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Medication Policy Manual

Policy No: dru160

Topic: Cimzia[®], certolizumab pegol

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Certolizumab pegol (Cimzia[®]) binds to and inhibits the activity of tumor necrosis factor (TNF), a chemical in the body that causes inflammation. Certolizumab pegol is used for the treatment of Crohn's disease and rheumatoid arthritis. Certolizumab pegol is administered as a subcutaneous injection, either by the patient or a health care professional.

Policy/Criteria

- I.** Most contracts require prior authorization approval of certolizumab pegol prior to coverage. Certolizumab pegol may be considered medically necessary in patients when criteria A or B below are met:

- A.** Crohn's disease when criteria 1 and 2 below are met:

- 1.** Acute treatment of an exacerbation of Crohn's disease when at least one of the following criteria a, b, or c below is met.

- a.** Treatment with an adequate course of systemic corticosteroids (e.g., 40 mg to 60 mg prednisone per day for 7 to 14 days) has been ineffective or is contraindicated.

OR

- b.** The patient has been unable to taper off of an adequate course of systemic corticosteroids without experiencing worsening of disease.

OR

- c.** The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least 2 months on an immunomodulatory medication (such as azathioprine, mercaptopurine, cyclosporine, or methotrexate).

AND

- 2.** Either criteria a or b below is met:

- a.** Infliximab (Remicade[®]) is not effective after at least an initial induction period (5 mg/kg on weeks 0, 2 and 6), except if not tolerated due to documented clinical side effects.

OR

- b.** Adalimumab (Humira[®]) is not effective after at least an initial 3-dose induction period, except if not tolerated due to documented clinical side effects.

OR

B. Rheumatoid Arthritis when criteria 1, 2, and 3 below are met:

- 1.** The diagnosis of RA has been established by a rheumatologist OR by the criteria in Appendix 1.

AND

- 2.** Methotrexate is ineffective after at least a 6 to 12 week treatment course based on documentation which includes one or more of the assessment components listed in Appendix 2 except if methotrexate is contraindicated or not tolerated based on clinical documentation.

AND

- 3.** Etanercept (Enbrel[®]) and adalimumab (Humira[®]) are each not effective after at least a 12-week treatment course except if not tolerated due to documented clinical side effects.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence considers certolizumab pegol to be a self-administered medication.

B. When prior authorization is approved, certolizumab pegol may be authorized in quantities as follows:

- 1.** Initial Authorization: When prior authorization is approved, certolizumab pegol may be covered in quantities up to 10 of the 200 mg vials in the first 12 weeks.
- 2.** Continued Authorization: If documentation is provided that the initial treatment period has been effective, certolizumab pegol may be covered in quantities of 2 of the 200 mg vials or syringes each month.

C. Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Certolizumab pegol is considered investigational when used for all other conditions including, but not limited to, ulcerative colitis.

Position Statement

Treatment of Crohn's disease and ulcerative colitis ^[1,5-8]

- There are many treatments for Crohn's disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
 - Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD.
 - When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies are often the best value.
- * First-line therapies to induce remission include:
 - Patients with CD: oral corticosteroids, methotrexate, aminosalicylates, azathioprine, mercaptopurine.
 - Patients with UC: oral aminosalicylates (e.g., sulfasalazine), topical mesalamine (i.e., rectally administered), topical corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
 - Due to the potential for severe adverse effects, the use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate-to-severe disease who failed to respond to first-line therapies. Use is generally limited in duration and frequency.
 - Corticosteroids such as prednisone are effective in both patients with Crohn's disease and patients with ulcerative colitis. Dosages in the range of 40 mg to 60 mg/day or 1 mg/kg/day of prednisone or equivalent are effective for induction of remission. ^[49-51]
 - * First-line therapies to maintain remission include:
 - Patients with CD: methotrexate and azathioprine.
 - Patients with UC: topical mesalamine (i.e., rectally administered), oral aminosalicylates (e.g., sulfasalazine), topical corticosteroids, or oral corticosteroids, depending on the extent and location of disease.

- When non-medical therapies and oral/topical medications are inadequate, the biologic medications, adalimumab (CD only) or infliximab (CD and UC) may be appropriate. Because of flaws in the clinical studies, the role of certolizumab and natalizumab in Crohn's disease remain uncertain.
- There is inadequate evidence to distinguish between the effectiveness of the TNF- α inhibitors adalimumab and infliximab for the management of patients with moderate-to-severe Crohn's disease. The evidence for certolizumab remains uncertain.
 - * Generally, these medications result in a remission of disease in about 1 in every 5 to 8 patients when compared with a placebo agent.
 - * There have been no direct comparative trials that have demonstrated a difference in clinical effect of safety of one agent over another.
 - * There is inadequate evidence to establish the efficacy of certolizumab in fistulizing Crohn's disease.
- Because of the risk of serious, sometimes fatal adverse events with natalizumab, it is recommended that it only be used after other treatment options have failed.
- In this class of medications, only infliximab has been adequately studied in the management of patients with ulcerative colitis. There is no reliable evidence that certolizumab or natalizumab are effective for ulcerative colitis.

