


PHARMACY / MEDICAL POLICY – 5.01.603

Epidermal Growth Factor Receptor (EGFR) Inhibitors

Effective Date:	April 1, 2019	RELATED MEDICAL POLICIES:
Last Revised:	March 19, 2019	5.01.517 Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Patients
Replaces:	N/A	5.01.518 BCR-ABL Kinase Inhibitors
		5.01.534 Multiple Receptor Tyrosine Kinase Inhibitors
		5.01.544 Prostate Cancer Targeted Therapies
		501.549 Off-Label Use of Drugs and Biologic Agents

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Introduction

Genes contain instructions for how a cell makes proteins. Proteins drive the functions within a cell. The EGFR gene produces a protein called epidermal growth factor, which instructs the cells to grow and divide. Changes to the EGFR gene, however, can result in too much EGFR protein. Too much EGFR protein causes cells to grow uncontrollably, leading to tumors. An EGFR inhibitor is a type of biological therapy that might stop cancer cells from growing. This policy discusses when EGFR 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 oral drugs listed below will be 3 months. Continued approval beyond the first 3 months will require documentation showing objective response to therapy.

Note: Initial approval period for injectable drugs listed below will be 12 months.

Small Molecule EGFR inhibitors

Drug	Medical Necessity
Oral Drugs	
Gilotrif® (afatinib)	<p>Gilotrif® (afatinib) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant epidermal growth factor receptor (EGFR) • Treatment of patients with metastatic, squamous NSCLC progressing after platinum-based chemotherapy <p>Note: Safety and efficacy of Gilotrif were not established in patients whose tumors have resistant EGFR mutations.</p>
Iressa® (gefitinib)	<p>Iressa® (gefitinib) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations <p>Note: Safety and efficacy of Iressa were not established in patients whose tumors have resistant EGFR mutations.</p>
Tagrisso® (osimertinib)	<p>Tagrisso® (osimertinib) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • Treatment of patients with metastatic non-small cell lung cancer (NSCLC) that have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations • The treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, whose disease has progressed on or after EGFR TKI therapy
Tarceva® (erlotinib)	<p>Tarceva® (erlotinib) may be considered medically necessary for:</p>



Drug	Medical Necessity
	<ul style="list-style-type: none"> Treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations receiving first-line, maintenance, or second or greater line treatment after progression following at least one prior chemotherapy regimen. <ul style="list-style-type: none"> Tarceva is not recommended for use in combination with platinum-based chemotherapy First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. <p>Note: Safety and efficacy of Tarceva were not established in patients with NSCLC whose tumors have other EGFR mutations.</p>
Vizimpro® (dacomitinib)	<p>Vizimpro® (dacomitinib) may be considered medically necessary for:</p> <ul style="list-style-type: none"> First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations. <p>Note: Safety and efficacy of Vizimpro were not established in patients whose tumors have resistant EGFR mutations.</p>

Investigational

All other uses of erlotinib, afatinib, gefitinib, dacomitinib and osimertinib not listed above are considered investigational.

Monoclonal Antibodies to EGFR Receptors

Drug	Medical Necessity
Injectable Drugs	
Erbitux® (cetuximab)	<p>Erbitux® (cetuximab) may be considered medically necessary for:</p> <ul style="list-style-type: none"> The treatment of unresectable, advanced, or metastatic



Drug	Medical Necessity
	<p>colorectal cancer (mCRC) when patient has not had prior panitumumab (Vectibix) therapy and when used:</p> <ul style="list-style-type: none"> ○ As a single agent in first or later line of therapy for documented KRAS and RAS wild-type mCRC <p>OR</p> <ul style="list-style-type: none"> ○ In combination with the FOLFIRI regimen in first or later line of therapy for documented KRAS and RAS wild-type mCRC <ul style="list-style-type: none"> • The treatment of locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) and when used: <ul style="list-style-type: none"> ○ In combination with radiation therapy <p>OR</p> <ul style="list-style-type: none"> ○ As a single agent in patients with prior radiation therapy for SCCHN who have either a local regional recurrence or distant metastases or both <p>OR</p> <ul style="list-style-type: none"> ○ As a single agent or in combination with a platinum based regimen for recurrent, second primary or metastatic SCCHN <ul style="list-style-type: none"> • The treatment of squamous cell carcinoma of the skin as a single agent for recurrent or distant metastases
Vectibix® (panitumumab)	<p>Vectibix® (panitumumab) may be considered medically necessary for:</p> <ul style="list-style-type: none"> • The treatment of unresectable or advanced mCRC when patient has not had prior cetuximab (Erbix) therapy and when used as a single agent in first or later line of therapy for documented KRAS and RAS wild-type mCRC <p>OR</p> <ul style="list-style-type: none"> • Second line therapy treatment of metastatic penile squamous cell carcinoma

Investigational

Use of Erbitux® (cetuximab) and Vectibix® (panitumumab) to treat other types of solid tumors and hematological malignancies not listed above is considered investigational.

