

PHARMACY POLICY – 5.01.518

BCR-ABL Kinase Inhibitors


Effective Date: May 1, 2018
 Last Revised: April 3, 2018
 Replaces: N/A

RELATED MEDICAL POLICIES:

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

Select a hyperlink below to be directed to that section.

[POLICY CRITERIA](#) | [CODING](#) | [RELATED INFORMATION](#)
[EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

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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

Note: Initial approval period for agents listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy.

Drug	Medical Necessity
Gleevec® (imatinib)	<p>Gleevec® (imatinib) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Treatment of adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase, accelerated phase or blast crisis; • Treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant; • Treatment of adult and pediatric patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL); • Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements; • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown; • Adult patients 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 patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown; • Adult patients 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 patients with Kit (CD117) positive GIST, melanoma and other tumors; • Treatment of patients with Ph+ NHL – Lymphoblastic lymphoma.
Sprycel® (dasatinib)	<p>Sprycel® (dasatinib) may be considered medically necessary in</p>



Drug	Medical Necessity
	<p>patients with resistance or intolerance to prior therapy with 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 patients with gastrointestinal stromal tumor (GIST) • Treatment of pediatric patients with Ph+CML in chronic phase
Tasigna® (nilotinib)	<p>Tasigna® (nilotinib) may be considered medically necessary in patients with resistance or intolerance to prior therapy with 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)
Bosulif™ (bosutinib)	<p>Bosulif™ (bosutinib) may be considered medically necessary in patients with resistance or intolerance to prior therapy with imatinib for treatment of adults with chronic, accelerated, or blast phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML).</p>
Iclusig™ (ponatinib)	<p>Iclusig™ (ponatinib) may be considered medically necessary in patients with resistance or intolerance to prior therapy with imatinib and an additional tyrosine kinase inhibitor (eg, dasatanib, nilotinib, and bosutinib) for:</p> <ul style="list-style-type: none"> • Treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+CML) • Treatment of adults with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
Synribo™ (omacetaxine)	<p>Synribo™ (omacetaxine) may be considered medically necessary in adult patients with resistance or intolerance to prior therapy with imatinib and an additional tyrosine kinase inhibitor (eg, dasatanib, nilotinib, bosutinib, ponatinib) for the treatment of chronic or accelerated phase chronic myeloid</p>



Drug	Medical Necessity
	leukemia.

Additional Information

Imatinib (Gleevec®)
 Patients that have not demonstrated objective response to imatinib therapy after three months are considered imatinib-resistant for purposes of prescribing an alternative therapy.

Bosulif™ (bosutinib), Iclusig™ (ponatinib), Sprycel® (dasatinib), Tasigna® (nilotinib)
 Patients that have not demonstrated objective response to bosutinib, dasatinib, or nilotinib therapy after three months are considered resistant for purposes of prescribing ponatinib therapy.

All other uses of imatinib, dasatinib, nilotinib, bosutinib, ponatinib, and omacetaxine not encompassed within this policy are considered investigational.

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 (eg, 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” (eg, 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 (eg, 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
Gleevec® (imatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL, PDGFR-



Drug Name	Pharmacology	How Given	FDA-approved Uses
			associated MDS/MPD, KIT+ (CD117) cancers
Sprycel® (dasatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL, KIT+ GIST
Tasigna® (nilotinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, KIT+ GIST
Bosulif™ (bosutinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML
Iclusig™ (ponatinib)	BCR-ABL kinase inhibitor	Oral (Rx)	Philadelphia chromosome +CML, ALL

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.

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 patients shows an 8-year event-free survival of 81%. However, 17% of patients 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 patients 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 patients do well on first-line agents and do not harbor mutations. Of patients that fail imatinib therapy, Parker et al. were able to detect mutations in 28% of patients by sequencing, and 32%



by mass spectrometry. Soverini et al. estimated that 29% of patients with imatinib failure harbor a detectable 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 patients, 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 patients 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 patients, mutation data were collected at baseline and thereafter. Patients 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 recently approved by the FDA as second-line therapy, and other potential treatments for imatinib-resistant patients are being tested.

As patients 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 patients 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 patients in all phases of CML, as well as BCR-ABL+ (Ph+) ALL.

Two Phase II studies evaluated the efficacy and safety of Sprycel® in patients with chronic phase CML who were previously treated with Gleevec® (imatinib). One randomized, non-comparative pilot study enrolled patients (N=150) after failure of low-dose Gleevec® (ie, <600 mg/day). One other single-arm study enrolled patients (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 patients achieved a MCyR at 12 weeks and 21% achieved a complete cytogenetic response (CCyR). In the single-arm study 39% of patients achieved a MCyR.

Three single-arm Phase II studies were performed to evaluate the safety and efficacy of Sprycel® in patients 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 patients. The first trial (N=51) examined newly diagnosed chronic phase CML patients, while the 2nd trial (n=46) looked at patients 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 patients 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 patients 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 use of either dasatinib or nilotinib in patients with imatinib-resistant or –intolerant Ph+ CML (all phases).

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 (eg, 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 is in agreement 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 patients suggests that response rates can be increased by careful attention to therapeutic drug monitoring. Hehlmann and colleagues randomized 1014 newly-diagnosed CML patients to receive 400mg/day, 800mg/day tolerability adjusted or 400mg/day plus alpha interferon. Patients 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.

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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.



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). ©2018 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 benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
 - Qualified sign language interpreters
 - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
 - Qualified interpreters
 - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀናት ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحتوي هذا الإشعار على معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تاريخ معينه للحفاظ على تغطيتك الصحية أو المساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):

Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):

Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):

Tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):

Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):

この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):

본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈ້ງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកកាមរយ: Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងដូចជា ធានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਕੱਠ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).