

PHARMACY / MEDICAL POLICY – 5.01.517


Use of Vascular Endothelial Growth Factor Receptor (VEGF) Inhibitors and Other Angiogenesis Inhibitors in Oncology Patients

Effective Date: Nov. 1, 2018
 Last Revised: Jan. 1, 2019
 Replaces: N/A

RELATED MEDICAL POLICIES:	
5.01.518	BCR-ABL Kinase Inhibitors
5.01.534	Multiple Receptor Tyrosine Kinase Inhibitors
5.01.544	Prostate Cancer Targeted Therapies
5.01.549	Off-Label Use of Drugs and Biologic Agents
5.01.603	Epidermal Growth Factor Receptor (EGFR) Inhibitors

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Introduction

Angiogenesis is the creation of new blood vessels. The body controls this process through chemical signals. Everything is usually in balance so that new blood vessels are created only when needed. In cancer, however, as a tumor grows it demands more oxygen and nutrients, which is delivered by blood vessels. Tumors can send signals to nearby normal cells to start creating more blood vessels. There are certain drugs that interfere with these signals. These drugs reduce or stop the blood vessel growth that tumors need. This policy describes when these drugs 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 the **injectable** drugs listed below will be 12 months.

No review is needed for eye-related injections; these are considered standard of care.

Drug	Medical Necessity
Injectable Drugs	
Avastin® (bevacizumab)	<p>Avastin® (bevacizumab) may be considered medically necessary no earlier than 28 days following major surgery and until surgical wound is fully healed.</p> <p>Avastin® (bevacizumab) may be considered medically necessary for patients with ECOG performance status 0-2 for the treatment of:</p> <ul style="list-style-type: none"> • Metastatic colorectal cancer, in combination with a 5FU-based or capecitabine-based regimen • Unresectable or metastatic non-squamous, non-small cell lung cancer, in combination with carboplatin and paclitaxel • Recurrent glioblastoma in adults • Metastatic renal cell carcinoma in combination with interferon alfa • Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan • Epithelial ovarian, fallopian tube, or primary peritoneal cancer: <ul style="list-style-type: none"> ○ In combination with carboplatin and paclitaxel, followed by Avastin ○ As a single agent, for stage III or IV disease following initial surgical resection ○ In combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens <p>Avastin® (bevacizumab) is considered investigational for all other uses, including advanced adenocarcinoma of the pancreas.</p>
Zaltrap® (ziv-aflibercept)	Zaltrap® (ziv-aflibercept) in combination with 5-fluorouracil,



Drug	Medical Necessity
Injectable Drugs	
	<p>leucovorin, irinotecan-(FOLFIRI) may be considered medically necessary for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen.</p> <p>Zaltrap® (ziv-aflibercept) is considered investigational for all other uses.</p>

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.

Drug	Medical Necessity
Oral Drugs	
Revlimid® (lenalidomide)	<p>Revlimid® (lenalidomide) may be considered medically necessary for the treatment of myelodysplastic syndrome in patients meeting the following criteria:</p> <ul style="list-style-type: none"> • Patient has transfusion-dependent anemia <p>AND</p> <ul style="list-style-type: none"> • The dose is limited to 10 mg daily. <p>Revlimid® (lenalidomide) may be considered medically necessary for the treatment of multiple myeloma:</p> <ul style="list-style-type: none"> • In combination with dexamethasone at a dose not to exceed 25mg/day <p>OR</p> <ul style="list-style-type: none"> • As maintenance therapy following hematopoietic stem cell transplantation (auto-HSCT). <p>Revlimid® (lenalidomide) may be considered medically necessary for the treatment of mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which includes bortezomib.</p> <p>Use of Revlimid® (lenalidomide) to treat other diagnoses is</p>



Drug	Medical Necessity
Oral Drugs	
	considered investigational.
Pomalyst™ (pomalidomide)	<p>Pomalyst™ (pomalidomide) may be considered medically necessary, in combination with dexamethasone, for treatment of multiple myeloma in patients meeting the following criteria:</p> <ul style="list-style-type: none"> • Patient has received at least two prior therapies, including lenalidomide and a proteasome inhibitor <p>AND</p> <ul style="list-style-type: none"> • Patient has demonstrated disease progression within 60 days of completion of the last prior therapy

Coding

Code	Description
HCPCS	
J9035	Injection, bevacizumab (Avastin®), 10 mg
J9400	Injection, ziv-aflibercept (Zaltrap®), 1 mg
Q5107	Injection, bevacizumab-awwb, biosimilar, (mvasi), 10 mg (new code effective 1/1/19)

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Related Information

N/A

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). These targets are typically preferentially located on/in tumor cells, thus these therapies have a higher specificity for tumor cells. 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.

