INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies including plans formerly administered by Great-West Healthcare, which is now a part of Cigna. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supercedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2012 Cigna

Coverage Policy

Cigna covers tocilizumab (Actemra®) as medically necessary for the treatment of active rheumatoid arthritis (RA) in an adult with EITHER of the following:

- history of beneficial clinical response to tocilizumab
- inadequate response, intolerance, or contraindication to at least ONE disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Leflunomide, Sulfasalazine) AND to TWO self administered preferred tumor necrosis factor (TNF) antagonists [adalimumab (Humira®) and etanercept (Enbrel®)]

Cigna covers tocilizumab (Actemra®) as medically necessary for the treatment of systemic juvenile idiopathic arthritis (JIA) in a child 2 years of age and older with EITHER of the following:

- history of beneficial clinical response to tocilizumab
- inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine)

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to tocilizumab (Actemra®).
FDA Approved Indications

Rheumatoid Arthritis (RA)
Actemra is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

Systemic Juvenile Idiopathic Arthritis (SJIA)
Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

FDA Recommended Dosing

RA
Actemra may be used as monotherapy or concomitantly with methotrexate or other DMARDs. The recommended dose of Actemra for adult patients is 4 mg per kg followed by an increase to 8 mg per kg based on clinical response given once every 4 weeks as a 60-minute single intravenous drip infusion for those who have had an inadequate response to one or more TNF antagonists and when used in combination with DMARDs or as monotherapy the recommended starting dose.

Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia. Doses exceeding 800 mg per infusion are not recommended in RA patients.

SJIA
Actemra may be used alone or in combination with methotrexate. The recommended dose of Actemra for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is as follows:

- Patients less than 30 kg weight at a dose of 12 mg per kg
- Patients at or above 30 kg weight at a dose of 8 mg per kg

A change in dose should not be made based solely on a single visit body weight measurement, as weight may fluctuate. Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia.

Black Box Warning

Patients treated with Actemra are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra until the infection is controlled. Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra use and during therapy. Treatment for latent infection should be initiated prior to Actemra use.
- Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Actemra should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Drug Availability

Actemra is supplied in single-use vials as a preservative-free, sterile concentrate (20 mg/mL) solution for intravenous infusion. The following packaging configurations are available: Individually packaged, single-use vials - 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL. Box of 4 single-use vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL.
General Background

Pharmacology
Tocilizumab is a humanized monoclonal antibody which competes with actions mediated by IL-6 signaling by binding to both soluble and membrane-bound IL-6 receptors. Steady state mean maximum plasma concentrations are 88.3 mcg/mL following a 4 mg/kg dose and 183 mcg/mL following an 8 mg/kg dose. Steady state area under the curve is reached following one 4 mg/kg dose and two 8 mg/kg doses. Tocilizumab has a steady state volume of distribution of 6.4 L. The route of tocilizumab metabolism is unknown. At steady state, the half-life of tocilizumab is approximately 11 to 13 days and is concentration dependent.

Tocilizumab is a monoclonal antibody labeled for the treatment of Rheumatoid Arthritis (RA). Tocilizumab is the first biologic agent to target the proinflammatory cytokine, interleukin 6 (IL-6). Tocilizumab is not labeled for first-line treatment of RA, but as a therapeutic option for adults who do not respond to treatment with anti-tumor necrosis factor (anti-TNF) agents. Tocilizumab alone or in combination with methotrexate or other disease modifying antirheumatic drugs (DMARDs) is more effective than methotrexate or other DMARDs alone.

Guidelines
American College of Rheumatology (ACR)
The ACR updated their 2008 recommendations for the use of DMARDs and biologic agents in the treatment of RA in April 2012. The updated recommendations follow the same methodology used to develop the 2008 recommendations. While the recommendations are extensive and include new areas and new agents not covered in 2008, they are not comprehensive and should be used as a guide for clinicians treating RA patients.

