Clinical Criteria

Subject:	Monoclonal Antibodies to Interleukin-6		
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Overview

This document addresses the use of monoclonal antibodies which bind to interleukin-6 (IL-6) receptors and inhibit release of proinflammatory cytokines. Indications are drug-specific but IL-6 inhibitors are approved for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular and systemic juvenile idiopathic arthritis, chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome, and other conditions as applicable. Agents addressed in this clinical guideline include:

- Actemra (tocilizumab)
- Kevzara (sarilumab)

Actemra is available in intravenous and subcutaneous injection formulations and Kevzara is available in a subcutaneous formulation.

Rheumatoid Arthritis: The American College of Rheumatology (ACR) guidelines recommend disease-modifying antirheumatic drug (DMARD) monotherapy [methotrexate (MTX) preferred] as first-line treatment in individuals with early or established RA. If disease activity remains high despite DMARD monotherapy, combination traditional DMARDs, TNFi +/- MTX, non-TNFi biologic +/- MTX, or Xeljanz +/- MTX should be utilized. Due to superior efficacy, biologic therapy should be used in combination with MTX when possible. If disease activity remains high despite TNFi monotherapy, one or two additional DMARDs should be added. If an individual has failed TNFi therapy, options include switching to another TNFi or non-TNFi biologic +/- MTX. Non-TNFi biologics (such as IL-6 or IL-1 inhibitors) are preferred over JAK inhibitors due to potential long-term safety concerns.

Juvenile Idiopathic Arthritis: The American College of Rheumatology (ACR) guidelines provide recommendations for juvenile idiopathic arthritis, including systemic disease (SJIA) and JIA with polyarthritis (PJIA). SJIA is an autoinflammatory condition marked by intermittent fever, rash, and arthritis. PJIA is marked by the presence of more than four affected joints in the first six months of illness. For children with active systemic features and varying degrees of synovitis, therapy with IL-1 inhibitors (anakinra or canakinumab) or tocilizumab may be considered after initial therapy with NSAIDs or corticosteroids. For children without active systemic features and varying degrees of synovitis, anakinra or tocilizumab may be considered after initial therapy with DMARDS (methotrexate or leflunomide). TNFi may be considered if polyarthritis is present (ACR 2013). For children with active polyarthritis, biologic therapy including TNFi, abatacept, or tocilizumab +/- DMARD is recommended following initial DMARD therapy (preferably methotrexate) (ACR 2019).

Chronic Antibody-Mediated Renal Transplant Rejection: Antibody-mediated rejection is caused by anti-donor-specific antibodies, mostly anti-HLA antibodies. Treatment for acute antibody-mediated rejection (AMR) generally consists of IVIG and rituximab, with or without plasma exchange. Although success has been reported with these therapies, chronic AMR (cAMR) and transplant glomerulopathy remain significant problems that are often unresponsive to current therapies. There is literature (Choi 2017) to support tocilizumab as a treatment option for cAMR and transplant glomerulopathy in human leucocyte antigen (HLA)-sensitive renal allograft recipients. Given limited alternative treatment options and supporting literature, tocilizumab may be an option for cAMR and transplant glomerulopathy who have failed standard therapy.

Other uses: The National Comprehensive Cancer Network® (NCCN) provides recommendations for off-label use of Actemra with a category 2A level of evidence. These include the use in steroid-refractory graft-versus-host-disease (Ganetsky 2019), immune checkpoint Inhibitor-related inflammatory arthritis, unicentric castleman's disease, and CRS related to blinatumomab therapy. High-quality evidence supporting its safety and efficacy in these conditions has not been reported.