Epidermal growth factor receptor (EGFR) and tyrosine kinases play a critical role in the modulation of growth factor signaling. The binding of a ligand to EGFR induces the phosphorylation and activation of tyrosine kinase signal pathways. The induction of the signaling pathways enhances activities such as up regulation of RAS, RAF and mitogen-activated phosphorylation which develops 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.

EGFR and/or VEGF over expression have been identified in a variety of solid and hematological malignancies (eg, colon, lung, breast, kidney, liver, CML). Furthermore, increasing VEGF levels have been correlated with poor prognosis in many of these same pathologies. As a result, VEGF and other angiogenesis 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.



The VEGF and miscellaneous angiogenesis inhibiting agents currently available are as follows:

Drug Name	Pharmacology	How Given	FDA-approved Uses
Bevacizumab (Avastin®)	VEGF receptor inhibitor (MAb)	IV (Clinic)	Metastatic colorectal cancer, non-squamous non-small cell lung cancer, metastatic breast cancer, glioblastoma and metastatic renal cell carcinoma
Ziv-aflibercept	VEGF trap	IV (Clinic)	Metastatic colorectal cancer
Lenalidomide (Revlimid®)	Not understood	Oral (Rx)	Myelodysplastic syndrome (MDS), Multiple Myeloma
Pomalidomide (Pomalyst™)	Not understood	Oral (Rx)	Multiple Myeloma

Revlimid® (lenalidomide) and Pomalyst™ (pomalidomide) are angiogenesis inhibitors with pharmacology similar to that of thalidomide. The mechanism by which lenalidomide and pomalidomide inhibit angiogenesis is not well understood. Both agents are approved for treatment of multiple myeloma. Lenalidomide is approved for treatment of MDS as well.

Avastin® (bevacizumab) is a recombinant humanized monoclonal antibody that inhibits angiogenesis and new blood vessel survival by binding and inhibiting the interaction of human vascular endothelial growth factor (VEGF) to its receptors on endothelial cells. VEGF is a key component of endothelial cell proliferation and new blood vessel formation that supports the growth of many tumor types, including colorectal cancer.

Zaltrap® (ziv-aflibercept) is a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1. Ziv-aflibercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) K-1 mammalian expression system. Ziv-aflibercept is a dimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa).

Ziv-aflibercept acts as a soluble receptor that binds to human VEGF-A (equilibrium dissociation constant KD of 0.5 pM for VEGF-A165 and 0.36 pM for VEGF-A121), to human VEGF-B (KD of 1.92 pM), and to human PlGF (KD of 39 pM for PlGF-2). By binding to these endogenous ligands, ziv-aflibercept can inhibit the binding and activation of their cognate receptors. This inhibition can result in decreased neovascularization and decreased vascular permeability.



National Comprehensive Cancer Center (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.

In June 2008, the NCCN Compendium became one of four references for Centers for Medicare & Medicaid Services (CMS) for oncology coverage policy.

In its Medicare Benefit Policy Manual (October 24, 2008), CMS describes this change and 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.”



Breast Cancer

Breast cancer is the most common cancer in women and is the leading cause of death for women 40-55 years of age. While advances have been made with the introduction of endocrine therapies, new chemotherapies, and biologics, and early detection has significantly improved the outlook for women with the disease, recurrence remains an ongoing concern. In addition, treatment of advanced breast cancer remains a challenge. VEGF levels are increased in approximately 30-60% of breast cancers and many studies show a link between VEGF and prognosis; hence the recent targeting of EGF inhibitors toward the disease.