Analysis	Medical Necessity
K-RAS mutation analysis	K-RAS mutation analysis may be considered medically



Analysis	Medical Necessity
	<p>necessary for predicting treatment response.</p> <p>Note: See the Erbix® (cetuximab) and Vectibix® (panitumumab) sections above.</p>
BRAF	<p>BRAF mutation analysis may be considered medically necessary to predict nonresponse in the treatment of metastatic colorectal cancer.</p>

Coding

Code	Description
HCPCS	
J9055	Injection, cetuximab (Erbix), 10 mg
J9303	Injection, panitumumab (Vectibix), 10mg
J9999	Not otherwise classified, antineoplastic drugs

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

The age for which Tagrisso® (osimertinib) is considered medically necessary in this policy is 18. This is because the safety and effectiveness of Tagrisso® in pediatric patients has not been established.

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, small molecule tyrosine kinase inhibitors) are the newest therapeutic approach. These agents have been designed to interfere with Epidermal Growth Factor Receptor proteins, which are molecular targets that have a role in tumor growth and progression. These target proteins are typically preferentially expressed in tumor cells, thus these therapies have a higher specificity for these cells than for normal tissues. The promise of these agents is 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 epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). EGFR plays a critical role in the modulation of growth factor signaling. The binding of a ligand such as epidermal growth factor to EGFR induces phosphorylation of several tyrosine residues near the C-terminal end of the EGFR protein and subsequent activation of several tyrosine kinase signal pathways such as the MAPK, Akt and JNK pathways. The induction of these signaling cascades enhances activities such as up regulation of RAS, RAF and mitogen-activated phosphorylation (MAP) which develop cellular growth and invasive capacity. EGFR activation also stimulates vascular endothelial growth factor (VEGF), which is the primary inducer of angiogenesis. As solid tumors cannot grow without the nutritional support provided by a blood supply, angiogenesis plays a key role in progression of these tumors. This feature makes the ErbB family of receptor proteins natural targets for development of novel antitumor compounds.



EGFR overexpression has been identified in a variety of solid tumors (eg, colorectal, lung, breast, kidney, liver). Furthermore, increasing VEGF levels have been correlated with poor prognosis in many of these same pathologies. As a result, EGFR, tyrosine kinase, and VEGF inhibitors have been developed and investigated for the treatment of these conditions. However, much remains to be learned regarding the rational integration of these therapies into cancer treatment regimens and methods to optimize the selection of patients most likely to benefit.

KRAS/BRAF

The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. RAS proteins are G-proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The GTPase KRas (KRAS) gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. KRAS mutations are found in approximately 30–50% of colorectal cancer tumors and are common in other tumor types.

Serine/threonine-protein kinase B-Raf (BRAF) encodes a protein kinase, and is involved in intracellular signaling and cell growth and is a principal downstream effector of KRAS. BRAF mutations occur in less than 10–15% of colorectal cancers, and appear to be a marker of poor prognosis.

Recent studies have discovered that EGFR inhibition is not effective in treating tumors that have a mutation in the K-RAS gene. It is thought that the mutant gene is in an activated state and therefore does not require signal initiation from the EGF Receptor, which is located earlier in the signaling pathway.

However, there are still patients with KRAS wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, BRAF mutations are now increasingly being investigated in metastatic colorectal cancer. KRAS and BRAF mutations are considered to be mutually exclusive.

The EGFR inhibiting agents currently available are as follows:

Drug Name	Pharmacology	How Given	FDA-Approved Uses
Small Molecules (acting inside the cell)			
Erlotinib (Tarceva®)	EGFR tyrosine	Oral (Rx)	* NSCLC, pancreatic cancer



Drug Name	Pharmacology	How Given	FDA-Approved Uses
Gefitinib (Iressa®)	kinase inhibitor	--	NSCLC
Osimertinib (Tagrisso®)	kinase inhibitor	Oral (Rx)	NSCLC
Monoclonal Antibodies (acting at the cell membrane surface)			
Cetuximab (Erbix®)	EGFR tyrosine	IV (Clinic)	Metastatic *CRC, Head/Neck
Panitumumab (Vectibix®)	kinase MAb	IV (Clinic)	Metastatic CRC

*NSCLC – Non-small cell lung cancer

*RCC – Renal cell carcinoma

*HCC – Hepatocellular carcinoma

*GIST – Gastrointestinal stromal tumor

*CRC – Colorectal cancer

One small molecule EGFR tyrosine kinase inhibitor is currently approved for use in the United States. Erlotinib (Tarceva®) is approved for the treatment of patients with metastatic NSCLC. Although its mechanism of action is not fully characterized, it is believed to selectively and reversibly inhibit the intracellular phosphorylation of EGFR tyrosine kinase. EGFR is expressed in NSCLC, as well as numerous other solid tumors.