Efficacy of biologic agents in Crohn's disease and ulcerative colitis ^[1,5-8]

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 1 summarizes the chances that certain biologic medications will improve disease symptoms such as the number and consistency of stools, pain, associated conditions, or weight loss, either initially or as on-going treatment, in patients with Crohn's disease or ulcerative colitis. ^{a,b}

Table 1: Chances of significantly improving symptoms of Crohn’s disease or ulcerative colitis with biologic medications (compared to no treatment).^[1,5-8]

Biologic Medications	Crohn’s Disease		Ulcerative Colitis
	Initial Treatment	Ongoing Treatment (6 months of treatment)	Ongoing Treatment (6 months of treatment)
infliximab (Remicade)	About 1 in 3 likely to benefit after 10 weeks of initial treatment NNT = 3	About 1 in 7 patients likely to benefit. NNT = 7 (range 5 - 8)	Uncertain
adalimumab (Humira)	About 1 in 7 patients likely to benefit after 6 weeks of treatment. NNT = 7 (range 5 – 8)	About 1 in 5 patients likely to benefit. NNT = 5	N/A
certolizumab (Cimzia)	Uncertain ^c		Not studied
natalizumab (Tysabri)	Uncertain ^c		Not studied

^a Crohn’s Disease: Benefit means control of symptoms, otherwise known as “remission”, defined as a total symptom score of no more than 150 on the Crohn’s Disease Activity Index (CDAI), a standard grading system for Crohn’s disease symptoms. This represents a significant improvement in Crohn’s disease symptoms.

^b Ulcerative colitis: Benefit means control of symptoms, otherwise known as “clinical response”, defined as a decrease from baseline in the Mayo score by 30% or more and 3 points or more, accompanied by a decrease in the rectal bleeding sub-score of 1 or more or a rectal bleeding sub-score of 0 or 1. These are standard measures of the severity of symptoms in ulcerative colitis, and represent a significant improvement in ulcerative colitis disease symptoms.

^c The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

Efficacy of certolizumab pegol in Crohn's disease

- Due to problems with study design, the efficacy of certolizumab pegol in the treatment of patients with moderate-to-severe Crohn's disease is uncertain. There are no head-to-head trials comparing certolizumab pegol with any other treatment for Crohn's disease. ^[2-4]
- In one 26-week double-blind study, 662 adults with moderate-to-severe Crohn's disease were randomized to receive either certolizumab pegol 400 mg (given as two – 200 mg injections) or placebo SC at weeks 0, 2, and 4, then every 4 weeks. ^[3]
 - * After 6 weeks, 35% of patients receiving certolizumab pegol experienced a response to treatment (defined as a decrease of 100 points or more on the Crohn's Disease Activity Index score – "CDAI") as compared with 27% of patients receiving placebo. This means that one of 13 patients treated with certolizumab pegol would have a meaningful response at 6 weeks, compared with giving placebo.
 - * Twenty-three percent of patients receiving certolizumab pegol experienced a response to treatment at both week 6 and 26, compared to 16% of patient receiving placebo. This means 15 patients would need to be treated with certolizumab pegol for up to 26 weeks for one patient to experience a sustained response to treatment, compared to placebo.
- Another 26 week double-blind, randomized controlled trial was conducted differently. In this trial, all patients (n=668) were administered certolizumab pegol 400 mg at weeks 0, 2 and 4. At week 6, 64% (n=428) of these patients experienced a response to therapy. These patients were then randomized to continue either certolizumab pegol 400 mg or placebo every 4 weeks. ^[3]
 - * At week 26, 63% of the patients continued on certolizumab experienced a response to therapy compared with 36% of the patients who continued on placebo. This means that, in patients that experienced a response to induction, 4 patients would need to be treated with certolizumab pegol instead of placebo to see one patient experience a response at 26 weeks.

Treatment of rheumatic disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis) ^[1,5,6, 11-16,19,20]

- There are many treatments for rheumatic disorders that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Nonmedical therapies, such as prescribed exercise therapy, physical therapy and weight loss, are important components in any treatment plan for patients suffering from a rheumatic disorder.
- When a systemic medication therapy is needed to manage one of the rheumatic disorders, oral therapies are usually the best value.
 - * Medications to control inflammation, such as nonsteroidal antiinflammatory medications (e.g., ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral and injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
 - * Orally administered disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine, are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
 - * Oral therapies have known potential risks. The management of these risks is well established.
- Methotrexate is considered effective in the treatment of RA and the standard reference DMARD to which newer DMARDs (etanercept, anakinra, adalimumab, and leflunomide) are compared for efficacy.
- When non-medical therapies and oral medications are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, certolizumab, or abatacept) may be appropriate. Rituximab has been studied in rheumatoid arthritis, but it's role in therapy remains uncertain at this time.
- No studies have shown that any of biologic medications is more effective than another in the treatment of rheumatic disorders, with the exception of indirect evidence that anakinra may be less effective than other alternatives.
 - * The biologic agents can decrease symptoms, help preserve joint functioning, and slow the progression of rheumatic disease.