Two randomized, controlled Phase III trials of Avastin® (bevacizumab) have been conducted in patients with metastatic breast cancer (Miller et al., 2002 and Miller et al., 2005). The earlier study examined the therapeutic benefit of adding bevacizumab 15 mg/kg every three weeks to daily capecitabine compared to capecitabine alone in 462 patients with metastatic breast cancer refractory to taxanes and anthracyclines. The primary endpoint of progression-free survival (PFS) was not met (4.86 versus 4.17 months, $P=0.857$). Although, RR was significantly higher for the combination compared with capecitabine alone independently assessed RR: 19.8 versus 9.1%, respectively, $P=0.001$; investigator-assessed RR: 30.2 versus 19.1%, respectively, $P=0.006$. The combination was well tolerated and the incidence and severity of capecitabine-related toxicities were not affected by concurrent use of bevacizumab, and bevacizumab-related adverse events were as expected. The latter study was a randomized, open-label study in patients with metastatic breast cancer who were receiving first-line paclitaxel with or without bevacizumab 10 mg/kg every two weeks. The primary objective of the study is PFS. A preliminary report for 715 patients randomized to the two treatments showed a significant increase in median PFS for the bevacizumab + paclitaxel group compared with the paclitaxel alone group (10.97 months versus 6.11 months, respectively, $P<0.001$). A significant two-fold increase in RR for the bevacizumab + paclitaxel group compared with paclitaxel alone (28.2 versus 14.2%, $P<0.0001$) was also observed. Adverse events were as expected based on data from previous trials of bevacizumab.

Bevacizumab is also being studied in patients with metastatic breast cancer in combination with Herceptin® (trastuzumab) and Tarceva® (erlotinib).

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%.



Currently, the use of two chemotherapy agents (doublet) is NCCN recommended 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 ≥ 25 -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 have 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. Recently, 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.

Recently, in a US Cooperative Group Phase III clinical trial (Sandler et al., 2005), 444 patients with Stage IIIB or IV non-squamous cell NSCLC were randomly assigned to paclitaxel plus carboplatin (PC) and 434 to PC plus bevacizumab 15 mg/kg every three weeks (PC+B). Most patients (86%) had Stage IV disease. Patients receiving PC+B had a higher response rate, and modestly longer progression-free (PFS) and overall survival (OS). See [Table 1](#) below.

Table 1. Study E4599: Response to bevacizumab plus paclitaxel/carboplatin in patients with advanced NSCLC (707 evaluable patients).

	PC Alone (n=350)	PC + B (n=357)	P-value
Response Rate, %	10.0	27.2	<0.0001
PFS, months	4.5	6.4	<0.0001
OS, months	10.2	12.5	0.0075

Both regimens were generally well tolerated. Selected adverse events (PC versus PC+B) included neutropenia (16.4% versus 24%), thrombocytopenia (0 versus 1.4%), hemorrhage (0.7% versus 4.5%), and hypertension (0.7% versus 6.0%). The incidence of hemoptysis was decreased



compared with an initial phase 2 trial in patients with NSCLC, but five of eight cases in the PC+B group were fatal.

Myelodysplastic Syndrome

The efficacy and safety of Revlimid® (lenalidomide) were evaluated in patients with transfusion dependent anemia in Low or Intermediate-1- risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single arm, multi-center study. The major study was not designed nor powered to prospectively compare the efficacy of the two dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity. This major study enrolled 148 patients who had RBC transfusion dependent anemia. RBC-transfusion dependence was defined as having received ≥ 2 units of RBCs within eight weeks prior to study treatment. The study enrolled patients with absolute neutrophil counts ≥ 500 cells/mm³, platelet counts $\geq 50,000$ /mm³, serum creatinine ≤ 2.5 mg/dL, serum SGOT/AST or SGPT/ALT ≤ 3.0 x upper limit of normal, and serum direct bilirubin ≤ 2.0 mg/dL. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. The frequency of RBC-transfusion independence was modified from the International Working Group (IWG) response criteria for MDS. RBC transfusion independence was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (eight weeks) during the treatment period.

Transfusion independence was seen in 99/148 (67%) patients (95% CI [59, 74]). The median duration from the date when RBC transfusion independence was first declared (ie, the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range of 0 to >67 weeks). Ninety percent of patients who achieved a transfusion benefit did so by completion of three months in the study. RBC-transfusion independence rates were unaffected by age or gender. The dose of lenalidomide was reduced or interrupted at least once due to an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean, 35.1 days; range, 2-253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2-265 days). A second dose reduction or interruption due to adverse events was required in 50 (33.8%) of the 148 patients. The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15-205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2-148 days).



