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POLICY Document for ACTEMRA

The overall objective of this policy is to support the appropriate and cost effective use of the medication, specific to use of preferred medication options, lower cost site of care and overall clinically appropriate use. This document provides specific information to each of the three sections of the overall policy.

Section 1: Preferred Product
- Policy information specific to preferred medications

Section 2: Site of Care
- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

Section 3: Clinical Criteria
- Policy information specific to the clinical appropriateness for the medication

Section 1: Preferred Product

EXCEPTIONS CRITERIA
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS PRODUCTS

PREFERRED PRODUCTS: ENTYVIO, ILUMYA, REMICADE, SIMPONI ARIA, STELARA IV

POLICY
This policy informs prescribers of preferred products and provides an exception process for targeted products through prior authorization.

I. PLAN DESIGN SUMMARY

This program applies to the disease-modifying antirheumatic drug (DMARD) products specified in this policy. Coverage for targeted products is provided based on clinical circumstances that would exclude the use of the preferred product and may be based on previous use of a product. The coverage review process will ascertain situations where a clinical exception can be made. For psoriasis, this program applies to all adult members requesting treatment with a targeted product. For all other indications, this program applies to adult members who are new to treatment with a targeted product for the first time.

Each referral is reviewed based on all utilization management (UM) programs implemented for the client.

Table. Disease-modifying antirheumatic drugs for autoimmune conditions

	Products	
Preferred	• **Entyvio** (vedolizumab) • **Ilumya** (tildrakizumab-asmn) • **Remicade** (infliximab)	• **Simponi Aria** (golimumab, intravenous) • **Stelara IV** (ustekinumab)*
Targeted	• **Actemra** (tocilizumab) • **Avsola** (infliximab-axxq) • **Cimzia** (certolizumab pegol)	• **Inflectra** (infliximab-dyyb) • **Orencia** (abatacept) • **Renflexis** (infliximab-abda)

*Stelara IV is indicated for a one time induction dose for Crohn's disease and ulcerative colitis.

II. EXCEPTION CRITERIA

This program applies to members requesting treatment for an indication that is FDA-approved for the preferred products.

Coverage for a targeted product is provided when any of the following criteria is met:

A. For Avsola, Inflectra and Renflexis, when member meets both of the following:
   1. Member has a documented intolerable adverse event with the preferred product, Remicade, and the adverse event was not an expected adverse event attributed to the active ingredient as described in the prescribing information.
   2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, and Simponi Aria where the product's indications overlap.

B. For Cimzia, when any of the following criteria are met:
   1. Member is currently receiving treatment with the requested targeted product, excluding when the requested targeted product is obtained as samples or via manufacturer's patient assistance programs, unless the request is for psoriasis.
   2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, Remicade, and Simponi Aria where the product's indications overlap
   3. Member is currently pregnant or breastfeeding

C. For all other targeted products, when any of the following criteria are met:
   1. Member is currently receiving treatment with the requested targeted product, excluding when the requested targeted product is obtained as samples or via manufacturer's patient assistance programs.
   2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, Remicade, and Simponi Aria where the product's indications overlap, unless there is a documented clinical reason to avoid TNF inhibitors (Appendix)

III. Appendix: Clinical reasons to avoid TNF inhibitors

- History of demyelinating disorder
- History of congestive heart failure
- History of hepatitis B virus infection
- Autoantibody formation/lupus-like syndrome
- Risk of lymphoma

Section 2: Site of Care

GUIDELINES FOR HOSPITAL OUTPATIENT SPECIALTY MEDICATION INFUSION

I. INTRODUCTION

There is a wide variation in the site-of-service utilization patterns for specific medications and therapy classes. This is driven by several factors. Some of these specialty medications are derived from pooled blood plasma, and therefore have the potential for an increased risk of infusion-related complications. These differences can affect patient tolerance and a physician's decision to utilize a more acute site of care such as the outpatient hospital. However, many patients that have been established on this treatment with one to several infusions safely administered may be candidates for infusions in a less acute lower-cost site of care.
Outpatient hospital infusion costs may be 2-3 times more compared to other sites of care suggesting an immediate opportunity exists for lowering spend on select specialty medications that require infusion.

Services for patients requiring infused specialty medications may be provided through a physician's in office infusion program or free standing ambulatory infusion center. These options provide access to quality care at a lower cost that may be more convenient for the patient. In addition, many patients who receive home or in office infusion therapy have been shown to experience better outcomes, fewer complications and, improved quality of life and preference, including more personalized attention which helps avoid stress.

This document describes the medical necessity criteria required for hospital outpatient infusion of the medications included in this policy.

II. GENERAL REQUIREMENTS: OUTPATIENT MEDICAL NECESSITY

Infusion in a hospital outpatient setting may be considered medically necessary for medications included in this policy when the criteria below OR individual medication policy criteria are met as outlined section III.

