

PHARMACY / MEDICAL POLICY – 5.01.563


Pharmacotherapy of Inflammatory Bowel Disorder

Effective Date: Jan. 1, 2019
Last Revised: Dec. 13, 2018
Replaces: Extracted from
5.01.550

RELATED MEDICAL POLICIES:
11.01.523 Site of Service: Infusion Drugs and Biologic Agents

Select a hyperlink below to be directed to that section.

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Introduction

Inflammatory bowel disorder describes several diseases where the lining of the digestive tract becomes chronically inflamed. Inflammation may cause internal sores or ulcers in the gut and symptoms of abdominal pain, cramping, diarrhea, bleeding, feeling tired, and weight loss. The two most common diseases include Crohn disease (CD) and ulcerative colitis (UC). In Crohn disease the entire digestive tract may be involved. In ulcerative colitis the disease is limited to the colon or large bowel only. Both disorders can be chronic; so far there is not a cure for either. However there are many different medications that can be used to treat these disorders. This policy describes treatment for the most common inflammatory bowel disease and which drugs may need pre-approval.

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 providers about when a service may be covered.

Policy Coverage Criteria

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician’s office, or at home.

Drugs subject to site of service review addressed in this policy are:

- Entyvio™ (vedolizuma)
- Inflectra® (infliximab-dyyb)
- Remicade® (infliximab)
- Renflexis® (infliximab-abda)

Click on the links below to be directed to the related medical necessity criteria:

[Crohn Disease](#)

[Ulcerative Colitis](#)

[Site of Service Infusion](#)

Site of Service Administration	Medical Necessity
Medically necessary sites of service <ul style="list-style-type: none">• Physician’s office• Infusion center• Home infusion	IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost effective site: <ul style="list-style-type: none">• These are the preferred medically necessary sites of service for specified drugs.
Hospital-based outpatient setting <ul style="list-style-type: none">• Outpatient hospital IV infusion department• Hospital-based outpatient clinical level of care	IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site. This site is considered medically necessary for the first 90 days for the following: <ul style="list-style-type: none">• The initial course of infusion of a pharmacologic or biologic agent



Site of Service Administration	Medical Necessity
	<p>OR</p> <ul style="list-style-type: none"> • Re-initiation of an agent after 6 months or longer following discontinuation of therapy* <p>*Note: This does not include when standard dosing between infusions is 6 months or longer</p> <p>This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.</p> <p>This site is considered medically necessary only when the patient has a clinical condition which puts him or her at increased risk of complications for infusions, including any ONE of the following:</p> <ul style="list-style-type: none"> • Known cardiac condition (eg, symptomatic cardiac arrhythmia) or pulmonary condition (eg, significant respiratory disease, serious obstructive airway disease, %FVC \leq 40%) that may increase the risk of an adverse reaction • Unstable renal function which decreases the ability to respond to fluids • Difficult or unstable vascular access • Acute mental status changes or cognitive conditions that impact the safety of infusion therapy • A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug
<p>Hospital-based outpatient setting</p> <ul style="list-style-type: none"> • Outpatient hospital IV infusion department • Hospital-based outpatient clinical level of care 	<p>These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.</p>



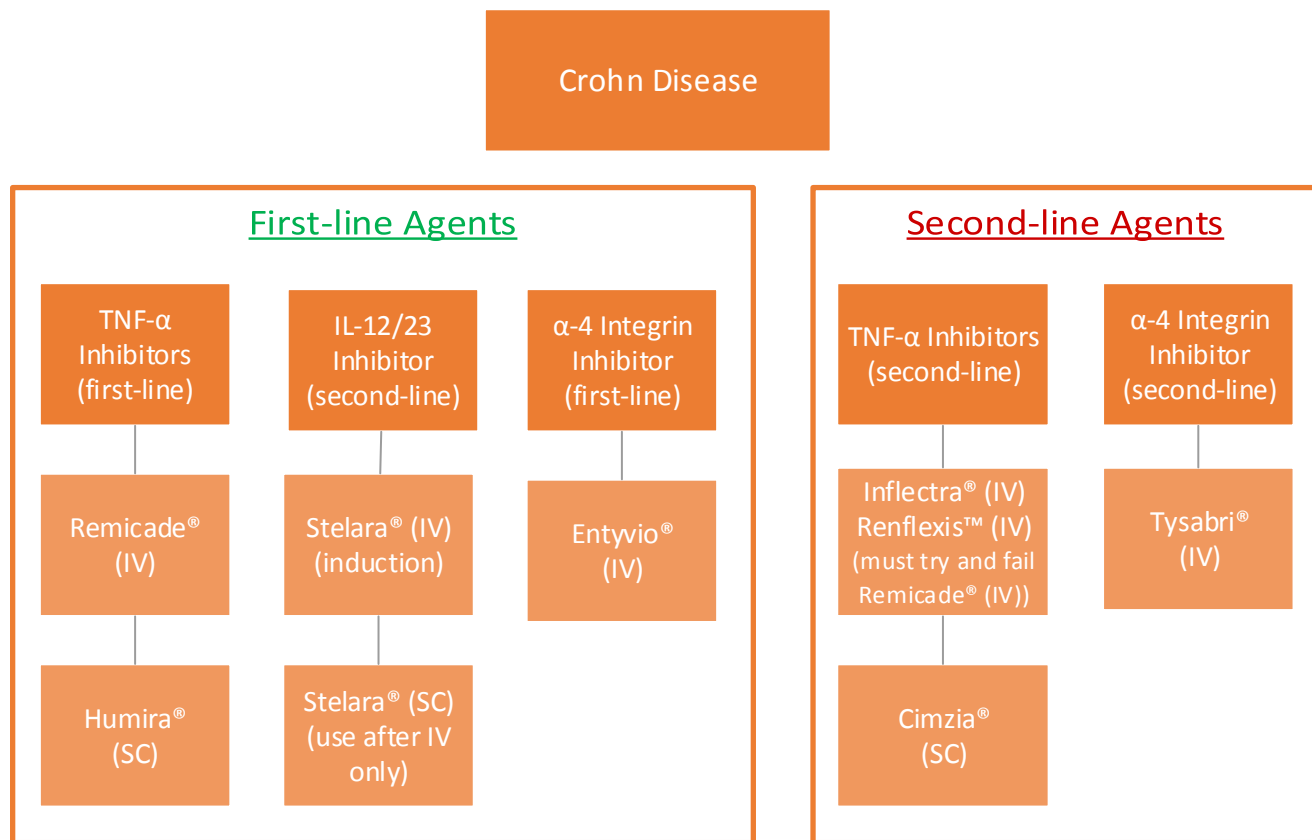
Medical and Biological Agents

Please note that claims billed for the drugs described in this policy that are administered via an intravenous route (IV) must be processed through a medical benefit only (not pharmacy).