Two additional growth factor inhibitors differ mechanistically from these, in that they are monoclonal antibodies to the receptors:

- Erbitux® (cetuximab) is a recombinant chimeric monoclonal antibody that binds and inhibits human epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on normal and tumor cells. This binding prevents the phosphorylation and activation of kinases, resulting in the inhibition of cell growth, induction of apoptosis, and decrease in VEGF production.
- Vectibix® (panitumumab) is a recombinant fully human monoclonal antibody that binds and inhibits human epidermal growth factor receptor (EGFR). It is produced in genetically engineered Chinese Hamster ovary cells.

NCCN Compendium

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.

Lung Cancer

Non-small cell lung cancer (NSCLC) is potentially curable if diagnosed early (Stage I or II). Unfortunately, approximately 75% of cases are not identified until the patient has locally advanced or metastatic disease (ie, Stage III or IV). Overall five year survival is only about 15%.

Two chemotherapy agents (doublet) are recommended by NCCN for first-line therapy of patients with advanced NSCLC and good performance status (ie, ECOG performance status 0-2). Patients with poor performance status (ie, 3 or 4) generally do not benefit from chemotherapy. Specifically, platinum-based regimens are recommended. Newer agents in combination with platinum agents have generated a plateau in overall response rate (ORR) of $\geq 25\text{-}35\%$, time to progression (TTP) of four to six months, median survival of eight to 10 months, and one-year survival of 30-40%. None of these newer combinations has been shown to be clearly superior.

As understanding of the pathophysiology of NSCLC has improved, and because most patients with advanced disease continue to progress following first-line chemotherapy and ultimately die within a year, newer therapies have been developed that have demonstrated value in prolonging survival in this setting. Single-agent docetaxel is considered the standard for comparison for second-line therapy of advanced or recurrent metastatic NSCLC. A large randomized head-to-head study showed pemetrexed 500 mg/m² provided similar response and survival rates with less severe adverse events and fewer hospitalizations compared to docetaxel 75 mg/m².



Iressa® (gefitinib)

The safety of Iressa® (gefitinib) is based on the data from 2462 patients with NSCLC who received IRESSA 250 mg daily monotherapy in three randomized clinical studies (Study 2, Study 3 and Study 4). Patients with a history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis that required steroid treatment or any evidence of clinically active interstitial lung disease were excluded from these studies.

Study 2 was a randomized, multicenter, open-label trial in which 1217 patients were randomized to receive first-line treatment for metastatic NSCLC; 607 patients received IRESSA 250 mg daily and 589 patients received carboplatin/paclitaxel. The median duration of treatment with IRESSA was 5.9 months. The study population characteristics were: median age 57 years, age less than 65 years (73%), female (79%), Asian (100%), NSCLC adenocarcinoma histology (100%), never smoker (94%), light ex-smoker (6%), ECOG PS 0 or 1 (90%).

Study 3 was a randomized, multicenter, double-blind, placebo-controlled trial in which 1692 patients were randomized to receive second- or third-line treatment for metastatic NSCLC; of which 1126 patients received IRESSA 250 mg daily and 562 patients received placebo. The median duration of treatment with IRESSA was 2.9 months. The study population characteristics were: median age 62 years, age less than 65 years (60%), female (33%), Caucasian (75%), Asian (21%), NSCLC adenocarcinoma histology (48%), never smoker (22%), ECOG PS 0 or 1 (65%), PS 2 (29%), PS 3 (5%) and two or more prior therapies (51%).

Study 4 was a randomized, multicenter, open-label trial in which 1466 patients were randomized to receive second-line treatment for metastatic NSCLC; 729 patients received IRESSA 250 mg daily and 715 patients received docetaxel. The median duration of treatment with IRESSA was 2.4 months. The study population characteristics were: median age 61 years, age less than 65 years (61%), female (36%), Caucasian (79%), Asian (21%), NSCLC adenocarcinoma histology (54%), never smoker (20%), ECOG PS 0 or 1 (88%) and two or more prior therapies (16%).

