

***Title: tocilizumab (Actemra)***

<b>Origination:</b> 03/10/10	<b>Revised:</b> 11/11/11	<b>Annual Review:</b> 12/15/11
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**Purpose:**

To provide guidelines and criteria for the review and decision determination of requests for medications that requires prior authorization.

**Background Information:**

***Reference Statement***

- Guidelines will be compiled from available US Food and Drug Administration (FDA) approved indications, general practice guidelines, and/or evidence-based uses established through phase III clinical studies without published conflicting data. Only clinical studies published in their entirety in reputable peer-reviewed journals will be evaluated.

***Medication Summary***

- Actemra (tocilizumab) is a monoclonal antibody that works as an interleukin-6 (IL-6) receptor antagonist. IL-6 is a cytokine produced by many different types of cells, including immune modulators and synovial cells. Production by synovial and endothelial cells increases the IL-6 concentrations in inflamed joints, as seen in rheumatoid arthritis (RA). Actemra binds to both soluble and bound IL-6 receptors to inhibit cytokine production and the signaling in the inflammatory pathway.
- Actemra is indicated for the treatment of moderately to severely active **rheumatoid arthritis (RA)** in adults who have an inadequate response to treatment with one or more tumor necrosis factor (TNF) antagonists and for the treatment of active systemic juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA).
- Actemra may be used alone, or in combination with, methotrexate (MTX) or Disease Modifying Anti-Rheumatic Drugs (DMARDs); however, Actemra should not be combined with biological DMARDs, including TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies, or selective costimulation modulators due to increased risk of infection.
- Actemra is administered as an intravenous (IV) infusion over sixty (60) minutes every four (4) weeks at a dose not to exceed 800mg per infusion. Actemra is available as a 20mg/mL solution in 4mL, 10mL, and 20mL single-use vials.

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**Background Information, continued:**

***Eligibility Criteria***

- Member must be eligible and have applicable benefits.
- Prior authorization requests that do not meet clinical criteria in this Procedure will be forwarded to a Clinical Pharmacist for review.

***Exclusions***

- Concurrent administration of multiple biological response modifiers [including, but not limited to: Kineret (anakinra), Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Rituxan (rituximab), Simponi (golimumab), or Orencia (abatacept)]. Only one (1) agent at a time will be covered for the treatment of rheumatoid arthritis.
- Members with a history of hypersensitivity to Actemra or any of its ingredients.
- Members experiencing clinically important, active infections including, but not limited to, sepsis, tuberculosis without treatment, local or opportunistic infections.

**Procedure:**

- 1.0 Request for *initial therapy* with Actemra for **rheumatoid arthritis (RA)** requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following:
  - 1.1 Requesting independent practitioner must be a rheumatologist; **AND**
  - 1.2 Member must be at least 18 years of age; **AND**
  - 1.3 Diagnosis of moderately to severely active RA of at least six (6) months duration as evidenced by at least one (1) of the following:
    - 1.3.1 Erythrocyte sedimentation rate (ESR)  $\geq$  28mm/hr;
    - 1.3.2 C-reactive protein (CRP)  $\geq$  1.0mg/dL;
    - 1.3.3 Morning stiffness;
    - 1.3.4 Swollen and/or tender joints;
    - 1.3.5 Synovitis;

**AND**

- 1.4 Member shows inadequate response to a three (3) to six (6) month minimum trial of an adequate dose of methotrexate; **OR**

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**Procedure, continued:**

1.0 Request for *initial therapy* with Actemra for **rheumatoid arthritis (RA)** requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following, continued:

1.4 Member has contraindication to methotrexate as evidenced by **at least one (1)** of the following:

- 1.4.1 Chronic liver disease;
- 1.4.2 Leukopenia;
- 1.4.3 Thrombocytopenia;
- 1.4.4 Creatinine clearance less than 40mL/minute;
- 1.4.5 Immunodeficiency;

**AND**

1.5 Member shows inadequate response to a three (3) to six (6) month minimum trial of an adequate dose of **OR** is not a candidate for at least (1) of the following DMARDs:

- 1.5.1 Oral or Injectable Gold;
- 1.5.2 Leflunomide (Arava);
- 1.5.3 Hydroxychloroquine (Plaquenil);
- 1.5.4 Sulfasalazine;
- 1.5.5 Azathioprine (Imuran);
- 1.5.6 D-Penicillamine;
- 1.5.7 Cyclosporine;

1.6 **For Commercial Members only – excludes Medicare or Miami Dade County** Member shows inadequate response, or intolerance to, an adequate dose of both Humira (adalimumab) **AND** Enbrel (etanercept);

**AND**

1.7 Current lab values (within the past 30 days) indicating all of the following:

- 1.7.1 Serum transaminase (AST and ALT) less than 1.5x the upper limit of normal (ULN); **AND**
- 1.7.2 Absolute neutrophil counts (ANC) greater than 2,000/mm<sup>3</sup>; **AND**
- 1.7.3 Platelet count greater than 100,000/mm<sup>3</sup>;

**AND**

1.8 Current weight for weight based dosing;

1.9 If all criteria are met, Actemra 4mg/kg every four (4) weeks may be approved for up to three (3) months (#3 infusions).