Drug	Investigational
As listed	All other uses of the below-named agents for conditions not outlined in this policy are considered investigational.

Medications listed in this policy may also be subject to quantity limits per the FDA labeled dosing.

Step therapy tiers are listed below, please refer to the Policy section for details:



Drug	Medical Necessity for Crohn Disease
First-line TNF-α Antagonists	
<p>Humira® (adalimumab) SC</p> <ul style="list-style-type: none"> First-line 	<p>Adalimumab may be considered medically necessary as the first-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> • Patient has had an adequate trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> ○ Corticosteroid (eg, prednisone, prednisolone, dexamethasone, budesonide, etc.) <p>OR</p> <ul style="list-style-type: none"> ○ Azathioprine, 6-mercaptopurine, methotrexate, certolizumab, infliximab, vedolizumab, or ustekinumab. <p>OR</p> <ul style="list-style-type: none"> ○ Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas <p>OR</p> <ul style="list-style-type: none"> ○ Patient has had ileocolonic resection (to reduce the chance of Crohn disease recurrence) <p>AND</p> <ul style="list-style-type: none"> • Adalimumab is being prescribed by or in consultation with a gastroenterologist
<p>Remicade® (infliximab) IV</p> <ul style="list-style-type: none"> First-line 	<p>Infliximab is subject to review for site of service administration.</p> <p>Infliximab may be considered medically necessary as a first-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> • Patient has had an adequate trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> ○ Corticosteroid (eg, prednisone, prednisolone, dexamethasone, budesonide, etc.) <p>OR</p> <ul style="list-style-type: none"> ○ Azathioprine, 6-mercaptopurine, methotrexate, certolizumab, adalimumab, vedolizumab, or ustekinumab <p>OR</p> <ul style="list-style-type: none"> • Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas <p>OR</p> <ul style="list-style-type: none"> • Patient has had ileocolonic resection (to reduce the chance of



Drug	Medical Necessity for Crohn Disease
	Crohn disease recurrence) AND <ul style="list-style-type: none"> Infliximab is being prescribed by or in consultation with a gastroenterologist
First-line α-4 Integrin Inhibitors	
Entyvio® (vedolizumab) IV <ul style="list-style-type: none"> First-line 	Vedolizumab is subject to review for site of service administration. <p>Vedolizumab may be considered medically necessary as a first-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> Patient has had a trial and treatment failure with at least one of the following: <ul style="list-style-type: none"> Corticosteroids (eg, prednisone, prednisolone, dexamethasone, budesonide, etc.) OR <ul style="list-style-type: none"> Azathioprine, 6-mercaptopurine, methotrexate, certolizumab, adalimumab, infliximab, or ustekinumab OR <ul style="list-style-type: none"> Patient has enterocutaneous (perianal or abdominal) or rectovaginal fistulas OR <ul style="list-style-type: none"> Patient has had ileocolonic resection (to reduce the chance of Crohn disease recurrence) AND <ul style="list-style-type: none"> Vedolizumab is being prescribed by or in consultation with a gastroenterologist
First-line IL-12 and IL-23 Antagonist	
Stelara® (ustekinumab) IV and Stelara® (ustekinumab) SC <ul style="list-style-type: none"> First-line Post-induction dose 	Ustekinumab IV may be considered medically necessary as a first-line agent in the treatment of moderate to severe active Crohn disease when: <ul style="list-style-type: none"> Patient has had an adequate trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> Corticosteroids (eg, prednisone, prednisolone, dexamethasone, or budesonide, etc.) OR <ul style="list-style-type: none"> Azathioprine, 6-mercaptopurine, methotrexate,



Drug	Medical Necessity for Crohn Disease
	<p>certolizumab, vedolizumab, adalimumab, or infliximab</p> <p>AND</p> <ul style="list-style-type: none"> Ustekinumab is being prescribed by or in consultation with a gastroenterologist <p>Ustekinumab SC may be considered medically necessary after patient has received a single induction dose with ustekinumab IV, presuming the above criteria are met.</p>
Second-line TNF-α Antagonists	
<p>Cimzia® (certolizumab) SC</p> <ul style="list-style-type: none"> Second-line 	<p>Certolizumab may be considered medically necessary as a second-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> Patient has had a trial and treatment failure of one of the following: <ul style="list-style-type: none"> Corticosteroid, azathioprine, 6-mercaptopurine, or methotrexate <p>OR</p> <ul style="list-style-type: none"> Patient has had trial and treatment failure with Humira or Stelara <p>AND</p> <ul style="list-style-type: none"> Certolizumab is being prescribed by or in consultation with a gastroenterologist
<p>Inflectra® (infliximab-dyyb) IV and Renflexis® (infliximab-abda)</p> <ul style="list-style-type: none"> Second-line 	<p>Infliximab-dyyb and infliximab-abda are subject to review for site of service administration.</p> <p>Infliximab-dyyb and infliximab-abda may be considered medically necessary as a second-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> Patient has had a trial and treatment failure with at least one of the following: <ul style="list-style-type: none"> Corticosteroids (eg, prednisone, prednisolone, dexamethasone, budesonide, etc.) <p>OR</p> <ul style="list-style-type: none"> Azthioprine, 6-mercaptopurine, methotrexate, certolizumab, vendolizumab, adalimumab, or ustekinumab <p>OR</p> <ul style="list-style-type: none"> Patient has enterocutaneous (perianal or abdominal) or