The pooled safety database from the three randomized trials was used to evaluate for serious and uncommon adverse drug reactions. Common adverse reactions were evaluated in Study 3. The most frequent adverse reactions in Study 3 (incidence of >20% and greater than placebo) reported in IRESSA-treated patients were skin reactions (47%) and diarrhea (29%). The most frequent fatal adverse reactions in IRESSA-treated patients were respiratory failure (0.9%), pneumonia (0.8%), and pulmonary embolism (0.5%).

Approximately 5% of IRESSA-treated patients and 2.3% of placebo-treated patients discontinued treatment due to an adverse event. The most frequent adverse reactions that led



to discontinuation in patients treated with IRESSA were nausea (0.5%), vomiting (0.5%) and diarrhea (0.4%).

Tarceva® (erlotinib)

Tarceva® (erlotinib) has proven survival benefit as a second- or third-line therapy for the treatment of patients with chemotherapy refractory (typically a platinum-based regimen) advanced or recurrent metastatic NSCLC compared to basic supportive care. It has a unique and milder side effect profile compared with traditional cytotoxics (eg, docetaxel) recommended for use in this setting. It also offers the convenience and potential advantages of oral versus invasive administration as a second-line therapy.

Use of Erbitux® (cetuximab), a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), has the potential to increase survival in patients with advanced NSCLC. In a 1125 patient multinational, multicenter, open-label, phase 3 trial, chemotherapy-naïve patients with advanced EGFR-expressing histologically or cytologically proven Stage IIIIB or Stage IV NSCLC were randomly assigned in a 1:1 ratio to chemotherapy plus cetuximab (n=557) or just chemotherapy (n=568). Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group.

A retrospective study of patients treated with first-line chemotherapy with and without erlotinib found that the median overall survival for all patients with mutations was significantly better (>20 months, P<.001) than overall survival for patients without mutations (10 months).

Gilotrif® (afatinib)

One single arm phase II study and two phase III open label studies compared Gilotrif® (afatinib) with standard chemotherapies as a first line treatment for patients with advanced or metastatic NSCLC. All patients were newly diagnosed, treatment naïve, stage IIIIB or IV with activating EGFR mutations. The results showed modest efficacy of afatinib compared with standard chemotherapy. There are no comparative efficacy data for afatinib vs. previous TKIs in common mutations (exon 19 deletion/L858R), or in preventing T790M resistance.

In the LUX-Lung 3 study, afatinib significantly prolonged PFS (11.1 months) vs. cisplatin/pemetrexed (6.9 month) (HR: 0.58 [95% CI: 0.43, 0.78]; P<0.001), but not overall survival. Median PFS was longer (13.6 months, HR: 0.47 [95% CI: 0.34, 0.65]; P<0.0001) with common EGFR mutations (Del19 and L858R). Afatinib significantly delayed the time to



deterioration for cough (HR: 0.60 [95% CI 0.41 to 0.87]; P= 0.007) and dyspnea (HR: 0.68 [95% CI 0.50 to 0.93]; P =0.015), but not pain (HR: 0.83 [95% CI 0.62 to 1.10]; P =0.19). However, the study included no maintenance therapy in chemotherapy group, and there was potential investigator bias due to the awareness of new NCCN guidelines and high cross over rates.

The LUX-Lung 6 study compared efficacy and safety of afatinib to gemcitabine/cisplatin as first-line treatment in an Asian population with EGFR positive mutations. The design and results were similar to LUX-Lung 3. Afatinib prolonged PFS as compared to gemcitabine/cisplatin (11 months vs. 5.6 months, HR 0.28 [95% CI 0.20, 0.39]; P=0.0001). LUX-Lung 2 is a single arm, phase II study of afatinib as first and second line therapy in patients from Taiwan and USA. Two doses of afatinib (50 mg and 40 mg) were tested in this study. The results were similar compared to LUX-Lung 3 and LUX-Lung 6: ORR was 61%, median PFS was 10.1 month and overall survival was 24.8 months for all patients.

The most common adverse events (AE) with afatinib were diarrhea (95.2%), rash (90%), dryness, and irritation of the skin, mucosa and nails. Although the discontinuation rate was lower in afatinib (8%) versus chemotherapy (12%), almost half of afatinib patients required dose reduction to less than 40 mg per day and 14% discontinued therapy due to AE. Diarrhea and rash occurred in more than 90% of patients. Serious AE included several cases of interstitial lung disease and 4 deaths potentially due to treatment related fatal toxicity. This suggests that afatinib may not be well tolerated, and more data are needed to ensure its safe use in a wider population. Afatinib improved PFS and quality of life as a first-line treatment for patients with metastatic NSCLC whose tumors have activating EGFR mutations. It is not metabolized by CYP450 enzymes as are other EGFR TKIs.