Multiple Myeloma

Two randomized studies were conducted to evaluate the efficacy and safety of lenalidomide. These multicenter, multinational, double-blind, placebo-controlled studies compared lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone, in patients with multiple myeloma who had received at least one prior treatment. In both studies, patients in the lenalidomide/dexamethasone group took 25 mg of lenalidomide orally once daily on days one to 21 and a matching placebo capsule once daily on days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took one placebo capsule on days one to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on days one to four, nine to 12, and 17 to 20 of each 28-day cycle for the first four cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days one to four of each 28-day cycle after the first four cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory findings. Sequential dose reductions to 15 mg daily, 10 mg daily and 5 mg daily were allowed for toxicity.

The primary efficacy endpoint in both studies was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease or death due to progressive disease. Preplanned interim analyses of both studies showed that the combination of lenalidomide/dexamethasone was significantly superior to dexamethasone alone for TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination. Pomalidomide is a newer agent similar to lenalidomide that offers potential to extend benefit in patients that have progressed on prior therapies.

Ovarian Cancer

Small prospective trials in ovarian cancer have established the single-agent activity of bevacizumab in recurrent ovarian cancer. In one study, 63 patients with recurrent ovarian cancer were treated with bevacizumab 15 mg/kg IV every three weeks. Patients had received up to two prior cytotoxic regimens. Forty-two percent entered had platinum-sensitive disease. Overall RR was 17.7%, median duration of response was 10.25 months, and 38.7% of patients were progression-free at six or more months. No gastrointestinal perforations were noted.

In a second study, reported by Cannistra et al., 44 patients with platinum-resistant disease were evaluated. Patients were required to progress on or within six months of platinum-based chemotherapy and then receive either liposomal doxorubicin or topotecan and progress on or



within three months of that therapy. Patients had received up to three prior regimens. The majority of patients had primary platinum-resistant ovarian cancer (83.7%), with 16.3% of patients entering with platinum-resistant disease after their second platinum-based regimen. Fifty-nine percent of patients received liposomal doxorubicin, 25% topotecan, and 16% both drugs prior to study entry. The response rate to bevacizumab in this refractory heavily pretreated population was 16% (7/44 patients, all partial responses). The expected response rate to cytotoxic chemotherapy in this poor prognosis patient population is less than 10%, establishing single-agent activity of bevacizumab. The original accrual goal of the trial was 53 patients. The study closed to accrual after the first 44 patients because of a gastrointestinal perforation rate of 11.4% (5/44 patients). One of these perforations was fatal. Perforations did not appear to correlate with response. On October 4, 2005, the National Cancer Institute (NCI) alerted investigators of the perforation risk with bevacizumab. Gastrointestinal perforation appeared to be associated with gastrointestinal tumor involvement, specifically bowel obstruction and bowel wall thickening.

In a third trial, NCI trial 5789, recurrent ovarian cancer patients with up to two prior regimens were treated with bevacizumab 10 mg/kg IV every two weeks in combination with metronomic oral cyclophosphamide (50 mg daily). Forty-two percent were platinum-sensitive. Overall response rate of 28% with 57% of patients being progression-free at six months was noted. Two patients (3%) experienced gastrointestinal perforation.

A retrospective case series of 32 patients treated with bevacizumab at 15 mg/kg IV every three weeks was reported. Patients had had a median of five prior regimens. The majority were treated with bevacizumab alone, although 10 patients received bevacizumab with chemotherapy or had chemotherapy added during the course of treatment. The response rate was 16%. One enterocutaneous fistula was noted.

The results of these studies clearly show that bevacizumab has single agent activity in patients with metastatic ovarian disease that is refractory to numerous prior regimens; however, the response rates are very modest, and are offset by a worrisome incidence of bowel perforations in this population. While it has been suggested that patients with bowel involvement of the tumor are at higher risk, there is to date insufficient evidence to confidently predict this. Given the very modest benefit and considerable risk, bevacizumab should be considered a potentially promising therapy for this population, and in need of further research to confirm that the benefits outweigh risk and to identify the population most suitable for treatment.



Renal Cell Carcinoma

Renal cell carcinoma (RCC) usually occurs in adults between the ages of 50 and 70 and is the most common cancer of the kidney, accounting for 3% of all human cancers and over 90% of malignant kidney tumors. Between 25 and 30% of patients have metastases at the time of diagnosis. RCC is classified into five subtypes, but most patients (70-80%) have the clear cell type.