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**Procedure, continued:**

- 2.0 Request for *continuation of therapy* with Actemra for RA requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following:
- 2.1 Improvement in Member's physical functioning; **OR**
  - 2.1 Reduction in signs and symptoms (ex. 20% improvement in American College of Rheumatology scores such as painful joint count, ESR, CRP, or morning stiffness); **AND**
  - 2.2 Repeat lab values indicating the following:
    - 2.2.1 Serum transaminase (AST and ALT) less than 5x the upper limit of normal (ULN); **AND**
    - 2.2.2 Absolute neutrophil counts (ANC) greater than 1000/mm<sup>3</sup>; **AND**
    - 2.2.3 Platelet count remains greater than 100,000/mm<sup>3</sup>;
  - 2.3 If all criteria are met, Actemra 4mg/kg every four (4) weeks (up to 8mg/kg with a maximum of 800mg per infusion) may be approved for up to one (1) year (#13 infusions).
- 3.0 Request for *initial therapy* with Actemra for **juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA)** requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following:
- 3.1 Requesting independent practitioner must be a rheumatologist; **AND**
  - 3.2 Member is at least two (2) years old; **AND**
  - 3.3 Diagnosis of moderately to severely active RA of at least six (6) months duration as evidenced by at least one (1) of the following:
    - 1.3.1 Erythrocyte sedimentation rate (ESR)  $\geq$  28mm/hr;
    - 1.3.2 C-reactive protein (CRP)  $\geq$  1.0mg/dL;
    - 1.3.3 Morning stiffness;
    - 1.3.4 Swollen and/or tender joints;
    - 1.3.5 Synovitis;
- AND**
- 3.4 Member shows inadequate response to a three (3) to six (6) month minimum trial of an adequate dose of methotrexate; **OR**

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**Procedure, continued:**

3.0 Request for *initial therapy* with Actemra for **juvenile rheumatoid arthritis/juvenile idiopathic arthritis (JRA/JIA)** requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following, continued:

3.4 Member has contraindication to methotrexate as evidenced by **at least one (1)** of the following:

- 1.4.1 Chronic liver disease;
- 1.4.2 Leukopenia;
- 1.4.3 Thrombocytopenia;
- 1.4.4 Creatinine clearance less than 40mL/minute;
- 1.4.5 Immunodeficiency;

**AND**

3.5 Member shows inadequate response to a three (3) to six (6) month minimum trial of an adequate dose of **OR** is not a candidate for at least (1) of the following DMARDs:

- 1.5.1 Injectable Gold;
- 1.5.2 Leflunomide (Arava);
- 1.5.3 Enteric Coated Sulfasalazine;
- 1.5.4 D-Penicillamine; **AND**

3.6 **For Commercial Members only – excludes Medicare or Miami Dade County:** Member shows inadequate response, or intolerance to, an adequate dose of both Humira (adalimumab) if older than 4 years of age **AND** Enbrel (etanercept); **AND**

3.7 Current lab values (within the past 30 days) indicating all of the following:

- 3.7.1 Serum transaminase (AST and ALT) less than 1.5x the upper limit of normal (ULN); **AND**
- 3.7.2 Absolute neutrophil counts (ANC) greater than 2,000/mm<sup>3</sup>; **AND**
- 3.7.3 Platelet count greater than 100,000/mm<sup>3</sup>;

**AND**

3.8 Current weight for weight based dosing;

3.9 If all criteria are met, Actemra may be approved for up to three (3) months at the following dosing: 8mg/kg every two (2) weeks for children greater than 30kg (#6 infusions) and 12mg/kg every 2 weeks (#6 infusions) for children less than 30kg.

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**Procedure, continued:**

4.0 Request for *continuation of therapy* with Actemra for JRA/JIA requires documentation from the Member's medical records maintained by the requesting independent practitioner verifying the following:

4.1 Improvement in Member's physical functioning; **OR**

4.1 Reduction in signs and symptoms (ex. 20% improvement in American College of Rheumatology scores such as painful joint count, ESR, CRP, or morning stiffness);

**AND**

4.2 Repeat lab values indicating the following:

4.2.1 Serum transaminase (AST and ALT) less than 5x the upper limit of normal (ULN); **AND**

4.2.2 Absolute neutrophil counts (ANC) greater than 1000/mm<sup>3</sup>; **AND**

4.2.3 Platelet count remains greater than 100,000/mm<sup>3</sup>;

4.3 If all criteria are met, Actemra may be approved for up to one (1) year at the following dosing:

4.3.1.1 8mg/kg every two (2) weeks for children greater than 30kg (#26 infusions);

4.3.1.2 12mg/kg every two (2) weeks (#26 infusions) for children less than 30kg.

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**References:**

1. Actemra (tocilizumab) Prescribing Information. Genentech, Inc. San Francisco, CA. January 2010.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2011. Available at: <http://www.clinicalpharmacology-ip.com/default.aspx>.
3. Emery, P et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomized placebo-controlled trial. *Annals of the Rheumatic Diseases*. 2008; 67(11): 1516-23.
4. Lexi-Drugs Online. Hudson, Ohio: Lexi-Comp, Inc.; 2007; March 1, 2010.
5. Nishimoto, N et al. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Annals of the Rheumatic Disease*. 2009; 68(10): 1580-84.
6. Smolen, J et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. *Lancet*. 2008; 371: 987-97.

**Disclaimer Information:**

Prior Authorization criteria are developed to determine coverage for AvMed Health Plans' benefits, and are published to provide a better understanding of the basis upon which coverage decisions are made. AvMed Health Plans makes coverage decisions based on the Member's benefit plan contract and these criteria. This guideline sets forth concise clinical coverage criteria which have been developed from a review of current literature, policies of the FDA and other government agencies, and other appropriate references, in consultation and with approval from practicing physicians who are members of AvMed's Pharmacy and Therapeutic committee. Treating providers are solely responsible for the medical advice and treatment of Members. This guideline may be updated and therefore is subject to change. The use of these criteria is neither a guarantee of payment nor a final prediction of how specific claim(s) will be adjudicated.