Tagrisso® (osimertinib)

The evidence base for the approval of osimertinib consists of 2 single-arm, open-label trials (Study 1, Study 2). The 2 studies were pooled for efficacy and adverse event outcomes because there were no substantial differences in the patient characteristics between studies. A total of 411 patients with metastatic, EGFR T790M mutation-positive NSCLC who had received prior EGFR TKI therapy were recruited and treated with osimertinib 80 mg until progression or unacceptable toxicity. The primary end points were ORR by RECIST criteria as assessed by central independent review and adverse events. Secondary end points included dose-limiting toxicity, duration of response, and PFS.

In Study 1, no patients achieved a complete response. Partial response was achieved in 115 patients, for an ORR of 57% (95% CI, 50% to 64%). Study 2 had 2 complete responses and 126



partial responses, with an ORR of 59% (95% CI, 54% to 64%). Among responders, most patients (96%) had ongoing responses, ranging from 1.1 to 5.6 months, with a median duration of follow-up of 4.2 months in study 1 and 4 months in study 2. Pooled overall ORR was 59% (95% CI, 54% to 64%).

Colorectal Cancer

Cetuximab has been studied as both a single agent and in combination with irinotecan in the treatment of metastatic colorectal cancer.²⁸

Pancreatic Cancer

In pancreatic cancer symptoms are typically minor until the disease has significantly progressed, and following diagnosis the tumor is often resistant to standard anticancer therapies. These factors contribute to a high mortality rate, with only 20% of patients surviving to one year. In patients with advanced pancreatic cancer, one-year survival drops to approximately 10%. The current standard of therapy in unresectable, advanced, and metastatic disease is gemcitabine.

A randomized, double-blind, placebo-controlled clinical trial added erlotinib 100 mg/day to gemcitabine in patients with inoperable advanced pancreatic cancer. The results showed modest survival benefit compared to those receiving gemcitabine alone. There was a significant difference in overall survival [$p=0.025$] that favored the erlotinib plus gemcitabine group with a hazard ratio of 0.81 [95% CI 0.67 - 0.97]. The corresponding one-year survival rates were 24% versus 17%. PFS was also significantly improved in the gemcitabine plus erlotinib treatment group with a hazard ratio of 0.76, $p=0.003$. The RR [CR/PR/SD] were 58% [CR/PR=9%] and 49% [CR/PR=8%] for the erlotinib and placebo groups, respectively. No unexpected adverse events or safety signals were reported.

Hepatocellular Carcinoma

Hepatocellular carcinoma is the third leading cause of cancer deaths worldwide. Surgical resection and liver transplantation are the only cures for hepatocellular carcinoma, but benefit only 15% of patients. Most cases are fatal within one year of diagnosis. Sorafenib is the only pharmacotherapy option available for advanced, inoperable hepatocellular carcinoma (HCC).



One Phase II study (N=137 patients) looked at the safety and efficacy of four week cycles of 400 mg twice daily sorafenib given to patients with inoperable HCC, no prior systemic treatment and Child-Pugh A or B scores. After independent assessment, three patients (2.2%) had a partial response, eight patients (5.8%) had minor response and 46 patients (33.6%) had stable disease for at least 16 weeks. The median time to progression was 4.2 months and median overall survival was 9.2 months. Adverse events included fatigue, diarrhea, and hand-foot skin reaction.

One Phase III study (N=602) looked at the efficacy and safety of 400 mg sorafenib twice daily compared to placebo in patients with advanced HCC, no prior systemic treatment, ECOG 0-2 and Child-Pugh A. Primary endpoints were median overall survival (OS) and time to symptomatic progression (TTSP). The hazard ratio for OS was 0.69 for sorafenib versus placebo which represented 44% improvement in OS. This was the basis for early stopping criteria. The median overall survival advantage was 10.7 months for sorafenib versus 7.9 months for placebo. The hazard ratio for TTSP was 0.58 and median TTP was 5.5 months for sorafenib vs 2.8 months for placebo. Adverse events incidences were similar between the two groups; however, more serious adverse events of diarrhea and hand-foot skin reactions were seen in the sorafenib group.

The 2008 NCCN Practice Guidelines for hepatocellular carcinoma reflects the results of the Phase III study and recommends sorafenib for patients with Child-Pugh Class A or B status as first line treatment for unresectable or inoperable HCC and in cases of HCC metastatic disease.