Treatment of RCC depends on disease staging and the patient's overall physical health. Surgery is typically performed in earlier/lower stages of the disease, and systemic therapy is reserved when there is recurrence or spread of the cancer. Unfortunately, RCC tends to be very resistant to chemotherapy. Consequently, various types of immunotherapy (eg, interferon alpha and interleukin-2) are currently preferred. However, immunotherapies have only resulted in modest improvements in median survival; therefore, new treatment options are needed.

In a randomized, double-blind, placebo-controlled Phase II trial, 116 patients with immunotherapy refractory RCC received bevacizumab 3 or 10 mg/kg every two weeks or placebo (Yang et al, 2003). Crossover from placebo to bevacizumab 3 mg/kg \pm thalidomide was permitted at progression. The two primary endpoints were time to progression (TTP) and response. OS was only a secondary endpoint because crossover therapy at progression was allowed. The trial was closed early because progression-free survival was significantly longer in patients treated with bevacizumab 10 mg/kg than in those receiving placebo (HR=2.55, $P < 0.001$). There were no life-threatening adverse events or deaths related to bevacizumab therapy. The most common adverse events reported were hypertension and proteinuria.

Two large Phase III clinical trials are also underway to investigate the use of bevacizumab in combination with immunotherapy in patients with metastatic RCC.

2008 Update

Glioblastoma

Fifty four patients with recurrent high grade glioma received therapy with bevacizumab at 10 mg/kg every two weeks for four doses in an eight week cycle along with Irinotecan at 125 mg/m². The survival was calculated from the time of starting bevacizumab-based therapy. The median PFS and OS were 5 (95% confidence interval, 1.0-6.9) and 9 (95% confidence interval, 7.5-10.5) months respectively. Radiological responses following therapy were noted in 72.2% of cases. The patients who received less than two cycles of bevacizumab-based therapy had a PFS



and OS of seven and 11 months compared to 3.5 and five months for the patients who received less than two cycles of therapy ($p=0.02$ and $P<0.0001$) respectively. Neither the grade of the tumor nor the surgical resection prior to therapy had an impact on survival.

2009 Update

Ovarian Cancer

Azad and colleagues stated that CA125 is an accepted indicator of epithelial ovarian cancer (EOC) response and is used to monitor patients treated with cytotoxic chemotherapy. However, it is uncertain how CA125 is affected by molecularly targeted drugs and so the authors analyzed the utility of CA125 to predict disease behavior in patients who were receiving sorafenib, a Raf-kinase/VEGFR2 inhibitor, and bevacizumab, an anti-VEGF monoclonal antibody. Fifteen of 42 patients had recurrent EOC. Patients received sorafenib 200 mg orally twice daily or D1-5 of seven and bevacizumab 5 mg/kg to 10 mg/kg intravenously every two weeks for 28-day cycles. Computed tomography (CT) scans were performed every two cycles for restaging, and CA125 was measured monthly. CA125 concentrations were retrospectively analyzed as a function of clinical behavior. They found that fourteen of 15 patients had abnormal CA125 concentrations at study entry. Seven (47%) patients had partial response by imaging criteria. Five of these seven patients had partial response by CA125 criteria (71% sensitivity). Eight (53%) patients would have had partial responses if CA125 criteria were used; only 5 were confirmed by CT (63 % specificity). Imaging and CA125 criteria combined yielded a higher total response rate of 10 of 15 (67%). Three patients with objective partial response by imaging lasting >20, >22, and >24 cycles would have terminated treatment prematurely if CA125 had been used. They concluded that CA125 changes may not correspond to imaging response criteria for EOC patients who are receiving sorafenib and bevacizumab. They stated that caution is recommended when using CA125 as a response criterion of molecularly targeted agents until prospective studies validate CA125 changes with objective imaging response results.

NCCN Drug Compendium

The National Comprehensive Cancer Network (NCCN, April 2009) Drugs and Biologics Compendium states that bevacizumab is recommended for use as recurrence therapy for ovarian cancer as a single agent for the following indications:

- Recurrence as evidenced by serially rising CA125 in patients who have received prior chemotherapy (2B category of evidence);



- Progressive or stable disease on primary therapy (2A category of evidence);
- Relapse after being in complete remission following primary chemotherapy (2B category of evidence); and
- Stage II to IV disease showing partial response to primary treatment (2A category of evidence).