It is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, evidence of radiographic erosions, elevated erythrocyte sedimentation rate, elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti–cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single “gold standard” measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

The ACR plans to periodically update RA treatment recommendations depending upon the availability of new therapies, new evidence on the benefits and harms of existing treatments, and changes in policies to reflect the rapidly evolving care of RA patients. The 2012 revision updates the 2008 recommendations in the following areas:

- indications for DMARDs and biologic agents
- switching between DMARD and biologic therapies
- use of biologic agents in high-risk patients (those with hepatitis, congestive heart failure [CHF], and malignancy)
- screening for TB in patients starting or currently receiving biologic agents
- vaccination in patients starting or currently receiving DMARDs or biologic agents

Though recommendations vary with each patient, the 2012 guidelines generally recommend physicians start treatment with a DMARD, proceed to therapy combining two or more DMARDs and then to a biologic when and if each option fails to control the disease. When switching from DMARDs to biologics, for example, physicians should use either an anti-TNF biologic or a non-TNF biologic if a patient has moderate or high disease activity after three months of methotrexate treatment or DMARD combination therapy.
For use in high-risk patients, the guideline recommendations go against the use of biologics in RA patients with untreated chronic hepatitis B or with treated chronic hepatitis B with Child-Pugh class B and higher because of the potential for strong side-effects. Etanercept is the only biologic recommended for use in RA patients with Hepatitis C.

RA patients with cancer may be treated with a biologic if their treatment for a solid malignancy was over 5 years ago or treated non-melanoma skin cancer was over 5 years ago. Rituximab is recommended for patients treated for a solid malignancy within the last 5 years or treated non-melanoma skin cancer within the last 5 years, treated skin melanoma, or treated lymphoproliferative malignancy.

Recommendations for patients with heart failure include a biologic if their case is not too severe. However, a biologic is not recommended for patients with a NYHA class III/IV rating and an ejection fraction of less than or equal to 50%.

Due to increasing awareness of the risk of preventable infections in RA patients, the recommendations place a priority on screening and vaccination. RA is an autoimmune disease in which the immune system attacks the body's own tissues. Treatments suppress the immune system and make those treated vulnerable to infections. For that reason, the 2012 guidelines recommend that all patients taking biologics for RA be screened for latent tuberculosis infection (LTBI) – statistics show that 5 to 10 percent of these patients will go on to develop active TB later.

The 2012 guidelines recommend that all killed (pneumococcal, influenza intramuscular, and hepatitis B), recombinant (human papillomavirus [HPV] vaccine for cervical cancer) and live attenuated (herpes zoster) vaccinations should be undertaken before starting a DMARD or a biologic agent. If not previously done, vaccination with indicated pneumococcal (killed), influenza intramuscular (killed), hepatitis B (killed), and HPV vaccine (recombinant) should be undertaken in RA patients already taking a DMARD or a biologic agent. Vaccination with herpes zoster vaccine in RA patients already taking a DMARD is recommended but is not recommended in patients taking a biologic agent. All vaccines should be given based on age and risk, and physicians should refer to vaccine instructions and CDC recommendations for details about dosing and timing issues related to vaccinations.

The 2012 guidelines literature search included eight DMARDs and nine biologic agents most commonly used for the treatment of RA. DMARDs included azathioprine, cyclosporine, hydroxychloroquine, lefunomide, methotrexate, minocycline, organic gold compounds, and sulfasalazine. Similar to 2008, azathioprine, cyclosporine, and gold were not included in the recommendations based on their infrequent use and lack of new data. The biologic agents included abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Anakinra was not included in the recommendations due to infrequent use and lack of new data.

Adverse Reactions
The most common side effects occurring in patients treated with tocilizumab or tocilizumab in combination with other DMARDs include an increase in alanine aminotransferase concentrations, hypertension, nasopharyngitis, headache, and upper respiratory tract infection. The most common serious adverse event associated with tocilizumab is serious infection as noted in the Black Box Warning. The overall rate of serious infection in clinical trials was 4.7 events per 100 patient-years. Other less common serious side effects include gastrointestinal perforation, demyelinating disorders, and malignancy. Do not administer tocilizumab in combination with biologic DMARDs such as TNF antagonists or rituximab. Tocilizumab may result in increased metabolism of CYP450 substrates. Do not administer live vaccines to patients receiving tocilizumab.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:
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