2008 Update

K-RAS Mutations and Their Impact on the Clinical Effectiveness EGFR Inhibitors

Many retrospective observational studies have been performed to evaluate the contribution of mutations downstream of the epithelial growth factor receptor (EGFR) on the efficacy of the anti-EGFR tyrosine kinase inhibitor oncology therapies such as cetuximab, panitumumab, and gefitinib. Studies differ in design, patient demographics, and therapeutic regimens. The majority of studies evaluating the association of K-RAS mutation with treatment resistance conclude that wild type status is associated with a more favorable response to treatment. Higher efficacy is often seen among tumors with wild-type K-RAS, including a higher percent and degree of response, overall survival, and time-to-progression. However, no single outcome is consistently statistically significant among all studies. Currently available evidence suggests that K-RAS mutation is associated with poor response to TKI therapy, with the most evidence being for



cetuximab. At this time, K-RAS mutation status neither predicts resistance to therapy, nor does the presence of wild-type allele predict good efficacy.

A statistically significant difference in overall response was seen in 10 of 13 studies in which response was an outcome. Response rates among K-RAS mutants ranged from 0% to 33%. Only 5 of 13 studies that measured response reported any response to TKI treatment, ranging from 9.5% to 33%. No studies assessing response to panitumumab reported any response to therapy in the K-RAS mutant group. In general, the presence of K-RAS mutation is associated with decreased response to TKI treatment. However, studies presenting response rates of approximately 10-30% suggest that the existence of K-RAS mutation is not the sole determinant of treatment response. In addition, the percent of K-RAS wild-type subjects with partial or complete response is still relatively low, ranging from 26-68%. This suggests that while K-RAS likely contributes the TKI resistance, other factors are involved.

Seven of 15 studies assessed overall survival as an outcome. Three of these found no statistically significant difference, and one found a difference in overall survival only among patients taking combination therapy of cetuximab with irinotecan, while no difference in overall survival was seen in the same patients taking cetuximab monotherapy. The remaining three found statistically significant differences in overall survival between K-RAS mutants and K-RAS wild-type. All three assessed response to cetuximab. Comparison of the overall survival of mutants versus wild-type found an overall median response rate of 6.9 months and 16.3 months, respectively ($p < 0.001$), 27.3 weeks versus 44.7 weeks, respectively ($p = 0.003$), and 10.1 months versus 14.3 months, respectively ($p = 0.026$). Overall, half of the studies that measured overall survival as an outcome reported a difference between K-RAS mutants and K-RAS wild type. The largest study performed with overall survival as an outcome, consisting of 427 patients, found that there was no difference in overall survival between K-RAS mutants and K-RAS wild type after treatment with panitumumab.

Eleven of 15 studies assessed progression-free-survival (PFS) or time-to-progression (TTP). Three of these directly compared TTP or PFS between K-RAS mutants and K-RAS wild type after treatment with cetuximab found no statistically significant difference. However, six studies directly comparing them confirmed that there was a difference. After treatment with cetuximab, TTP for K-RAS mutants and K-RAS wild type were 10.1 weeks [95% CI, 8 to 16 weeks] and 31.4 weeks [95% CI, 19.4 to 36 weeks], respectively. PFS was 6.9 months versus 16.3 months for mutants and wild-type, respectively ($p = 0.016$). One study found a statistically significant difference in progression-free survival only with cetuximab combined with irinotecan (12 weeks versus 34 weeks, $p = 0.016$), but not for cetuximab monotherapy. When randomized to best supportive care or best supportive care and panitumumab, subjects with K-RAS mutations showed no difference in PFS between the two treatment arms. In K-RAS wild-type patients, a



statistically significant difference in PFS was seen (HR 0.45, 95%CI -.34-0.59). One study with patients taking either cetuximab or panitumumab reported difference in PFS of 8.6 weeks in K-RAS mutants versus 32 weeks in K-RAS wild type ($p < 0.001$). Two abstracts presented at the American Society of Clinical Oncology (ASCO) 2008 Annual Meeting evaluated the benefit of cetuximab as adjunct therapy to the standard regimen for metastatic colorectal cancer, FOLFIRI. Both studies found that the addition of cetuximab to standard therapy only resulted in increased median PFS in K-RAS wild-type patients. K-RAS mutants showed no improvement in PFS. Overall, the evidence shows that K-RAS mutation is associated with shorter TTP and PFS after treatment with TKI than K-RAS wild type. However, K-RAS mutation has been independently associated with disease progression and this may contribute to differences in disease progression regardless of therapy.

Karapetis et al. published a study that used tissue samples from the CO.17 trial of cetuximab versus supportive care in treating refractory advanced stage metastatic colorectal cancer patients. Five hundred seventy-two patients were enrolled in the original clinical trial, of which tissue samples were examined for 394 patients (69%). The remainder was unavailable for logistic reasons, or due to lack of consent. The authors observed a five-month improvement in median overall survival (9.5 months in the cetuximab group versus 4.8 months with supportive care) for patients with wild type K-RAS. There was no difference in survival between cetuximab and supportive care groups for patients with K-RAS mutations.