The Company recognizes indications and uses of bevacizumab 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.

2010 Update

Avastin® (bevacizumab) and Advanced Adenocarcinoma of the Pancreas

This summary is adapted from a 2009 TEC Assessment. The objective of the Assessment was to evaluate the use of bevacizumab in advanced adenocarcinoma of the pancreas to identify any incremental benefit of using bevacizumab in these patients taking into account potential increases in survival and quality of life as well as the effects of adverse events caused by the treatment.

Because VEGF appears to play a role in pancreatic cancer, bevacizumab was considered a promising therapy and results of two of the phase 2 trials seemed to indicate potential benefit as well. About 89–93% of pancreatic patients have a VEGF mutation, which is associated with early recurrence after surgery, liver metastases, and poor prognosis. Finding VEGF in tumors is also correlated with tumor size.

Five studies were identified for review as part of the Assessment that tested the use of bevacizumab in patients with advanced adenocarcinoma. These studies consisted of two phase 3 trials, two phase 2 trials and one phase 1 trial. In all trials, bevacizumab was added to gemcitabine which is considered the current standard of care. Some trials also included other agents as well including cisplatin and erlotinib.

The two Phase III studies, one by Kindler et al. and the second by van Cutsem et al.(21), provided the strongest evidence because of their design. Neither study demonstrated that the addition of bevacizumab resulted in a statistically significant difference in the primary outcome of overall



survival. For the secondary outcome of progression-free survival, the van Cutsem study appeared to show benefit while the Kindler study did not.

Kindler et al. randomized 590 patients with advanced cancer (local or metastatic) to gemcitabine with or without bevacizumab. The trial was stopped early when it was determined that the combination of gemcitabine plus bevacizumab could not achieve longer survival than the gemcitabine alone arm of the trial. The results have not been published in a peer-reviewed journal; however they were presented at the American Society for Clinical Oncology (ASCO) annual meeting in 2007.

Van Cutsem et al. randomized 607 patients with metastatic adenocarcinoma of the pancreas to gemcitabine plus erlotinib with or without bevacizumab. There was no statistically significant difference between the two groups in the primary outcome of overall survival. The median survival was 7.1 months for the treatment group and 6.0 months for the control group (hazard ratio=0.73; 95% confidence interval 0.74–1.07; p=0.21). The study reported a statistically significant difference in progression-free survival of 4.6 months in the treatment arm and 3.6 months in the control group. Although this secondary outcome was significant, there were few details given regarding the methods used to assess progression-free survival, which may be subject to greater measurement error than overall survival.

It was anticipated that bevacizumab may offer benefit in advanced adenocarcinoma of the pancreas because the drug targets VEGF, which is thought to play an important role in pancreatic cancer, and because of an apparently positive effect in a phase 2 clinical trial. Unfortunately, the results of two phase 3 trials, one of which was stopped early because of lack of overall survival benefit, and the second recently released trial also showed no incremental benefit in overall survival.

Treatment of advanced adenocarcinoma of the pancreas with bevacizumab is not an FDA-approved indication. The available evidence does not clearly demonstrate that addition of bevacizumab to chemotherapy regimens for advanced adenocarcinoma of the pancreas improves the net health outcome of those patients. Therefore, bevacizumab for patients with advanced adenocarcinoma of the pancreas is considered investigational.

Avastin® (bevacizumab) and Revlimid® (lenalidomide)

As a result of NCCN Drug Compendium revisions, policy statements were revised to reflect additional medically necessary statements for bevacizumab and lenalidomide.



2011 Update

Avastin®

The FDA posted the following information on their website on December 16, 2010: "FDA is proposing that the breast cancer indication for Avastin be removed based on results from required clinical studies of the drug, including the AVADO and RIBBON1 studies, which established the following:

- The addition of Avastin to chemotherapy resulted in only a small delay in tumor growth (ie, progression-free survival, PFS), and the average time it took for tumors to progress seen in these trials was much shorter than had been expected based on the data from an earlier trial that led to accelerated approval.
- The addition of Avastin to chemotherapy did not prolong the lives of women with breast cancer (ie, overall survival, OS).

