RATIONALE FOR INCLUSION IN PA PROGRAM

Background
Actemra is an agent in the class of drugs known as biologic disease modifiers. It is used to treat adult onset rheumatoid (RA) arthritis, polyarticular juvenile idiopathic arthritis (PJIA), systemic juvenile idiopathic arthritis (SJIA), giant cell arteritis, and cytokine release syndrome (CRS). Biologic disease modifiers are genetically engineered drugs that are used to modify imbalances of the immune system in autoimmune disease. Some of these agents block, or modify, the activity of selected cells in the immune system, while others (including Actemra) work by blocking certain messenger proteins, known as cytokines, that send signals between those cells (1).

Actemra works by blocking a cytokine known as interleukin 6, or IL-6, which is believed to be one of the factors that cause inflammation in rheumatoid arthritis. Actemra is an antibody that blocks the spot where IL-6 attaches to the surface of cells. When IL-6 is unable to attach to these cells, it is unable to activate them or turn them on. As a result, the cells are unable to drive inflammation in rheumatoid arthritis (1).

Regulatory Status
FDA-approved indication: Actemra is an interleukin-6 (IL-6) receptor antagonist indicated for: (2)

1. Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
2. Adult patients with giant cell arteritis
3. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
4. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
5. Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Off Label Indications:
Per the NCCN compendium, Actemra has been found to be effective in the following disease states: (3-5)
1. Unicentric Castleman’s Disease: Second-line therapy as a single agent for relapsed or refractory unicentric CD for patients who are human immunodeficiency virus-negative and human herpesvirus-8-negative at a dose of 8mg/kg every 2 weeks

2. Multicentric Castleman’s Disease: Subsequent therapy as a single agent for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease at a dose of 8mg/kg every 2 weeks

Actemra should not be administered in patients with an active infection, including localized infections. Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving Actemra. If a serious infection develops, interrupt Actemra until the infection is controlled. Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections (2).

Patients should be tested for latent TB infection prior to initiating Actemra. Anti-tuberculosis therapy should also be considered prior to initiation of Actemra in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy (2).

Gastrointestinal (GI) perforation may occur, primarily as complications of diverticulitis in RA patients. Actemra should be used with caution in patients who may be at increased risk for gastrointestinal perforation (2).

Laboratory monitoring is recommended prior to and monitored every 4 to 8 weeks due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests (2).

Treatment with Actemra was associated with a higher incidence of neutropenia. Initiation of Actemra treatment is not recommended in patients with an absolute neutrophil count (ANC) below 2000 per mm3. Actemra treatment must be withheld if the ANC is 500-1000 cells per mm3 and
resumed at a decreased dose when the ANC is >1000 mm$^3$. Actemra treatment must be discontinued if the ANC is less than 500 cells per mm$^3$ (2).

Treatment with Actemra was associated with a reduction in platelet counts. Actemra treatment is not recommended in patients with a platelet count below 100,000 per mm$^3$ (2).

Treatment with Actemra was associated with a higher incidence of transaminase elevations. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with Actemra (2).

Treatment with Actemra was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol. Patients should be managed according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP) for the management of hyperlipidemia (2).

Actemra has not been studied and its use should be avoided in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection. Actemra may be used as monotherapy or concomitantly with methotrexate or other non-biological DMARDs such as hydroxychloroquine, leflunomide, azathioprine, and cyclosporine (2).

Treatment with Actemra is not recommended in patients with active hepatic disease or hepatic impairment, including patients with positive hepatitis B virus (HBV) and hepatitis C virus (HCV) (2).

Safety and effectiveness of Actemra in pediatric patients with conditions other than PJIA, SJIA, or cytokine release syndrome have not been established. Children under the age of two have not been studied (2).

Actemra doses exceeding 800 mg per infusion are not recommended in RA or CRS patients (2).

**Summary**

Actemra is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of moderately to severely active rheumatoid arthritis in adults who have had an inadequate response to one or more
disease-modifying anti-rheumatic drugs (DMARDs); in patients 2 years of age or older with active polyarticular juvenile idiopathic arthritis (PJIA), active systemic juvenile idiopathic arthritis (SJIA), giant cell arteritis, or cytokine release syndrome (CRS). Actemra should not be administered in patients with an active infection, including localized infections. Laboratory monitoring is recommended prior to and monitored every 4 to 8 weeks due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. Treatment with Actemra is not recommended in patients with active hepatic disease or hepatic impairment. Actemra has not been studied and its use should be avoided in combination with biological DMARDs. Actemra may be used as monotherapy or concomitantly with methotrexate or other non-biological DMARDs (1-3). Additionally, Actemra has shown efficacy in the off-label treatment of Unicentric and Multicentric Castleman’s Disease (4).

Prior authorization is required to ensure the safe, clinically appropriate and cost effective use of Actemra while maintaining optimal therapeutic outcomes.

References
1. American College of Rheumatology. American College of Rheumatology website.
   http://www.rheumatology.org/Practice/Clinical/Patients/Medications/Tocilizumab_(Actemra)/