2009 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 2 or phase 3 studies demonstrating treatment effectiveness.

Schneider et al. studied the effect of various polymorphisms involving the EGFR signaling pathway in 311 patients receiving erlotinib in NSCLC. None of 17 patients with a KRAS mutation had a tumor response, but the impact of KRAS mutation status on survival outcomes was of borderline statistical significance. Similarly, Miller et al. studied a series of 101 patients with bronchioalveolar carcinoma, of which no patient (zero of 18; 95% CI, 0% to 19%) whose tumor harbored a KRAS mutation responded to erlotinib.



2010 Update

This policy is updated in agreement with March 2010 NCCN Drugs and Biologics Compendium recommendations of 1 and 2A.

2011 Update – KRAS/BRAF

Technology Assessments, Guidelines and Position Statements

The National Comprehensive Cancer Network (NCCN) guidelines (1.2011) on the treatment of colon cancer recommend that tumor KRAS gene status testing be performed for all patients with metastatic colon cancer. This testing would be done on archived specimens of primary tumor or a metastasis, at the time of diagnosis of metastatic disease. The guidelines indicate that cetuximab and panitumumab are only indicated for patients with tumors that express the wild-type KRAS gene (category 2A recommendation). The guidelines state that there is the option of BRAF genotyping of tumor tissue at the diagnosis of KRAS wild-type stage IV disease, but that data regarding BRAF as a predictor of response (or lack of) to anti-EGFR therapy remain inconclusive.

Summary

Clinical trial data show that patients with KRAS-mutated metastatic colorectal cancer do not benefit from cetuximab or panitumumab, either as monotherapy or in combination with other treatment regimens. These data support the use of KRAS mutation analysis of tumor DNA before considering use of cetuximab or panitumumab in a treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs and unnecessary drug toxicities, and expedite the use of alternative therapies. Thus, KRAS mutation analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.

The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter PFS and OS regardless of treatment. The data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies.



However, recent data (currently unpublished) from the CRYSTAL trial suggest that patients with KRAS wild-type/BRAF mutant tumors may respond to anti-EGFR therapy. Therefore, it may be considered an option in the diagnosis of KRAS wild-type Stage IV disease. Non-concurrent subgroup analyses of BRAF mutations in patients previously randomized in the large trials in which KRAS mutations predicted nonresponsiveness to anti-EGFR therapy will be helpful to confirm the current data available for BRAF mutations.

2013 Update

This policy is updated in agreement with November 2013 NCCN Drugs and Biologics Compendium recommendations of 1 and 2A. Criteria for afatinib, a new oral EGFR inhibitor, were added. A literature search from January 1, 2013 did not identify further required changes.

2014 Update

This policy is updated with a literature search from 7/1/13 to 10/31/14. No further required changes.

2015 Update

This policy is updated with a literature search from 7/1/14 to 10/31/15. No further required changes. Revision is planned for first quarter 2016. Reviewed by the Pharmacy and Therapeutics committee November 19, 2015.

2016 Update

This policy was updated to include a new kinase inhibitor, Tagrisso® (osimertinib) used for the treatment of NSCLC. A revised indication for Tarceva® (erlotinib) used for the treatment of NSCLC was added.

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History

Date	Comments
03/08/05	Add to Prescription Drug Section - New Policy. Hold for notification, publish June 1, 2005
10/01/05	Replace Policy - Medco issue resolved, approved text being added back into Policy Statement and Policy Guidelines. No review needed by MPC.
02/14/06	Replace Policy - Policy reviewed and revised per Pharmacy and Therapeutics Committee on 1/31/06. Title changed from Epidermal Growth Factor Receptor Inhibitors
06/16/06	Update Scope and Disclaimer - No other changes.
06/21/06	Update codes only. - No other changes.
08/08/06	Replace Policy - Policy reviewed by Pharmacy and Therapeutics Committee on 7/25/06; no changes in policy statement; policy guidelines updated.
03/13/07	Replace Policy - Policy updated with literature review; references updated. Indications for Sprycel, Nexavar, Sutent and Vectibix added to policy statement; indications for Avastin in the treatment of ovarian cancer added as an investigational policy statement, and medically necessary in the treatment of diabetic retinopathy. Policy Guidelines and Rationale updated.
04/10/07	Replace Policy - Policy reviewed by P&T March 27, 2007. Policy statement updated to clarify the indications and criteria for medically necessary treatment with Gleevec and Sprycel. Policy Guidelines updated.
12/11/07	Replace Policy - Policy updated with literature review; policy statement updated to include bullet point "treatment of patients with advanced hepatocellular carcinoma (HCC)" as medically necessary under Sorafenib (Nexavar®). Rationale and references updated to support change in statement.
08/12/08	Replace Policy - Policy updated with literature search. Policy statement revised to indicate that Erbitux may be considered medically necessary for head and neck cancer. Comment on testing for K-RAS mutations added to Policy Guidelines. Rationale section updated, references added. Reviewed by P&T July 24, 2008
11/11/08	Update Description Section - No other changes.