The addition of Avastin to various chemotherapies leads to an increase in incidence of serious adverse events from Avastin, as well as the serious side effects related to chemotherapy. Serious adverse events are toxicities that are severe or life-threatening, require medical intervention, hospitalization, or even result in death.

Considering all information from these clinical trials, FDA concluded that the risks of this drug outweigh its benefits in the treatment of patients with metastatic breast cancer. Under the accelerated approval process, the agency must provide the company with the chance to request a hearing by issuing a Notice of Opportunity for a Hearing (NOOH). The agency issued the NOOH today. Genentech will have 15 days to request a hearing in writing. If Genentech does not request a hearing, the indication will be removed from the label. If Genentech requests a hearing, it must, within 30 days of receiving the NOOH, submit to FDA the data and information upon which it intends to rely at a hearing. If a hearing is requested and granted, it will be open to the public."

Genentech has requested a hearing. The hearing is scheduled for June 28-29, 2011.



2012 Update

Avastin®

Clarified grade requirement for bevacizumab treatment of gliomas. A literature search and review of NCCN compendium listings failed to identify other new information that would change these policy requirements.

Although FDA has withdrawn the indication of bevacizumab for treatment of breast cancer it remains as an option in NCCN guidelines; therefore, the Plan will continue to approve off-label use for this indication as medically necessary.

Zaltrap®

Added this newly approved agent for treatment of metastatic colorectal cancer. Efficacy of ziv-aflibercept for the treatment of metastatic colorectal cancer that is resistant to or has progressed following an oxaliplatin-containing regimen was demonstrated in the Phase III multinational trial (VELOUR). The 1,226 patients were randomized (1:1) to receive ziv-aflibercept 4 mg/kg (n=612) or placebo (n=614) by intravenous (IV) infusion every 2 weeks in conjunction with the standard FOLFIRI regimen. Baseline characteristics were balanced between treatment groups at. The majority of patients were from Western and Eastern Europe. Approximately 11% were in the U.S. Approximately 30% had prior treatment with bevacizumab. Median follow-up was 22.3 months. Median OS was significantly higher in the ziv-aflibercept group than in the placebo group (13.5 versus 12.1 months; hazard ratio [HR] 0.82 [95.3% confidence interval (CI): 0.71, 0.94]; p=0.003). The ziv-aflibercept group also had greater median PFS (6.9 versus 4.7 months, HR 0.76 [95% CI: 0.66, 0.87]; p<0.001). Response rate was also higher in the ziv-aflibercept group.

2013 Update

Updated to include indication for recurrent or metastatic cervical cancer, based on a recent abstract of a Phase 3 trial by Tewari et al., and NCCN Category 2A recommendation. A literature search from 01/01/2012 to 04/30/2013 and review of NCCN compendium listings failed to identify new information that would change these policy requirements. Clarified policy by adding ependymoma as a specific example of coverage for gliomas.



2014 Update

Updated with new indications per NCCN compendium listings: bevacizumab for anaplastic glioma and endometrial carcinoma and lenalidomide for AIDS-related B-cell lymphoma, CLL/SLL and Hodgkin lymphoma. A literature search from 01/01/13 to 10/28/14 failed to identify other new information that would change these policy requirements.

2015 Update

Updated with new indications per FDA approval and NCCN compendium listings: bevacizumab for second line treatment of metastatic CRC, mesothelioma and rectal cancer; and lenalidomide for mantle cell lymphoma, non-Hodgkin lymphoma; and lenalidomide or pomalidomide for systemic light chain amyloidosis. A literature search from 01/01/14 to 8/31/15 failed to identify other new information that would change these policy requirements.

2018 Update

Updated with new labeled indications. A literature search from 05/01/17 to 05/31/18 failed to identify additional new information that would change the policy criteria.