IL-6 inhibitors have a black box warning for serious infections. Individuals treated with IL-6 inhibitors are at increased risk for developing serious infections that may lead to hospitalization or death. Most individuals who developed these infections were taking concomitant

immunosuppressants such as methotrexate or corticosteroids. IL-6 inhibitors should be discontinued if an individual develops a serious infection or sepsis. Individuals should be tested for latent tuberculosis (TB) before IL-6 inhibitor use and during therapy. Treatment for latent TB should be initiated prior to use. Risks and benefits of Il-6 inhibitors should be carefully considered prior to initiation of therapy in individuals with chronic or recurrent infection.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Actemra (tocilizumab)

Initial ~~R~~requests for Actemra (tocilizumab) may be approved for the following:

I. Giant cell arteritis (GCA) when each of the following criteria are met:
   A. Individual is 18 years of age or older with GCA; **AND**
   B. Agent is used in combination with a tapering course of corticosteroids (such as prednisone); **OR**
   C. Agent is used as a single agent following discontinuation of corticosteroids;

OR

II. Rheumatoid arthritis (RA) when each of the following criteria are met:
   A. Individual is 18 years of age or older with moderate to severe RA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine)] or a tumor necrosis factor (TNF) antagonist (ACR 2015);

OR

III. Polyarticular juvenile idiopathic arthritis (PJIA) when each of the following criteria are met:
   A. Individual is 2 years of age or older with moderate to severe PJIA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate)];

OR

IV. Systemic juvenile idiopathic arthritis (SJIA) when each of the following criteria are met:
   A. Individual is 2 years of age or older with SJIA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs);

OR

V. Multicentric Castleman Disease when each of the following criteria are met (NCCN 2A):
   A. Individual with a diagnosis of relapsed/refractory or progressive multicentric Castleman disease; **AND**
   B. Used as a single agent; **AND**
   C. Human immunodeficiency virus negative; **AND**
   D. Human herpes-8 negative; **AND**
   E. No concurrent clinically significant infection (for example, Hepatitis B or C); **AND**
   F. No concurrent lymphoma;

OR

VI. Cytokine Release Syndrome when the following criteria are met:
   A. Individual is 2 years of age or older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome;

OR

VII. Chronic Antibody-Mediated Renal Transplant Rejection when the following criteria are met (Choi 2017):
   A. Individual has chronic active antibody-mediated rejection plus donor-specific antibodies and transplant glomerulopathy; **AND**
   B. Individual has failed to respond to intravenous immune globulin (IVIG) plus rituximab therapy (with or without plasma exchange).

Continuation requests for Actemra (tocilizumab) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease.

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Requests for Actemra (tocilizumab) may not be approved for the following:

I. All other indications not included above; **OR**
II. In combination with JAK inhibitors, apremilast, or other biologic drugs (such as anti-CD20 monoclonal antibodies, IL-1 inhibitors, selective co-stimulation modulators, or TNF antagonists); **OR**
III. At initiation of therapy, absolute neutrophil count less than 2000/mm3, platelet count less than 100,000/mm3, or alanine aminotransferase or aspartate aminotransferase greater than 1.5 times the upper limit of normal; **OR**
IV. Tuberculosis, other active serious infections or a history of recurrent infections; **OR**

V. Prior to initiating therapy, ~~I~~individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis ~~prior to initiating tocilizumab~~(unless switching therapy from another targeted immune modulator and no risk factors) ~~{~~[in the setting of non-emergent use only~~}~~].

Kevzara (sarilumab)

Initial ~~R~~requests for Kevzara (sarilumab) may be approved for the following:

I. Rheumatoid arthritis (RA) when each of the following criteria are met:
   A. Individual is 18 years of age or older with moderate~~ly~~ to severe RA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine)] or a tumor necrosis factor (TNF) antagonist (ACR 2015).

Continuation requests for Kevzara (sarilumab) may be approved if the following criterion is met:
I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease.