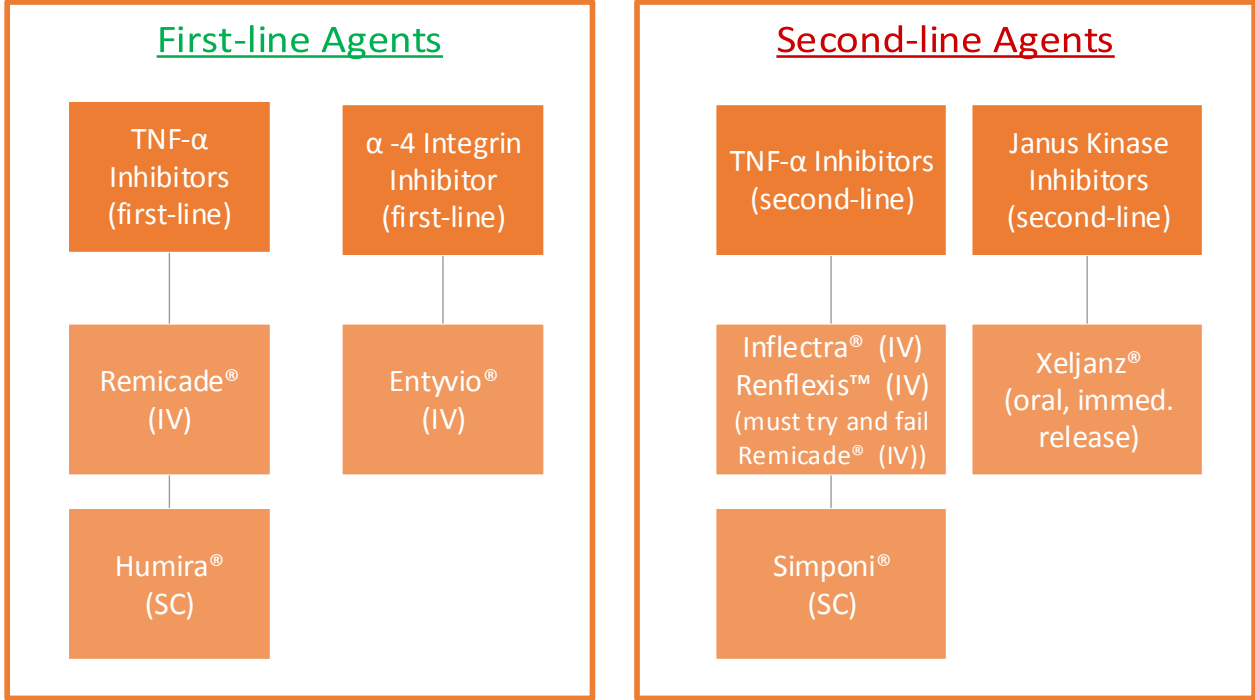


Drug	Medical Necessity for Crohn Disease
	<p>rectovaginal fistulas</p> <p>OR</p> <ul style="list-style-type: none"> • Patient has had ileocolonic resection (to reduce the chance of Crohn disease recurrence) <p>AND</p> <ul style="list-style-type: none"> • The patient has had an inadequate response or intolerance to infliximab (Remicade®) <p>AND</p> <ul style="list-style-type: none"> • Infliximab-dyyb or infliximab-abda is being prescribed by or in consultation with a gastroenterologist
Second-line α-4 Integrin Inhibitors	
<p>Tysabri® (natalizumab) IV</p> <ul style="list-style-type: none"> • Second-line 	<p>Natalizumab may be considered medically necessary as a second-line agent in the treatment of Crohn disease when:</p> <ul style="list-style-type: none"> • Natalizumab is being prescribed by or in consultation with a gastroenterologist



Step therapy tiers are listed below, please refer to the Policy section for details:

Ulcerative Colitis



Drug	Medical Necessity for Ulcerative Colitis
First-line TNF-α Antagonists	
Humira® (adalimumab) SC <ul style="list-style-type: none"> First-line 	<p>Adalimumab may be considered medically necessary as the first-line agent in the treatment of ulcerative colitis when:</p> <ul style="list-style-type: none"> • Patient has had a trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> ○ Azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, infliximab, golimumab, or a corticosteroid OR • Patient has pouchitis AND • Patient has tried therapy with one of the following medications: <ul style="list-style-type: none"> ○ an antibiotic (eg metronidazole, ciprofloxacin), probiotic, corticosteroid enema/suppository, mesalamine



Drug	Medical Necessity for Ulcerative Colitis
	<p>enema/suppository</p> <p>AND</p> <ul style="list-style-type: none"> Adalimumab is being prescribed by or in consultation with a gastroenterologist
<p>Remicade® (infliximab) IV</p> <ul style="list-style-type: none"> First-line 	<p>Infliximab is subject to review for site of service administration.</p> <p>Infliximab may be considered medically necessary as a first-line agent in the treatment of ulcerative colitis when:</p> <ul style="list-style-type: none"> Patient has had a trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, golimumab, adalimumab, or a corticosteroid <p>OR</p> <ul style="list-style-type: none"> Patient has pouchitis <p>AND</p> <ul style="list-style-type: none"> Patient as tried therapy with one of the following medications: <ul style="list-style-type: none"> an antibiotic (eg metronidazole, ciprofloxacin), probiotic, corticosteroid enema/suppository, mesalamine enema/suppository <p>AND</p> <ul style="list-style-type: none"> Infliximab is being prescribed by or in consultation with a gastroenterologist
First-line α-4 Integrin Inhibitor	
<p>Entyvio® (vedolizumab) IV</p> <ul style="list-style-type: none"> First-line 	<p>Entyvio® (vedolizumab) is subject to review for site of service administration.</p> <p>Vedolizumab may be considered medically necessary as a first-line agent in the treatment of ulcerative colitis when:</p> <ul style="list-style-type: none"> Patient has had a trial and treatment failure with one of the following agents: <ul style="list-style-type: none"> Azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, infliximab, adalimumab, golimumab, or a corticosteroid <p>OR</p> <ul style="list-style-type: none"> Patient has pouchitis <p>AND</p>



Drug	Medical Necessity for Ulcerative Colitis
	<ul style="list-style-type: none"> • Patient as tried therapy with one of the following medications: <ul style="list-style-type: none"> ○ an antibiotic (eg metronidazole, ciprofloxacin), probiotic, corticosteroid enema/suppository, mesalamine enema/suppository <p>AND</p> <ul style="list-style-type: none"> • Vedolizumab is being prescribed by or in consultation with a gastroenterologist
Second-line TNF-α Antagonists	
<p>Simponi® (golimumab) SC</p> <ul style="list-style-type: none"> • Second-line 	<p>Simponi® (golimumab) may be considered medically necessary as a second-line agent in the treatment of ulcerative colitis when:</p> <ul style="list-style-type: none"> • The patient has had a trial and treatment failure with at least three of the following: <ul style="list-style-type: none"> ○ Corticosteroids (eg, prednisone, prednisolone, dexamethasone, budesonide, etc.) <p>AND/OR</p> <ul style="list-style-type: none"> ○ Sulfasalazine <p>AND/OR</p> <ul style="list-style-type: none"> ○ Immunomodulatory drugs (eg, azathioprine, mercaptopurine, cyclosporine) <p>AND/OR</p> <ul style="list-style-type: none"> ○ Pentasa, Rowasa, or Asacol <p>AND</p> <ul style="list-style-type: none"> • The patient has had an inadequate response or intolerance to adalimumab <p>AND</p> <ul style="list-style-type: none"> • Golimumab is being prescribed by or in consultation with a gastroenterologist
<p>Inflectra® (infliximab-dyyb) IV and Renflexis® (infliximab-abda)</p> <ul style="list-style-type: none"> • Second-line <p>Note: Infliximab-dyyb (Inflectra®) and infliximab-abda are not approved for use in</p>	<p>Inflectra® (infliximab-dyyb) IV and Renflexis® (infliximab-abda) are subject to review for site of service administration.</p> <p>Infliximab-dyyb and infliximab-abda may be considered medically necessary as a second-line agent in the treatment of ulcerative colitis when:</p> <ul style="list-style-type: none"> • Patient has had a trial and treatment failure with one of the following agents:



Drug	Medical Necessity for Ulcerative Colitis
<p>pediatric ulcerative colitis.</p>	<ul style="list-style-type: none"> ○ Azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, adalimumab, golimumab, or a corticosteroid <p>OR</p> <ul style="list-style-type: none"> • Patient has pouchitis <p>AND</p> <ul style="list-style-type: none"> • Patient as tried therapy with one of the following medications: <ul style="list-style-type: none"> ○ an antibiotic (eg metronidazole, ciprofloxacin), probiotic, corticosteroid enema/suppository, mesalamine enema/suppository <p>AND</p> <ul style="list-style-type: none"> • Patient has had an inadequate response or intolerance to Remicade® (infliximab) <p>AND</p> <ul style="list-style-type: none"> • Infliximab-dyyb or infliximab-abda is being prescribed by or in consultation with a gastroenterologist
<p>Xeljanz® (tofacitinib) (oral, immediate-release ONLY)</p> <ul style="list-style-type: none"> • Second-line <p>Note: Xeljanz XR is not approved for use in ulcerative colitis.</p>	<p>Xeljanz® (tofacitinib) immediate-release may be considered medically necessary as a second-line agent in the treatment of adult patients with ulcerative colitis when:</p> <ul style="list-style-type: none"> • The patient has had a trial and treatment failure with one systemic agent (eg, 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone) or was intolerant to one of these agents for ulcerative colitis. • NOTE: A previous trial of a biologic [eg, adalimumab (Humira), infliximab IV (Remicade, Renflexis, Inflectra), golimumab SC (Simponi), or vedolizumab IV (Entyvio)] also counts as a trial of one systemic agent for UC. <p>AND</p> <ul style="list-style-type: none"> • Tofacitinib (Xeljanz) is prescribed by or in consultation with a gastroenterologist.

Coding



Code	Description
HCPCS	
J0135	Injection, adalimumab (Humira®), 20mg
J0717	Injection, certolizumab pegol (Cimzia®), 1 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J1745	Injection, infliximab (Remicade®), 10mg
J2323	Injection, natalizumab, (Tysabri®), 1mg
J3357	Injection, ustekinumab (Stelara®), 1 mg
J3358	Ustekinumab (Stelara®), for intravenous injection, 1 mg
J3380	Injection, vedolizumab (Entyvio®), 1 mg
Q5102	Injection, infliximab (Inflectra®) (Renflexis™), 10 mg (code terminated 4/1/18)
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra®), 10 mg (new code effective 4/1/18)
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis™), 10 mg (new code effective 4/1/18)
Q5109	Injection, infliximab-qbtx, biosimilar, (ixifi), 10 mg (new code effective 1/1/19)

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 described in this policy for medical necessity of select intravenous and injectable therapy services is 13 years of age or older. The age criterion is based on the following: Pediatric patients are not small adults. Pediatric patients differ physiologically, developmentally, cognitively, and emotionally from adult patients, and vary by age groups from infancy to teen. Children often require smaller doses than adults, lower infusion rates, appropriately sized equipment, the right venipuncture site determined by therapy and age, and behavioral management during administration of care. Specialty infusion training is therefore necessary for pediatric IV insertions and therapy. Due to pediatrics unique physiology and psychology, site of service review is limited to patients above the age of 13.



The ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for this drug.

Evidence Review

Crohn Disease (CD)

The American College of Gastroenterology indicates current therapeutic recommendations depend on disease location, disease severity, and the presence of disease-associated complications. Pharmacologic approaches include various 5-aminosalicylates (5-ASAs), corticosteroids, and immunosuppressants. While the effectiveness of the 5-ASAs is less than corticosteroids, their side effect profile is more favorable. Azathioprine and sulfasalazine are also associated with clinically significant long-term toxicity, according to the National Cooperative Crohn's Disease Study. Azathioprine, sulfasalazine, and prednisone have not been demonstrated to prevent recurrence of disease flares.

Surgical resection is a common occurrence in CD, with up to 57% of patients requiring at least one surgery in any given year. Within 10 years of disease onset, 71% of patients undergo this therapy.

Clinical trials with Remicade® (infliximab) in patients with moderate to severe CD have shown that Remicade significantly reduces symptoms, improves quality of life, provides endoscopic evidence of mucosal healing, and reduces recurrence rates allowing for fewer hospitalizations and invasive procedures. Additionally, patients with fistulizing disease were able to achieve a reduction in the number of draining enterocutaneous and rectovaginal fistulas.

Inflectra® (infliximab-dyyb) is a biosimilar to Remicade® (infliximab) approved for the same indications, with the exception of ulcerative colitis in pediatric patients. For a full list of indications and details on the clinical trials information please refer to the package insert for Inflectra®. The safety and efficacy of adalimumab (Humira) for the induction and/or maintenance of remission in patients with moderately to severely active CD (Crohn Disease Activity Index [CDAI] ≥ 220 and ≤ 450) was evaluated in four randomized placebo-controlled studies. Two of these studies evaluated Humira for induction of remission (defined as a CDAI < 150), one study in patients who were TNF antagonist naïve (CLASSIC-I) and the other in patients who had lost response or were intolerant to Remicade (GAIN). Two of these studies evaluated Humira for maintenance of remission, both studies in patients who were TNF antagonist naïve (CLASSIC-II and CHARM).