Date	Comments
07/14/09	Replace Policy - Policy updated with literature search. Policy statements extensively revised. References added.
09/15/09	Minor updates, code updates - 3rd bullet added under Tarceva's policy statement "documentation of susceptibility to EGFR mutation or gene amplification". No other changes. Code S3713 added.
10/13/09	Replace Policy - Policy updated with literature search. Two bullets added under the Nexavar medically necessary statement regarding gastrointestinal stromal tumors and soft-tissue sarcoma. References added.
01/12/10	Replace Policy - Policy updated with literature search; no change to the policy statement. Policy guidelines updated.
05/11/10	Replace Policy - Policy updated with literature search. Policy statement updated to include med nec statement for Erbitux. Reference added. Reviewed by OAP on February 18, 2010. Reviewed by P&T committee on March 2010.
9/14/10	Replace Policy - Policy statement for Erbitux updated with removal of IIIB pleural effusion/IV. Policy guidelines for Erbitux updated with removal of guidelines under NSCLC in accordance with NCCN guidelines. Reviewed by OAP on 8/19/10.
03/08/11	Replace Policy - Policy updated with literature search. BRAF, previously not addressed, may now be considered medically necessary in colon cancer. Reviewed by OAP 02/17/11.
05/10/11	Replace Policy - Policy updated with the abstraction of soratenib (Nexavar®) and sinitinib (Sutent®) which are now addressed in 5.01.534; reference to these drugs and their ability to treat renal cell and thyroid cancers have been removed, along with associated references.
06/26/12	Replace policy. Literature review; no change in policy statements.
06/29/12	Coding update: CPT codes, 81275, 81403 and 88363 added to the policy.
12/19/12	Update Related Policy to add 5.01.01 and 9.03.504.
12/09/13	Replace policy. Policy updated in agreement with November 2013 NCCN Drugs and Biologics Compendium recommendations of 1 and 2A. Criteria for afatinib, a new oral EGFR inhibitor, were added. References 50 – 55 added. CPT codes 81275 and 88363 removed; they are not specific to this policy. Deleted code S3713 removed.
12/17/14	Annual review. Policy updated with literature review; no change in policy statements.
12/08/15	Annual Review. Policy updated with literature review; no change in policy statements. Reviewed by P & T November 2015.
04/01/16	Interim update, approved March 8, 2016. Addition of a new kinase inhibitor, osimertinib and its criteria to the policy.
05/01/16	Annual Review, approved April 12, 2016. Addition of recently revised indication for EGFR inhibitor, gefitinib and its criteria to the policy.



Date	Comments
10/01/16	Interim Update, approved September 13, 2016. Inclusion of a new indication for Gilotrif. Potential update of criteria for Erbitux and Vectibix.
12/01/16	Minor update, approved November 8, 2016. A notation was added that this policy applies only to those 18 and older because data does not support efficacy and safety in those under 18.
06/01/17	Annual review, approved May 23, 2017. A statement outlining the length of therapy for initial approval has been added to the policy.
02/01/18	Interim Review, approved January 30, 2018. Inclusion of a new indication for Gilotrif.
07/01/18	Annual Review, approved June 12, 2018. Tagrisso and Gilotrif criteria were updated with new literature. Erbitux and Vectibix criteria were re-written for clarity and use of Erbitux for NSCLC was removed due to a large trial (S0819) of previously untreated advanced NSCLC patients randomized to paclitaxel plus carboplatin vs. paclitaxel plus carboplatin plus bevacizumab, with or without cetuximab failed to show overall or disease free survival advantage in the cetuximab arms. Removed HCPCS codes J8565 and J8999.
11/01/18	Interim Review, approved October 9, 2018. Added dacomitinib. Updated indications for all drugs based on labels. Remove code 81403, added code J9999.
04/01/19	Interim Review, approved March 19, 2019. Updated criteria for Tagrisso and Tarceva.

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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. Beeksisni 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):

Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnu 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-ato 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 ដល់កំណត់ថ្លៃជាក់លាក់នានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ដុល្លារចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងដុល្លារនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ 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 (کلیر بران 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 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 คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย 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).