with Ph+ CML in chronic phase.

2020 Update

Reviewed prescribing information for all drugs. Indications for Gleevec were updated in August 2020, but were already included in medical policy. No other new developments were found. Reference list updated.



2021 Update

Reviewed prescribing information for all drugs. Added to Iclusig (ponatinib) coverage for T315I-positive Ph+ CML and T315I-positive Ph+ ALL. Iclusig is the only TKI with significant activity against the T315I mutation. Added the standard Investigational and Length of Approval tables to policy. Captured information listed in a separate Additional Information table as a “Note” to applicable drugs in policy and deleted the Additional Information table.

2022 Update

Reviewed prescribing information for all drugs in policy. No new evidence was identified that required changes to coverage criteria.

2023 Update

Reviewed prescribing information for all drugs in policy. Updated Gleevec criteria to have trial and failure to generic imatinib. Added a new coverage criterion for generic imatinib. Updated Gleevec (imatinib) and generic imatinib criteria to update statement “Treatment of adult and pediatric individuals with Philadelphia Chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy” and Sprycel (dasatinib) criteria to include “Sprycel (dasatinib) may be considered medically necessary for the treatment of newly diagnosed pediatric and adult individuals with Ph+ ALL in combination with chemotherapy.” Updated Bosulif (bosutinib) criteria to include coverage for individuals 1 year of age or older with chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (CML) that is newly diagnosed or resistant or intolerant to prior therapy.

2024 Update

Reviewed prescribing information for all drugs in policy. Added coverage criteria for Phyrago (dasatinib). Removed Synribo (omacetaxine) coverage criteria as it has been withdrawn from the market. Clarified that the imatinib step therapy requirement is limited to generic imatinib for Sprycel (dasatinib), Scemblix (asciminib), Tassigna (nilotinib), and Iclusig (ponatinib). Updated Iclusig (ponatinib) to include coverage criteria for certain adults with newly diagnosed acute lymphoblastic leukemia.



References

1. Shah N, Rousselot P, Pasquini D et al. Dasatinib vs imatinib in patients with chronic phase chronic myeloid leukemia resistant to imatinib: results of the CA180017 START-R randomized trial [Presentation]. American Society of Clinical Oncology (ASCO) Annual Meeting. Atlanta, GA. June 2-6, 2006.
2. Hochhaus A, Baccarani M, Sawyers CL et al. Efficacy of dasatinib in patients with chronic phase Ph+ CML resistant or intolerant to imatinib: first results of the CA180013 START-C phase II study [Presentation]. American Society of Hematology (ASH) 47th Annual Meeting and Exposition. Atlanta, GA December 10-13, 2005.
3. Guilhot F, Apperley JF, Shah N et al. A phase II study of dasatinib in patients with accelerated phase chronic myeloid leukemia who are resistant or intolerant to imatinib: first results of the CA 18005 START-A study. American Society of Hematology (ASH) 47th Annual Meeting and Exposition. Atlanta, GA December 10-13, 2005.
4. Talpaz M, Rousselot P, Kim DW et al. A phase II study of dasatinib in patients with chronic myeloid leukemia in myeloid blast crisis: first results of the CA 180006 START-B study. American Society of Hematology (ASH) 47th Annual Meeting and Exposition. Atlanta, GA December 10-13, 2005.
5. Ottmann OG, Martinelli G, Dombret H et al. A phase II study of dasatinib in patients with chronic myeloid leukemia in lymphoid blast crisis: the START-L CA 180015 study. American Society of Hematology (ASH) 47th Annual Meeting and Exposition. Atlanta, GA December 10-13, 2005.
6. Sprycel (dasatinib) Prescribing Information. Bristol Myers Squibb. Princeton, NJ. Revised February 2023.
7. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Chronic Myeloid Leukemia. V.1.2023. Available at: http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf Accessed April 2, 2024.
8. National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Drug and Biologics Compendium Available at: <http://www.nccn.org/> Accessed April 2, 2024.
9. Hehlmann R, Lauseker M, Jung-Munkwitz S, et al. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon- α in newly diagnosed chronic myeloid leukemia. *J Clin Oncol.* 2011 Apr 20;29(12):1634-42.
10. Guilhot F, Hughes TP, Cortes J, et al. Plasma exposure of imatinib and its correlation with clinical response in the Tyrosine Kinase Inhibitor Optimization and Selectivity Trial. *Haematologica* 2012;97(5):731-8. Ibrahim AR, Clark RE, Holyoake TL, et al. Second generation tyrosine kinase inhibitors improve the survival of patients with chronic myeloid leukemia in whom imatinib therapy has failed. *Haematologica* 2011;96(12):1779-82.
11. Deininger M, O'Brien SG, Guilhot F, et al. International randomized study of interferon vs. STI571 (IRIS) 8-year follow up: sustained survival and low risk for progression or events in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) treated with imatinib [abstract]. *Blood* 2009;114. Abstract 1126.
12. Jelinek J, Gharibyan V, Estecio M, et al. Aberrant DNA methylation is associated with disease progression, resistance to imatinib and shortened survival in chronic myelogenous leukemia. *PLoS One.* 2011;6(7):e22110.
13. Apperley JF. Mechanisms of resistance to imatinib in chronic myeloid leukaemia. *Lancet Oncol* 2007;8(11):1018-29.
14. Parker WT, Lawrence RM, Ho M et al. Sensitive detection of BCR-ABL1 mutations in patients with chronic myeloid leukemia after imatinib resistance is predictive of outcome during subsequent therapy. *J Clin Oncol.* 2011 Nov 10;29(32):4250-9.
15. Soverini S, Hochhaus A, Nicolini FE, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood* 2011 118:1208-1215.