In CLASSIC-I, 299 patients with moderately to severely active CD, including patients with draining fistulas, were randomized to two subcutaneous injections at Weeks 0 and 2 with Humira 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo. Enrollees were also able to maintain existing therapy with immunomodulatory agents, corticosteroids, and/or aminosalicylates. The primary efficacy endpoint was induction of remission (CDAI <150) at Week 4. The rate of remission was significantly higher in the 160 mg/80 mg group (36%, $p=0.001$), but not for the 40 mg/20 mg (18%, $p=0.36$) or 80 mg/40 mg (24%, $p=0.06$) groups compared with placebo (12%). Injection site reactions occurred more frequently in Humira-treated patients, otherwise adverse events occurred at similar frequencies in all four treatment groups.

In GAIN, 325 patients with moderately to severely active CD who were intolerant of, who had lost response, or who had an inadequate response to Remicade were randomized to two subcutaneous injections at Weeks 0 and 2 with Humira 160 mg/80 mg or placebo. Primary efficacy endpoint was induction of remission (CDAI <150) at Week 4. Clinical response (decrease in CDAI score ≥ 70 or 100) at Week 4 was also assessed. More Humira-treated patients (21%, $p<0.001$) achieved clinical remission compared to those treated with placebo (7%). More Humira-treated patients (52%, $p<0.01$) achieved a clinical response-70 compared with the placebo group (34%).

A total of 276 patients participating in CLASSIC-I enrolled in CLASSIC-II and received open-label Humira 40 mg subcutaneously at Weeks 0 (Week 4 of CLASSIC-I) and 2. Those patients ($n=55$) in remission at both Week 0 and Week 4 were re-randomized to Humira 40 mg QOW, 40 mg QW, or placebo for 52 additional weeks. Patients who were not in remission at both Weeks 0 and 4 were treated with open-label Humira 40 mg QOW. These patients were allowed to have their dose increase to 40 mg QW for non-response or disease flare. The re-randomized patients were also allowed to "escape" into this open-label arm with disease flare. The primary efficacy endpoint was maintenance of remission (CDAI <150) in randomized patients through week 56. Of the 55 patients randomized at Week 4, a greater proportion receiving Humira (79% of the Humira 40 mg QOW group and 83% of the 40 mg QW group, both $p<0.05$) were in remission compared to the placebo group (44%). Of 204 patients entering the open-label arm, 46% were in remission at Week 56. Humira was generally well-tolerated.

In CHARM, a total of 854 patients with moderately to severely active CD were treated with open-label Humira 80 mg at Week 0 followed by 40 mg at Week 2 as induction therapy. At Week 4, patients were stratified by clinical response (decrease of CDAI ≥ 70) and randomized to double-blind treatment with subcutaneous Humira 40 mg QOW, Humira 40 mg QW, or placebo weekly for 52 additional weeks. The proportion of randomized clinical responders achieving clinical remission at Week 26 and 56 were coprimary endpoints. At Week 4, 499/854 (58%) of patients achieved a clinical response-70 and were randomized to Humira or placebo. The percentage of



randomized responders in remission was significantly greater in the Humira 40 mg QOW and 40 mg QW groups compared to the placebo group at Week 26 (40%, 47%, and 17%, respectively; $p < 0.001$) and at Week 56 (36%, 41%, and 12%, respectively; $p < 0.001$). No significant differences in efficacy were observed between the two active treatment groups. Patients who did not achieve clinical response after 12 weeks were unlikely to achieve response. The safety profile for Humira was consistent with previous experience with the drug. More patients receiving placebo (13.4%) discontinued treatment for an adverse event than those receiving Humira (6.9% in the 40 mg QOW and 4.7% in the 40 mg QW group).

Two randomized controlled Phase III trials, PRECiSE 1 and PRECiSE 2, demonstrated the safety and efficacy of Cimzia 400 mg SC at Weeks 0, 2, 4 and then every four weeks versus placebo for up to 24 weeks. In the induction study, patients who had C-reactive protein (CRP) levels > 10 mg/L at baseline who were treated with certolizumab had higher response rates than placebo-treated patients (37% versus 26%; $p = 0.04$) at Week 6. In the overall population, response rates were significantly higher with certolizumab vs. placebo (23% versus 16%; $p = 0.02$). There were no significant differences in remission rates at Week 6 or 26 between certolizumab and placebo. Overall, certolizumab was well tolerated. The other trial investigated the efficacy of maintenance therapy in patients that had completed a standard induction course. In this study 64% of all initially enrolled patients achieved a clinical response (decrease in CDAI ≥ 150) at 6-weeks. Certolizumab produced significantly better maintenance of clinical response than placebo through Week 26 (62% versus 34%, $p < 0.001$) in patients with CRP ≥ 10 mg/L. Maintenance treatment with CIMZIA showed significantly better remission rates than placebo at Week 26 (48% versus 29%, $p < 0.001$) in the ITT population. The adverse event profiles observed in these studies was similar to that seen with other anti-TNF agents.

The ENCORE, ENACT-1 and ENACT-2 trials found that the use of Tysabri in adults with moderate to severe CD significantly increased the percent of patients with a clinical response and those in clinical remission. In patients shown to be responders after 12-weeks of induction therapy, response rates and remission rates were significantly greater with Tysabri.

The percent of patients with sustained remission after withdrawal of oral steroids was also significantly greater with Tysabri versus placebo at Weeks 36 and 60. For assessment of quality of life, patients treated with Tysabri experienced statistically and clinically significant improvements in both general measures (SF-36) and disease specific measures (IBDQ) beginning at Week 24 and continuing through Week 60 compared with placebo. From Week 24 through 60, patients treated with Tysabri had quality of life scores consistent with remission.

A 12-week trial in CD patients found a significantly higher incidence of headache, nasopharyngitis, and hypersensitivity-like reactions at Week 12. Development of anti-natalizumab antibodies at any post-baseline visit through Week 12 was more common with



natalizumab vs. placebo. Exacerbation of CD and discontinuations due to adverse events were more common with placebo than with Tysabri at Week 60. There was a higher incidence at Week 60 of influenza with natalizumab compared to placebo. Viral infections were more common with natalizumab compared to placebo. At Week 12, there was a higher incidence of hypersensitivity reactions during infusion with natalizumab versus placebo.

Tysabri was initially approved for the treatment of multiple sclerosis in November 2004. It was withdrawn from the market by the manufacturer in February 2005 after three patients in clinical trials developed progressive multifocal leukoencephalopathy (PML). The FDA stopped clinical trials for the product in February 2005. Following no new cases of PML, the FDA allowed Tysabri to return to the market in June 2006 with the requirement of a risk minimization program to be in place to limit use. Patient registration and periodic follow-up is also required. In August 2008, two additional cases of PML were reported in European Tysabri patients, bringing the total to five. Both patients were taking the drug for multiple sclerosis. Both had received at least one year of therapy and neither was receiving any other biologic immunomodulator concurrently. The implications for Crohn patients remain unclear.

