certolizumab pegol (Cimzia®)

Policy # 00200
Original Effective Date: 06/18/2008
Current Effective Date: 03/19/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Crohn’s Disease
Based on review of available data, the Company may consider certolizumab pegol (Cimzia®) for the treatment of Crohn’s disease to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of certolizumab pegol (Cimzia) for the treatment of Crohn’s disease will be considered when all of the following criteria are met:
- Patient is 18 years of age or older; and
- Patient has moderately to severely active Crohn’s disease; and
- Patient has failed treatment with conventional therapies such as corticosteroids, 6-mercaptopurine (6 MP) and Azathioprine; and
- Patient has failed treatment with adalimumab (Humira®) after at least two months of therapy (unless there is clinical evidence or patient history that suggests that the this product will be ineffective or cause an adverse reaction to the patient); and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Patient has a negative purified protein derivative (PPD) test prior to treatment.

Rheumatoid Arthritis
Based on review of available data, the Company may consider certolizumab pegol (Cimzia) for the treatment of adult rheumatoid arthritis to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of certolizumab pegol (Cimzia) for the treatment of rheumatoid arthritis will be considered when all of the following criteria are met:
- Patient is 18 years of age or older; and
- Patient has moderately to severely active rheumatoid arthritis; and
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
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- Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel®) after at least two months of therapy with each product (unless there is clinical evidence or patient history that suggests that these products will be ineffective or cause an adverse reaction to the patient); and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Patient has a negative purified protein derivative (PPD) test prior to treatment.

Psoriatic Arthritis
Based on review of available data, the Company may consider the use of certolizumab pegol (Cimzia) for the treatment of psoriatic arthritis to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of certolizumab pegol (Cimzia) for the treatment of psoriatic arthritis will be considered when all of the following criteria are met:

- Patient is 18 years of age or older; and
- Patient has active psoriatic arthritis; and
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product (unless there is clinical evidence or patient history that suggests that these products will be ineffective or cause an adverse reaction to the patient); and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Patient has a negative purified protein derivative (PPD) test prior to treatment.

Ankylosing Spondylitis
Based on review of available data, the Company may consider the use of certolizumab pegol (Cimzia) for the treatment of active ankylosing spondylitis to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of certolizumab pegol (Cimzia) for the treatment of active ankylosing spondylitis will be considered when all of the following criteria are met:

- Patient is 18 years of age or older; and
- Patient has active ankylosing spondylitis; and
- Patient has failed treatment with non steroidal anti-inflammatory drugs (NSAIDs) or has documented contraindications to non steroidal anti-inflammatory drug (NSAID) usage; and
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product (unless there is clinical evidence or patient history that suggests that these products will be ineffective or cause an adverse reaction to the patient); and
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(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)

- Patient has a negative purified protein derivative (PPD) test prior to treatment.

Note: The FDA approved prescribing information recommends:

- That Cimzia not be prescribed with biological disease-modifying anti-rheumatic drugs (DMARDs) and other tumor necrosis factor (TNF) blocker therapy

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of certolizumab pegol (Cimzia) when patient selection criteria are not met to be investigational* (with the exception of those denoted above as not medically necessary**).

Based on review of available data, the Company considers the use of certolizumab pegol (Cimzia) for indications other than those listed above to be investigational.*

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of certolizumab pegol (Cimzia) when any of the following criteria for their respective disease state listed below (and denoted in the patient selection criteria above) are not met to be not medically necessary**:

- For rheumatoid arthritis and psoriatic arthritis:
  - Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs)
  - Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product

- For Crohn’s disease:
  - Patient has failed treatment with adalimumab (Humira) after at least two months of therapy

- For active ankylosing spondylitis:
  - Patient has failed treatment with non steroidal anti-inflammatory drugs (NSAIDs) or has documented contraindications to non steroidal anti-inflammatory drug (NSAID) usage
  - Patient has failed treatment with adalimumab (Humira) AND etanercept (Enbrel) after at least two months of therapy with each product

Background/Overview
Cimzia
Cimzia is a TNF blocker indicated for reducing signs and symptoms of Crohn’s disease and maintaining clinical response in adult patients with moderately to severely active disease who have had inadequate response to conventional therapy. Cimzia also carries indications for the treatment of adults with moderately to severely active rheumatoid arthritis, treatment of adults with psoriatic arthritis, and the treatment of adults with ankylosing spondylitis. Cimzia is supplied as a sterile, white, lyophilized powder for reconstitution in a
single use vial for subcutaneous injection. Cimzia is also available in a 200mg/mL solution in a single-use prefilled syringe.