A. Clinical documentation that supports one or more of the following:

1. History of repeated moderate adverse reactions not responding to conventional interventions OR,
2. Laboratory confirmation of autoantibody development
3. The patient is medically unstable which may include respiratory, cardiovascular, or renal conditions that may predispose the member to a severe adverse event that cannot be managed in an alternate setting without appropriate medical personnel and equipment.
4. The patient has previously experienced a severe adverse event during or immediately after an infusion including but not limited to: anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures.
5. Significant venous access issues requiring phlebotomy

B. Patient specific criteria that meets the following:

1. All alternate non-hospital outpatient settings are not within a reasonable distance from the member's home (10-30miles) AND,
2. The patient's home has been determined to be inappropriate for home infusion by a social worker, case manager or previous home nurse assessment or home infusion services are not available due to limited network access

III. MEDICATION SPECIFIC CRITERIA FOR HOSPITAL OUTPATIENT MEDICAL NECESSITY

In addition to the general criteria in Section II, the following guidelines will be applied:

A. TOCILIZUMAB
One or more of the following criteria must be met:

1. To determine tolerance of the therapy, the first two infusions may be permitted in the hospital outpatient setting.
2. Pediatric patients who are less than 21 years of age. The use of non-hospital based alternate site infusion services are at the discretion of the prescribing physician.
3. Patients who have experienced moderate infusion reactions including hypertension, hypotension, tachycardia, syncope, etc that have not responded to standard interventions including infusion rate adjustment and premedication.

IV. GENERAL CONSIDERATIONS: HOME INFUSION

Home Infusion therapy has the potential to deliver cost-effective, quality care.
Efforts to support patients who can receive infused medications care in a lower-cost setting versus an inpatient or clinic-based setting seems appealing, particular if that lower-cost setting is the patient's home.
The home infusion provider will complete an assessment to determine the appropriateness of a patient, caregiver if applicable, and their home prior to initiating care. This assessment may include an evaluation of the following:

- **A.** Accessibility to 911 services and urgent care. Volunteer services may be acceptable if urgent care is readily available.
- **B.** Adequate refrigeration is available if required.
- **C.** Home is not located in a high crime area as determined by local authorities
- **D.** Home environment does not meet general cleanliness standards determined by onsite home nursing assessment

V. BACKGROUND

Therapeutic monoclonal antibodies are laboratory-engineered substances that recognize and bind to a protein on the surface of a cell. Each mAB recognizes a different protein, or antigen. mAB's may be administered alone, in combination with other drugs, or as a carrier of agents. There are four types of antibodies defined by their source: Murine, chimeric (30:70 ratio of mouse to human sequences), humanized (~90% human sequences) and human. Monoclonal antibodies induce moderate acute infusion reactions in 5-10% of patients. Reactions may occur with any dose of therapy; however, they are more common with the first two doses. The mAB's with the highest risk include murine and chimeric. The humanized and human mAB's carry a lesser risk because they carry fewer non-human components.

Tocilizumab is an interleukin-6 receptor inhibitor indicated in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying antirheumatic drug (DMARD) therapies. Tocilizumab may be used as monotherapy or may be combined with methotrexate or other DMARDs. Tocilizumab is indicated as monotherapy or in combination with methotrexate for the treatment of active systemic juvenile idiopathic arthritis in children age 2 years and older.

Serious adverse reactions that have been reported include: gastrointestinal perforation, decreased platelet count (1% to 4%), neutropenia (rheumatoid arthritis, 1.8% to 3.7%; polyarticular or systemic juvenile idiopathic arthritis, 3.7% to 17%), anaphylaxis, hypersensitivity reaction (0% to 0.9%), opportunistic infection, tuberculosis, upper respiratory infection (rheumatoid arthritis, 6% to 8%; systemic juvenile idiopathic arthritis, 5% or higher), cancer, and severe infectious disease.
Infusion reactions have been reported as follows: (Rheumatoid arthritis, 7% to 8%; polyarticular juvenile idiopathic arthritis, 16% to 20.2%)

Section 3: Clinical Criteria

ACTEMRA (tocilizumab)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDS).
2. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.
3. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.
4. Adult patients with giant cell arteritis.
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.

B. Compendial Uses
1. Unicentric Castleman's disease
2. Multicentric Castleman's disease
3. Oligoarticular juvenile idiopathic arthritis
4. Refractory/severe immunotherapy-related inflammatory arthritis not responding to corticosteroids and anti-inflammatory agents

All other indications are considered experimental/investigational and are not medically necessary.

II. CRITERIA FOR INITIAL APPROVAL

A. Moderately to severely active rheumatoid arthritis (RA)

1. Authorization of 12 months may be granted for members who have previously received a biologic or targeted synthetic DMARD (e.g., Rinvoq, Xeljanz) indicated for moderately to severely active rheumatoid arthritis.