The TOUCH® program requires distribution of Tysabri only through centralized or specialty pharmacies that have registered and follow the strict requirements of patient assessment, monitoring, education, and follow-up. Tysabri is currently only approved for monotherapy as it is unclear if the risks of PML increase with concurrent use of other immunosuppressives. Notably, the use of concomitant immunosuppressives was associated with PML in three cases, of which two patients were being treated for MS and one for CD.

The safety and efficacy of vedolizumab (Entyvio™) were evaluated in 3 Phase III, double blinded, placebo controlled, multicenter, randomized clinical trials—two in Crohn disease and one in ulcerative colitis. There were total of 3,326 patients participated in these trials. There were high discontinuation rates across all arms of the trials (51% to 62%), most often for a lack of efficacy (59% to 69%). Discontinuation did not appear to be different between placebo and drug arms and intention-to-treat efficacy analysis was performed to generate the data.

GEMINI 2 trial shows efficacy of vedolizumab in patients with Crohn disease. The study populations had a mean duration of disease of 9 (SD: 7.8) years and 51% of patients were on glucocorticoids with median prednisone dose of 20 mg. At week 6, 15% of patients in the vedolizumab arm and 7% of the patients in the placebo arm had a clinical response ($p=0.02$). In the maintenance trial, which included only those responded to the induction therapy, 39% of those assigned to VDZ Q8W were in clinical remission at week 52, compared with 22% assigned to placebo ($p<0.001$). Clinical remission is defined as CDAI score ≤ 150 . Durable clinical remission was 21% in the VDZ Q8W group compared with 14% in the placebo group ($p=NS$).



Glucocorticoid-free remission was 32% in the VDZ Q8W compared with 16% in the placebo group (p=0.02).

GEMINI 3 trial tested the efficacy of vedolizumab in patients with Crohn disease but it was discontinued after the induction phase due to lack of efficacy. The study authors explained that the statistically non-significant effect of vedolizumab as induction therapy could be related to the baseline disease severity and heavily pretreated disease state in the study population. Only the abstract is available on GEMINI 3 trial.

During the trial, 56 of 1434 (4%) of patients treated with vedolizumab had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects with persistently positive anti-vedolizumab antibody, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

In April 2013, Feuerstein, et al., reported results of a systematic review of treatment recommendations by international guidelines for Crohn disease. Of the 89% of guidelines that graded evidence, only 23% of treatment recommendations were supported by level A evidence, and 28% by level B; thus, approximately half the recommendations were based on lower quality evidence or expert opinion. This reflects the difficulties encountered in treating this perplexing disease. Policy updated to include new labeled indication of golimumab to treat ulcerative colitis. A full review of this policy will be scheduled later in the year.

August 2013: As the most recent US and European guidelines for the treatment of adults with Crohn disease call into question the efficacy of 5-ASAs for induction or maintenance of remission for this condition, their use prior to approval of a TNF- α inhibitor is no longer a requirement in Crohn disease. The efficacy of 5-ASAs for induction or maintenance of remission in ulcerative colitis remains established and use prior to approval of a TNF α inhibitor remains a requirement in this condition.

However, several new themes or trends have been identified and should be followed. These included a potential new therapeutic goal of "deep remission", defined as a Crohn disease activity index (CDAI) score <150 and complete mucosal healing on endoscopy. A Crohn Disease Digestive Damage Score (Lémann score) has been developed to measure cumulative bowel damage in patients with this condition. Similar to the Sharp score for assessing joint damage in rheumatoid arthritis (RA), the Lémann score may be used to assess the effect of various pharmacological therapies, function as a clinical trial endpoint, and allow better identification of high-risk patients in regard to identification or progression of bowel damage. Also analogous to



RA, there is momentum growing in Crohn for use of disease modifying agents (eg, TNF- α inhibitors) early in the disease course to avoid later complications and need for surgery, particularly in patients with poor prognostic factors. Combination therapy with an immunosuppressive and a TNF- α inhibitor is also promising. However, robust supporting scientific evidence for these emerging trends is still lacking. New compounds currently in phase II and/or III development for use in IBD include ustekinumab (Stelara®), Xeljanz® (tofacitinib), and vedolizumab.

Stelara® (ustekinumab)

Stelara® (ustekinumab) is a human IgG1 κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring cytokines that are involved in inflammatory and immune responses, such as naturalkiller cell activation and CD4+ T-cell differentiation and activation. In in vitro models, ustekinumab was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-12R β 1. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn Disease. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab, was shown to be protective.

Stelara® (ustekinumab) was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn disease (Crohn Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy. Studies CD-1 and CD-2 In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n=741; CD-2, n=627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of Stelara® at either approximately 6 mg/kg, placebo, or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the



patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 319 in the Stelara® approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-mercaptopurine, azathioprine, methotrexate; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). The median baseline CDAI score was 286 in the STELARA® and 290 in the placebo group. In these induction studies, a greater proportion of patients treated with Stelara® achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo. Clinical response and remission were significant as early as Week 3 in Stelara® treated patients and continued to improve through Week 8.

Study CD-3

The maintenance study (CD-3), evaluated 388 patients who achieved clinical response (≥ 100 point reduction in CDAI score) at Week 8 of induction with Stelara® in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg STELARA® every 8 weeks or placebo for 44 weeks. At Week 44, 47% of patients who received STELARA® were corticosteroid-free and in clinical remission, compared to 30% of patients in the placebo group. At Week 0 of Study CD-3, 34/56 (61%) Stelara® treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44. At Week 0 of Study CD-3, 46/72 (64%) Stelara® treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of Stelara® treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm. Patients who were not in clinical response 8 weeks after STELARA® induction were not included in the primary efficacy analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of Stelara®



upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

Ulcerative Colitis (UC)

The safety and efficacy of Remicade were assessed in two randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) with an inadequate response to conventional oral therapies.¹⁵ In both studies, patients were randomized to receive either placebo, 5 mg/kg Remicade or 10 mg/kg Remicade at Weeks 0, 2, 6, 14 and 22.

Patients in study 1 had failed to respond or were intolerant to oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). Patients in study 2 had failed to respond or were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients in studies 1 and 2 were receiving corticosteroids (61% and 51%, respectively), 6-MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in study 2 than 1 were taking solely aminosalicylates for UC (26% versus 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by 30% and 3 points, accompanied by a decrease in the rectal bleeding subscore of 1 or a rectal bleeding subscore of 0 or 1.