Cimzia is a recombinant, humanized antibody Fab’ fragment, with specificity for human tumor necrosis factor alpha (TNFα), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). The Fab’ fragment is manufactured in E. coli and is subsequently subjected to purification and conjugation to PEG2MAL40K, to generate certolizumab pegol. The Fab’ fragment is composed of a light chain with 214 amino acids and a heavy chain with 229 amino acids. The molecular weight of certolizumab pegol is approximately 91 kilodaltons.

Crohn’s Disease
Crohn's disease is a chronic autoimmune disease that can affect any part of the gastrointestinal tract but most commonly occurs in the ileum. As a result of the immune attack, the intestinal wall becomes thick, and deep ulcers may form. In addition to the bowel abnormalities, CD can also affect other organs in the body. Typically, first line treatments such as corticosteroids, 6-mercaptopurine (6 MP) and Azathioprine are used to treat this condition.

Rheumatoid Arthritis
Rheumatoid Arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Psoriatic Arthritis
Psoriatic arthritis is an arthritis that is often associated with psoriasis of the skin. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Ankylosing Spondylitis
Ankylosing spondylitis is a chronic inflammatory disease that affects the joints between the vertebrae of the spine, and the joints between the spine and the pelvis. It eventually causes the affected vertebrae to fuse or grow together. Nonsteroidal anti-inflammatory drugs such as aspirin are used to reduce inflammation and pain associated with the condition. Corticosteroid therapy or medications to suppress the immune system may be prescribed to control various symptoms.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
In April of 2008, The FDA granted approval to Cimzia (certolizumab pegol), a new drug to treat adults with moderate to severe Crohn's disease who have not responded to conventional therapies. In May 2009, Cimzia was granted approval for the treatment of adults with moderately to severely active rheumatoid arthritis. In September and October 2013, Cimzia was given approval to treat adults with psoriatic arthritis and ankylosing spondylitis, respectively.
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The most common side effects of Cimzia that were seen in the controlled studies included headache, upper respiratory infections, abdominal pain, injection-site reactions and nausea. In addition, because Cimzia blocks TNF, patients taking Cimzia are at increased risk for more serious adverse effects, including fatal infections and increased risk of lymphomas and other malignancies. Julie Beitz, M.D., director of the Office of Drug Evaluation III for the FDA’s Center for Drug Evaluation and Research states; “This drug works to reduce the signs and symptoms of Crohn’s, but it also carries risks that will require patients on it to be closely monitored by their health care professionals.” The FDA noted that patients taking Cimzia should be educated regarding how to identify an infection and be instructed to contact their healthcare professional at the first sign of infection while on Cimzia. In cases of serious infections, the drug should be discontinued immediately. Postmarketing studies and clinical trials will be required to obtain long-term safety data.

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies and accredited national guidelines.

Crohn’s Disease
The efficacy and safety of Cimzia were assessed in two double-blind, randomized, placebo-controlled studies (CD1 and CD2) in patients aged 18 years and older with moderately to severely active Crohn’s disease, as defined by a Crohn’s Disease Activity Index (CDAI) of 220 to 450 points, inclusive. Cimzia was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn’s disease were permitted.

Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn’s disease. Cimzia or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower. At Week 6, the proportion of clinical responders was statistically significantly greater for Cimzia-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn’s disease. All patients who entered the study were dosed initially with Cimzia 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either Cimzia 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the Cimzia-treated group compared to the group treated with placebo.
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Rheumatoid Arthritis
The efficacy and safety of Cimzia were assessed in four randomized, placebo-controlled, double blind studies (RA-I, RA-II, RA-III, and RA-IV) in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had its diagnosis according to the American College of Rheumatology (ACR)verely baseline. Cimzia was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in Studies RA-I, RA-II, and RA-III. Cimzia was administered as monotherapy in Study RA-IV. Study RA-I and Study RA-II evaluated patients who had received MTX for at least 6 months prior to study medication, but had an incomplete response to MTX alone. Patients were treated with a loading dose of 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg or 400 mg of Cimzia or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at Week 52 (RA-I). The open-label extension follow-up study enrolled 846 patients who received 400 mg of Cimzia every other week. Study RA-III evaluated 247 patients who had active disease despite receiving MTX for at least 6 months prior to study enrollment. Patients received 400 mg of Cimzia every four weeks for 24 weeks without a prior loading dose. Patients were evaluated for signs and symptoms of RA using the ACR20 at Week 24. Study RA-IV (monotherapy) evaluated 220 patients who had failed at least one DMARD use prior to receiving Cimzia. Patients were treated with Cimzia 400 mg or placebo every 4 weeks for 24 weeks. Patients were evaluated for signs and symptoms of active RA using the ACR20 at Week 24.