16. Branford S, Melo JV, Hughes TP. Selecting optimal second-line tyrosine kinase inhibitor therapy for chronic myeloid leukemia patients after imatinib failure: does the BCR-ABL mutation status really matter? *Blood* 2009; 114(27):5426-5435.
17. Schumacher JA, Szankasi P, Bahler DW, et al. A pyrosequencing-based test for detection and relative quantification of the BCR-ABL1 T315I point mutation. *J Clin Pathol* 2011; 64:618-25.
18. Hughes T, Saglio G, Branford S, et al. Impact of baseline BCR-ABL mutations on response to nilotinib in patients with chronic myeloid leukemia in chronic phase. *J Clin Oncol* 2009; 27:4204-4210.
19. Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010 Nov;11(11):1029-35.
20. European LeukemiaNet. Available at: <https://www.leukemia-net.org> Accessed April 2, 2024.
21. Hanfstein B, Müller MC, Hochhaus A. Response-related predictors of survival in CML. *Ann Hematol*. 2015 Apr;94 Suppl 2:S227-39.
22. Mahon FX. Discontinuation of tyrosine kinase inhibitor therapy in CML. *Ann Hematol* 2015 Apr;94 Suppl 2:S187-93.
23. Hochhaus A, Ernst T, Eigendorff E, et al. Causes of resistance and treatment choices of second- and third-line treatment in chronic myelogenous leukemia patients. *Ann Hematol*. 2015 Apr;94 Suppl 2:S133-40.
24. Casado LF, García-Gutiérrez JV, Massagué I, et al. Switching to second-generation tyrosine kinase inhibitor improves the response and outcome of frontline imatinib-treated patients with chronic myeloid leukemia with more than 10% of BCR-ABL/ABL ratio at 3 months. *Cancer Med*. 2015 Mar 10. doi: 10.1002/cam4.440. [Epub ahead of print]
25. Brümmendorf TH, Cortes JE, de Souza CA, et al. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. *Br J Haematol*. 2015 Jan;168(1):69-81.
26. Deininger MW, Kopecky KJ, Radich JP, et al. Imatinib 800 mg daily induces deeper molecular responses than imatinib 400 mg daily: results of SWOG S0325, an intergroup randomized PHASE II trial in newly diagnosed chronic phase chronic myeloid leukaemia. *Br J Haematol*. 2014 Jan;164(2):223-32.
27. Reviewed by Company Pharmacy and Therapeutics Committee (P&T) on March 7, 2013; May 2014; May 2015.
28. Soverini, et al. In Chronic Myeloid Leukemia Patients on Second-line Tyrosine Kinase Inhibitor Therapy, Deep Sequencing of BCR=ABL1 at the Time of Warning May Allow Sensitive Detection of Emerging Drug-Resistant Mutants. *BMC Cancer*. Aug 2, 2016. doi: 10.1186/s12885-016-2635-0.
29. Tekgunduz E, et al. Adult Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in Daily Practice: A Multicenter Experience. *Clin Lymphoma Myeloma Leuk*. May, 2016. doi: 10.1016/j.clml.2016.01.007. Epub 2016 Feb 4.
30. Inklusig (ponatinib) Prescribing Information. Takeda Pharmaceutical Company Limited. Cambridge, MA. Revised March 2024.
31. Bosulif (bosutinib) Prescribing Information. Pfizer Inc. New York, NY. Revised September 2023.
32. Tasigna (nilotinib) Prescribing Information. Novartis. East Hanover, NJ. Revised February 2024.
33. Gleevec (imatinib) Prescribing Information. Novartis. East Hanover, NJ. Revised March 2024.
34. Scemblix (asciminib) Prescribing Information. Novartis. East Hanover, NJ. Revised November 2023.
35. Synribo (omacetaxine mepesuccinate) Prescribing Information. Teva. North Wales, PA. Revised May 2021.
36. Imatinib Mesylate. Prescribing Information. Sun Pharmaceutical Industries, Inc. Cranbury, NJ. Revised November 2018.
37. Phyrago (dasatinib) Prescribing Information. Nanocopoeia LLC. New Brighton, MN. Revised December 2023.