2. Authorization of 12 months may be granted for treatment of moderately to severely active RA when any of the following criteria is met:
   a. Member has experienced an inadequate response to at least a 3-month trial of methotrexate despite adequate dosing (i.e., titrated to 20 mg/week).
   b. Member has an intolerance or contraindication to methotrexate (see Appendix A).

B. Active articular juvenile idiopathic arthritis

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for active articular juvenile idiopathic arthritis.

2. Authorization of 12 months may be granted for the treatment of active articular juvenile idiopathic arthritis when any of the following criteria are met:
   a. The member had an inadequate response to methotrexate or another non-biologic DMARD administered at an adequate dose and duration.
   b. The member has risk factors (See Appendix B) and the member also meets one of the following:
      i. High-risk joints are involved (e.g., cervical spine, wrist, or hip).
      ii. High disease activity.
      iii. Are judged to be at high risk for disabling joint disease.

C. Active Systemic Juvenile Idiopathic Arthritis (sJIA)

Authorization of 12 months may be granted for members who have previously received a biologic indicated for active systemic juvenile idiopathic arthritis.

Authorization of 12 months may be granted for the treatment of active sJIA when any of the following criteria is met:
a. Member has an inadequate response to at least a 1-month trial of NSAIDs.

b. Member has an inadequate response to at least a 2-week trial of corticosteroids.
c. Member has an inadequate response to at least a 3-month trial of methotrexate or leflunomide.

D. Giant Cell Arteritis
Authorization of 12 months may be granted for the treatment of giant cell arteritis when the patient's diagnosis was confirmed by the following:
1. Temporal artery biopsy or cross-sectional imaging; or
2. Acute-phase reactant elevation (i.e., high erythrocyte sedimentation rate [ESR] and/or high serum C-reactive protein [CRP])

E. Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome
Authorization of 1 month may be granted for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

F. Unicentric Castleman's Disease
Authorization of 12 months may be granted for treatment of unicentric Castleman's disease when all of the following are met:
1. The member is HIV-negative.
2. The member is human herpesvirus-8-negative.
3. The requested drug will be used as monotherapy.
4. The requested drug is being used as second-line therapy for relapsed/refractory disease.

G. Multicentric Castleman's Disease
Authorization of 12 months may be granted for treatment of multicentric Castleman's disease when both of the following are met:
1. The requested drug will be used as monotherapy.
2. The requested drug is being used as second-line therapy for relapsed/refractory or progressive disease.

H. Immunotherapy-related Inflammatory Arthritis
Authorization of 12 months may be granted for treatment of severe/refractory immunotherapy-related inflammatory arthritis that is not responding to corticosteroids and anti-inflammatory agents.

III. CONTINUATION OF THERAPY

Chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome and immunotherapy-related inflammatory arthritis
All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

All other diagnoses
Authorization of 12 months may be granted for all members (including new members) who are using Actemra for an indication outlined in section II and who achieve or maintain a positive clinical response as evidenced by low disease activity or improvement in signs and symptoms of the condition.

IV. OTHER

For all indications: Member has had a documented negative TB test (which can include a tuberculosis skin test [PPD], an interferon-release assay [IGRA], or a chest x-ray)* within 6 months of initiating therapy for persons

who are naïve to biologic DMARDs or targeted synthetic DMARDs (e.g., Rinvoq, Xeljanz), and repeated yearly for members with risk factors** for TB that are continuing therapy with biologics.

* If the screening testing for TB is positive, there must be documentation of further testing to confirm there is no active disease. Do not administer tocilizumab to members with active TB infection. If there is latent disease, TB treatment must be started before initiation of tocilizumab.

** Risk factors for TB include: Persons with close contact to people with infectious TB disease; persons who have recently immigrated from areas of the world with high rates of TB (e.g., Africa, Asia, Eastern Europe, Latin America, Russia); children less than 5 years of age who have a positive TB test; groups with high rates of TB transmission (e.g., homeless persons, injection drug users, persons with HIV infection); persons who work or reside with people who are at an increased risk for active TB (e.g., hospitals, long-term care facilities, correctional facilities, homeless shelters).

For all indications: Member cannot use Actemra concomitantly with any other biologic DMARD or targeted synthetic DMARD.

V. APPENDIX A: Examples of contraindications to methotrexate

1. Alcoholism, alcoholic liver disease or other chronic liver disease
2. Breastfeeding
3. Blood dyscrasias (e.g., thrombocytopenia, leukopenia, significant anemia)
4. Elevated liver transaminases
5. History of intolerance or adverse event
6. Hypersensitivity
7. Interstitial pneumonitis or clinically significant pulmonary fibrosis
8. Myelodysplasia
9. Pregnancy or planning pregnancy
10. Renal impairment
11. Significant drug interaction

APPENDIX B: Risk factors for articular juvenile idiopathic arthritis

1. Positive rheumatoid factor
2. Positive anti-cyclic citrullinated peptide antibodies
3. Pre-existing joint damage

VI. REFERENCES

REFERENCES:

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