Cimzia-treated patients had higher ACR20, 50 and 70 response rates at 6 months compared to placebo-treated patients. The results in study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-III (247 patients) were similar to those seen in study RA-IV. Over the one-year Study RA-I, 13% of Cimzia-treated patients achieved a major clinical response, defined as achieving an ACR70 response over a continuous 6-month period, compared to 1% of placebo-treated patients. Among patients receiving Cimzia, clinical responses were seen in some patients within one to two weeks after initiation of therapy.

In Study RA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score, at Week 52, compared to baseline. In the placebo group, 52% of patients experienced no radiographic progression (mTSS ≤0.0) at Week 52 compared to 69% in the Cimzia 200 mg every other week treatment group. Study RA-II showed similar results at Week 24. In studies RA-I, RA-II, RA-III, and RA-IV, CIMZIA-treated patients achieved greater improvements from baseline than placebo-treated patients in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 (RA-II, RA-III and RA-IV) and at Week 52 (RA-I).

Psoriatic Arthritis
The efficacy and safety of Cimzia were assessed in a multi-center, randomized, double-blind, placebo controlled trial (PsA001) in 409 patients aged 18 years and older with active psoriatic arthritis despite DMARD therapy. Patients in this study had ≥ 3 swollen and tender joints and adult-onset PsA of at least 6 months' duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, and increased acute phase reactants. Patients had failed one or more DMARDs. Previous treatment with one
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anti-TNF biologic therapy was allowed, and 20% of patients had prior anti-TNF biologic exposure. Patients receiving concomitant NSAIDs and conventional DMARDs were 73% and 70 % respectively. Patients received a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either Cimzia 200 mg every other week or Cimzia 400 mg every 4 weeks or placebo every other week. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 12 and modified Total Sharp Score (mTSS) at Week 24.

ACR20 response rates at weeks 12 and 24 were higher for each CIMZIA dose group relative to placebo (95% confidence intervals for Cimzia 200 mg minus placebo at weeks 12 and 24 of (23%, 45%) and (30%, 51%), respectively and 95% confidence intervals for Cimzia 400 mg minus placebo at weeks 12 and 24 of (17%, 39%) and (22%, 44%), respectively). Patients with enthesitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI). Cimzia-treated patients receiving either 200 mg every 2 weeks or 400 mg every 4 weeks showed a reduction in enthesitis of 1.8 and 1.7, respectively as compared with a reduction in placebo-treated patients of 0.9 at week 12. Similar results were observed for this endpoint at week 24.

**Ankylosing Spondylitis**

The efficacy and safety of Cimzia were assessed in one multicenter, randomized, double-blind, placebo-controlled study (AS-1) in 325 patients ≥18 years of age with adult-onset active axial spondyloarthritis for at least 3 months. The majority of patients in the study had active AS. Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or active disease as defined by the Bath Ankylosing Spole (NRS). Patients must have been intolerant to or had an inadequate response to at least one NSAID. Patients were treated with a loading dose of Cimzia 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of Cimzia every 2 weeks or 400 mg of Cimzia every 4 weeks or placebo. Concomitant NSAIDs were received by 91% of the AS patients. The primary efficacy variable was the proportion of patients achieving an ASAS20 response at Week 12. In study AS-1, at Week 12, a greater proportion of AS patients treated with Cimzia 200 mg every 2 weeks or 400 mg every 4 weeks achieved ASAS 20 response compared to AS patients treated with placebo. Responses were similar in patients receiving Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks.
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References

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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Policy History
Original Effective Date: 06/18/2008
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06/04/2008 Medical Director review
06/04/2009 Medical Director review
06/17/2009 Medical Policy Committee approval. FDA prescribing information added to policy criteria.
07/01/2010 Medical Policy Committee approval
07/21/2010 Medical Policy Implementation Committee approval. Negative cancer screening changed to negative cancer history in the coverage section Note. No change to coverage.
11/03/2011 Medical Policy Committee approval
11/16/2011 Medical Policy Implementation Committee approval. Added an additional company requirement to the patient selection criteria. Added a Not Medically Necessary section to the policy.
11/01/2012 Medical Policy Committee approval
11/28/2012 Medical Policy Implementation Committee approval. No change to coverage eligibility.

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10/10/2013 Medical Policy Committee approval
10/16/2013 Medical Policy Implementation Committee approval. Added the new indication for psoriatic arthritis. Changed to requirement to try both Humira AND Enbrel prior to Cimzia for Rheumatoid Arthritis and Psoriatic Arthritis. Modified the not medically necessary section to reflect changes.
03/06/2014 Medical Policy Committee approval
03/19/2014 Medical Policy Implementation Committee approval. Added indication for Ankylosing Spondylitis to match FDA package insert. Humira and Enbrel will need to be used prior. Reworded background, FDA approval, and rationale sections.

Next Scheduled Review Date: 03/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other non-affiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient’s illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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