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Requests for Kevzara (sarilumab) may not be approved for the following:

I. All other indications not included above; **OR**
II. In combination with JAK inhibitors, apremilast, or other biologic drugs (such as anti-CD20 monoclonal antibodies, IL-1 inhibitors, selective co-stimulation modulators, or TNF antagonists); **OR**
III. At initiation of therapy, absolute neutrophil count less than 2000/mm3, platelet count less than 150,000/mm3, or alanine aminotransferase or aspartate aminotransferase greater than 1.5 times the upper limits of normal; **OR**
IV. Tuberculosis, other active serious infections or a history of recurrent infections; **OR**
V. Prior to initiating therapy, ~~I~~individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis ~~prior to initiating sarilumab~~(unless switching therapy from another targeted immune modulator and no risk factors).

Quantity Limits

Actemra (tocilizumab) Quantity Limit

Drug	Limit
Actemra (tocilizumab) 80 mg, 200 mg, & 400 mg vial for intravenous infusion	8 mg/kg* as frequently as every 4 weeks
Override Criteria	
I. For polyarticular juvenile idiopathic arthritis (PJIA), may approve up to 10 mg/kg every 4 weeks for individuals weighing less than 30 kg II. For systemic juvenile idiopathic arthritis (SJIA), may approve up to 12 mg/kg every 2 weeks for patients weighing less than 30 kg and up to 8 mg/kg every 2 weeks for patients at or above 30 kg. III. For cytokine release syndrome (CRS), may approve a total of up to four intravenous doses at least 8 hours apart; each dose up to 8 mg/kg for individuals weighing at or above 30 kg and up to 12 mg/kg in individuals weighing less than 30 kg *For rheumatoid arthritis and CRS, Each dose should not exceed 800mg total	

Drug	Limit
Actemra (tocilizumab) 162 mg/0.9 mL ACTPen prefilled autoinjector	4 autoinjectors per 28 days
Actemra (tocilizumab) 162 mg/0.9 mL prefilled syringe	4 syringes per 28 days

Kevzara (sarilumab) Quantity Limit

Drug	Limit
Kevzara (sarilumab) 150 mg, 200 mg prefilled pen/syringe	2 pens/syringes per 28 days

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J3262	Injection, tocilizumab, 1 mg [Actemra]
C9399	Unclassified drugs or biologicals Hospital Outpatient Use ONLY) [when specified as sarilumab (Kevzara)]
J3490	Unclassified drug [when specified as sarilumab (Kevzara)]
J3590	Unclassified biologics [when specified as sarilumab (Kevzara)]

ICD-10 Diagnosis

C90.00-C95.92	Leukemias
D47.Z2	Castleman disease
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor
M06.4	Inflammatory polyarthropathy
M06.80-M06.89	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.20-M08.29	Juvenile rheumatoid arthritis with systemic onset
M08.3	Juvenile rheumatoid polyarthritis (seronegative)
M31.5	Giant cell arteritis with polymyalgia rheumatica
M31.6	Other giant cell arteritis
R65.10-R65.11	Systemic inflammatory response syndrome (SIRS) of non-infectious origin [cytokine release syndrome]
T86.11	Kidney transplant rejection
T86.12	Kidney transplant failure
T86.19	Other complication of kidney transplant
Z94.0	Kidney transplant status

Document History

Revised: 11/20/2020
Document History:

- 11/20/2020 – Annual Review: Add continuation of use section; update tuberculosis testing language. Coding Reviewed: No changes.
- 11/15/2019 – Annual Review: Wording and formatting changes; update combination therapy criteria for consistency with other agents. Coding Reviewed: No Changes.
- 09/23/2019 - Administrative update to add drug specific quantity limit.
- 12/10/2018 – Select Review: Add new QL for Actemra ACTPen autoinjector per label.
- 11/16/2018 – Annual Review: Initial P&T review of Monoclonal Antibodies to Interleukin-6 Clinical Guideline - combined Actemra (tocilizumab) and Kevzara (sarilumab) policies. Update clinical criteria to delete "active" disease wording. Update criteria to delete requirement agent is being used "to reduce signs and symptoms, maintain clinical response", etc. Add examples of conventional therapy to approval criteria for clarity. Update sarilumab QL for clarity. Wording and formatting changes to criteria for consistency. HCPCS coding updated: Added C9399. No ICD-10 changes.

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