In both studies, greater percentages of patients in both Remicade groups achieved a clinical response, a sustained clinical response (response at both Weeks 8 and 30), clinical remission and other assessed clinical outcomes than in the placebo group. Of patients on corticosteroids at baseline, greater proportions of patients in the Remicade treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in Remicade treatment groups vs. 10% in placebo group in study 1; 23% in Remicade treatment groups vs. 3% in placebo group in study 2). Clinical outcomes were generally similar in the Remicade 5 mg/kg and 10 mg/kg dose groups.

After positive reports in small open-label trials, the safety and efficacy of adalimumab (Humira) was assessed in a multicenter, double-blinded randomized controlled trial in patients with moderate to severe ulcerative colitis who were anti-TNF naïve and on stable suppressive therapy with oral corticosteroids and/or immunomodulators. A total of 576 patients were randomized to receive either placebo, high dose (HD), or low dose (LD) adalimumab. HD was 180/60/40/40mg and LD was 80/40/40/40mg of adalimumab at Weeks 0, 2, 4, 6, respectively. Clinical remission was defined as a Mayo score \leq 2 with subscores no greater than 1. Secondary outcomes included absolute score decrease plus decrease in rectal bleeding subscore, proportion with mucosal healing, and proportion with mild disease (including physician global assessment [PGA],



rectal bleeding, and stool frequency subscores). Because the European regulatory authorities wanted to include a LD of adalimumab, there were two parts to the study, a 1:1 with HD (n=186) and a 1:1:1 portion of the study (n=390); results were pulled from the latter.

Twice as many patients reached clinical remission at Week 8 with HD ($p=0.031$) therapy, while LD patients were not significantly different versus placebo. Of the secondary outcomes, subscores in rectal bleeding and PGA showed improvement with significance vs. placebo in the HD arm. Patients with higher baseline CRP levels had less instances of remission, and higher placebo rates were seen in Canadian and Eastern European centers than those in the US. Discontinuation rates were similar in each arm, with UC being the most common reason. Injection site pain was minimal and infection incidence was similar across groups, and malignancy was only seen in the placebo arm.

The safety and efficacy of golimumab (Simponi) were evaluated in two multi-center, randomized, double-blind, placebo-controlled clinical trials in patients ≥ 18 years of age (Trials UC-1 and UC-2). Trial UC-1 was an induction trial conducted in patients with moderately to severely active UC, defined as a Mayo score of 6 to 12 [the Mayo score ranges from 0 to 12 and has four subscales that are each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment]. At baseline, subjects also had an endoscopy subscore of 2 or 3 on a 3-point scale (an endoscopy score of 2 is defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 is defined by spontaneous bleeding, ulceration). Patients were corticosteroid dependent (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response to or had failed to tolerate at least one of the following therapies: oral aminosaliclates, oral corticosteroids, azathioprine, or 6-mercaptopurine.

Trial UC-1 was divided into 2 parts. In Part 1 (dose finding), patients were randomized to one of 4 treatment groups: 400 mg golimumab administered subcutaneously (SC) at Week 0 and 200 mg at Week 2 (400/200 mg), 200 mg golimumab SC at Week 0 and 100 mg at Week 2 (200/100 mg), 100 mg golimumab SC at Week 0 and 50 mg at Week 2 (100/50 mg), or placebo SC at Weeks 0 and 2. In Part 2 (dose confirming), 771 patients were randomized to receive either 400 mg golimumab SC at Week 0 and 200 mg at Week 2, 200 mg golimumab SC at Week 0 and 100 mg at Week 2, or placebo SC at Weeks 0 and 2. golimumab 100/50 mg SC was not evaluated in Part 2; its safety and effectiveness has not been established in UC. Concomitant stable doses of oral aminosaliclates (5-ASA), oral corticosteroids (less than 40 mg/day), azathioprine (AZA), 6-mercaptopurine (6-MP), and/or methotrexate (MTX) were permitted. Patients who received previous TNF inhibitors were excluded. The primary endpoint was the percent of patients in clinical response at Week 6, defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and



≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 (no blood seen) or 1 (streaks of blood with stool less than half the time).

Trial UC-2 was a randomized-withdrawal maintenance trial that evaluated 463 patients who achieved clinical response with golimumab induction and tolerated golimumab treatment. Patients were randomized to receive golimumab 50 mg, golimumab 100 mg or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, azathioprine, 6-mercaptopurine, and/or methotrexate were permitted. Corticosteroids were to be tapered at the start of the maintenance trial. The primary endpoint was the percent of patients maintaining clinical response through Week 54.

In Trial UC-1, a greater proportion of patients achieved clinical response, clinical remission and had improvement of endoscopic appearance of the mucosa at Week 6 in the golimumab 200/100 mg group compared with the placebo group. The golimumab 400/200 mg group did not demonstrate additional clinical benefit over the golimumab 200/100 mg group. Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore > 1. Improvement of endoscopic appearance of the mucosa was defined as a Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern, mild friability).

In Trial UC-2, a greater proportion of patients maintained clinical response through Week 54 in the golimumab 100 mg group compared with the placebo group. In Trial UC-2, golimumab-treated patients in clinical response (which included the subset of patients in clinical remission) in Trial UC-1, were again assessed for clinical remission at Week 30 and Week 54. A greater proportion of patients achieved clinical remission at both Weeks 30 and 54 without demonstrating a loss of response at any time point through Week 54 in the golimumab 100 mg group compared with the placebo group.

The GEMINI 1 trial tested the efficacy of vedolizumab in patients with ulcerative colitis. The study populations had a mean duration of disease of 6.9 (SD: 6.4) years and 53% of patients were on glucocorticoids with median prednisone dose of 20 mg. At week 6, 47.1% of patients in the vedolizumab arm and 25.5% of the patients in the placebo arm had a clinical response ($p < 0.001$). In the maintenance trial, which included only those responded to the induction therapy, 41.8% of those assigned to VDZ Q8W were in clinical remission at week 52, compared with 15.9% assigned to placebo ($p < 0.001$). Clinical remission is defined as complete Mayo score of ≤2 points and no individual subscore >1 point. Durable clinical remission was 20.5% in the VDZ Q8W group compared with 8.7% in the placebo group ($p = 0.008$). Glucocorticoid-free remission was 31.4% in the VDZ Q8W compared with 13.9% in the placebo group ($p < 0.001$).