History



Date	Comments
08/12/08	Add to Prescription Drug Section - New PR policy.
12/16/08	Minor Update - Corrected table under description.
12/08/09	Replace Policy - Additional wording regarding NCCN added to Description and Rationale. No change to policy statements. Reference added.
11/09/10	Replace Policy - Reviewed by OAP in August 2010 – The policy statement has been reworded for purposes of clarification, listing the specific types of tumors covered under the medically necessary indication; the intent remains the same. A literature review was conducted; references added. Reviewed by P&T in September 2010.
11/10/11	Replace Policy – Policy updated with literature review; no change in policy statement. Reference 11 added. Reviewed by P&T on September 27, 2011.
11/13/12	Replace policy. Policy updated with literature review; no change in policy statements. References 12 and 13 added.
03/11/13	Replace policy. Policy section updated with medically necessary statements for dasatinib, dasatinib, nilotinib and omacetaxine. The medical necessity criteria for imatinib, dasatinib and nilotinib were updated to include currently labeled indications, and indications were added for bosutinib and ponatinib. Policy Guidelines and Rationale sections updated; references added. Reviewed by P&T on March 7, 2013. HCPCS codes C9297, 9399 and J9999 added.
08/15/13	Update Related Policies. Add 5.01.534.
12/06/13	Update Related Policies. Add 5.01.544.
07/31/14	Annual review. Policy updated with literature review. No change in policy statements.
12/03/14	Update Related Policies. Add 5.01.517.
06/09/15	Annual review. Policy updated with literature review. No change in policy statements.
01/01/17	Annual review, changes approved December 13, 2016. Policy updated with literature review. No change in policy statements. Note added that coverage is managed through the Pharmacy benefit.
05/01/17	Annual Review, changes approved April 11, 2017. A statement outlining the length of therapy for initial and subsequent approval has been added to the policy.
10/24/17	Policy moved to new format; no change to policy statements.
05/01/18	Annual Review, approved April 3, 2018. Literature search from 5/1/2017 to 3/6/2018. Updated pediatric indication on dasatinib and revised wording in tables. Removed HCPCS codes J8999, J9999, and S0088 (oral) from policy.
03/01/19	Interim Review, approved February 12, 2019. Updated criteria for dasatinib.
05/01/19	Annual Review, approved April 9, 2019. Updated criteria for Tasigna (nilotinib).



Date	Comments
10/01/20	Annual review, approved September 17, 2020. No change to policy statements.
02/01/21	Annual Review, approved January 6, 2021. Added to Iclusig (ponatinib) coverage for T315I-positive Ph+ CML and T315I-positive Ph+ ALL.
02/01/22	Interim Review, approved January 11, 2022. Added coverage criteria for Scemblix (asciminib) for the treatment of Ph+ CML in chronic phase after intolerance to prior therapy with imatinib and an additional tyrosine kinase inhibitor and for the treatment of Ph+ CML in chronic phase with the T315I mutation.
01/01/23	Annual Review, approved December 23, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
08/01/23	Annual Review, approved July 11, 2023. Reviewed prescribing information for all drugs in policy. Updated Gleevec criteria to have trial and failure to generic imatinib. Added a new coverage criterion for generic imatinib. Updated Gleevec (imatinib) and generic imatinib criteria to update statement "Treatment of adult and pediatric individuals with Philadelphia Chromosome positive acute lymphoblastic leukemia (Ph+ ALL) in combination with chemotherapy" and Sprycel (dasatinib) criteria to include "Sprycel (dasatinib) may be considered medically necessary for the treatment of newly diagnosed pediatric and adult individuals with Ph+ ALL in combination with chemotherapy."
12/01/23	Interim Review, approved November 14, 2023. Updated Bosulif (bosutinib) criteria to include coverage for individuals 1 year of age or older with chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia (CML) that is newly diagnosed or resistant or intolerant to prior therapy.
05/01/24	Annual Review, approved April 9, 2024. Added coverage criteria for Phyrago (dasatinib). Removed Synribo (omacetaxine) coverage criteria as it has been withdrawn from the market. Clarified that the imatinib step therapy requirement is limited to generic imatinib for Sprycel (dasatinib), Scemblix (asciminib), Tasisa (nilotinib), and Iclusig (ponatinib). Updated Iclusig (ponatinib) to include coverage criteria for certain adults with newly diagnosed acute lymphoblastic leukemia.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member



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Language Assistance

- ATENCIÓN:** si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 844-722-4661 (TTY: 711).
- 注意:** 如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 844-722-4661 (TTY: 711)。
- CHÚ Ý:** Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 844-722-4661 (TTY: 711).
- 주의:** 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 844-722-4661 (TTY: 711) 번으로 전화해 주십시오.
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- XIYYEEFFANNA:** Afaan dubbattu Oroomiffa, tajaajjila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 844-722-4661 (TTY: 711).
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- ACHTUNG:** Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 844-722-4661 (TTY: 711).
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