- * There have been no reliable, direct-comparative trials that have demonstrated a difference in clinical effect or safety of one agent over another.
- * Individual responses and tolerability are unpredictable and may vary between patients.
- * Because responses vary, if one of the biologic agents provides an inadequate response, another biologic medication may yet be effective.
- * In RA, the best response is seen when methotrexate is used concomitantly with any of the biologics. Infliximab has been shown to be effective only when used with methotrexate. Treatment options other than infliximab should be considered for patients who cannot take methotrexate.

Efficacy of biologic agents in rheumatic conditions ^[1,5,6, 11-16,19,20]

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 1 summarizes the chances that certain biologic rheumatologic medications will improve joint pain and stiffness in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:

Table 1: Chances of improving joint pain and stiffness by at least 20% after three to six months of treatment with biologic medications (compared to no treatment).

Biologic Medications (when used with methotrexate)	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis
adalimumab (Humira)	About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4)	About 1 in 3 likely to benefit ^a	About 1 in 4 likely to benefit ^a
etanercept (Enbrel)			
infliximab (Remicade)		NNT = 3	NNT = 4 (Range 3-4)
certolizumab (Cimzia)		N/A	N/A
golimumab (Simponi)	About 1 in 5 likely to benefit NNT = 5	About 1 in 3 likely to benefit NNT = 3	About 1 in 3 likely to benefit NNT = 3
abatacept (Orencia)	About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4)	N/A	N/A
anakinra (Kineret)	About 1 in 7 likely to benefit ^a NNT = 7	N/A	N/A
rituximab (Rituxan)	Uncertain ^b	N/A	N/A

^a Benefit = at least 20% improvement in joint pain and stiffness after six months of treatment.

^b The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

- There is reliable evidence that etanercept, adalimumab, and abatacept (when given with methotrexate) are effective in the management of patients with juvenile idiopathic arthritis (JIA). The design of the clinical studies prevents calculation of “number-needed-to-treat” (NNT) for this use. [1,5,6, 11-16,19,20]

Efficacy of certolizumab pegol in rheumatic disorders

- In two double-blind, placebo-controlled trial a total of 1,601 patient patients were randomized to receive certolizumab pegol 200 mg, 400 mg, or placebo every 2 weeks (following a loading dose of 400 mg at weeks 0, 2, and 4) along with methotrexate for 24 weeks. At the end of 24 weeks, 57% to 59% of patients who received certolizumab pegol plus methotrexate experienced at least a 20% improvement in the symptoms of their rheumatoid arthritis, compared to only 9 to 14% of patients receiving a methotrexate treatment alone.. [1,9,10]

Safety of certolizumab pegol

- Certolizumab pegol carries a black-box warning for tuberculosis (TB) (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections that have been observed in patients receiving certolizumab. [1,4]
- Serious adverse events observed with the use of certolizumab in the treatment of Crohn’s disease include serious infections, tuberculosis, hepatitis B virus reactivation, malignancies, hypersensitivity reactions, neurologic and hematologic reactions, use with anakinra, heart failure, autoimmunity, immunizations, and immunosuppression. [1,4]
- The most common issues observed with the use of certolizumab in the treatment of Crohn’s disease include (incidence \geq 5% and higher than placebo): upper respiratory tract infection (20%), urinary tract infection (7%), and worsening joint pain (6%). [1,4]

Dosing and administration of certolizumab pegol

- For the treatment of moderate-to-severe Crohn’s disease: 400 mg subcutaneously (given as two SC injections of 200 mg each) initially and at weeks 2 and 4. If response occurs, follow with 400 mg SC (given as two SC injections of 200 mg each) every four weeks. ^[1,4]
- For the treatment of rheumatoid arthritis: 400 mg initially subcutaneously (given as two SC injections of 200 mg each) and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, 400 mg every 4 weeks can be considered. ^[1,4]
- There is no evidence that higher doses of certolizumab (Cimzia) result in improved response to therapy. ^[1,4]

Appendix 1: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) ^[21]	
Diagnosis of RA requires the presence of at least 4 of 7 criteria below:	
1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3.	Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4.	Symmetric (bilateral joint) involvement for > 6 weeks.
5.	Presence of rheumatoid nodules.
6.	Positive serum rheumatoid factor.
7.	Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 2: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) ^[14]

-	Tender joint count.
-	Swollen joint count.
-	Patient's assessment of pain.
-	Patient's global assessment of disease activity.
-	Physician's global assessment of disease activity.
-	Patient's assessment of physical function.
-	Acute phase-reactant measures (erythrocyte sedimentation rate or C-reactive protein levels).

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Cross References
Enbrel [®] , etanercept dru035
Humira [®] , adalimumab dru081
Remicade [®] , infliximab dru036
Kineret [®] , anakinra dru049
Tysabri [®] , natalizumab dru111
Orencia [®] , abatacept dru129
Simponi [®] , golimumab dru183

Codes	Number	Description
HCPCS	J3590	Unclassified biologics