Xeljanz® (tofacitinib)

Xeljanz® (tofacitinib) 10mg twice daily was studied in two eight-week induction trials, OCTAVE Induction 1 (n=598) and Induction 2 (n=541), in moderate-severe ulcerative colitis in patients previously treated with TNF- α antagonists. The primary end point was remission at 8 weeks. Patients achieving remission were randomized to continue on maintenance therapy with either 5 or 10 mg twice daily or placebo. The primary end point was remission at 52 weeks. In OCTAVE Induction 1, remission at 8 weeks occurred in 18.5% of the tofacitinib patients versus 8.2% in the placebo group (P = 0.007); in OCTAVE Induction 2, remission occurred in 16.6% versus 3.6% (P<0.001). In the OCTAVE Sustain trial, 34.3% of the patients in the 5-mg group and 40.6% in the 10-mg group versus 11.1% in the placebo group (P<0.001 for both comparisons with placebo). In OCTAVE Induction, rates of serious infection were higher with tofacitinib than placebo. In OCTAVE Sustain, the rate of serious infection was similar across the three treatment groups, and the rates of overall infection and herpes zoster infection were higher with tofacitinib than placebo. Across all three trials, nonmelanoma skin cancer occurred in five tofacitinib patients and one placebo patient. Cardiovascular events occurred in five tofacitinib and no placebo patients. Tofacitinib was associated with increased lipid levels versus placebo.

Toxicities of TNF- α Antagonists

There have been no prospective trials evaluating safety among the TNF- α inhibitors. The risk of malignancies and serious infections has been studied to some depth retrospectively with the three older agents (adalimumab, etanercept and infliximab). The FDA did a meta-analysis of the available data in 2006 and found that the malignancy rates of patients on TNF- α inhibitors are no higher than what is to be expected in this patient population. Another study done in 2007 found a higher incidence of cutaneous cancers among the TNF- α inhibitor treated patients, irrespective of the agent. The newer agents are limited in their data breadth to demonstrate safety with respect to malignancies, but so far they compare similarly to the older agents. Long-term safety evaluations are necessary to validate this finding.

With regards to serious infections and tuberculosis, there are higher rates of serious infections while on the TNF- α inhibitors, compared to MTX alone. However, the retrospective studies do not come to an agreement on the actual risk. Infliximab showed higher rates of any infection compared to etanercept and adalimumab, and also showed higher rates of serious infections with the 10mg/kg dosing regimen versus the 3mg/kg dosing regimen. The newer agents (certolizumab and golimumab) showed increased risk of serious infections, but this data is not



comparable with the older agents. This class of agents also has been associated with hepatitis B reactivation, CHF exacerbations, and new onset or exacerbation of demyelinating disorders.

2018 Update

A literature search was conducted from 3/1/2017 to 3/5/2018. No new studies were found that would require changes to policy. Toxicities of TNF inhibitors section revised to exclude non-IBD disease states.

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History

Date	Comments
07/01/16	New policy, approved June 14, 2016. Add to Prescription Drug section. Policy content removed from 5.01.550. This policy addresses the medically necessary pharmacological treatment for IBD and includes site of service IV therapy administration criteria for applicable drugs.
11/01/16	Interim review, approved October 11, 2016. Clarified age criteria language indicating that site of service review is applicable to only those age 13 and older; drug criteria review applies to all ages. Inclusion of Stelara with its new indication for use in Crohn's disease (along with the description and clinical trials information).
12/01/16	Interim review, approved November 8, 2016. Clarification added regarding Inflectra's covered indications: not approved for pediatric UC.
03/14/17	Annual review, changes to be come effective April 1, 2017. Added administration route to each drug, as well as included a statement on the status of IV agents being processed exclusively through the medical benefit.
03/22/17	Interim update. Cimzia in the setting of Crohn disease now has an extra step that requires a trial and failure of either Humira or Stelara. Effective April 1, 2017.
04/10/17	Interim update. Policy section updated with infliximab (Remicade®) IV and vedolizumab (Entyvio®) moving to first-line agents, considered medically necessary as when criteria are met.
05/05/17	Minor update; added hyperlinks and step therapy graphs.
07/01/17	Interim review, approved June 13, 2017. Added coverage criteria for Renflexis® (infliximab-abda). Added adalimumab step to Stelara SC.
07/14/17	Coding updated, added HCPCS code Q9989 (new code effective 7/1/17).
09/01/17	Interim review, approved August 15, 2017 Added coverage criteria for Xeljanz (tofacitinib) in Ulcerative Colitis. Clarified second line status of Stelara in Crohn's.



Date	Comments
	Added Renflexis coding.
11/01/17	Interim Review, approved October 3, 2017. Clarified site of service exception criterion related to access: There is no outpatient infusion center within 50 miles of the patient's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.
01/01/18	Coding update; added HCPCS code J3358 (new code effective 1/1/18).
02/14/18	Interim Review, approved February 6, 2018. Stelara has been moved from second line agent to first line agent for Crohn Disease with removal of mandatory step through Humira in criteria. Approved February 13, 2018, to update hospital based outpatient coverage from 30 days to 90 days.
04/01/18	Coding update; added new HCPCS codes Q5103 and Q5104 (effective 4/1/18), noted that Q5102 terminated 4/1/18.
05/01/18	Annual Review, approved April 18, 2018. A literature search was conducted from 3/1/2017 to 3/5/2018. No new studies were found that would require changes to policy. Toxicities of TNF inhibitors section revised to exclude non-IBD disease states. Added suppositories as one of the options for corticosteroid and mesalamine products for ulcerative colitis. Dosing table was removed.
06/01/18	Interim Review approved May 17, 2018. Removed ulcerative colitis indication for Xeljanz as it is not FDA approved indication.
08/01/18	Interim Review, approved July 13, 2018. Added criteria and references for tofacitinib to treat ulcerative colitis.
11/01/18	Minor update, the Site of Service criteria was updated for clarity.
01/01/19	Interim Review, approved December 13, 2018. Clarified criteria for Humira under the ulcerative colitis section. Minor clarification to Consideration of Age statement. Added new HCPCS code Q5109 (new code effective 1/1/19). Removed code Q9989 from policy as it was terminated 1/1/18.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



Discrimination is Against the Law

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

Premera:

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

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

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

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

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

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

Getting Help in Other Languages

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

አማርኛ (Amharic):

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

العربية (Arabic):

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

中文 (Chinese):

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

Oromoo (Cushite):

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

Français (French):

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

Kreyòl ayisyen (Creole):

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

Deutsche (German):

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

Hmoob (Hmong):

Tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas pab kom koj ua tsis pub dhau cov caij nyuog 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).

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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).

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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。

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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 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.

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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 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. 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).