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History

Date	Comments
08/12/08	Add to Prescription Drug Section - New PR Policy.
12/16/08	Updated Rationale Section - No other changes.
05/12/09	Replace Policy - Policy updated with literature search. Policy statement regarding ovarian cancer revised to reflect change from investigational to medically necessary for certain uses. NCCN categories of evidence added to Description and Rationale. References added.
10/13/09	Replace Policy - Policy statement revised for Avastin to allow as either first or second line treatment for kidney cancer and deleted requirement of combo therapy with Irinotecan for CNS cancer. Revisions for Revlimid: In multiple myeloma, deleted requirement for concurrent dexamethasone or needing one prior therapy. In myelodysplastic syndrome, added requirement for no chromosomal abnormality. In NHL/mantle cell lymphoma, changed from investigational to medically necessary.
01/12/10	Replace Policy - Policy updated with literature search. Policy statement revised to change carboplatin to "carboplatin-like agent". Policy statement also now specifically indicates that Avastin for advanced adenocarcinoma of the pancreas is investigational, incorporating data from BC.5.01.18. Rationale and References revised.
09/14/10	Replace Policy - Policy statement on Avastin revised to add capecitabine-based regimen as medically necessary for CRC, add continuous maintenance therapy as medically necessary for NSCLS, and angiosarcoma and solitary fibrous tumor/hemangiopericytoma as medically necessary. Guidelines on Avastin revised to add unresected or stage IV disease and no untreated CNS metastasis. Policy statement



Date	Comments
	and Guidelines on Revlimid revised to add seven types of lymphoma as medically necessary.
12/14/10	Replace Policy - Policy guidelines updated with medically necessary indications for Avastin in the treatment of ovarian cancer recurrence as a single therapy agent.
05/10/11	Replace Policy - Reviewed and recommended by OAP on February 17, 2011. Rationale updated with FDA information regarding their action to remove Breast Cancer as a labeled indication for Avastin.
04/10/12	Replace policy. Policy updated with clarification on grade requirements for bevacizumab treatment of gliomas.
12/11/12	Replace policy. Policy statement updated: ziv-aflibercept (Zaltrap®) in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI) may be considered medically necessary for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen; investigational for all other uses. Reviewed by P&T on 11/27/12. HCPCS code J1725 added to the policy. Add Related Policy 5.01.01.
05/28/13	Replace policy. Policy reviewed with literature search; no change to policy statements. Clarified policy by adding ependymoma as a specific example of coverage for gliomas.
08/12/13	Replace policy. Policy statement added indicating Pomalidomide (Pomalyst™) may be medically necessary for the treatment of multiple myeloma when criteria are met. Policy Guidelines section also updated. Policy statement for Avastin® updated to include indication for recurrent or metastatic cervical cancer.
11/20/13	Update Related Policies. Delete 5.01.01 and replace it with 5.01.549, add 5.01.544.
11/20/14	Annual Review. Policy section updated with new medically necessary indications per NCCN compendium listings: bevacizumab for anaplastic glioma and endometrial carcinoma and lenalidomide for AIDS-related B-cell lymphoma, CLL/SLL and Hodgkin lymphoma. HCPCS code J9400 added to the policy; this is a new code.
01/13/15	Minor update. Clarification made to the medically necessary policy statement for Avastin in the treatment of ovarian cancer; the word "recurrence" was removed.
10/13/15	Annual Review. Updated policy with new NCCN guidelines and indications from updated FDA labels.
12/08/15	Interim Update. Relapsed or refractory mantle cell lymphoma now requires step-therapy when treated with Revlimid. Pomalyst may be considered medically necessary to treat systemic light chain amyloidosis. Approved by P&T on November 19, 2015.
01/04/16	Minor edit. Formatting change to list of indications for off-label use of lenalidomide (Revlimid®).
10/01/16	Annual Review, approved September 13, 2016. Updating indication and criteria for bevacizumab.
12/09/16	Minor edit. Formatting correction to indicate that treatment of endometrial carcinoma



Date	Comments
	is a standalone criterion for use of Avastin, not a subset of ovarian carcinoma.
06/01/17	Annual Review, approved May 16, 2017. Policy moved into new format. A statement outlining the length of therapy for initial approval has been added to the policy. Note added to confirm that eye-related injections do not require a review; these are standard of care.
06/01/18	Annual Review, approved May 3, 2018. A literature search from 05/01/17 to 05/31/18 failed to identify additional new information that would change the policy criteria. Updated per labeled indications.
06/15/18	Minor edit, reformatted the Avastin medical necessity criteria but statements were unchanged.
11/01/18	Interim Review, approved October 9, 2018. Updated Avastin criteria for ovarian cancer per label revised (6/13/18). Removed HCPCS codes J8499 and J8999.
01/01/19	Coding update, added new HCPCS code Q5107 (new code effective 1/1/19).

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አማርኛ (Amharic):

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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-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 ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວົ້ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកតាមរយៈ 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 ਇਛੁੱਕ 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. 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).